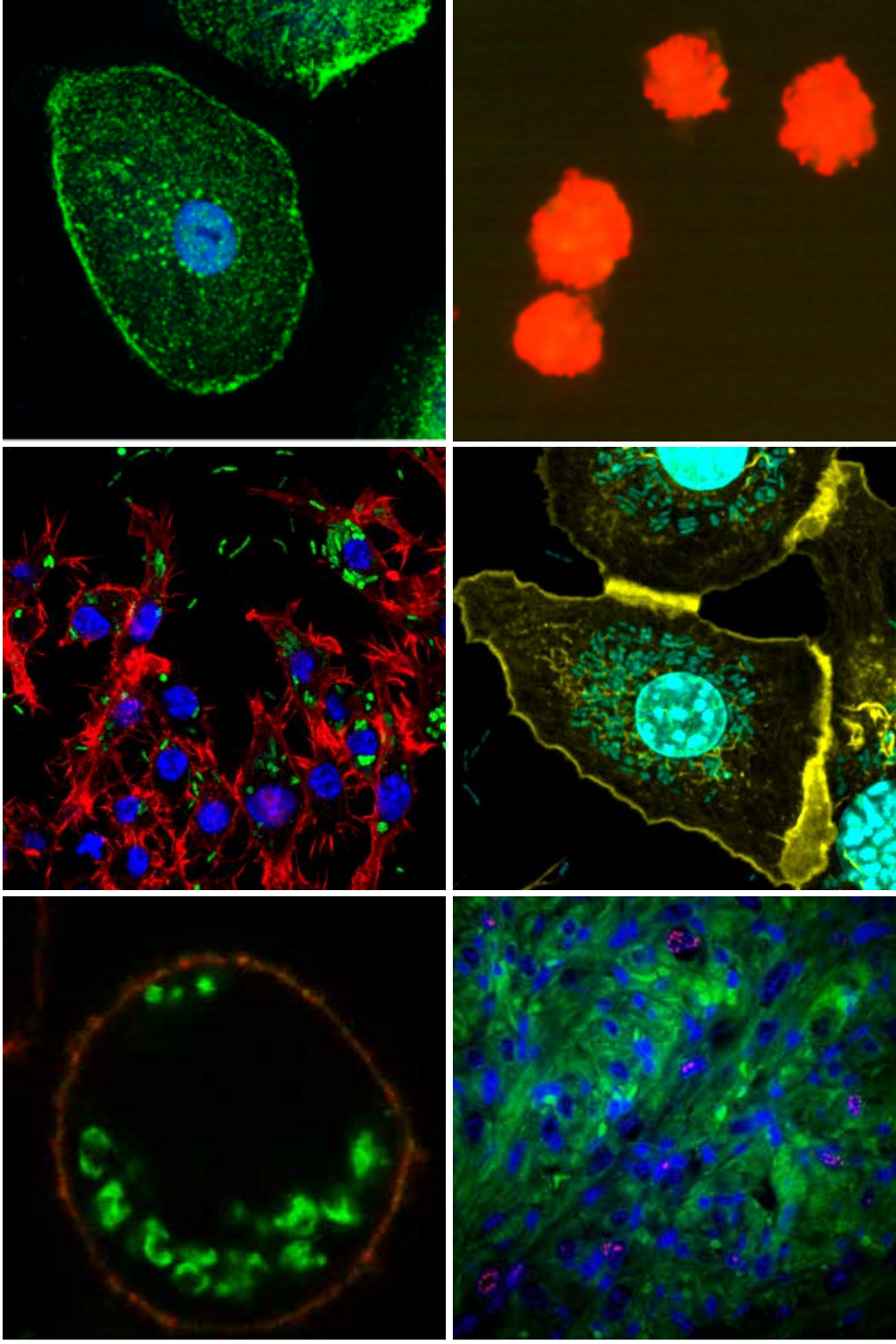

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine

Clinical Research 2020

Sections

Cover images (from bottom left, clockwise):

Image 1: Staining of a novel anti-frizzled7 monoclonal antibody directed at tumor stem Cells. Credit: Benjamin Dekel lab.

Image 2: Growing adult kidney spheroids and organoids for cell therapy. Credit: Benjamin Dekel lab.

Image 3 & 4: Vibrio proteolyticus bacteria infecting macrophages. Credit: Dor Salomon.

Image 5: K562 leukemia cells responding to complement attack (red-complement C9, green-mitochondrial stress protein mortalin) Credit: Niv Mazkereth, Zvi Fishelson.

Image 6: Cardiomyocyte proliferation in newborn mouse heart by phosphohistone 3 staining (purple). Credit: Jonathan Leor.

Editor: Prof. Karen Avraham
Graphic design: Michal Semo Kovetz, TAU Graphic Design Studio
October 2020

The Sackler Faculty of Medicine

The Sackler Faculty of Medicine is Israel's largest medical research and training complex. The Sackler Faculty of Medicine of Tel Aviv University (TAU) was founded in 1964 following the generous contributions of renowned U.S. doctors and philanthropists Raymond, and the late Mortimer and Arthur Sackler. Research at the Sackler Faculty of Medicine is multidisciplinary, as scientists and clinicians combine efforts in basic and translational research. Research is conducted in the laboratories on the TAU campus, and in the clinical facilities affiliated to the Faculty. The Faculty of Medicine includes the Sackler School of Medicine, the School of Health Professions, the School of Public Health, and the School of Dental Medicine. Education takes place in all these schools and in the Graduate School of Medicine, School of Continuing Medical Education, the New York State American Program and the B.Sc. Program in Medical Life Sciences. This network of preclinical and clinical teams helps realize the ultimate goals of the research: the basic understanding of human pathophysiology and the prevention, diagnosis and treatment of disease. The research of clinical faculty members from the Sackler School of Medicine are featured in this research brochure.

The Faculty of Medicine engages in joint teaching and research programs with nearly every faculty at TAU, including the Wise Faculty of Life Sciences, the Sagol School of Neuroscience, the Edmond J. Safra Bioinformatics Center, the TAU Center for Nanoscience and Nanotechnology, and the Edmond J. Safra Center for Ethics, and multi-nationally with schools, hospitals and research centers throughout the world. The Sackler faculty is known for research in the following areas: cancer biology, stem cells, diabetes, neurodegenerative diseases, infectious diseases and genetic diseases, including but not imited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians in 181 Sacker affiliated departments and institutes in 17 hospitals hold academic appointments at TAU. The Gitter-Smolarz Life Sciences and Medicine Library serves students and staff and is the center of a consortium of 15 hospital libraries.

The student body is made up of 750 Israeli students enrolled in the 6-year M.D. degree program, 300 American and Canadian students enrolled in a 4-year M.D. program chartered by the State of New York and accredited by the State of Israel, and a 4-year program for Israeli students for the M.D. degree, with 260 students. Approximately 200 students study dental medicine in a six-year program where they are awarded the D.M.D. degree and another 2,000 students are enrolled in the health professions programs where they will earn degrees in Communications Disorders, Nursing, Physical Therapy and Occupational Therapy. Sackler's Graduate School for Advanced Studies trains approximately 800 masters and doctoral level students in the biomedical disciplines, with a special emphasis on a multidisciplinary approach and application of fundamental knowledge to important biomedical problems.

The Sackler Faculty of Medicine is led by the Dean, Prof. Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Ami Fishman, Prof. Arnon Wiznitzer, and Assistant to the Dean, Michal Gilboa.

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Cancer

K562 leukemia cells responding to complement attack
(red-complement C9, green- Rab11, blue- mitochondria mitotracker)
Credit: Niv Mazkereth, Zvi Fishelson

Prof. Nadir Arber, M.D., M.Sc., MHA

Integrated Cancer Prevention Center
Djerassi Oncology Center
Tel Aviv Sourasky Medical Center

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Cancer Prevention Research Laboratory

Positions

Professor of Medicine & Gastroenterology

Yechiel and Helen Leiber Professor for Cancer Research

Chair, Israeli Gastroenterological Association

Head, Integrated Cancer Prevention Center, Tel Aviv Sourasky Medical Center

Head, Promotion Center and Integrated Cancer Prevention Center Head, Djerassi Oncology Center

Former head, Cancer Research Center, Tel Aviv University

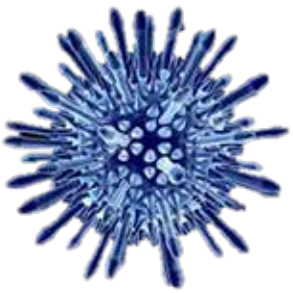
Former head, Dotan Center for Hemato-oncology, Tel Aviv University

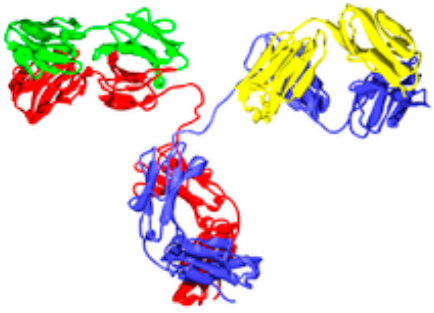
Research

Laboratory of Molecular Biology – ICPC

The Integrated Cancer Prevention Center (ICPC) has diverse and broad experience in translational research focused on early detection, prevention and therapy of cancer, particularly in tumors of the gastrointestinal (GI) tract. The team is highly experienced in clinical studies, molecular epidemiology as well as in molecular and cell biology studies of cancer.

Currently, on-going researches at the ICPC focus on translational research, bridging between basic researches in the lab and clinicians and patients in the clinical center. The center has a long history of planning, developing, and conducting clinical trials, with a main focus on investigator-initiated and cooperative group trials investigating the activity of





drugs for the prevention and treatment of colorectal cancer (CRC).

Basic research takes place at the Laboratory of Molecular Biology, headed by Dr. Shiran Shapira, a senior scientist and member of the academic staff at Tel Aviv University. Dr. Shapira devotes herself to cancer research in the fields of early detection, prevention, and cancer therapy. She possesses extensive experience in wide range of biology areas with foucing on cancer research, biochemistry, molecular biology, signal transduction, antibody engineering, protein expression and purification and gene delivery.

Research Team

Prof. Nadir Arber, MD, MSc, MHA, Head of ICPC; Dr. Shiran Shapira, PhD, Head of Laboratory; Dina Kazanov, MSc; Dr. Eliezer Liberman, MD; Ilana Bostenai, PhD student; Ahmad Fokra, PhD student; Sally Zigdon, MSc; Lina Tiklan

Projects

1. Early detection – development of new methods for the early detection of CRC and colorectal adenomas as well as other types of solid and hematological cancers. The tested samples taken from humans, blood and urine.

2. Prevention – Serving as the PI of several international, multicenter trials in the prevention of GI tumors, and in particular sporadic and familial CRC.

3. Identifying high risk subjects through molecular epidemiology – We have identified a new polymorphism in the APC gene (E1317Q), which is more common in Sephardic Jews and Arabs and is associated with a HR of ~4. When it is combined with another polymorphisms in the CD24 gene (V248A) the OR is 7.8.

4. Detection of new oncogenes that play a role in the multistep process of CRC carcinogenesis.

The research team at the Laboratory of Molecular Biology has been exploring, for several years, the hypothesis that CD24 is a potential oncogene in GI malignancies and may serve as a biomarker and target for the treatment of cancer and cancer-related chronic inflammatory disorders such as, inflammatory bowel diseases (IBD).

5. Treatment - Development of novel therapeutic strategies for cancer treatment with a main focus on immunotherapy using humanized anti-CD24 monoclonal Abs, immunotoxin and bi-specific

6. Design of novel therapeutic agents targeting Ras and Wnt pathways that play an important role in GI carcinogenesis, based on gene therapy using adenoviruses and highly sophisticated viral vectors such as adenoviruses, lentiviruses and adeno-associated viruses.

7. Wound healing- CD24 may represent a novel clinical intervention strategy to accelerate the healing of wounds both acute and chronic injuries for patients. The proposed treatment may enable faster recovery from injuries while reducing the risk of infection, toxicity and other possible side

Publications

Mikus M, Drobin K, Gry M, Bachmann J, Lindberg J, Yimer G, Aklillu E, Makonnen E, Aderaye G, Roach J, Fier I, Kampf C, Göpfert J, Perazzo H, Poynard T, Stephens C, Andrade RJ, Lucena MI, **Arber N**, Uhlén M, Watkins PB, Schwenk JM, Nilsson P, Schuppe-Koistinen I. Elevated levels of circulating CDH5 and FABP1 in association with human drug-induced liver injury. *Liver Int*. 2016 May 25. doi: 10.1111/liv.13174. [Epub ahead of print]

Moshkowitz, M., Fokra, A., Itzhak, Y., **Arber, N**. & Santo, E. Feasibility study of minimal prepared hydroflush screening colonoscopy. *United European Gastroenterology Journal*, 4(1):105-9, (2016).

Leshno, A., **Shapira, S**., Liberman, E., Kraus, S., Sror, M., Harlap-Gat, A., Avivi, D., Galazan, L., David, M., Maharshak, N., Moanis, S., **Arber, N.** and Moshkowitz, M. The APC I1307K allele conveys a significant increased risk for cancer. *Int J Cancer*, 138(6):1361-7, (2016).

Leshno, A., Moshkowitz, M., David, M., Galazan, L., Neugut, Al., **Arber, N.** and Santo, I. Prevalence of colorectal neoplasms in young, average risk individuals: A turning tide between East and West. *World J Gastroenterol,* 22(32): 00000-0000, (2016)

Pillar, N., Isakov, O., Weissglas-Volkov, D., Botchan, S, Friedman, E, **Arber, N.**, Shomron, N. Actionable clinical decisions based on comprehensive genomic evaluation in asymptomatic adults. *Molecular Genetics & Genomic Medicine,* 3(5),433-9, (2015).

Kraus, S., Shapira, S., Kazanov, D., Naumov, I., Moshkowitz, M., Santo, E., Galazan, L.,Geva, R., Shmueli, E., Hallack, A., **Arber, N.** Predictive Levels of CD24 in Peripheral Blood Leukocytes for the Early Detection of Colorectal Adenomas and Adenocarcinomas. *Disease Markers*, 2015:916098 (2015)

Kaplan, I., Nabiochtchikov, I., Leshno, A., Moshkowitz, M., Shlomi, B., Kleinman, S., Dagan, Y., Galazan, L., Avivi, L., Kraus, S., **Arber, N.** Association of CD24 and the Adenomatous Polyposis Coli (APC) Gene Polymorphisms with Oral Lichen Planus. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology (TRIPLEO)*, 120(3):378-85 (2015)

Shamai, S., Nabiochtchikov, I., Zigdon, S., Kraus, S., Kazanov, D., tzhak-Klutch, M., Eizner, C., **Arb**er, **N.,** Geva, R. CD24 and APC genetic polymorphisms in pancreatic cancers as potential biomarkers for clinical outcome. *PLoS One*, 10(9):e0134469 (2015)

Shapira, S., Ben-Amotz, O., Sher, O., Kazanov, D., Mashiah, J., Kraus, S., Gur, E., **Arber, N**. Delayed Wound Healing in Heat Stable Antigen (HSA/CD24)-Deficient Mice. *PLoS One,* 10(10):e0139787 (2015) Gluck, N., Shpak, B., Brun, R., Rösch, T., **Arber, N.**, Moshkowitz, M. A novel prepless X-ray imaging capsule for colon cancer screening. *Gut,* 65(3):371-3 (2015)

Kaplan I, Nabiochtchikov I, Leshno A, Moshkowitz M, Shlomi B, Kleinman S, Dagan Y, Meshiach Y, Galazan L, **Arber N**, Avivi-Arber L, Kraus S. Association of CD24 and the adenomatous polyposis coli gene polymorphisms with oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2015 Sep;120(3):378-85.

Kraus S, Sion D, **Arber N**. Can We Select Patients for Colorectal Cancer Prevention with Aspirin? *Curr Pharm Des*. 2015;21(35):5127-34.

Shapira S, Pleban S, Kazanov D, Tirosh P, **Arber N**. Terpinen-4-ol: A Novel and Promising Therapeutic Agent for Human Gastrointestinal Cancers. *PLoS One*. 2016 Jun 8;11(6):e0156540.

Kimchy Y, Lifshitz R, Lewkowitz S, Bertuccio G, **Arber N**, Gluck N, Pickhardt PJ. Radiographic capsule-based system for non-cathartic colorectal cancer screening. *Abdom Radiol (NY)*. 2017 Jan 4.

Dr. Osnat Ashur-Fabian, Ph.D.

Translational Oncology; Meir Medical Center
Department of Human Molecular Genetics and Biochemstry, Sackler Faculty of Medicine

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Investigating Hormone Metabolism in Cancer

Positions

Senior Lecturer, Sackler Faculty of Medicine

Principle Investigator, Translational Oncology Laboratory, Sapir Medical Center, Kfar- Saba

Research

Our research deals with the role of thyroid hormones in cancer progression and on the development of a novel class of targeted cancer therapy. A set of small molecules that specifically block the thyroid-cancer axis were developed. Our research group is the first to show the potent elimination of various cancer types by these novel drugs.

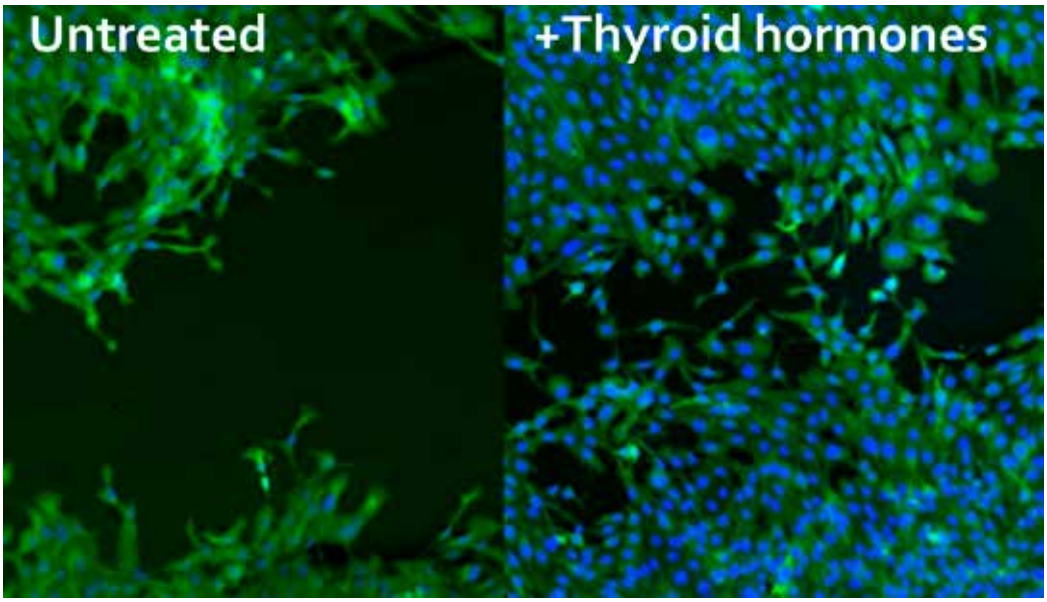
Publications

Cohen K, Ellis M, Khoury S, Davis PJ, Hercbergs A and **Ashur-Fabian O.** Thyroid hormone effects on myeloma bone marrow and cell lines: avb3-integrin mediated signaling with relevance to the action of bortezomib. *Leuk & Lymph*, 20:1-8, 2015.

Davis PJ, Glinsky GV, Lin HY, Leith JT, Hercbergs A, Tang HY, **Ashur-Fabian O**, Incerpi S, Mousa SA. Cancer Cell Gene Expression Modulated from Plasma Membrane Integrin αvβ3 by Thyroid Hormone and Nanoparticulate Tetrac. Front Endocrinol (Lausanne). 5:1-7, 2015.

Hercbergs A, Johnson RE, **Ashur-Fabian O**, Garfield DH, Davis PJ. Medically Induced Euthyroid Hypothyroxinemia May Extend Survival in Compassionate Need Cancer Patients: An Observational Study. The Oncologist, 20(1):72-6, 2015.

Pereg D, Cohen K, Mosseri M, Berlin T, Steinberg DM, Ellis M and **Ashur-Fabian O**. Cell free expression of stress-inducible mRNA in the peripheral blood of acute myocardial infarction patients. *Journal of Arteriosclerosis and Thrombosis*, 22(9):981-98, 2015.



Ovarian cancer cell proliferation and migration is enhanced by thyroid hormones

Fabian ID, Rosner M, Fabian I, Vishnevskia-Dai V, Zloto O, Shinderman E, Cohen K, Ellis M, Hung-Yun Lin, Hercbergs A, Davis PJ and **Ashur-Fabian O**. The Impact of Thyroid Hormone Levels on Survival in a Uveal Melanoma Murine Model. *Oncotarget*, 6(13): 6(13):11038-46, 2015

Shinderman-Maman E, Cohen K, Weingarten C, Nabriski D, Twito O, Baraf L, Hercbergs A, Davis PJ, Werner H, Ellis M and **Ashur-Fabian O**. The thyroid hormone-avb3 integrin axis in ovarian cancer: Regulation of gene transcription and MAPK-dependent proliferation. *Oncogene*,35(15):1977-87, 2016.

Yacobovich S, Tuchinsky L, Kirby M, Kardash T, Agranioni O, Nesher E, Redko B, Gellerman G, Tobi D, Gurova K, Koman I, **Ashur-Fabian O** and Pinhasov A. Novel synthetic cyclic integrin αvβ3 binding peptide ALOS4: Antitumor activity in mouse melanoma models. *Oncotarget*, 7(39):63549-63560, 2016.

Ellis M, Stern O and **Ashur-Fabian O**. The double benefit of Spalax p53: surviving underground hypoxia while defying lung cancer cells in vitro via autophagy and caspase-dependent cell death. *Oncotarget*, 7(39):63242-63251, 2016.

Ellis M, Krashin E, Hamburger-Avnery O, Gan S, Elis A and **Ashur-Fabian O**. The anti-leukemic and lipid lowering effects of imatinib are not hindered by statins in CML: a retrospective clinical study and in vitro assessment of lipid-genes transcription. *Leuk. & Lymph*, 58(5):1172-1177, 2017.

Redko B, Tuchinsky H, Segal T, Tobi D, Luboshits G, **Ashur-Fabian O**, Pinhasov A, Gerlitz G, Gellerman G.Toward the development of a novel non-RGD cyclic peptide drug conjugate for treatment of human metastatic melanoma. Oncotarget. 8(1):757-768, 2017.

Shinderman-Maman E, Cohen K, Moskovich D, Hercbergs A, Werner H, Davis PJ, Ellis M, **Ashur-Fabian O**. Thyroid hormones derivatives reduce proliferation and induce cell death and DNA damage in ovarian cancer. Scientific Reports 28;7(1):16475, 2017.

Weingarten C, Jenudi Y, Tshuva RY, Moskovich D, Alfandari A, Hercbergs A, Davis PJ, Ellis M and **Ashur-Fabian O**. The interplay between epithelial-mesenchymal transition (EMT) and the thyroid hormones-avb3 axis in ovarian cancer. Hormones and Cancer, 2017.

Krashin E, Ellis M, Cohen K, Viner M, Neumark E, Rashid G and **Ashur-Fabian O**. Chemical and Metabolic Profile of the Bone Marrow Interstitial Fluid in Plasma Cell Dyscrasias and Other Hematologic Disorders. Hematological Oncology, 2017.

Shinderman-Maman E, Weingarten C, Moskovich D, Werner H, Hercbergs A, Davis PJ, Ellis M, **Ashur-Fabian O**. Molecular insights into the transcriptional regulatory role of thyroid hormones in ovarian cancer. Mol Carcinog. 57(1):97-105, 2018.

Cohen K, Abadi U, Hercbergs A, Davis PJ, Ellis M, Ashur-Fabian O. The induction of myeloma cell death and DNA damage by tetrac, a thyroid hormone derivative. Endocr Relat Cancer. 25(1):21-34, 2018.

Mousa SA, Glinsky GV, Lin HY, Ashur-Fabian O, Hercbergs A, Keating KA, Davis PJ. contributions of thyroid hormone to cancer metastasis. Biomedicines, 6, 2018.

Ashur-Fabian O, Zloto O, Fabian I, Tsarfaty G, Ellis M, Steinberg DM, Hercbergs A, Davis PJ, Fabian ID. Tetrac delayed the onset of ocular melanoma in an orthotopic mouse model. Front Endocrinol (Lausanne), 9:775, 2019.

Dayan A, Fleminger G, Ashur-Fabian O. Targeting the Achilles' heel of cancer cells via integrin-mediated delivery of ROS-generating dihydrolipoamide dehydrogenase. Oncogene, 38:5050-5061, 2019.

Reviews

Krashin E, Piekiełko-Witkowska A, Ellis M, Ashur-Fabian O. Thyroid hormones and cancer: A comprehensive review of preclinical and clinical studies. Front Endocrinol (Lausanne), 10:59, 2019.

Davis PJ, Ashur-Fabian O, Incerpi S, Mousa SA. Editorial: Non genomic actions of thyroid hormones in cancer. Front Endocrinol (Lausanne), 10:847, 2019.

Grants

2015-2019 The Dotan Research Center, Tel Aviv University, Nuclear integrin in cancer

2018-2019 Sackler school of Medicine, Tel Aviv University, Selenoproteins in platelets

Prof. Iris Barshack, M.D.

Department of Pathology
Sheba Medical Center, Tel-Hashomer

TEL AVIV UNIVERSITY

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Investigating Markers of Inflammation and of Neoplastic Processes for Diagnosis and Treatment

Positions

Professor of Pathology

Vice Dean, Head of School of Medicine, Sackler Faculty of Medicine, Tel Aviv University

Head, Department of Pathology

Co-director, Tumor Tissue Bank, Molecular Diagnostic Service, Precision Medicine Project (diagnostic service), Digital Pathology Project, Sheba Medical Center, Tel Hashomer

Research

The profession of Pathology encompasses three main constituents: diagnostics, teaching and research. Within the department, description, processing and examination of the macroscopic specimen is performed by the doctors of the department. The specimens undergo histochemical staining. If necessary for the sake of diagnosis, additional specialized histochemical and immunohistochemical stains are carried out. Furthermore, the department executes other techniques that enable precise diagnosis such as: FISH, PCR, In-situ hybridization and Electron Microscopy visualization. The department delves in a large array of research projects with the cooperation of other departments within and outside of the hospital, and intrinsic research of the department itself.

The department encompasses a laboratory specific for histochemical staining, a laboratory for immunohistochemical staining that performs in-situ hybridization, as well as a laboratory for PCR, Electron Microscopy, FISH and for Molecular Pathology. Moreover, we are leading the tumor tissue bank of the Sheba Medical Center, and the Molecular Diagnostic Service of the Sheba Medical Center, using an advanced NGS platform for diagnostic and research purposes. We also perform on a routine and research basis immunohistochemical stainings and molecular methods for precision medicine and immunotherapy. Furthermore, the department includes an advanced system for photographing and processing both macroscopic and microscopic constituents, and leads the Digithal Pathology Project of the Sheba medical Center.

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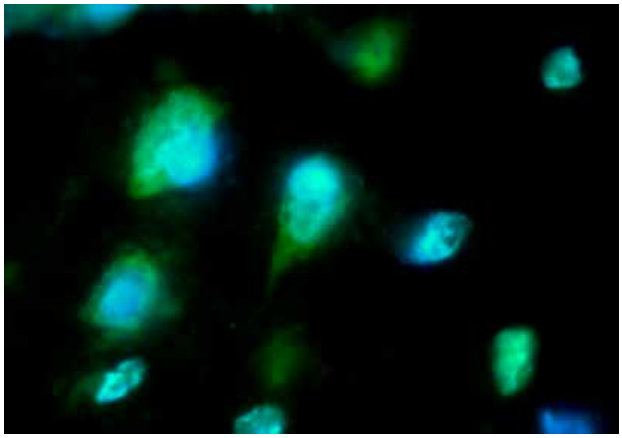

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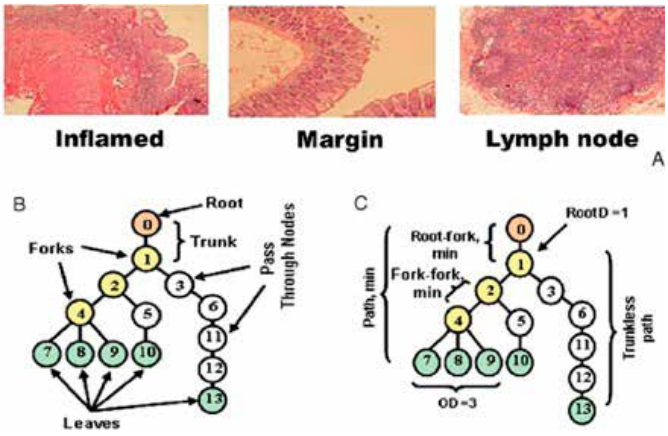

Fish of miR124 in normal brain. B. B-cell clonal diversification and gut-lymph node trafficking in ulcerative colitis revealed using lineage tree analysis. *Eur J Immunol* 38: 2600-2609 (2008).

Another branch is that of independent research. One of the great accomplishments has been the conceptual implementation of the use of microRNAs to aid in the identification of different tissues and the application of this knowledge to identify metastases of unknown origin. In situ hybridization of microRNAs is an important methodology used in our research for studing the pathogenesis of inflammatory and of neoplastic processes. Another area of research in which the department is leading is the development of the technology of tissue microarrays. The department leads the investigation of inflammatory processes and lymphoproliferative tumors according to the production and study of heavy chain B lymphocytes within the tissue. In light of this investigation, the department received a number of important research grants.

Publications

Zippel D, Barlev H, Ortenberg R, **Barshack I**, Schachter J, Markel G. A longitudinal study of CEACAM1 expression in melanoma disease progression. Oncol Rep. 2015;33(3):1314-8.

Carvalho S, Lindzen M, Lauriola M, Shirazi N, Sinha S, Abdul-Hai A, Levanon K, Korach J, **Barshack I**, Cohen Y, Onn A, Mills G, Yarden Y. An antibody to amphiregulin, an abundant growth factor in patients' fluids, inhibits ovarian tumors. Oncogene. 2016;35(4):438-47.

Grossman C*, **Barshack I***, Bornstein G, Ben-Zvi I. Is temporal artery biopsy essential in all cases of suspected giant cell arteritis? Clin Exp Rheumatol. 2015;33(2 Suppl 89):84-9.* *both authors contributed equally to the manuscript*

Kandel-Kfir M, Almog T, Shaish A, Shlomai G, Anafi L, Avivi C, **Barshack I**, Grosskopf I, Harats D, Kamari Y. Interleukin-1α deficiency attenuates endoplasmic reticulum stress-induced liver damage and CHOP expression in mice. J Hepatol. 2015; 63(4):926-33.

Svetlicky N, Kivity S, Odeh Q, Shovman O, Gertel S, Amital H, Gendelman O, Volkov A, **Barshack I**, Bar-Meir E, Blank M, Shoenfeld Y. Anti-citrullinated-protein-antibody-specific intravenous immunoglobulin attenuates collagen-induced arthritis in mice. Clin Exp Immunol. 2015; 182(3):241-50.

Sarit Aviel-Ronen, Tami Rubinek, Oranit Zadok, Aya Vituri, Camila Avivi, Ido Wolf, **Barshack I**. Klotho expression in cervical cancer: differential expression in adenocarcinoma and squamous cell carcinoma. J Clin Pathol. 2016;69(1):53-7.

Leibowitz A, Volkov A, Voloshin K, Shemesh C, **Barshack** I, Grossman E. Melatonin prevents kidney injury in a high salt diet-induced hypertension model by decreasing oxidative stress. J Pineal Res. 2016;60(1):48-54.

Tabibian-Keissar H, Hazanov L, Schiby G, Rosenthal N, Rakovsky A, Michaeli M, Shahaf GL, Pickman Y, Rosenblatt K, Melamed D, Dunn-Walters D, Mehr R, **Barshack** I. Aging affects B-cell antigen receptor repertoire diversity in primary and secondary lymphoid tissues. Eur J Immunol. 2016;46(2):480-92.

Aviel-Ronen S, Zadok O, Vituri A, Nass D, Schwartz I, Avivi C, **Barshack** I. α-methylacyl-CoA racemase (AMACR) expression in chordomas differentiates them from chondrosarcomas. Sci Rep. 2016;6:21277.

Pozniak Y, Balint-Lahat N, Rudolph JD, Lindskog C, Katzir R, Avivi C, Pontén F, Ruppin E, **Barshack** I, Geiger T. System-wide clinical proteomics of breast cancer reveals global remodeling of tissue homeostasis. Cell Syst. 2016;2(3):172-84.

Dror S, Sander L, Schwartz H, Sheinboim D, Barzilai A, Dishon Y, Apcher S, Golan T, Greenberger S, **Barshack** I, Malcov H, Zilberberg A, Levin L, Nessling M, Friedmann Y, Igras V, Barzilay O, Vaknine H, Brenner R, Zinger A, Schroeder A, Gonen P, Khaled M, Erez N, Hoheisel JD, Levy C. Melanoma miRNA trafficking controls tumour primary niche formation. Nat Cell Biol. 2016;18(9):1006-17.

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Investigating the Microenvironment Interactions and B-cell Receptor Signaling in Chronic Lymphocytic Leukemia

Positions

Senior Lecturer, Sackler Faculty of Medicine

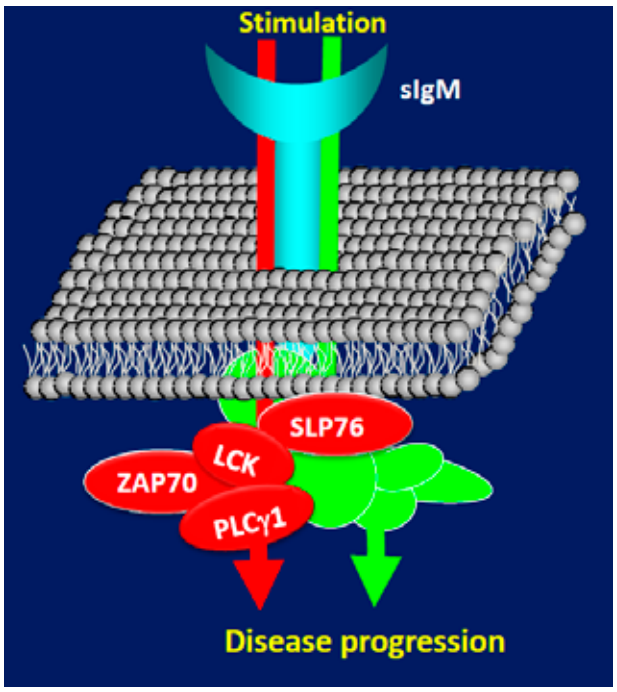
Head, CLL Service, Tel Aviv Sourasky Medical Center

Secretary, Israeli CLL Study Group

Committee Member, Israel Society of Hematology

Research

We study interactions between the CLL cells and the tissue microenvironment and explore new aspects of the B-cell receptor (BCR) signaling in CLL cells. Our previous work characterized distinct *in vivo* gene expression signatures of CLL cells derived from the different compartments of blood, bone marrow and lymph nodes. Recently, we have shown that SLP76, an adaptor protein of the T-cell receptor pathway, is ectopically expressed in CLL cells and mediates alternative signaling downstream of the BCR (Figure). Our research is aimed to discover novel targets of therapy of CLL. Our group is well experienced in performing cell biology assays, flow cytometry and image analysis, protein analysis and gene silencing in primary CLL cells, and is highly skillful in studying signaling in CLL cells.



CLL cells ectopically express T-cell receptor associated signaling molecules, which potentiates their B-cell receptor responsiveness.

Publications

Ofran Y, Filanovsky K, Gafter-Gvili A, Vidal L, Aviv A, Gatt ME, Silbershatzl, **Herishanu Y**, Arad A, Tadmor T, Dally N, Nemets A, Rouvio O, Ronson A, Herzog Tzarfati K, Akria L, Braester A, Hellmann I, Yeganeh S, Nagler A, Leiba R, Mittelman M, Merkel D. Higher infection rate after 7- compared with 5-day cycle of azacitidine in patients with higher-risk myelodysplastic syndrome. Clin Lymphoma Myeloma Leuk 15:e95-9, 2015.

Herishanu Y, Goldschmidt N, Bairey O, Ruchlemer R, Fineman R, Rahimi-Levene N, Shvidel L, Tadmor T, Ariel A, Braester A, Joffe E and Aaron Polliack. Efficacy and safety of frontline therapy with "FCR" regimen for chronic lymphocytic leukemia outside clinical trials: the Israeli CLL Study Group experience. Haematologica 100:662-9, 2015.

Sarid N, Kay S, Angel A, Trakhtenbrot L, Amit O, **Herishanu Y**, Perry C. diagnosis of relapsed burkitt's lymphoma in a urine sample: an unusual "FISHing" expedition. Isr Med Assoc J 17:648-9, 2015.

Herishanu Y and Katz BZ. Cryoglobulins mimicking platelet recovery in a mantle cell lymphoma patient treated with chemo-immnotherapy. Blood 125:1047, 2015.

Perry C, Lerman H, Joffe E, Sarid N, Amit O, Avivi I, Kesler M, Ben-Ezra J, Even-Sapir E and **Herishanu Y.** The value of PET-CT in detecting bone marrow

involvement in patients with follicular lymphoma. Medicine (Baltimore) 95:e2910, 2015.

Dezorella N, Kay S, Baron S, Shapiro M, Porat Z, Naparstek E, Deutsch V, **Herishanu Y**, and Katz BZ. Measurement of lymphocyte aggregation by flow cytometry physiological implications in chronic lymphocytic leukemia. Cytometry B Clin Cytom 90:257-66, 2016.

Sarid N, Joffe E, Polliack A, Avivi I, Perry C and **Herishanu Y**. Reduced-dose ICE chemotherapy ± rituximab is a safe and effective salvage therapy for fit elderly patients with diffuse large B-cell lymphoma. Leuk Lymphoma 57:1633-9, 2016.

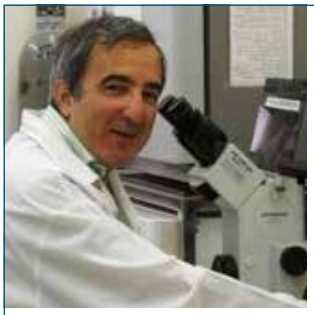
Gentile M, Zirlik K, Ciolli S, Francesca R, Mauro FR, Di Renzo N, Mastrullo L, Angrilli F, Molica S, Tripepi G, Specchia G, Di Raimondo F, Selleri C, Coscia M, Musso M, Orsucci L, Mannina D, Cimino G, Melpignano A, Ferrara F, **Herishanu Y**, et al. Bendamustine plus rituximab for untreated patients with Chronic Lymphocytic Leukemia: a multicenter, retrospective, real-life trial. Eur J Cancer 60:154-65, 2016.

Marom A, Barak AF, Kramer MP, Lewinsky H, Binsky-Ehrenreich I, Cohen S, Sitsou-Kampeli A, Kalchenko V, Kuznetsov Y, Mirkin V, Dezorella N, Shapiro M, Schwartzberg PL, Cohen Y, Shvidel L, Haran M, Becker-Herman S, **Herishanu Y**, Shachar I. CD84 mediates CLL-microenvironment interactions. Oncogene. 2016 Jul 25. [Epub ahead of print]

Dezorella N, Katz BZ, Shapiro M, Polliack A, Perry C and **Herishanu Y**. SLP76 integrates into the B-Cell receptor signaling cascade in chronic lymphocytic leukemia cells and is associated with aggressive disease course. Haematologica. 2016 Jul 21. [Epub ahead of print]

Mittelman M, Filanovsky K, Ofran Y, Rosenbaum H, Raanani P, Braester A, Goldschmidt N, Kirgner I, **Herishanu Y**, Perri C, Ellis M, Oster HS; Israel Myelodysplastic Syndrome Working Group (MDS-WG). Azacitidine-lenalidomide (ViLen) combination yields a high response rate in higher risk myelodysplastic syndromes (MDS)-ViLen-01 protocol. Ann Hematol 95:1811-8, 2016.

Herishanu Y, Polliack A, Shenhar-Tsarfaty S, Weinberger R, Gelman R, Ziv-Baran T, Zeltser D, Shapira I, Berliner S, and Rogowski O. Increased serum C-reactive protein levels are associated with shorter survival and development of second cancers in chronic lymphocytic leukemia. Ann Med. 2016 Sep 5:1-22. [Epub ahead of print]



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Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions

Professor, Sackler Faculty of Medicine

Chair, MD-PhD program

Research

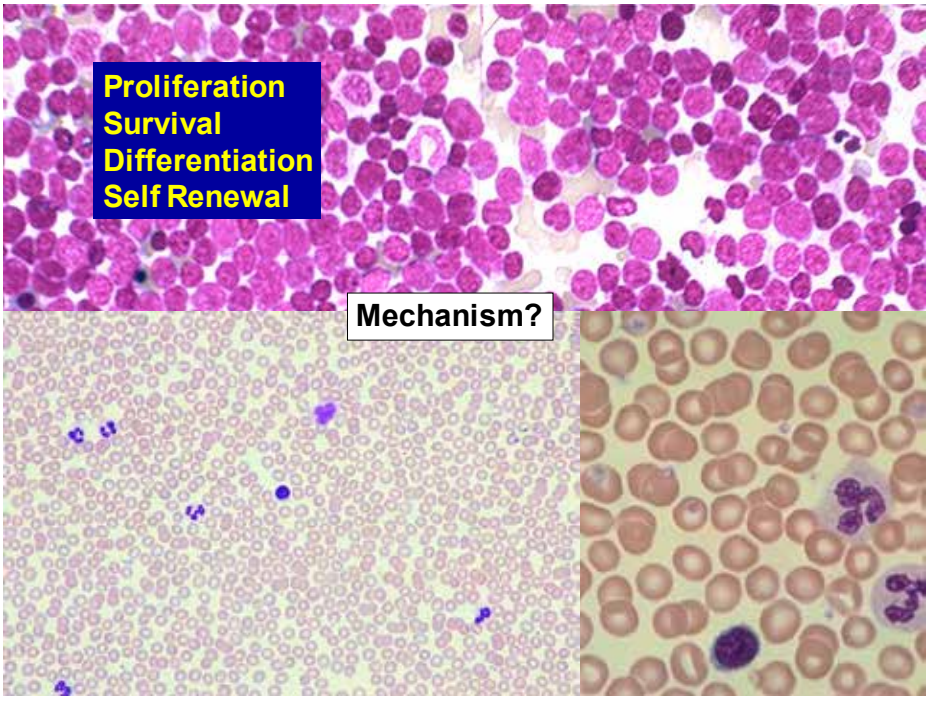
We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

Our research is divided into two major topics:

1. Basic, translational and clinical research of leukemia.

2. The role of SIL (STIL) protein in mitosis, centrosomal biology and cancer.

Cancer is the deadliest disease of children and leukemia is the most common childhood cancer.



Carboxypeptidase E (CPE), a novel Wnt inhibitor, is excluded from the colonic crypt bottom.

We are interested in the fundamental question how normal blood development is diverted into leukemia. What are the genetic and biochemical abnormalities that block cell differentiation, enhance proliferation and survival and confer the unique stem cell properties of self renewal to leukemia stem cells? We focus on chromosome 21 because of the mysterious association of leukemia with Down Syndrome. We utilize advanced genomic technologies, cell based assays of transformation of primary human and mouse stem cells, mouse models including transgenic, transplantation and explants of human leukemia. Our recent discoveries of the major involvement of the TSLP-IL7R-JAK2 pathway in leukemogenesis have lead to clinical trials with novel inhibitors of this pathway for high-risk leukemias in children and adults. The spread of leukemia to the brain is a major clinical problem as preventive therapy to the brain consisting of chemotherapy or irradiation causes long term side effects. We are therefore studying how leukemia cells spread to the central nervous system and developing mouse models to study this challenging problem.

We have discovered that SIL, a gene cloned from childhood leukemia, is required for centrosomal biogenesis and for survival of cancer cells. Targeting SIL by siRNA cause cancer cell death at mitotic entry in-vitro and in-vivo. Current research focuses on the fundamental role of the SIL protein in centrosome generation in normal and malignant cells and on developing approaches for its targeting for cancer therapy.

Publications

David, A., H. Amartely, N. Rabinowicz, M. Shamir, A. Friedler, and **S. Izraeli**. Molecular basis of the STIL coiled coil oligomerization explains its requirement for de-novo formation of centrosomes in mammalian cells. *Sci Rep*, 2016. **6**: 24296.

Townsend, E.C., M.A. Murakami, A. Christodoulou, **S. Izraeli**, …J.C. Aster, M.A. Shipp, J.D. Griffin, and D.M. Weinstock. The public repository of xenografts enables discovery and randomized phase ii-like trials in mice. *Cancer Cell*, 2016. 29: 574-86.

Williams, M.T., Y.M. Yousafzai, A. Elder, K. Rehe, S. Bomken, L. Frishman-Levy, S. Tavor, P. Sinclair, K. Dormon, D. Masic, T. Perry, V.J. Weston, P. Kearns, H. Blair, L.J. Russell, O. Heidenreich, J.A. Irving, **S. Izraeli**, J. Vormoor, G.J. Graham, and C. Halsey. The ability to cross the blood-cerebrospinal fluid barrier is a generic property of acute lymphoblastic leukemia blasts. *Blood*, 2016. 127: 1998-2006.

Amar, D., T. Hait, **S. Izraeli**, and R. Shamir. Integrated analysis of numerous heterogeneous gene expression profiles for detecting robust disease-specific biomarkers and proposing drug targets. *Nucleic Acids Res*, 2015. 43: 7779-89.

Bugarin, C., J. Sarno, C. Palmi, A.M. Savino, G. te Kronnie, M. Dworzak, A. Shumich, B. Buldini, O. Maglia, S. Sala, I. Bronzini, J.P. Bourquin, E. Mejstrikova, O. Hrusak, D. Luria, G. Basso, **S. Izraeli,** A. Biondi, G. Cazzaniga, G. Gaipa, and I.B.s. group. Fine tuning of surface CRLF2 expression and its associated signaling profile in childhood B-cell precursor acute lymphoblastic leukemia. *Haematologica*, 2015. 100: e229-32.

Frishman-Levy, L., A. Shemesh, A. Bar-Sinai, C. Ma, Z. Ni, S. Frenkel, V. Muench, H. Bruckmueller, C. Vokuhl, K.M. Debatin, C. Eckert, M. Stanulla, M. Schrappe, K.S. Campbell, R. Loewenthal, D.M. Schewe, J. Hochman, L.H. Meyer, D. Kaufman, G. Cario, A. Porgador, and **S. Izraeli.** Central nervous system acute lymphoblastic leukemia: role of natural killer cells. *Blood*, 2015. 125: 3420-31.

Lellouche, E., L.L. Israel, M. Bechor, S. Attal, E. Kurlander, V.A. Asher, A. Dolitzky, L. Shaham, **S. Izraeli**, J.P. Lellouche, and S. Michaeli. MagRET nanoparticles: An iron oxide nanocomposite platform for gene silencing from micrornas to long noncoding RNAs. *Bioconjug Chem*, 2015. 26: 1692-701.

Mansour, M.R., C. Reed, A.R. Eisenberg, J.C. Tseng, J.C. Twizere, S. Daakour, A. Yoda, S.J. Rodig, N. Tal, C. Shochat, A. Berezovskaya, D.J. DeAngelo, S.E. Sallan, D.M. Weinstock, S. **Izraeli**, A.L. Kung, A. Kentsis, and A.T. Look. Targeting oncogenic interleukin-7 receptor signalling with N-acetylcysteine in T cell acute lymphoblastic leukaemia. *Br J Haematol*, 2015. 168: 230-8.

Shaham, L., E. Vendramini, Y. Ge, Y. Goren, Y. Birger, M.R. Tijssen, M. McNulty, I. Geron, O. Schwartzman, L. Goldberg, S.T. Chou, H. Pitman, M.J. Weiss, S. Michaeli, B. Sredni, B. Gottgens, J.D. Crispino, J.W. Taub, and **S. Izraeli**. MicroRNA-486-5p is an erythroid oncomiR of the myeloid leukemias of Down syndrome. *Blood*, 2015. 125: 1292-301.

Tursky, M.L., D. Beck, J.A. Thoms, Y. Huang, A. Kumari, A. Unnikrishnan, K. Knezevic, K. Evans, L.A. Richards, E. Lee, J. Morris, L. Goldberg, **S. Izraeli**, J.W. Wong, J. Olivier, R.B. Lock, K.L. MacKenzie, and J.E. Pimanda. Overexpression of ERG in cord blood progenitors promotes expansion and recapitulates molecular signatures of high ERG leukemias. *Leukemia*, 2015. 29: 819-27.

Reviews

Izraeli, S., The acute lymphoblastic leukemia of Down Syndrome - Genetics and pathogenesis. *Eur J Med Genet*, 2016. 59:158-61.

Savino, A.M. and **S. Izraeli**, On mice and humans: the role of thymic stromal lymphopoietin in human B-cell development and leukemia. *Haematologica*, 2016. 101: 391-3.

Pui, C.H., J.J. Yang, S.P. Hunger, R. Pieters, M. Schrappe, A. Biondi, A. Vora, A. Baruchel, L.B. Silverman, K. Schmiegelow, G. Escherich, K. Horibe, Y.C. Benoit, **S. Izraeli**, A.E. Yeoh, D.C. Liang, J.R. Downing, W.E. Evans, M.V. Relling, and C.G. Mullighan. Childhood Acute Lymphoblastic Leukemia: Progress through collaboration. *J Clin Oncol*, 2015. 33: 2938-48.

Grants

2016-2019 German Israel Foundation

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Development of B-Cell Malignancies

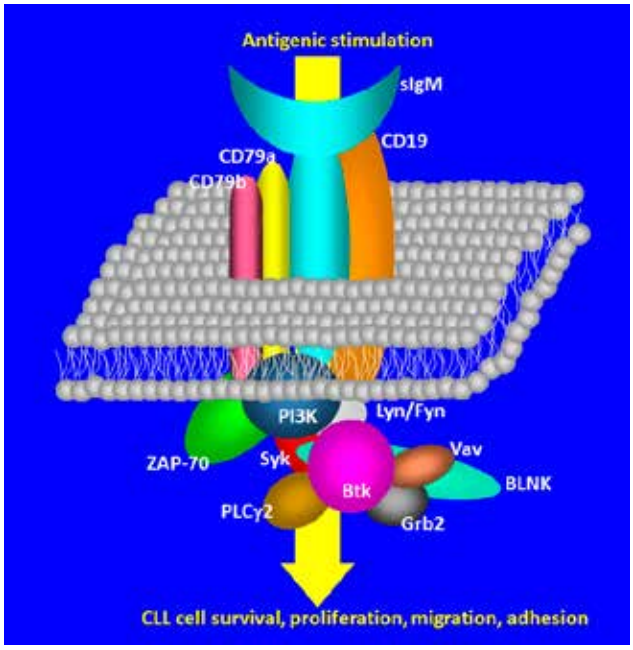
Positions

Senior Lecturer, Sackler Faculty of Medicine

Deputy Director, The Hematology Laboratory, Tel Aviv Sourasky Medical Center

Research

The focus of the research in the laboratory is on B-cell malignancies, their developmental processes, and the clinical significance of the malignant B-cells physiological and molecular phenotypes. We utilize a wide range of both clinical and basic research laboratory techniques, and study tissue culture model systems, as well as primary patient-derived samples.



Specific research programs
A) The role of microenvironmental interactions in the pathogenesis of chronic lymphocytic leukemia.
B) The function of CD19 and CD38 in the physiology of malignant B-cells.
D) Development of novel laboratory methodologies to study B-cell malignancies
The complexity of the B-cell receptor.

Publications

Herishanu, Y., **Katz, B.-Z**. *Cryoglobulins mimicking platelet recovery in a mantle cell lymphoma patient treated with chemoimmunotherapy.* (2015) Blood 125:1047.

Sarid, N., **Katz, B.-Z**. *Dividing plasma cells in the cerebrospinal fluid of a patient with refractory multiple myeloma.* (2015) Blood 126:2162.

Dezorella, N., Kay, S., Baron, S., Shapiro, M., Porat, Z., Deutsch, V., Herishanu, Y., **Katz, B.-Z**. *Measurement of lymphocyte aggregation by flow cytometry-physiological implications in chronic lymphocytic leukemia.* (2016) Cytometry B Clin. Cytom. 90:257-266.

Dezorella, N.*, **Katz, B.-Z**.*, Shapiro, M., Polliack, A., Perry, C., Herishanu, Y. *SLP76 integrates into the B-Cell receptor signaling cascade in chronic lymphocytic leukemia cells and is associated with aggressive disease course.* (2016) Haematologica 101:1553-1562. * Equal contributors

Shapiro, M., Herishanu, Y., **Katz, B.-Z**., Dezorella, N., Sun, C., Kay, S., Polliack, A., Avivi, I., Wiestner, A., Perry, C. *Lymphocyte activation gene 3- A novel therapeutic target in chronic lymphocytic leukemia.* (2017) Haematologica In press.

Katz, B.-Z., Herishanu, Y. Fragility of sub-cellular structures in chronic lymphocytic leukemia. (2017) Int. J. Hematol. In press.

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Tumor-Microenvironment Cellular Interactions in Cancer Progression and Metastasis

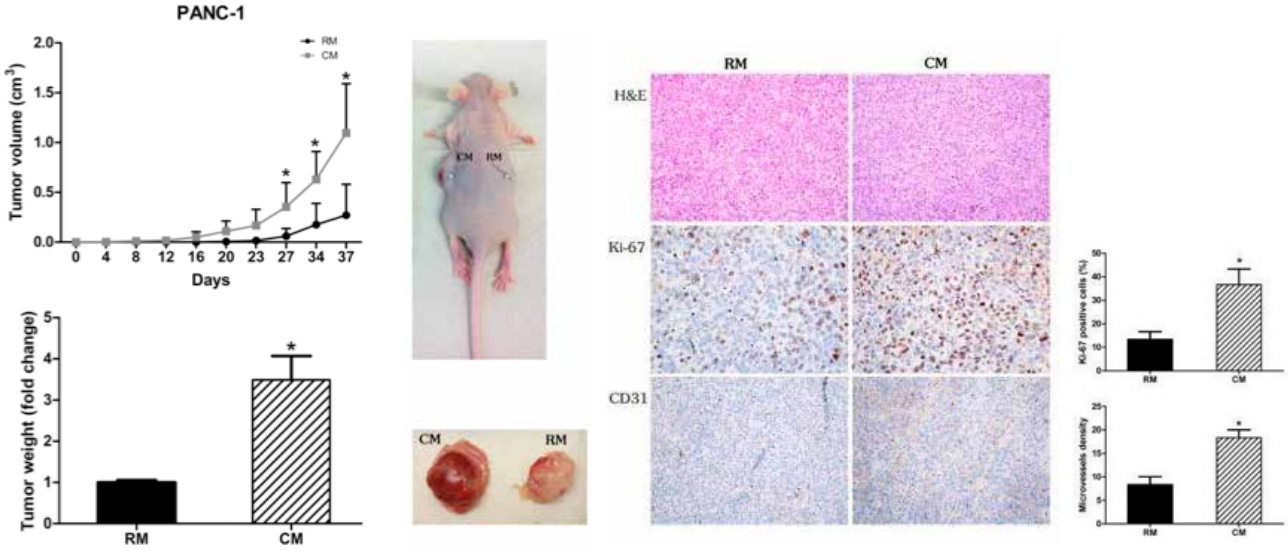
Positions

Chair, Department of Surgery A

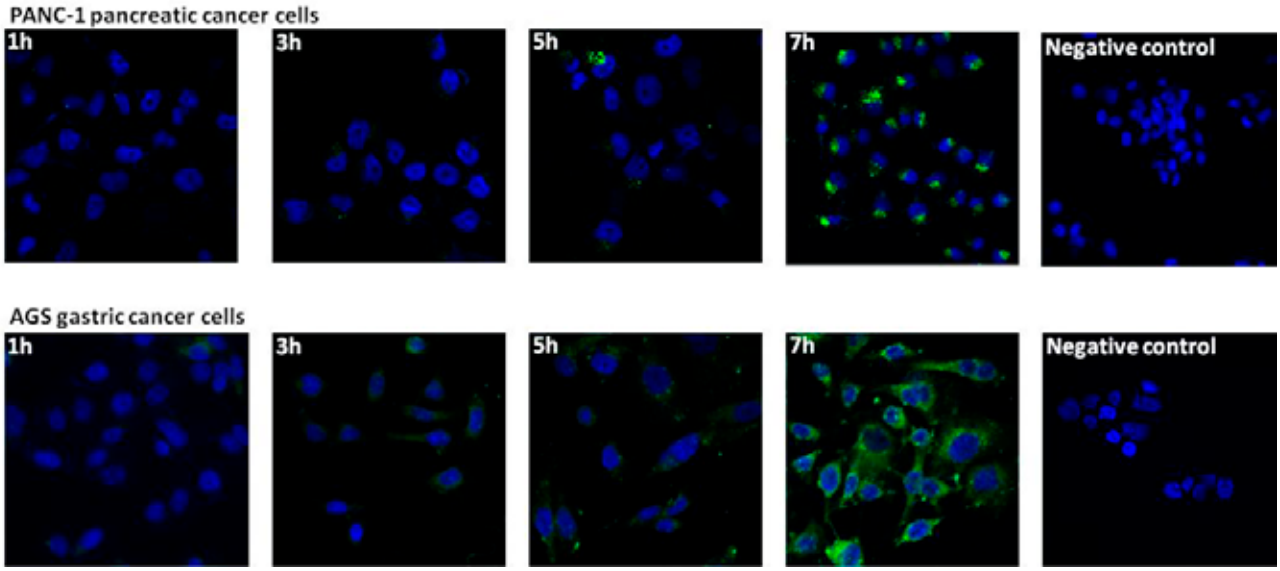
Senior Lecturer, Sackler Faculty of Medicine

Research

The surgical oncology research lab was established in order to conduct clinical and basic science research in order to further understand disease patterns and mechanisms, thus, trying to improve diagnosis and treatment outcomes of the patients we operate on. Moreover, the lab is a platform for the development of future academic surgeons, passionate about both research and the field of surgery. We focus on patient-driven translational research, studying the molecular basis of various soft tissue sarcoma (STS) tumors, and gastrointestinal malignancies. We aim to explore distinct signaling pathways and molecules that may play a role in cancer progression and metastasis. Specifically, we investigate the cross talk between metastatic GI cancer cells and the omentum. We also investigate the potential role of miRNAs as molecular biomarkers for staging, prognosis, and pattern of future spread. For these purposes we frequently utilize in-vitro and in-vivo models, human cancer specimens from our clinically annotated tissue bank, as well as various advanced molecular and bioinformatic approaches.



Tumor growth is promoted by omental fat in vivo. PANC-1 pancreatic cancer cells were initially pretreated in vitro with human omental fat conditioned medium (CM) or control regular medium (RM) for 24h. The tumor cells were then injected subcutaneously into the flank of nude mice. (A) Tumor growth and weight of PANC-1 tumors was facilitated in mice following pre-treatment with omental fat CM (n=15); (B) Representative mice and tumor images; (C) Marked increase in proliferation (Ki-67) and microvessel density (CD31) by human omental fat CM.



Uptake of omental fat exosomes by cancer cells. PKH67-labeled omental fat exosomes were incubated with PANC-1 pancreatic cancer cells (upper panel) and AGS gastric cancer cells (lower panel), reaction was stopped at different time points (1, 3, 5 and 7 hours) and cells were analyzed by confocal microscopy. The nucleus of PANC-1 and AGS cells was stained with dapi. Negative control- PANC-1 and AGS cells with no addition of labeled exosomes.

Publications

Papoulas M, Weiser R, Rosen G, Gerstenhaber F, Merimsky O, Lubezky N, Klausner JM, **Lahat G**. Visceral Fat Content Correlates with Retroperitoneal Soft Tissue Sarcoma (STS) Local Recurrence and Survival. World J Surg. 2015.

Nachmany I, Pencovich N, Ben-Yehuda A, **Lahat G**, Nakache R, Goykhman Y, Lubezky N, Klausner JM. Laparoscopic Distal Pancreatectomy: Learning Curve and Experience in a Tertiary Center. J Laparoendosc Adv Surg Tech A. 2016;26(6):470-4.

Loewenstein S, Lubezky N, Nizri E, Zemel M, Levin Y, Savidor A, Sher O, Klausner JM, **Lahat G.** Adipose-induced Retroperitoneal Soft Tissue Sarcoma (RSTS) Tumorigenesis: A Potential Crosstalk between Sarcoma and Fat Cells. Molecular Cancer Research. 2016.

Lahat G, Lubezky N, Gerstenhaber F, Nizri E, Gysi M, Rozenek M, , Goichman Y, Nachmany I, Nakache R, Wolf I, Klausner JM. Number of evaluated lymph nodes and positive lymph nodes, lymph node ratio, and log odds evaluation in early-stage pancreatic ductal adenocarcinoma: numerology or valid indicators of patient outcome? World journal of surgical oncology 2016;14(1):254.

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Investigating the Immuno-Proteome in Cancer

Positions

Senior Physician, Institute of Pulmonary Medicine, Sheba Medical Center

Senior Lecturer, Sackler Faculty of Medicine

Research

We study the proteins and peptides involved in the interaction between immune cells and tumor cells. While genomics has boosted our knowledge on the molecular basis of human disease, both DNA sequencing and gene expression analysis report on indirect effects that often do not correlate with the actual expression and activity of proteins in cells and tissues. Importantly, proteins are the most prevalent drug targets. Thus, we employ advanced high-throughput immuno-proteomics, using mass-spectrometry-based methods, cell biology, biochemistry and *in vivo* models to reveal proteins with a novel immuno-regulatory function that can serve as drug targets in cancer and autoimmune diseases.

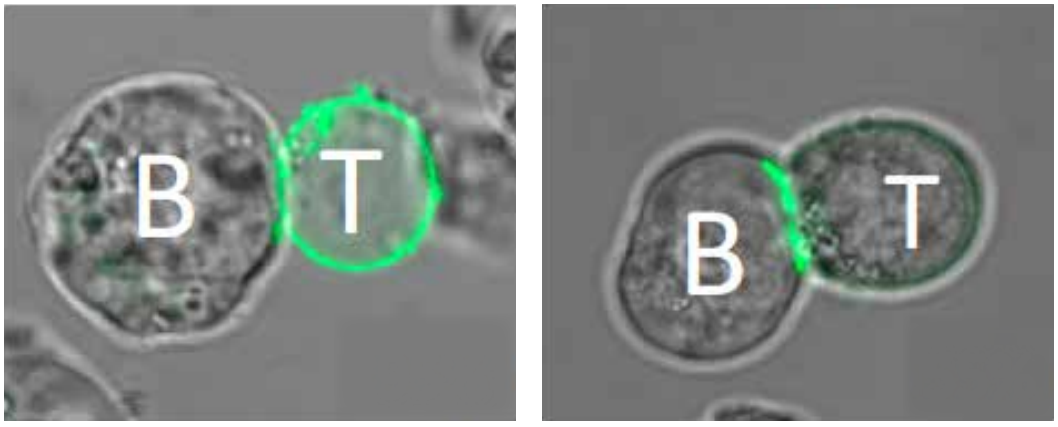
Publications

Tocheva AS, **Peled M**, Strazza M, Nayak S, Dragovich MA, Azoulay-Alfaguter I, Philips EA, Adam K, Neel BG, Uberheide B, Mor A. Quantitative phosphoproteomic analysis reveals involvement of PD-1 in multiple T cell functions. Preprint, J Biol Chem, 2020.

Reuveny R, DiMenna FJ, Gunaratnam C, Arad AD, McElvaney GN, Susta D, **Peled M**, Moyna NM. High-intensity interval training accelerates oxygen uptake kinetics and improves exercise tolerance for individuals with cystic fibrosis. BMC Sports Sci Med Rehabil. 2020;12:9.

Sultan M, Ben-Shushan D, **Peled M**, Kamari Y, Isman S, Barshack I, Kuban RJ, Kühn H, Harats D, Shaish A. Specific overexpression of 15-lipoxygenase in endothelial cells promotes cancer cell death in an in vivo Lewis lung carcinoma mouse model. Adv Med Sci. 2020;65:111-119.

Magri V, Gottfried T, Di Segni M, Urban D, **Peled M**, Daher S, Stoff R, Bar J, Onn A. SLAMF6 clustering



EFHD2 is required for PD-1 clustering at the immunological synapse. Freshly isolated human T cells were transfected with non-targeting siRNA (siControl) (**A**) or siRNA targeting EFHD2 (siEFHD2) (**B**) and with GFP–PD-1 expression plasmid, followed by co-culturing with Raji B cells expressing PDL1 and loaded with SEE. Cells were subjected to real-time imaging by confocal microscopy.

is required to augment T cell activation. Cancer Manag Res. 2019;11:8201-8207.

Dragovich MA, Adam K, Strazza M, Tocheva AS, **Peled M**, Mor A.PLoS One. 2019 Jun 14;14(6):e0218109.

Peled M, Onn A, Herbst RS. Tumor-infiltrating lymphocytes-location for prognostic evaluation. Clin Cancer Res. 2019;25(5):1449-1451.

Peled M, Strazza M, Mor A. Co-immunoprecipitation assay for studying functional interactions between receptors and enzymes. J Vis Exp. 2018;(139):58433.

Peled M, Tocheva AS, Sandigursky S, Nayak S, Philips EA, Nichols KE, Strazza M, Azoulay-Alfaguter I, Askenazi M, Neel BG, Pelzek AJ, Ueberheide B, Mor A. Affinity purification mass spectrometry analysis of PD-1 uncovers SAP as a new checkpoint inhibitor. Proc Natl Acad Sci US A. 2018; 115(3):E468-e477.

Peled M, Dragovich MA, Adam K, Strazza M, Tocheva AS, Vega IE, Mor A. EF Hand Domain family member D2 is required for T cell cytotoxicity. J Immunol. 2018;201(9):2824-2831.

Azoulay-Alfaguter I, Strazza M, **Peled M**, Novak HK, Muller J, Dustin ML, Mor A. The tyrosine phosphatase SHP-1 promotes T cell adhesion by activating the adaptor protein CrkII in the immunological synapse. Sci Signal. 2017;10(491):eaal2880.

Peled M, Nishi H, Weinstock A, Barrett TJ, Zhou F, Quezada A, Fisher EA. A wild-type mouse-based model for the regression of inflammation in atherosclerosis. PLoS One. 2017;12(3):e0173975.

Strazza M, Azoulay-Alfaguter I, **Peled M**, Smrcka AV, Skolnik EY, Srivastava S, Mor A. PLCε1 regulates SDF-1α-induced lymphocyte adhesion and migration to sites of inflammation. Proc Natl Acad Sci USA. 2017;114(10):2693-2698.

Strazza M, Azoulay-Alfaguter I, **Peled M**, Mor A. assay of adhesion under shear stress for the study of T lymphocyte-adhesion molecule interactions. J Vis Exp. 2016;(112):54203.

Peled M, Strazza M, Azoulay-Alfaguter I, Silverman GJ, Scher JU, Mor A. Erratum to: Analysis of programmed death-1 in patients with psoriatic arthritis. Inflammation. 2015;38(4):1580.

Peled M, Strazza M, Azoulay-Alfaguter I, Silverman GJ, Scher JU, Mor A. Analysis of programmed death-1 in patients with psoriatic arthritis. Inflammation. 2015;38(4):1573-9.

Grants

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Immunotherapy of Brain Tumors: From Basic Mechanisms to Clinical Translation

Positions – Zvi Ram

Chairman, The Neurosurgery Section, Tel Aviv Sourasky Medical Center

Full Professor, Sackler Faculty of Medicine

Former Chairman, Tumor Section of European Association of Neurosurgical Societies

Positions – Ilan Volovitz

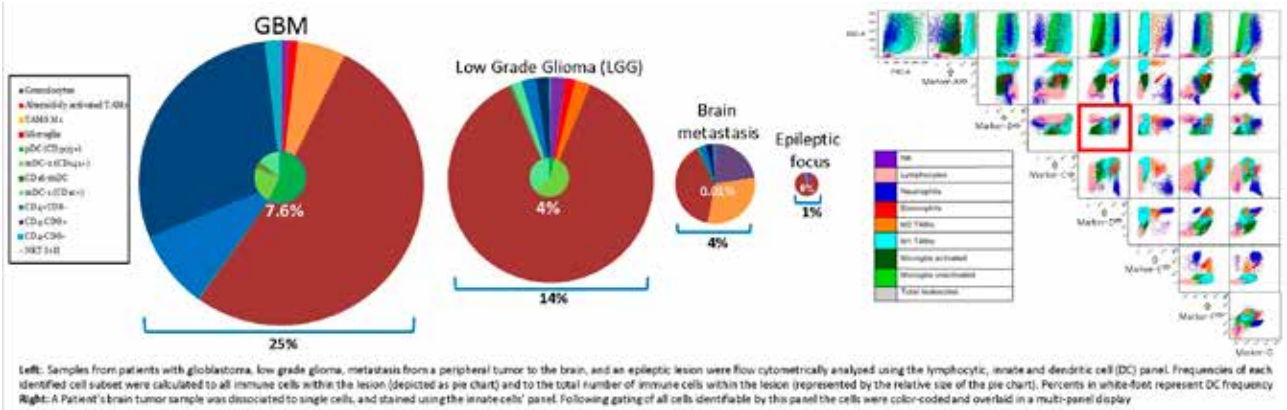
Lab Head, Cancer Immunotherapy Lab, Neurosurgery Department, Tel Aviv Sourasky Medical Center

Research

Our laboratory studies the unique immunology of brain tumors by combining basic-science with clinically-applied investigation. Utilizing the discrepancy between the relatively weak immune surveillance inside the brain and the potent one outside it, the lab has developed a novel method to treat brain tumors utilizing a concept we termed 'Split Immunity'. The concept was recently translated from rats to human glioblastoma (GBM) patients. To monitor the post-therapy changes in the anti-tumor immune response, the lab has developed a unique set of high resolution immune assays that follow the peripheral (outside the tumor) and the intratumoral immune response.

Main research interests

- Development of scientific and clinical insights into the concept of 'Split Immunity' and how it affects the treated patients.
- Mapping of the entire adaptive and innate cellular immune milieu found inside human brain tumors



Left: Samples from patients with glioblastoma, low grade glioma, metastasis from a peripheral tumor to the brain, and an epileptic lesion were flow cytometrically analyzed using the lymphocytic, innate and dendritic cell (DC) panel. Frequencies of each identified cell subset were calculated to all immune cells within the lesion (depicted as pie chart) and to the total number of immune cells within the lesion (represented by the relative size of the pie chart). Percents in white-font represent DC frequency
Right: A Patient's brain tumor sample was dissociated to single cells, and stained using the innate cells' panel. Following gating of all cells identifiable by this panel the cells were color-coded and overlaid in a multi-panel display

using advanced multicolor (up to 12-color) flow cytometry.

- Using a cell-centered approach called "Immune Cytomics" to study the network of interactions formed between the different intra-tumoral immune cells and between immune and tumor cells.
- Evaluating how novel, non-immune-based, treatments for brain tumors affect the anti-tumoral immune responses.

Publications

Gelerstein E, Berger A, Jonas-Kimchi T, Strauss I, Kanner AA, Blumenthal DT, Gottfried M, Margalit N, **Ram Z**, Shahar T. Regression of intracranial meningioma following treatment with nivolumab: Case report and review of the literature. J Clin Neurosci. 2017

Blumenthal DT, Dvir A, Lossos A, Tzuk-Shina T, Lior T, Limon D, Yust-Katz S, Lokiec A, **Ram Z**, Ross JS, Ali SM, Yair R, Soussan-Gutman L, Bokstein F. Clinical utility and treatment outcome of comprehensive genomic profiling in high grade glioma patients. J Neurooncol. 2016;130:211-219.

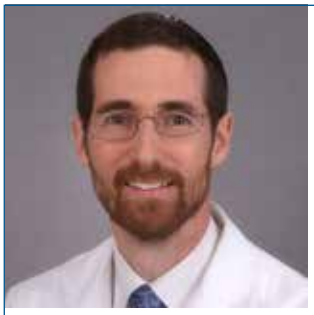
Shahar T, Granit A, Zrihan D, Canello T, Charbit H, Einstein O, Rozovski U, Elgavish S, **Ram Z**, Siegal T, Lavon I. Expression level of miRNAs on chromosome 14q32.31 region correlates with tumor aggressiveness and survival of glioblastoma patients. J Neurooncol. 2016

Ofek P, Calderón M, Mehrabadi FS, Krivitsky A, Ferber S, Tiram G, Yerushalmi N, Kredo-Russo S, Grossman R, **Ram Z**, Haag R, Satchi-Fainaro R. Restoring the oncosuppressor activity of microRNA-34a in glioblastoma using a polyglycerol-based polyplex. Nanomedicine. 2016

Volovitz I, Shapira N, Ezer H, Gafni A, Lustgarten M, Alter T, Ben-Horin I, Barzilai O, Shahar T, Kanner A, Fried I, Veshchev I, Grossman R, **Ram Z**. A non-aggressive, highly efficient, enzymatic method for dissociation of human brain-tumors and brain-tissues to viable single-cells. BMC Neurosci. 2016

Volovitz I, Melzer S, Amar S, Bocsi J, Bloch M, Efroni S, **Ram Z**, Tárnok A. Dendritic Cells in the Context of Human Tumors: Biology and Experimental Tools. Int Rev Immunol. 2016

Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, Taylor LP,Lieberman F, Silvani A, Fink KL, Barnett GH, Zhu JJ, Henson JW, Engelhard HH, Chen TC, Tran DD, Sroubek J, Tran ND, Hottinger AF, Landolfi J, Desai R, Caroli M, Kew Y, Honnorat J, Idbaih A, Kirson ED, Weinberg U, Palti Y, Hegi ME, **Ram Z**. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA. 2015



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Radiation Biology: Translating Biological Insights from the Lab to Impact Cancer Patient Care

Positions (Dr. Lawrence)

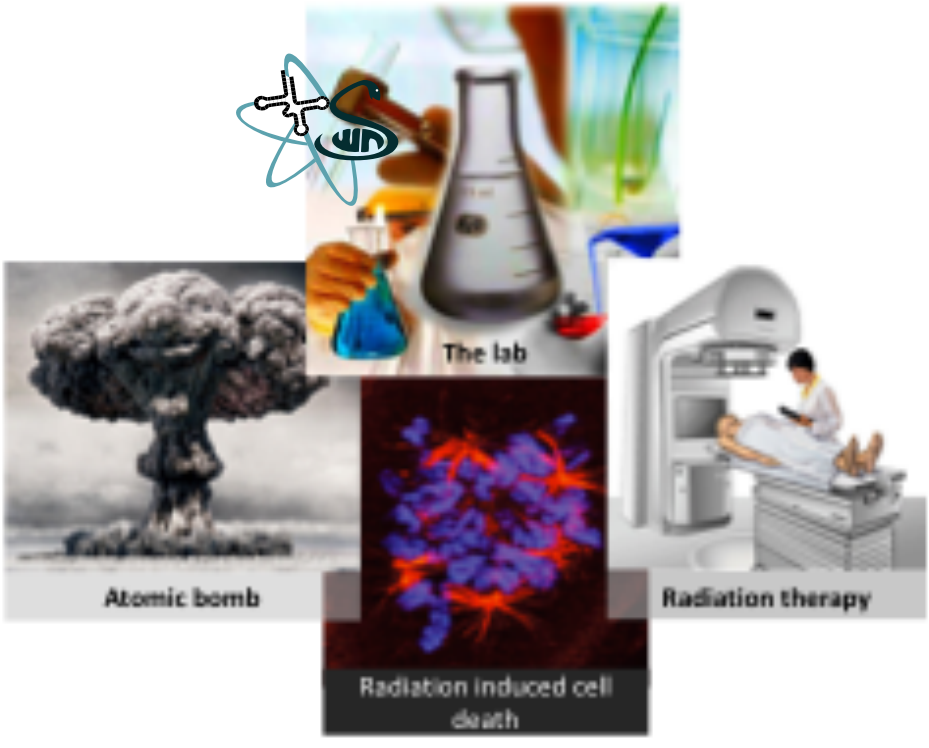
Director, Center for Translational Research in Radiation Oncology

Senior Lecturer (regular track), Sackler Faculty of Medicine

Assistant Professor (adjunct), Dep. Radiation Oncology, Thomas Jefferson University

Research

Radiation therapy is a cornerstone of modern cancer care. Ionizing radiation kills cancer cells by generating reactive oxygen species, damaging DNA, and inducing chromosomal damage. Yet many aspects of radiation biology remain unknown. The lab focusses on understating cells' ability to survive ionizing radiation, a phenomenon known as radioresistance. We seek to answer the question of how some tumors are able to withstand very large doses of radiation.



We hypothesize that cells withstand the intense onslaught of DNA damage by adapting their metabolic processes, diverting biosynthesis pathways to nucleotide synthesis and REDOX management. Another explanation of why cells in-vivo appear to resist radiation is the result of the interaction between tumor cells and the microenvironment. Ongoing projects in the lab are challenging and developing both these concepts.

The research center also performs clinical research, initiating and running clinical trials. Hence, a particular strength of the lab is the ability for our findings to impact patient care through the performance of clinical trials.

Publications

Amit U, Kain D, Sahu A, Nevo-Caspi Y, Gonen N, Molotski N, Konfino T, Landa N, Naftali-Shani N, Blum G, Merquiol E, Karo-Atar D, Kanfi Y, Peret G, Munitz A, Cohen HY, Ruppin E, Hannenhalli S, Leor J. A New Role for Interleukin-13 Receptor α1 in Myocardial Homeostasis and Heart Failure. Journal of the American Heart Association. 2017; 20: 6(5)

Nishanth N, Sahu A, **Amit U**, Robinson W.P, Seung G, Basu ML, Leor J, Ruppin E, Hannenhalli S. Putative Functional Genes in Idiopathic Dilated Cardiomyopathy. Scientific Reports. Manuscript accepted. In press.

Golan T, Sella T, Margalit O, **Amit U**, Halpern N, Aderka D, Shacham-Shmueli E, Urban D, **Lawrence YR**. Short- and Long-Term Survival in Metastatic Pancreatic Adenocarcinoma, 1993-2013. J Natl Compr Canc Netw. 2017;15(8):1022-1027

Naftali-Shani N, Levin-Kotler L, Palevski D, **Amit U**, Kain D, Landa N, Hochhauser E, Leor J. Heart failure switches resident and transplanted mesenchymal stromal cells toward a pro-inflammatory phenotype and impairs their reparative properties via Toll-like Receptor-4. Circulation. 2017;6: 135(23):2271-2287

Davidson T, Ben David M, Haskin T, Howes M, Scaife R, Kanana N, **Amit U**, Galper S, Ben Haim S, Symon Z, Goldstein J. The Use of 18F–FDG PET-CT Imaging to Determine Internal Mammary Lymph Node Location for Radiation Therapy Treatment Planning in Breast Cancer Patients. Practical Radiation Oncology. 2017;7(6):373-381

Alpert E, **Amit U**, Guranda L, Mehagnea R, Bentancur A. Point-of-care ultrasound by emergency physicians versus delayed diagnosis of tamponade and large pericardial effusions. Clinical and Experimental Emergency Medicine. 2017;4(3):128-132

Roichman A, Kanfi Y, Glazz R, Naiman S, **Amit U**, Landa N, Tinman S, Stein I, Pikarsky E, Leor J, Cohen HY. SIRT6 overexpression improves various aspects of mouse healthspan. Journal of Gerontology series A. 2017;1;72(5):603-615

Appel S, Goldstein J, Perelman M, Rabin T, Urban D, Onn A, Shulimzon TR, Weiss I, Lieberman S, Marom EM, Golan N, Simansky D, Ben-Nun A, **Lawrence YR**, Bar J, Symon Z. Neo-adjuvant Chemo-Radiation to 60 Gray Followed by Surgery for Locally Advanced Non-Small Cell Lung Cancer Patients: Evaluation of Trimodality Strategy. Isr Med Assoc J. 2017;19(10):614-619.

Lawrence YR, Moughan J, Magliocco AM, Klimowicz AC, Regine WF, Mowat RB, DiPetrillo TA, Small W Jr, Simko JP, Golan T, Winter KA, Guha C, Crane CH, Dicker AP. Expression of the DNA repair gene MLH1 correlates with survival in patients who have resected pancreatic cancer and have received adjuvant chemoradiation: NRG Oncology RTOG Study 9704. Cancer. 2017

Appel S, **Lawrence YR**, Goldstein J, Pfeffer RM, Weiss I, Rabin T, Felder S, Ben-Ayun M, Tzvang L, Alezra D, Simansky D, Ben-Nun A, Bar J, Symon Z. Stereotactic Ablative Body Radiation for Stage I Lung Cancer in Israel: A Retrospective Single-Center Report. Isr Med Assoc J. 2017;19(1):39-43.

Spieler B, Goldstein J, **Lawrence YR**, Saad A, Berger R, Ramon J, Dotan Z, Laufer M, Weiss I, Tzvang L, Poortmans P, Symon Z Salvage Radiation Therapy for Biochemical Failure Following Radical Prostatectomy. Isr Med Assoc J. 2017;19(1):19-24.

Saad A, Goldstein J, **Lawrence YR**, Spieler B, Leibowitz-Amit R, Berger R, Davidson T, Urban D, Tsang L, Alezra D, Weiss I, Symon Z. Classifying high-risk versus very high-risk prostate cancer: is it relevant to outcomes of conformal radiotherapy and androgen deprivation? Radiat Oncol. 2017;12(1):5

Symon Z, Ben-Bezalel G, Spieler B, Tsvang L, Alezra D, Berger R, Dotan Z, **Lawrence YR**, Goldstein J. A Retrospective Feasibility Study of Salvage Pelvic Nodal Radiation in 6 Patients with Biochemical Failure Following Prostate Fossa Radiation: An Alternative to Androgen Deprivation Therapy (ADT). Am J Clin Oncol. 2016;39(5):479-483.

Shi W, Palmer JD, Werner-Wasik M, Andrews DW, Evans JJ, Glass J, Kim L, Bar-Ad V, Judy K, Farrell C, Simone N, Liu H, Dicker AP, **Lawrence YR**. Phase I trial of panobinostat and fractionated stereotactic re-irradiation therapy for recurrent high grade gliomas. J Neurooncol. 2016;127(3):535-9.

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miRNAs in Solid Malignancies / Immunotherapy Research / Clinical Cancer Research

Positions

Senior Lecturer, Sackler Faculty of Medicine

Senior Medical Oncologist, Clinician-investigator, Oncology Institute & Cancer Research Center, Sheba Medical Center, Tel Hashomer

Research

As a clinician-investigator and a practicing medical oncologist, our lab is engaged in basic, translational and clinical cancer research.

Basic research: Our lab at the Cancer Research Center at the Sheba campus studies the role of microRNAs in solid malignancies. We were the first to show that a large micr-RNA cluster on chromosome 14q32 is silenced in melanoma. This cluster was later dubbed 'the larger tumor suppressor miRNA cluster' and was shown to be down-regulated in a wide range of malignancies. We showed the involvement of three miRNAs from this cluster in melanoma progression, and continue to study the role of this cluster in the pathogenesis of this disease. In the last year, we have also studyed the involvement of miRNAs in bladder cancer; specifically, preliminary results suggest that a family of miRNAs are associated with the development of resistance to chemotherapy in bladder cancer; research is currently ongoing.

Translational research: Immunotherapy, namely the activation of the immune system against cancer, is revolutionizing cancer treatment, yet not all cancers, and not all patients within a given cancer, respond to immunotherapy. Currently, the biomarkers associated with response to immunotherapy are unknown. In collaboration with Dr. Irit Gat-Viks from the Faculty of Life Sciences at TAU, we are embarking on a clinical trial in which we will prospectively search for immune cell populations within the systemic circulation that are associated with response to immunotherapy. We will perform RNA sequencing of immune cells before and following immunotherapy treatment and analyze the cell populations using deconvolution algorithms developed at the Gat-Viks lab.

Clinical research: Whereas the list of anti-neoplastic treatments is constantly growing across the cancer spectrum, currently there are almost no proven predictive biomarkers of response to treatment with any of these agents, and clinical decisions are generally empirical and based on 'trial and error'. We are interested in finding associations between lab variables/plasma biomarkers and response to anti-neoplastic treatment in genito-urinary malignancies; specifically, we recently addressed the following clinical questions:

1. We described clinical and laboratory variables associated with response to the hormonal agent abiraterone in prostate cancer.

2. We showed that the neutrophil-lymphocyte ratio is associated with response to chemotherapy in bladder cancer, and that a high lymphocyte count is associated with pathological complete response at cystectomy following neo-adjuvant treatment.

3. We described the patterns of change of a several plasma biomarkers following treatment with the biological agent cabozantinib in prostate cancer.

4. We summarized our clinical experience with the immunotherapeutic anti-PD1 antibody pembrolizumab, showing that low lymphocyte counts are associated with lack of response.

These clinical works, taken together, show that the adaptive arm of the immune response is imperative in amounting response to both chemo and immuno-therapy.

Publications

Leibowitz-Amit R, Shapira-Frommer R, Golan T, Israel A, Shacham-Shmueli E, Gluck I, Aderka D, Onn

A, Zach L, Nili Gal-Yam E, Kaufman B, Urban D, Bar J, Berger R. Clinical experience with pembrolizumab in metastatic pre-treated patients with solid cancers. *In preparation*.

Leibowitz-Amit R, Israel A, Gal M, Atenafu E A, Symon Z, Portnoy O, Laufer M, Dotan Z, Ramon J, Fridman E, Berger R. Association between the Absolute Baseline Lymphocyte Count and Response to Neoadjuvant Platinum-based Chemotherapy in Muscle-invasive Bladder Cancer. Clin Oncol (R Coll Radiol). 2016;28(12):790-796.

Leibowitz-Amit R, Pintilie M, Khoja L, Azad AA, Berger R, Laird AD, Aftab DT, Chi KN, Joshua AM. Changes in plasma biomarkers following treatment with cabozantinib in metastatic castration-resistant prostate cancer: a post hoc analysis of an extension cohort of a phase II trial. J Transl Med. 2016. 14:12.

Zehavi L, Schayek H, Jacob-Hirsch J, Sidi Y, **Leibowitz-Amit R***, Avni D*. MiR-377 targets E2F3 and alters the NF-kB signaling pathway through MAP3K7 in malignant melanoma. Mol Cancer. 2015. 14:68.* equal contribution.

Seah JA, **Leibowitz-Amit R***, Atenafu EG, Alimohamed N, Knox JJ, Joshua AM, Sridhar SS. Neutrophil-Lymphocyte Ratio and Pathological Response to Neoadjuvant Chemotherapy in Patients with Muscle-Invasive Bladder Cancer. Clin Genitourin Cancer. 2015:e229-33. *equal contribution.

Leibowitz-Amit R, Khoja L, Tannock IF, Joshua AM. Choosing a better endpoint for trials of bone-protecting agents. Ann Oncol. 2015. 26(5):1032-3.

Leibowitz-Amit R, Templeton AJ, Alibhai SM, Knox JJ, Sridhar SS, Tannock IF, Joshua AM. Efficacy and toxicity of abiraterone and docetaxel in octogenarians with metastatic castration-resistant prostate cancer. J Geriatr Oncol. 2015. 6(1):23-8.

Azad AA, Eigl BJ, **Leibowitz-Amit R**, Lester R, Kollmannsberger C, Murray N, Clayton R, Heng DY, Joshua AM, Chi KN. Outcomes with abiraterone acetate in metastatic castration-resistant prostate cancer patients who have poor performance status. Eur Urol. 2015. 67(3):441-7.

Leibowitz-Amit R, Templeton AJ, Omlin A, Pezaro C, Atenafu EG, Keizman D, Vera-Badillo F, Seah JA, Attard G, Knox JJ, Sridhar SS, Tannock IF, de Bono JS, Joshua AM. Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. Ann Oncol. 2014. 25(3):657-62.

Templeton AJ, Vera-Badillo FE, Wang L, Attalla M, De Gouveia P, **Leibowitz-Amit R**, Knox JJ, Moore M, Sridhar SS, Joshua AM, Pond GR, Amir E, Tannock IF. Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. Ann Oncol. 2013. 24(12):2972-7.

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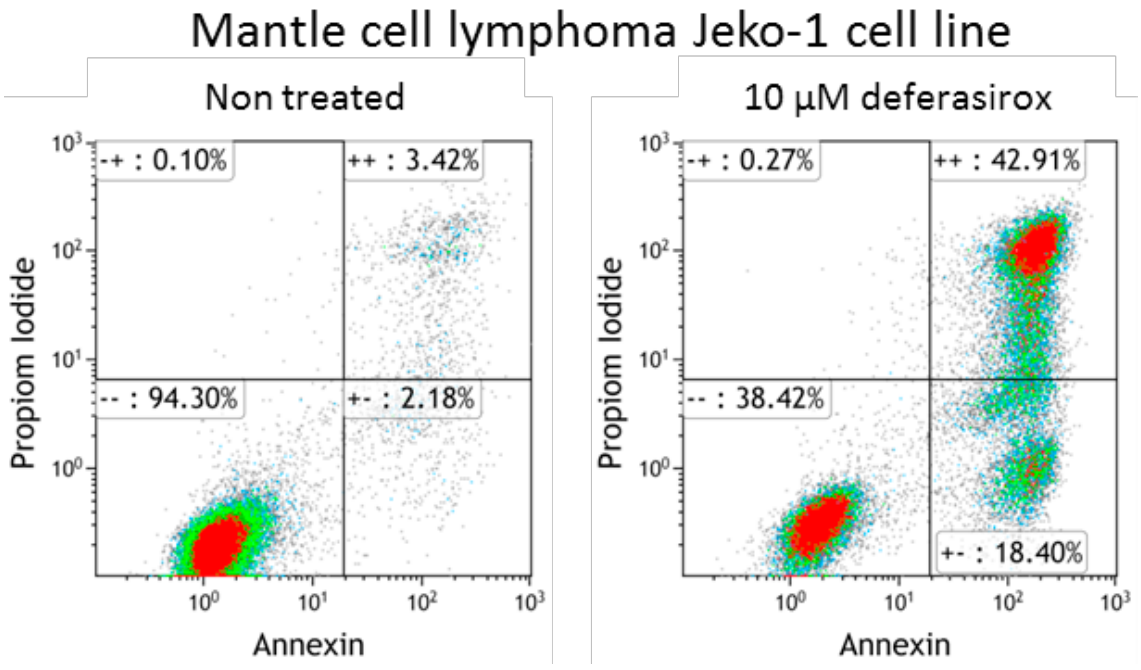
Hematological Malignancies

Positions

Prof. Raanani, Clinical Full Professor in Hematology, Sackler Faculty of Medicine

Research

Our primary field of interest is finding new therapies or better therapies for the treatment of incurable hematological malignancies. Our projects focus on exploring the effect of new agents on different leukemia and lymphoma cell lines and patient samples. We study the molecular pathways involved in the initiation and maintenance of hematological tumorigenesis and try to understand the effect of the different agents on these molecular pathways. We apply cutting-edge technologies including, molecular protein and cellular biology, microarray and NGS analysis. Understanding normal hematological development and understanding the molecular effect of different chromosomal abnormalities



Deferasirox is a rationally-designed oral iron chelator used to reduce chronic iron overload in patients who receive long-term blood transfusions. We showed that this agent can induce apoptosis in mantle cell lymphoma.

(translocations, deletion, etc.) is essential for understanding the the processes leading to the induction and maintenance of hematological malignancies and for designing targeted treatments for these malignancies.

Publications

Gover-Proaktor A, **Granot G**, Shapira S, Raz O, Pasvolsky O, Nagler A, Lev DL, Inbal A, Lubin I, **Raanani P**, Leader A. Ponatinib reduces viability, migration, and functionality of human endothelial cells. Leuk Lymphoma. 2017;58(6):1455-1467

Gover-Proaktor A*, **Granot G***, Shapira S, Raz O, Pasvolsky O, Nagler A, Lev DL, Inbal A, Lubin I, **Raanani P**, Leader A. Ponatinib reduces viability, migration, and functionality of human endothelial cells. Leuk Lymphoma. 2016;12:1-13.

Hershkovitz-Rokah O, Modai S, Pasmanik-Chor M, Toren A, Shomron N, **Raanani P**, Shpilberg O, **Granot G**. Restoration of miR-424 suppresses BCR-ABL activity and sensitizes CML cells to imatinib treatment. Cancer Lett. 2015;360(2):245-56.

Hershkovitz-Rokah O, Modai S, Pasmanik-Chor M, Toren A, Shomron N, **Raanani P**, Shpilberg O, **Granot G**. MiR-30e induces apoptosis and sensitizes K562 cells to imatinib treatment via regulation of the BCR-ABL protein. Cancer Lett. 2015;356(2 Pt B):597-605.

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Investigating Mechanisms of Hepatitis B Virus Persistence and Its Link to Liver Cancer

Positions

Head, Department of Medicine D and the Laboratory of Liver Research

Senior Lecturer, Sackler Faculty of Medicine

Research

Current research interests focus on the role of the innate immune system in HBV infection and the role of HBV infection in liver carcinogenesis.

1. Studying the molecular mechanisms by which HBV confers resistance to sorafenib in order to get a deeper understanding of HBV oncogenicity and to gain insight into possible molecular targets for HCC interventions.
2. Characterizing the molecular signature of type I interferon induction and response following HBV infection.
3. Characterizing the interferon-response genes (ISGs) induced by HBV and their effect on HBV life cycle.
4. Investigating the mechanism(s) of HBV inhibition by the innate immune response.

Publications

Ramanan, V.*, **Shlomai, A.***, Cox, D.B.T.*, Schwartz, R.E., Michailidis, E., Bhatta, A., Scott, D.A., Zhang, F., Rice, C.M., and Bhatia, S.N. 2015. CRISPR/Cas9 cleavage of viral DNA efficiently suppresses hepatitis B virus. *Sci. Rep.* 5. (*equal contribution)

Ricardo-Lax, I., Ramanan, V., Michailidis, E., Shamia, T., Reuven, N., Rice, C.M., **Shlomai, A.**, and Shaul, Y. 2015. Hepatitis B virus induces RNR-R2 expression via DNA damage response activation. *J. Hepatology*. 63(4):789-96

March, S., Ramanan, V., Trehan, K., Ng, S., Galstian, A., Gural, N., Scull, M.A., **Shlomai, A.**, Mota, M.M., Fleming, H.E., et al. 2015. Micropatterned coculture of primary human hepatocytes and supportive cells for the study of hepatotropic pathogens. *Nat. Protocols* 10:2027-2053.

Scheel, Troels K.H., Luna, Joseph M., Liniger, M., Nishiuchi, E., Rozen-Gagnon, K., **Shlomai, A.**, Auray, G., Gerber, M., Fak, J., Keller, I., et al. 2016. A Broad RNA Virus Survey Reveals Both miRNA Dependence and Functional Sequestration. *Cell Host Microbe 19:409-423.*

Billerbeck, E., Mommersteeg, M.C., **Shlomai, A.**, Xiao, J.W., Andrus, L., Bhatta, A., Vercauteren, K., Michailidis, E., Dorner, M., Krishnan, A., et al. 2016. Humanized mice efficiently engrafted with fetal hepatoblasts and syngeneic immune cells develop human monocytes and NK cells. *J. Hepatology* 65(2):334-43.

Leibovici-Weissman Y, Mor E, Leshno M, **Shlomai A**. Patients' age rather than Model of End stage Liver Disease score predicts survival after liver transplantation. *Digestive Diseases Sci***.** 2017 Jan 4. doi: 10.1007/s10620-016-4423-8.

Gozlan Y.*, Ben-Ari Z*, Moscona R, Kabat A, Shirazi R, Rakovsky A, Veizman E, Berdichevski T, Weiss P, Cohen-Ezra O, Luria Y, Gafanovich I, Brown M, Cohen-Naftali M, **Shlomai A**, Shibolet O, Zigmond E, Zuckerman E, Carmiel M, Hazan R, Nimer A, Maor Y, Kitay- Cohen Y, Shemer Y, Kra-Oz A, Schreiber L, Peleg O, Mendelson E, Mor O. Analysis of HCV Genotype 1 Subtypes and of Drug Resistance Substitutions at Baseline and in Patients Failing Direct Acting Antiviral Treatments in Israel. *Antiviral Ther***.** 2017 Jan 9. doi: 10.3851/IMP3123.

Grants

	Israeli Science Foundation (ISF)/ Physician-Scientist Grant
2016-2020	US-Israel Binational Science Foundation (BSF) Grant (with CM Rice)

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Pediatric Brain Tumors, Leukemias and Lymphomas

Research

Targeted therapies aimed at new targets identified by in-house analysis of genetic panels studing pediatric cancer patients' DNA.

Immunotherapy with new bispecific antibodies.

Incorporation of checkpoint inhibitors.

T-CARs for patients with relapse/refractory ALL. This innovative treatment has been performed in only a few centers in the USA and was successfully given to 5 patients. Pediatric brain tumors and neuroblastoma studies in the lab including pathogenesis, innovative therapies, discovery of new molecular aberrations, new biomarkers, new therapeutic targets the effect of new drugs on cell lines, primary cells and xenografts, studying the influence of changes in the levels of non-coding RNA's (mirs and link-RNA) on the tumor. Improvement of the activity of cytokine induced killer cells stemming from alfa/beta depleted T cells left over after haploidentical transplantations. Studying the effects of phytocannabinoids, synthetic cannabinoids and endocannabinoid-like substances on pediatric glioblastomas and neuroblastoma.

Main research areas:

1. T-CARS therapy for relapsed/reistant CD19 expressing leukemias and lymphomas
2. The effects of cannabinoids on pediatric tumors
3. Cytokine induced killer cells against pediatric tumors
4. Pediatric brain tumors research

Publications

Zinc enhances temozolomide cytotoxicity in glioblastoma multiforme model systems. **Toren A**, Pismenyuk T, Yalon M, Freedman S, Simon AJ, Fisher T, Moshe I, Reichardt JK, Constantini S, Mardor Y, Last D, Guez D, Daniels D, Assoulin M, Mehrian-Shai R. Oncotarget. 2016.

Yalon M, Tuval-Kochen L, Castel D, Moshe I, Mazal I, Cohen O, Avivi C, Rosenblatt K, Aviel-Ronen S, Schiby G, Yahalom J, Amariglio N, Pfeffer R, Lawrence YR, **Toren A**, Rechavi G, Paglin S Correction: Overcoming Resistance of Cancer Cells to PARP-1 Inhibitors with Three Different Drug Combinations.. PloS One. 2016.

Yalon M, Tuval-Kochen L, Castel D, Moshe I, Mazal I, Cohen O, Avivi C, Rosenblatt K, Aviel-Ronen S, Schiby G, Yahalom J, Amariglio N, Pfeffer R, Lawrence Y, **Toren A**, Rechavi G, Paglin S. Overcoming Resistance of Cancer Cells to PARP-1 Inhibitors with Three Different Drug Combinations. PloS One. 2016.

Fisher T, Golan H, Schiby G, PriChen S, Smoum R, Moshe I, Peshes-Yaloz N, Castiel A, Waldman D, Gallily R, Mechoulam R, **Toren A**. In vitro and in vivo efficacy of non-psychoactive cannabidiol in neuroblastoma. Curr Oncol. 2016.

Mehrian-Shai R, Yalon M, Moshe I, Barshack I, Nass D, Jacob J, Dor C, Reichardt JK, Constantini S, **Toren A**. Identification of genomic aberrations in hemangioblastoma by droplet digital PCR and SNP microarray highlights novel candidate genes and pathways for pathogenesis. BMC Genomics. 2016.

Mehrian-Shai R, Yalon M, Simon AJ, Eyal E, Pismenyuk T, Moshe I, Constantini S, **Toren A**.High metallothionein predicts poor survival in glioblastoma multiforme. BMC Med Genomics. 2015

Keidan I, Ben-Menachem E, Berkenstadt H, **Toren A**. A Simple Diagnostic Test to Confirm Correct Placement of Dysfunctional Central Venous Catheters Before Chemotherapy in Children. J Pediatr Hematol Oncol. 2016.

Hutt D, Nehari M, Munitz-Shenkar D, Alkalay Y, **Toren A**, Bielorai B Hematopoietic stem cell donation: psychological perspectives of pediatric sibling donors and their parents. Bone Marrow Transplant. 2015.

Mehrian-Shai R, Freedman S, Shams S, Doherty J, Slattery W, Hsu NY, Reichardt JK, Andalibi A, **Toren**

A. Schwannomas exhibit distinct size-dependent gene-expression patterns. Future Oncol. 2015.

Goldstein G, Shemesh E, Frenkel T, Jacobson JM, **Toren A**. Abnormal body mass index at diagnosis in patients with Ewing sarcoma is associated with inferior tumor necrosis. Pediatr Blood Cancer. 2015.

Goldstein G, Keller N, Bilik R, Bielorai B, **Toren A**. Do immunocompromised children benefit from having surgical lung biopsy performed? Acta Haematol. 2015.

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Cell to Cell Communication in Cancer: The Role of Exosomes

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Exosomes are nanosized particles that are formed in different types of cells, travel in blood and other body fluids and carry a cargo of prtoeins and nucleic acids. This cargo is delivered to neighbouring cells. Our lab studies the role of exosomes in cell to cell communication and the potential use of exosomal cargo as biomarkers for diagnostics and followup of patients with cancer. Previously, we found that exosomes derived from various neoplastic cells contain hTERT transcript of telomerase, an enzyme that is unique to cancer cells and is only rarely found on non-neoplastic cells. Furthermore, this transcript is actively translated and mediates canonical and non-canonical functions in the recipient cells. In parallel we have found that in cancer patients, about 2/3 of the sera derived exosomes contain detectable telomerase transcript.

Currently we are focused on the potential use of exosomal hTERT as a cancer biomarker. We follow the presence of telomerase in exosomes isolated from patients with cancer in response to treatment. This followup is conducted on exosomes derived from patients with lung cancer, breast cancer and

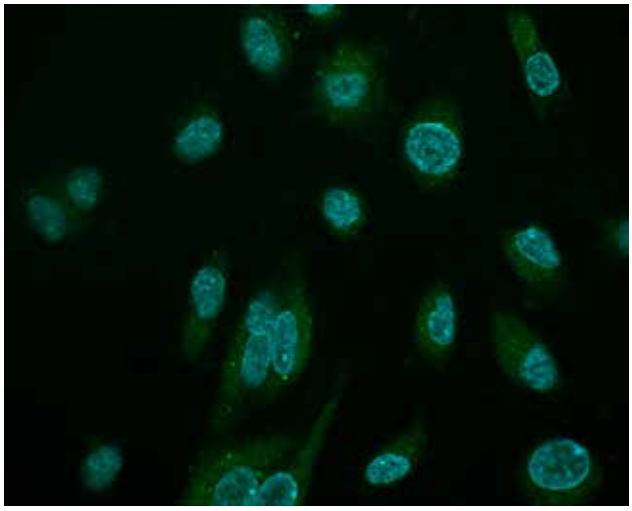

Figure 1. FITC-stained exosomes are taken up by HUVEC cells analyzed by fluoresent microscopy.

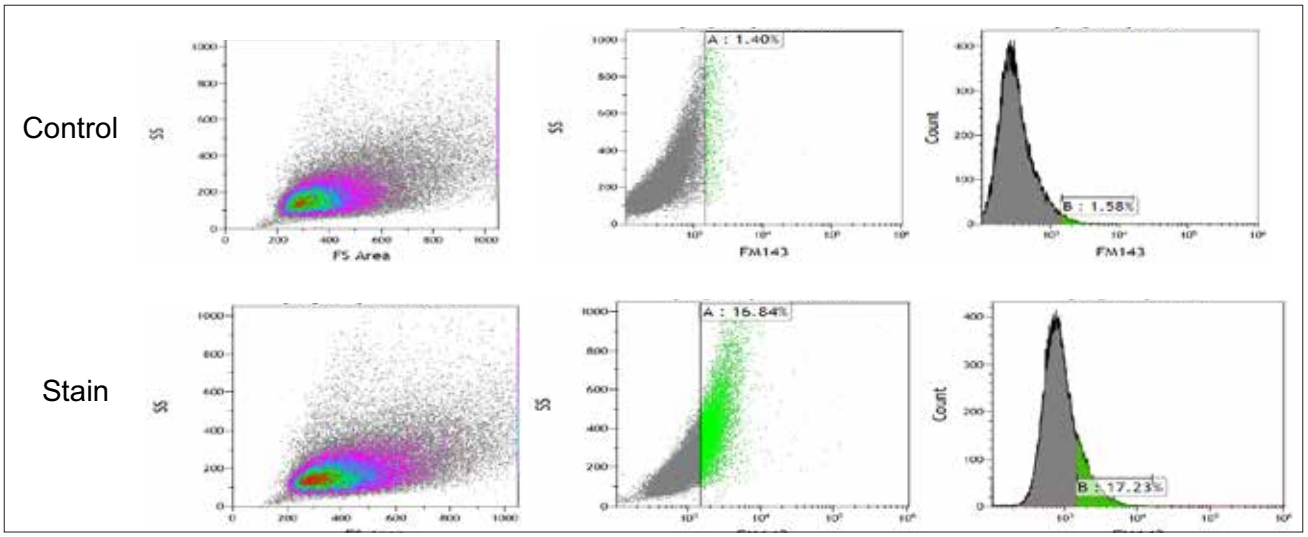

Figure 2. FM-134 stained exosomes are taken up by HUVEC cells analysed by flow cytometry.

glioblastoma multiforme in which we also correlate the disease stage with the presence of mutations present at telomerase promoter as well. We study also other types of cargos that are delivered by exosomes as well.

Additionally, we are studying the crosstalk of exosomes isolated from cancer cells and cells of their microenvironment. In figure 1, the uptake of FITC-stained cancer cell exosomes by HUVEC (Human Umbilical Vein Endothelial Cells) is shown. In figure 2, the same uptake is shown by FACS analysis.

Publications

Uziel O, Gutkin A, Beery E, Lahav M. Exosomes as mediators for cell- cell comunicastion: the relevance to cancer and to the enzyme telomerase. Harefua. 156, 710-714, 2017.

Goldvaser H, Gutkin A, Beery E, Edel Y, Nordenberg J, Wolach O, Rabizadeh E, **Uziel O**, Lahav M. Characterisation of blood-derived exosomal hTERT mRNA secretion in cancer patients: a potential pan-cancer marker. Br J Cancer. 2017 Jun 22. [Epub ahead of print]

Solomon Z, Tsur N, Levin Y, **Uziel O**, Lahav M, Ohry A. The implications of war captivity and long-term psychopathology trajectories for telomere length. Psychoneuroendocrinology. 81, 122-128, 2017.

Kliminski V, **Uziel O**, Kessler-Icekson G. Popdc1/Bves Functions in the Preservation of Cardiomyocyte Viability While Affecting Rac1 Activity and Bnip3 Expression. J Cell Biochem. 118, 1505-1517, 2017.

Gutkin A, **Uziel O,** Beery E, Nordenberg J, Pinchasi M, Goldvaser H, Henick S, Goldberg M, Lahav M. Tumor cells derived exosomes contain hTERT mRNA and transform nonmalignant fibroblasts into telomerase positive cells. Oncotarget. 7, 59173-88, 2016.

Uziel O, Yerushalmi R, Zuriano L, Beery E, Nordenberg J, Lubin I, Adel Y, Shepshelovich D, Pery S, Rizel S, Pasmanik-Chor M, Frumkin D, Lahav M. The role of BRCA1 in telomere regulation: implications for genomic stability and malignant transformation. Oncotarget. 7, 2433-54, 2016.

Uziel O, Lahav M. Proteomic and microRNA data clarifying the effects of telomere shortening on Cancer cells. Data in Brief. 48–51, 2015.

Shepshelovich D, Ram R, **Uziel O**, Kushnir M, Lithwick Yanai G, Hoshen M, Feinmesser M, Beeri O, Lahav M. MicroRNA signature is indicative of long term prognosis in diffuse large B cell lymphoma. Leukemia Research. 39, 632-7, 2015.

Uziel O, Yosef N, Sharan R, Ruppin E, Kupiec M, Kushnir M, Beery E, Cohen-Diker T, Nordenberg J, Lahav M. Effects of telomere shortening on cancer cells: Network model of proteomic and microRNA analysis. Genomics. 105, 5–16, 2015.

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Dr. Tami Rubinek, Ph.D.

Head - Oncology Division Research Lab, Tel Aviv Sourasky Medical Center
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Deciphering Endocrine Aspects of Cancer Development

Positions

Prof. Ido Wolf, Associate Professor, Sackler Faculty of Medicine

Head, Oncology Division, Tel Aviv Sourasky Medical Center

Dr. Tami Rubinek, Senior Lecturer, Sackler Faculty of Medicine

Head – Oncology Division Research Lab, Tel Aviv Sourasky Medical Center

Klotho: the hormone that links longevity, metabolism and cancer

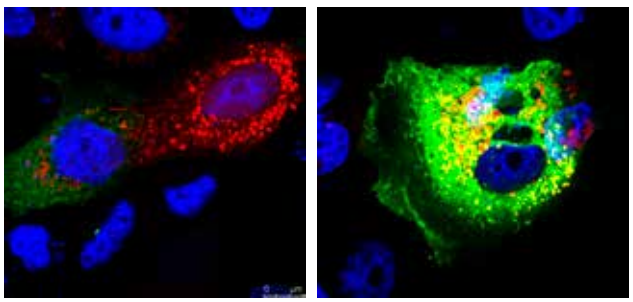
Klotho is a hormone that regulates physiologic processes, including kidney functions amd metabolism. Reduced klotho levels are associated with aging. We discovered that klotho is a potent tumor suppressor in breast, pancreatic and ovarian cancers. Current projects:

- Characterization of klotho activity in cancer by generation of transgenic mice, structure-function analyses and biochemical analyses of enzymatic activities
- Deciphring the role of klotho as a regulator of calcium fluxes, mitochondrial activity and tumor metabolism
- Discovering the role of klotho in regulator of the GH/IGF axis

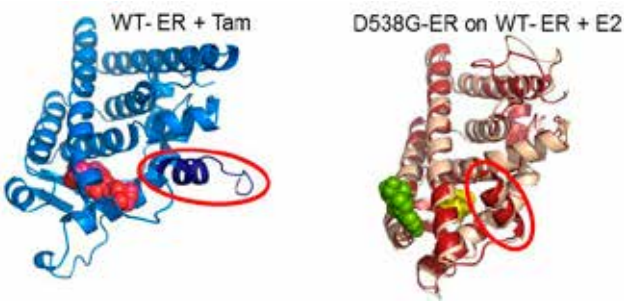
The estrogen receptor (ESR1) mutations in breast cancer

Our lab was the first to discover mutations in ESR1 that confer resistance to hormonal therapies in >40% of patients with metastatic breast cancer. Current projects:

- Styding the mutations as mediators of aggressive phenotype of breast cancer



Co-localization of klotho (green) with mitochondria (red) in MCF-7 breast cancer cells.



Structural model of D538G mutated ESR1

- Studiyng the unique metabolic activity of cance cells harboring thr mutations
- Development of novel treatment strategies in breast cancer

How do cancer cells choose were to metastasize- or what regulates tropism?

We are tackling the role of specific mutations in mediating homing of cancer cells to specific organs:

- Deciphering the mechanism of homing of pancreatic tumors to different organs
- Revealing metabolic pathways enabling colon cancer cells to form brain metastasis

Publications

Waissengrin B, Urban D, Leshem Y, Garty M, **Wolf I**. Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. J Pain Symptom Manage. 2015; 49(2):223-30.

Lojkin I, **Rubinek T**, Orsulik S, Schwarzmann O, Karlan B, Bose S, **Wolf I**. Reduced expression and growth inhibitory activity of the aging suppressor klotho in epithelial ovarian cancer. Cancer Lett. 2015 362(2):149-57.

Kamari Y, Fingrut O, Shaish A, Almog T, Kandel-Kfir M, Harats D, **Rubinek T, Wolf I**. The effect of klotho treatment on atherogenesis, blood pressure and metabolic parameters in experimental rodent models. Hormone and Metabolic Research, 2015 48(3):196-200.

Ligumsky H, **Rubinek T**, Merenbakh-Lamin K, Yeheskel A, Sertchook R, Shahmoon S, Aviel-Ronen S, **Wolf I**. Tumor suppressor activity of Klotho in breast cancer is revealed by structure-function analysis. Mol Cancer Res. 2015 13(10):1398-407 .

Aviel-Ronen S*, **Rubinek T***, Zadok O*, Vituri A, Avivi C, **Wolf I****, Barshack I**. Klotho expression in cervical cancer: differential expression in adenocarcinoma and squamous cell carcinoma. *first co-author, **equal supervisors. J Clin Pathol. 2016 ;69(1):53-7.

Wolf I *, Stein D*, Shahmoon S, Ziv SI, Hemi R, Kanety H, **Rubinek T****, Modan-Moses D**. Alteration in Serum Klotho Levels in Anorexia Nervosa. *first co-author, ** Co-supervision. Clin Nutr. 2015. pii: S0261-5614(15)00192-2.

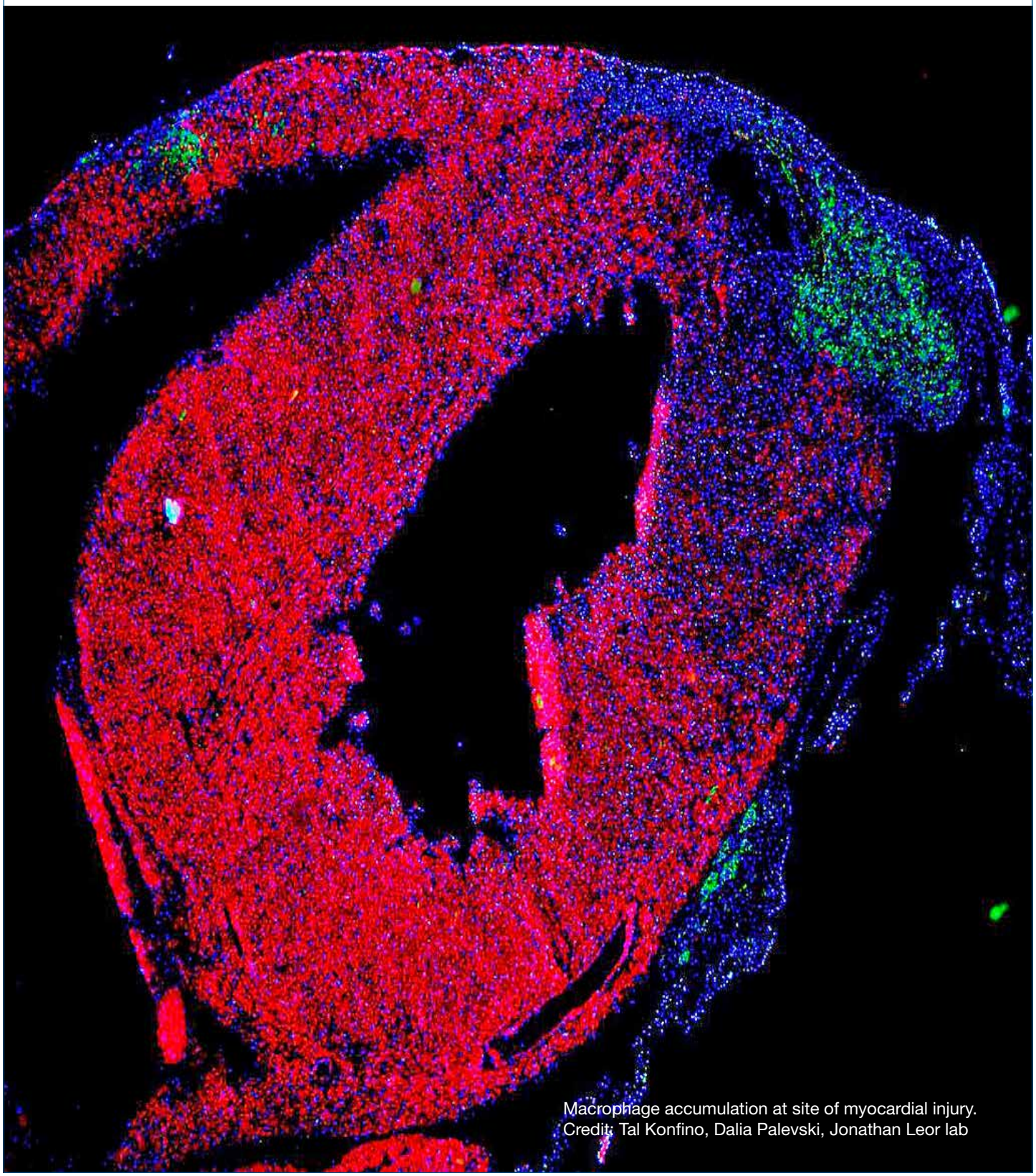
van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, Perez D, Robinson BA, Strickland AH, Ferguson T, Rodrigez J, Kröning H, **Wolf I**, Ganju V, Walpole E, Boucher E, Tichler T, Shacham-Shmueli E, Powell A, Eliadis P, Isaacs R, Price D, Moeslein F, Taieb J, Bower G, Gebski V, Van Buskirk M, Cade DN, Thurston K, Gibbs P. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 20;34(15):1723-31.

Rubinek T, Shahmoon S, Shabtay-Orbach A, Ben Ami M, Levy-Shraga Y, Mazor-Aronovitch K, Yeshayahu Y, Doolman R, Hemi R, Kanety H, **Wolf I**, Modan-Moses D. Klotho response to treatment with growth hormone and the role of IGF-I as a mediator. Metabolism, 2016;65(11):1597-1604.

Grants

2017-2022 Orion Scholarship

Cardiovascular System



Macrophage accumulation at site of myocardial injury.
Credit: Tal Konfino, Dalia Palevski, Jonathan Leor lab

Prof. Ehud Grossman, M.D.

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Investigating Hypertension, Diabetes Mellitus and Metabolic Syndrome

Positions (Prof. Grossman)

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Professor of Medicine, Sackler Faculty of Medicine, Tel Aviv University

Dean, Sackler Faculty of Medicine, Tel Aviv University

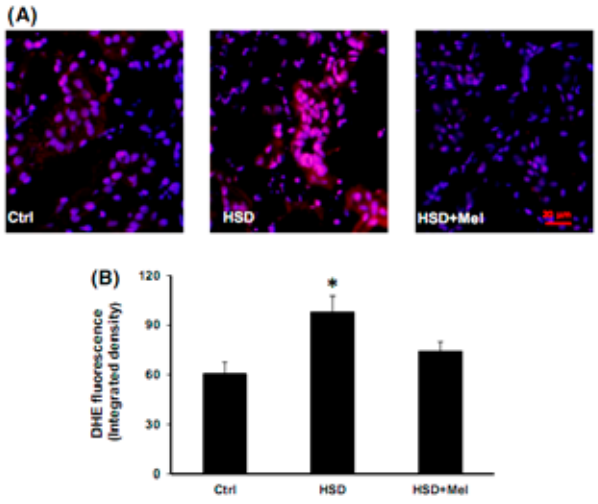

Fig. 3. Melatonin abolished high salt diet (HSD)-induced superoxide formation in the kidney. Dihydroethidium (DHE) staining demonstrating reactive oxygen species production determined in rats' kidneys. (A) Representative images of DHE-stained kidney sections and (B) quantification are presented. $*P < 0.05$ HSD versus Ctrl and HSD + Mel, n = 5, 20× magnification. Blue staining represents nuclear DAPI staining. Ctrl, control; HSD, high salt diet; Mel, melatonin.

Leibowitz A, Volkov A, Voloshin K, Shemesh C, Barshack I, **Grossman E.** J Pineal Res. 2016;60:48-54.

Research

Our research concentrates on the impact of coronary calcifications on cardiovascular morbidity and mortality in hypertensive patients. We showed that the presence of coronary calcifications is associated with increased mortality and that diabetic patients without coronary calcifications have a good prognosis. Our team also studied the effect of blood pressure control and stroke outcomes. We showed that elevated systolic blood pressure in acute stroke is associated with poor outcome and that change in BP during the first week after stroke has no effect on outcome. Our main basic research is on metabolic syndrome. How can we improve metabolic syndrome? We also studied the effect of melatonin on the cardiovascular system. Our recent paper in *J Pineal Res* showed that melatonin prevents kidney injury in a high salt diet-induced hypertension model by decreasing oxidative stress.

Publications

Shlomai G, Kopel E, Goldenberg I, **Grossman E.** The association between elevated admission systolic blood pressure in patients with acute coronary syndrome and favorable early and late outcomes. J Am Soc Hypertens. 2015;9:97-103.

Grossman C, Ehrlich S, Shemesh J, Koren-Morag N, **Grossman E.** Coronary Artery Calcium and Exercise Electrocardiogram as Predictors of Coronary Events

in Asymptomatic Adults. Am J Cardiol. 2015;115:745-50.

Lavan O, Rimon U, Simon D, Khaitovich B, Segal B, **Grossman E**, Kleinbaum Y, Steinberg DM, Salomon O. The use of optional inferior vena cava filters of type Optease in trauma patients- a single type of filter in a single Medical Center. Thromb Res. 2015;135:873-6.

Grossman A, Messerli FH, **Grossman E**. Drug induced hypertension--An unappreciated cause of secondary hypertension. Eur J Pharmacol. 2015;763:15-22.

Shlomai G, Haran-Appel T, Sella T, Grossman Y, Hauschner H, Rosenberg N, **Grossman E**. High-risk type-2 diabetes mellitus patients, without prior ischemic events, have normal blood platelet functionality profiles: a cross-sectional study. Cardiovasc Diabetol. 2015;14:80.

Weiss A, Grossman A, Bellosesky Y, Koren-Morag N, Green H, **Grossman E**. Inter-arm blood pressure difference in hospitalized elderly patients is not associated with excess mortality. J Clin Hypertens. 2015;17:786-91.

Berger A, **Grossman E**, Katz M, Kivity S, Klempfner R, Segev S, Goldenberg I, Sidi Y, Maor E. Exercise blood pressure and the risk for future hypertension among normotensive middle-aged adults. Journal of the American Heart Association. 2015: 4(4).

Keren S, **Leibowitz A**, **Grossman E**, Sharabi Y. Limited reproducibility of 24-h ambulatory blood pressure monitoring. Clin Exp Hypertens. 2015;37:599-603.

Rosman Y, Kopel E, Shlomai G, Goldenberg I, **Grossman E**. The association between admission systolic blood pressure of heart failure patients with preserved systolic function and mortality outcomes. Eur J Intern Med. 2015;26:807-12.

Berkovitch A, Maor E, Sabbag A, Chernomordik F, Elis A, Arbel Y, Goldenberg I, **Grossman E**, Klempfner R. Precipitating Factors for Acute Heart Failure Hospitalization and Long-Term Survival. Medicine (Baltimore). 2015;94:e2330.

Shopen N, Schiff E ,Koren-Morag N, **Grossman E.** Factors That Predict the Development of Hypertension in Women With Pregnancy-Induced Hypertension. Am J Hypertens. 2016;29:141-6.

Weiss A, Beloosesky Y, Kenett RS, **Grossman E**: Change in Systolic Blood Pressure During Stroke, Functional Status, and Long-Term Mortality in an Elderly Population. Am J Hypertens. 2016;29:432-8.

Eizenberg Y, Koton S, Tanne D, **Grossman E**. Association of age and admission mean arterial blood pressure in patients with stroke-data from a national stroke registry. Hypertens Res. 2016; 39:356-61.

Leibowitz A, Volkov A, Voloshin K, Shemesh C, Barshack I, **Grossman E.** Melatonin prevents kidney injury in a high salt diet-induced hypertension model by decreasing oxidative stress. J Pineal Res. 2016;60:48-54.

Koton S, Eizenberg Y, Tanne D, **Grossman E**. Trends in admission blood pressure and stroke outcome in patients with acute stroke and transient ischemic attack in a National Acute Stroke registry. J Hypertens. 2016;34:316-22.

Rock W, Zbidat K, Schwartz N, Elias M, Minuhin I, Shapira R, **Grossman E**. Pattern of Blood Pressure Response in Patients With Severe Asymptomatic Hypertension Treated in the Emergency Department. J Clin Hypertens . 2016;18:796-800.

Leiba A, Cohen-Arazi O, Mendel L, Holtzman EJ, **Grossman E**. Incidence, aetiology and mortality secondary to hypertensive emergencies in a large-scale referral centre in Israel (1991-2010). J Hum Hypertens. 2016;30:498-502.

Giladi O, Steinberg DM, Peleg K, Tanne D, Givon A, **Grossman E**, Klein Y, Avigdori S, Greenberg G, Katz R, Shalev V, Salomon O. Head trauma is the major risk factor for cerebral sinus-vein thrombosis. Thromb Res. 2016;137:26-9.

Shlomai G, Berkovitch A, Pinchevski-Kadir S, Bornstein G, **Leibowitz A**, Goldenberg I, **Grossman E**. The association between normal-range admission potassium levels in Israeli patients with acute coronary syndrome and early and late outcomes. Medicine (Baltimore). 2016;95:e3778.

Weiss A, Beloosesky Y, Grossman A, Shlesinger A ,Koren-Morag N, **Grossman E**. The association between orthostatic hypertension and all-cause mortality in hospitalized elderly persons. J Geriatr Cardiol. 2016;13:239-43.

Grossman C, Bornstein G, **Leibowitz A**, Ben-Zvi I, **Grossman E**. Effect of tumor necrosis factor-alpha inhibitors on ambulatory 24-h blood pressure. Blood Press. 2016:1-6.

Berger A, **Grossman E**, Katz M, Kivity S, Klempfner R, Segev S, Goldenberg I, Sidi Y, Maor E. Exercise systolic blood pressure variability is associated with increased risk for new-onset hypertension among normotensive adults. J Am Soc Hypertens. 2016;10: 535-527e2.

Solini A, **Grossman E**. What Should Be the Target Blood Pressure in Elderly Patients With Diabetes? Diabetes Care. 2016;39 Suppl 2:S234-43.

Shafran I, Greenberg G, **Grossman E, Leibowitz A**. Diabetic striatopathy-Does it exist in non-Asian subjects? Eur J Intern Med. 2016.

Grossman C, Bornstein G, Leibowitz A, Ben-Zvi I, **Grossman E***. Effect of tumor necrosis factor-alpha inhibitors on ambulatory 24-h blood pressure. Blood Press. 2017:26:24-29.*

Koton S, Tanne D, **Grossman E**. Prestroke treatment with beta-blockers for hypertension is not associated with severity and poor outcome in patients with ischemic stroke: data from a national stroke registry. J Hypertens. 2017;35(4):870-876.

Leiba A, Twig G, Vivante A, Skorecki K, Golan E, Derazne E, Tzur D, **Grossman E**, Dichtiar R, Kark JD and Shohat T. Prehypertension among 2.19 million adolescents and future risk for end-stage renal disease. J Hypertens. 2017;35(6):1290-1296.

Segal O, Segal G, **Leibowitz A**, Goldenberg I, **Grossman E**, Klempfner R. Elevation in systolic blood pressure during heart failure hospitalization is associated with increased short and long-term mortality. Medicine (Baltimore). 2017;96(5):e5890.

Israel A and **Grossman E**. Elevated High Density Lipoprotein Cholesterol is associated with hyponatremia in hypertensive patients. Am J Med. 2017.

Grossman C, Levin M, Koren-Morag N, Bornstein G, **Leibowitz A**, Ben-Zvi I, Shemesh J, **Grossman E**. Left ventricular hypertrophy predicts cardiovascular events in hypertensive patients with coronary artery calcifications. Am J Hypertens. 2017

Leibowitz A, **Grossman E**, Berkovitch A, Levartovski M, Appel S, Sharabi Y, Gluck I. The Effect of Head and Neck Radiotherapy on Blood Pressure and Orthostatic Hypotension in Patients with ith Head and Neck Tumors. Am J Hypertens. 2017.

Eizenberg Y, **Grossman E**, Tanne D, Koton S. Pre admission treatment with Beta-blockers in hypertensive patients with acute stroke and 3-month outcome - data from a national stroke registry. J Clin Hypertens. 2018

Botzer A, **Grossman E**, Moult J, Unger R. A system view and analysis of essential hypertension. J Hypertens. 2018

Prof. Giris Jacob, M.D., D.Sc.

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J. Recanati Autonomic Dysfunction CTR
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Cardiovascular Regulatory Systems Focusing on the Autonomic Nervous System in Human (*Translational Science*)

Position

Associate Professor, Medicine and Physiology

Research

Recanati Autonomic Dysfunction Center

The effect of adrenoceptors activation on the coagulation system

Insight into the regulatory mechanisms of mesenteric flow

Organ-specific flow regulation, e.g. cerebral and penile blood flow

Autonomic nervous system dysregulation in CVD

Autonomic nervous system and pain regulation, including fMRI studies

Postural tachycardia Syndrome (POTS)

Collaborations: Vanderbilt University, Nashville, TN, USA, Milano University, Italy, and Eurospace Center, Germany.

Publications

Ali-Saleh M, Sarig G, Ablin JN, Brenner B and **Jacob G**. Inhalation of a Short-Acting beta2-Adrenoreceptor Agonist Induces a Hypercoagulable State in Healthy Subjects. PLoS One 11: e0158652, 2016.

Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D and **Jacob G**. Pain Modulation and Autonomic Function: The Effect of Clonidine. Pain Med 2016.

Kaufmann H and **Jacob G**. Early and delayed orthostatic hypotension: Time tells. *Neurology* 85: 1358-1359, 2015.

Dayan L, Brill S, Hochberg U and **Jacob G**. Is adenosine a modulator of peripheral vasoconstrictor responses? *Clin Auton Res* 26: 141147,, 2016.

Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D and **Jacob G**. (365) Pain modulation and autonomic function: the effect of clonidine. *J Pain* 17: S66, 2016.

Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D and **Jacob G**. Sex differences in the relationships between parasympathetic activity and pain modulation. *Physiol Behav* 154: 40-48, 2016.

Nahman-Averbuch H, Sprecher E, **Jacob G** and Yarnitsky D. The Relationships Between Parasympathetic Function and Pain Perception: The Role of Anxiety. *Pain Pract* 2016.

Alshiek JA, Dayan L, Asleh R, Blum S, Levy AP, **Jacob G**. Anti-oxidative treatment with vitamin E improves peripheral vascular function in patients with diabetes mellitus and Haptoglobin 2-2 genotype: A double-blinded cross-over study. Diabetes Res Clin Pract. 2017;131:200-207.

Dayan L, Hochberg U, Nahman-Averbuch H, Brill S, Ablin JN, **Jacob G**. Increased sympathetic outflow induces adaptation to acute experimental pain. Pain Pract. 2017. doi: 10.1111/papr.12606.

Jahshan S, Dayan L, **Jacob G.** Nitric oxide-sensitive guanylyl cyclase signaling affects CO2-dependent but not pressure-dependent regulation of cerebral blood flow. Am J Physiol Regul Integr Comp Physiol. 2017;312(6):R948-R955.

Hellou R, Häuser W, Brenner I, Buskila D, **Jacob** G, Elkayam O, Aloush V, Ablin JN. Self-reported childhood maltreatment and traumatic events among israeli patients suffering from fibromyalgia

and rheumatoid arthritis. Pain Res Manag. 2017;2017:3865249.

Grants

2016-2019 Yahel Foundation (Recanati), NYC, USA

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Atherosclerosis – Research, Treatment and Prevention

Positions

Professor of Medicine, Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine

Acting Vice President of Research and Development and Academy and Chairman, IRB Committee

President, The Bert W. Strassburger Lipid Center, Sheba Medical Center

Chairman, IRB Committee of the Sheba Medical Center

CEO, Vascular Biogenics Ltd (VBL)

Research

We investigate lipid metabolism, atherosclerosis and vascular biology. In our research, we apply advanced research tools, utilizing in-vitro and in-vivo models and performing clinical trials. In our studies, we focus on basic aspects in atherosclerosis progression and developing new treatments for prevention of the disease.

The current research projects are:

The effect of carotenoids and their cleavage products on the activation of the nuclear receptor RXR and atherosclerosis in mouse models.

The effect of carotenoids on Retinitis Pigmentosa.

The effect of carotenoids on Alzheimer in transgenic mice.

The role of the coagulation Factor XI in early and advanced atherosclerosis by using apolipoproteinE/ FactorXI double knock-out mice.

The role of apoA5 in atherosclerosis development by using apolipoproteinE/apoAVI transgenic mice.

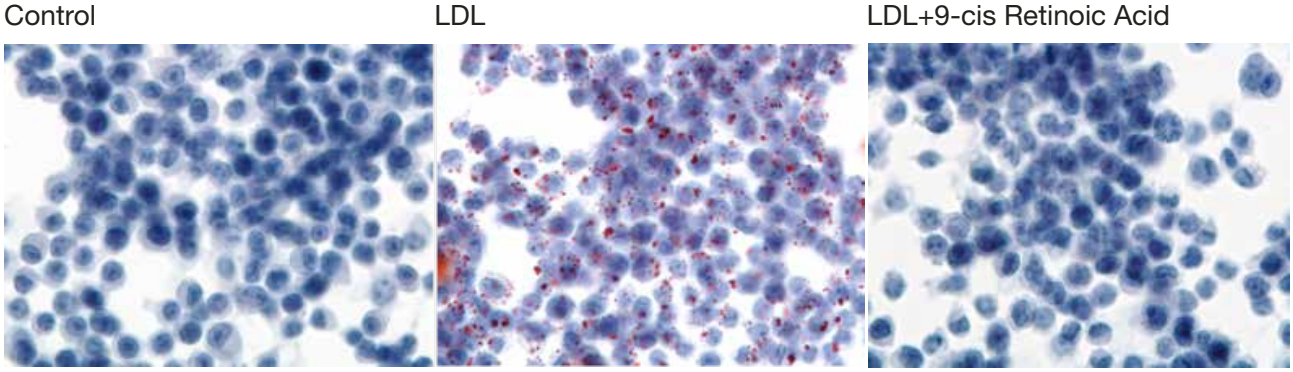
Publications

Mendel I, Yacov N, **Harats D**, Breitbart E. Therapies targeting innate immunity for fighting inflammation in atherosclerosis. Curr Pharm Des. 2015;21(9):1185-95.

Zolberg Relevy N, Bechor S, Harari A, Ben-Amotz A, Kamari Y, **Harats D**, Shaish A. The inhibition of macrophage foam cell formation by 9-cis β-carotene is driven by BCMO1 activity. PLoS One. 2015;10(1):e0115272.

Almog T, Kandel-Kfir M, Shaish A, Dissen M, Shlomai G, Voronov E, Apte RN, **Harats D**, Kamari Y. Knockdown of interleukin-1α does not attenuate LPS-induced production of interleukin-1β in mouse macrophages. Cytokine. 2015;73(1):138-143.

Relevy NZ, **Harats** D, Harari A, Ben-Amotz A, Bitzur R, Rühl R, Shaish A. .Vitamin A-Deficient Diet Accelerated Atherogenesis in Apolipoprotein E(-/-) Mice and Dietary β-Carotene Prevents This Consequence. Biomed Res Int. 2015;2015:758723



Macrophage foam cell formation is inhibited by 9-cis retinoic acid

Kandel-Kfir M, Almog T, Shaish A, Shlomai G, Anafi L, Avivi C, Barshack I, Grosskopf I, **Harats D**, Kamari Y. Interleukin-1α deficiency attenuates endoplasmic reticulum stress-induced liver damage and CHOP expression in mice. J Hepatol. 63(4):926-33, 2015.

Bitzur R, Rozenman Y, Vinker S, Dikerl D, Shemesh J, Lahad A, Gavishl D, **Harats D**, KnobLer H; Society for Research, Prevention and Treatment of Atherosclerosis, Israel; Israel Heart Society; Israel Association of Family Physicians; Israel Society of Internal Medicine. Israeli guidelines for the treatment of hyperlipidemia – 2014 update Harefuah 154(5):330-3, 337-8, 2015.

Rosenzweig B, Barshack I, **Harats D**, Shaish A. Thoracic Duct Narrowing-Innovative Technique Restraining Weight Gain in Rats. Obes Surg. 25(12):2443-50, 2015.

Shnerb Ganor R, **Harats D**, Schiby G, Gailani D, Levkovitz H, Avivi C, Tamarin I, Shaish A, Salomon O. Factor XI Deficiency Protects Against Atherogenesis in Apolipoprotein E/Factor XI Double Knockout Mice. Arterioscler Thromb Vasc Biol. 36(3):475-81, 2016.

Grosskopf I, Shaish A, Charach G, **Harats D**, Kamari Y. Nifedipine Treatment for Hypertension is Associated with Enhanced Lipolytic Activity and Accelerated Clearance of Postprandial Lipemia. Horm Metab Res. 2016 Feb 5. [Epub ahead of print]

Bechor S, Zolberg Relevy N, Harari A, Almog T, Kamari Y, Ben-Amotz A, **Harats D**, Shaish A. 9-cis β-Carotene Increased Cholesterol Efflux to HDL in Macrophages. Nutrients. 19;8(7), 2016.

Boehm-Cagan A, Bar R, **Harats D**, Shaish A, Levkovitz H, Bielicki JK, Johansson JO, Michaelson DM. Differential Effects of apoE4 and Activation of ABCA1 on Brain and Plasma Lipoproteins. PLoS One. 8;11(11), 2016.

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Elucidating the Molecular & Pathophysiological Mechanisms Leading to the Initiation and Progression of Cardiovascular Diseases

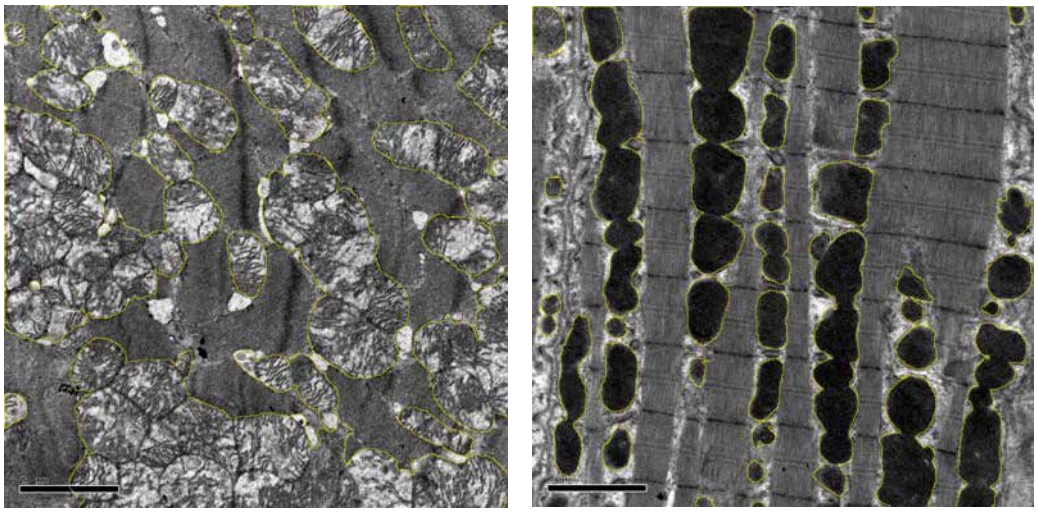
Positions (Prof. Keren)

Head, Cardiology Division, Tel Aviv Sourasky Medical Center

Professor, Department of Cardiology

Research

We study the molecular networks leading to the initiation and progression of acute versus chronic presentation of various cardiac diseases. Currently we mainly focus on studying the following cardiac pathologies: 1. Acute myocardial infarction leading to left ventricular dysfunction; 2. cardiac volume overload- a prominent pathology in valvular diseases and chronic heart failure; 3. the prevalent presentation of cardio-renal syndrome. Utilizing the appropriate in vivo models as well as various molecular and cellular techniques, we have been trying to identify novel therapeutic targets for attenuating disease progression and to improve the clinical presentation of these devastating conditions.



Captures of transmitted electron microscopy demonstrating the organized structure of cardiac mitochondria in sham-operated control rats (A) compared to the swallawed unorganized structure of the mitochondria in the heart tissue of animals with chronic kidney disease (B).

Main ongoing research topics

The potential involvement of the cation channel TRPV2, which is highly abundant on peri-infarct immune cells, in the recovery processes following an acute myocardial infarction.

Elucidating the therapeutic potential of anti-metalloproteinase antibodies as well as reagents holding anti- histone deacetylase activity for the treatment of cardiac volume overload.

Cardiac mitochondria as a promising target for attenuation of cardiac dysfunction and progression to cardiorenal syndrome in patients with chronic kidney disease.

Publications

Rofe MT, Levi1 R, Hertzberg-Bigelman E, Goryainov P, Barashi R, Ben-Shoshan J, **Keren G, Entin-Meer M**. Chronic kidney disease leads to cardiac hypertrophy with no apparent induction of cardiac cell death. Isr Med Assoc J. 2015, 17(12):744-9.

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, **Entin-Meer M**, Gur E, Loewenstein A, Barak A. Power-Assisted Liposuction Versus Tissue Resection for the Isolation of Adipose Tissue-Derived Mesenchymal Stem Cells: Phenotype, Senescence, and Multipotency at Advanced Passages. Aesthet Surg J. 2015, 35(7):NP230-40.

Hertzberg-Bigelman E, Entin-Meer M, Aharon-Hananek G, Saada A, Levy R, Cohen L, Rozenbaum Z, Keren G. Reduced number of active mitochondria in a rat model for long-term kidney disease. Supp to Eur Heart J. 2015;951, P5463.

Margolis G, Levy R, **Keren G, Entin-Meer M**. Differential effects of colchicine on cellular viability of cardiac cells in an in vitro model simulating myocardial infarction. Cardiology. 2016, 134(1):57-64.

Cohen L, Entin-Meer M, Rephaeli A, Tarasenko N, Ben Shoshan J, Hertzberg-Bigelman E, Keren G. Histone deacetylase inhibitor AN7 increases survival and may attenuate LV dilatation in mice with chronic volume overload. Suppl to Eur Heart J. 2016; 1097, P5387.

Ben Shoshan J, Steinvil A, Arbel Y, Topilsky Y, Barak L, **Entin-Meer M**, Levy R, Schwartz AL, Keren G, Finkelstein A, Banai S. Sustained Elevation of Vascular Endothelial Growth Factor and Angiopoietin 2 Levels Following Transcatheter Aortic Valve Replacement. Can J Cardiol. 2016, 32:1454-1461.

Hertzberg-Bigelman E, Barashi R, Levy R, Cohen L, Ben-Shoshan J, **Keren G, Entin-Meer M**. Down-Regulation of Cardiac Erythropoietin Receptor and its Downstream Activated Signal Transducer Phospho-STAT-5 in a Rat Model of Chronic Kidney Disease. Isr Med Assoc J. 2016, 18(6):326-30.

Entin-Meer M, Cohen L, Hertzberg-Bigelman E, Levy R, Ben-Shoshan J, Keren G. TRPV2 knockout mice demonstrate an improved cardiac performance following myocardial infarction due to attenuated activity of peri-infarct macrophages. PLoS One. 2017, 12(5): e0177132.

Ben-Shoshan J, Jubran A, Levy R, Keren G, Entin-Meer M. Increased CD11b+ cells and Interleukin-1 (IL-1) alpha levels during cardiomyopathy induced by chronic adrenergic activation. Isr Med Assoc J. 2017, 19(9):570-575.

Rozenbaum Z, Cohen L, Bigelman E, Shscham J, Keren G, Entin-Meer M. Downregulated expression of TRPV2 in peripheral blood cells following acute myocardial infarction is inversely correlated to sera levels of CRP and Troponin I. Cardiology. 2018, 139(3):169-174.

Bigelman E, Cohen L, Aharon-Hananel G, Levy R, Rozenbaum Z, Saada A, Keren G, Entin-Meer M. Pathological presentation of cardiac mitochondria in a rat model of chronic kidney disease. PLoS ONE. 2018, 13:e0198196.

Cohen L, Bigelman E, Sagi I, Keren G, Entin-Meer M. Specific MMP-9 and MMP-2 inhibition by novel MMP antibody attenuates LV remodeling secondary to volume overload. Suppl to Eur Heart J. 2018; 586, P2821.

Rozenbaum Y, Topilsky I, Khoury S, Milwidsky A, Balchyunayte A, Laufer-Perl M, Berliner S, Pereg D, Entin-Meer M*, Havakuk O* (equal authorship). Relationship between climate and hemodynamics according to echocardiography. J Appl Physiol. 2018; 126 (2):322-329.

Rozenbaum Z, Topilsky Y, Aviram G, Entin Meer M, Granot Y, Pereg D, Berliner S, Steinvil A, Biner S. Prognostic implications of small left arteria on hospitalized patients. Eur Heart J- Cardiovascular Imaging, 2019; 20(9):1051-1058.

Entin-Meer M, Keren G. Potential roles in cardiac physiology and pathology of the cation channel TRPV2 expressed in cardiac cells and cardiac macrophages: a mini-review. Am J Physiol Heart Circ Physiol. 2020;318:H181-H188.

Cohen L, Sagi I, Bigelman E, Solomonov I, Aloshin A, Ben-Shoshan J, Rozenbaum Z, Keren G, Entin-Meer M. cardiac remodeling secondary to chronic

volume overload is attenuated by a novel MMP9/2 blocking antibody. PloS One 2020;15(4):e0231202.

Grant

2018-2020 Ichilov-Weizmann Joint Fund

2018-2020 Ministry of Health (Chief Scientist)

2020-2022 Israel Innovation Authority-Kamin

Prof. Ran Kornowski, M.D., FESC, FACC

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Positions

Full Professor, Sackler Faculty of Medicine

Rena Favaloro Chair for Heart Surgery and Interventional Cardiology

Chairman, Division of Cardiology and Cardiac Catheterizations, Rabin Medical Center

President, Israeli Society of Cardiology

Research

Prof. Kornowski has been involved in multiple technology developments and innovative treatment techniques in cardiology. The research activities include:

Development of new techniques geared towards catheter valve interventions, examining feasibility, safety and treatment outcomes.

Innovative imaging techniques of the coronary arteries and physiology.

Study of the cardiac effects of caloric restriction and neuro-hormonal pathways of weight reduction.

Translational studies of coronary thrombosis and progenitor endothelial cells.

Translational cardiovascular research of stem cells and gene therapy.

Development of new medications during and after cardiac catheterizations.

Research of novel drug-eluting stents and biodegradable scaffolds implanted within the coronary arteries.

Development of methods of “hybrid” cardiac interventions combined with minimal invasive cardiac surgery to treat structural and coronary diseases.

Mentoring and guiding students and young cardiologists in the early stage of their career.

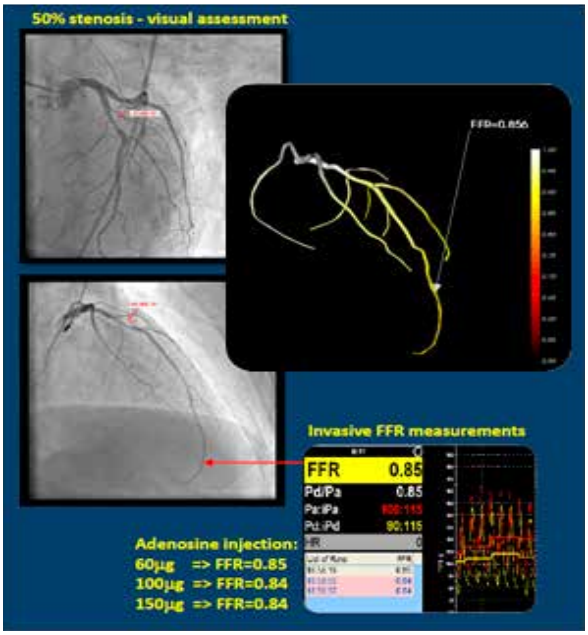

Image display of coronary angiography (Ref. Kornowski R. et al. J Am Coll Cardiol 2016;68:2235-2237)

Publications

Kornowski R, Lavi I, Pellicano M, Xaplanteris P, Vaknin-Assa H, Assali A, Valtzer O, Lotringer Y, De Bruyne B. Fractional Flow Reserve Derived From Routine Coronary Angiograms. J Am Coll Cardiol. 2016;68(20):2235-2237.

Landes U, Barsheshet A, Finkelstein A, Guetta V, Assali A, Halkin A, Vaknin-Assa H, Segev A, Bental T, Ben-Shoshan J, Barbash IM, **Kornowski R**. Temporal trends in transcatheter aortic valve implantation, 2008-2014: patient characteristics, procedural issues, and clinical outcome. Clin Cardiol. 2016.

Codner P, Levi A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, **Kornowski R**. Impact of Renal Dysfunction on Results of Transcatheter Aortic Valve Replacement Outcomes in a Large Multicenter Cohort. Am J Cardiol. 2016.

Landes U, **Kornowski R**, Bental T, Assali A, Vaknin-Assa H, Lev E, Iakobishvili Z. Long-term outcomes after percutaneous coronary interventions in cancer survivors. Coron Artery Dis. 2016.

Orvin K, Bental T, Assali A, Lev EI, Vaknin-Assa H, **Kornowski R**. Usefulness of the CHA2DS2-VASC Score to Predict Adverse Outcomes in Patients Having Percutaneous Coronary Intervention. Am J Cardiol. 2016;117(9):1433-8.

Landes U, Orvin K, Codner P, Assali A, Vaknin-Assa H, Schwartznberg S, Levi A, Shapira Y, Sagie A, **Kornowski R**. Urgent Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis and Acute Heart Failure: Procedural and 30-Day Outcomes. Can J Cardiol. 2016;32(6):726-31.

Levy E, **Kornowski R**, Gavrieli R, Fratty I, Greenberg G, Waldman M, Birk E, Shainberg A, Akirov A, Miskin R, Hochhauser E. Long-Lived αMUPA Mice Show Attenuation of Cardiac Aging and Leptin-Dependent Cardioprotection. PLoS One. 2015;10(12):e0144593.

Barbash IM, Finkelstein A, Barsheshet A, Segev A, Steinvil A, Assali A, Ben Gal Y, Vaknin Assa H, Fefer P, Sagie A, Guetta V, **Kornowski R**. Outcomes of Patients at Estimated Low, Intermediate, and High Risk Undergoing Transcatheter Aortic Valve Implantation for Aortic Stenosis. Am J Cardiol. 2015;116(12):1916-22.

Codner P, Orvin K, Assali A, Sharony R, Vaknin-Assa H, Shapira Y, Schwartzenberg S, Bental T, Sagie A, **Kornowski R**. Long-Term Outcomes for Patients with Severe Symptomatic Aortic Stenosis Treated With Transcatheter Aortic Valve ImplantationAm J Cardiol. 2015;116(9):1391-8.

Lakobishvili Z, **Kornowski R**. Can cardio-oncology deliver better care internationally? Future Oncol.;11(16):2259-62.

Landes U, Bental T, Orvin K, Vaknin-Assa H, Rechavia E, Iakobishvili Z, Lev E, Assali A, **Kornowski R**. Type 2 myocardial infarction: A descriptive analysis and comparison with type 1 myocardial infarction. J Cardiol. 2016;67(1):51-6.

Prof. Jonathan Leor, M.D.

Neufeld Cardiac Research Institute, Tel Aviv University; Tamman Cardiovascular Institute, Sheba Medical Center; Sheba Center of Regenerative Medicine, Stem Cells and Tissue Engineering

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Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions

Professor of Cardiology, Sackler Faculty of Medicine

Director, Neufeld Cardiac Research Institute, Tel Aviv University

Director, Tamman Cardiovascular Research Institute, Sheba Medical Center

Director, Sheba Center of Regenerative Medicine, Stem Cells and Tissue Engineering

Research

Our lab is focused on translational research. Specifically, we study cardiovascular regenerative medicine, stem cells and tissue engineering. In addition, we aim to target cardiovascular inflammation and fibrosis using novel nano-medicine and a theranostic (therapy + diagnosis) approach. We use a combination of gene profiling, new biomaterials, liposomes, tissue engineering, physiological testing, and molecular imaging technologies, to understand heart cell biology in vitro and in vivo. Particularly, we work on the development of novel nano-therapies for cardiovascular disease.

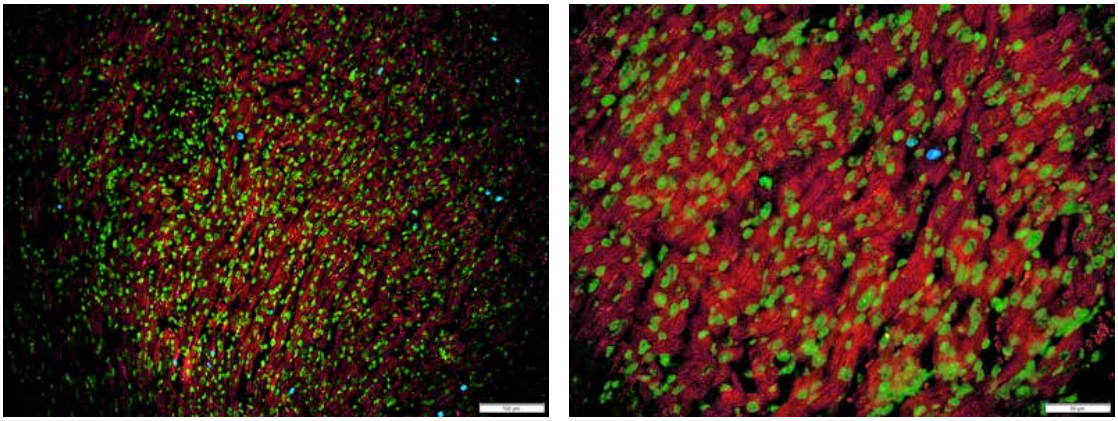
Publications (selected)

Brzezinski RY, Ovadia-Blechman Z, Lewis N, Rabin N, Zimmer Y, Levin-Kotler L, Tepper-Shaihov O, Naftali-Shani N, Tsoref O, Grossman E, Leor J and Hoffer O. Non-invasive thermal imaging of cardiac remodeling in mice. Biomed Opt Express. 2019;10:6189-6203.

Tsoref O, Tyomkin D, Amit U, Landa N, Cohen-Rosenboim O, Kain D, Golan M, Naftali-Shani N, David A and Leor J. E-selectin-targeted copolymer reduces atherosclerotic lesions, adverse cardiac remodeling, and dysfunction. J Control Release. 2018;288:136-147.

Naftali-Shani N, Molotski N, Nevo-Caspi Y, Arad M, Kuperstein R, Amit U, Huber I, Zeltzer LA, Levich A, Abbas H, Monserrat L, Paret G and Leor J. Modeling peripartum cardiomyopathy with human induced pluripotent stem cells reveals distinctive abnormal function of cardiomyocytes. Circulation. 2018;138:2721-2723.

Perrino C, Barabasi AL, Condorelli G, Davidson SM, De Windt L, Dimmeler S, Engel FB, Hausenloy DJ, Hill JA, Van Laake LW, Lecour S, Leor J, Madonna R, Mayr M, Prunier F, Sluijter JPG, Schulz R, Thum



Myocardial regeneration in a neonatal heart of a mouse, 3 days after apical resection. We used the heart of a newborn mouse to study the mechanism of myocardial regeneration and repair. The regenerating myocardium is characterized by cardiomyocyte (cardiac actin, red) dedifferentiation, and proliferation. Phospho-histone 3 immunostaining detects dividing nuclei (blue) and mitotic activity. Nuclei are stained green with DAPI

T, Ytrehus K and Ferdinandy P. Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. Cardiovasc Res. 2017;113:725-736.

Amit U, Kain D, Wagner A, Sahu A, Nevo-Caspi Y, Gonen N, Molotski N, Konfino T, Landa N, Naftali-Shani N, Blum G, Merquiol E, Karo-Atar D, Kanfi Y, Paret G, Munitz A, Cohen HY, Ruppin E, Hannenhalli S and Leor J. New role for interleukin-13 receptor alpha 1 in myocardial homeostasis and heart failure. J Am Heart Assoc. 2017;6.

Palevski D, Levin-Kotler LP, Kain D, Naftali-Shani N, Landa N, Ben-Mordechai T, Konfino T, Holbova R, Molotski N, Rosin-Arbesfeld R, Lang RA and **Leor J**. Loss of Macrophage Wnt Secretion Improves Remodeling and Function After Myocardial Infarction in Mice. *J Am Heart Assoc*. 2017;6.

Ben-Mordechai T, Kain D, Holbova R, Landa N, Levin LP, Elron-Gross I, Glucksam-Galnoy Y, Feinberg MS, Margalit R and Leor J. Targeting and modulating infarct macrophages with hemin formulated in designed lipid-based particles improves cardiac remodeling and function. *J Control Release*. 2017.

Zager Y, Kain D, Landa N, **Leor J** and Maor E. Optimization of Irreversible Electroporation Protocols for In-vivo Myocardial Decellularization. *PLoS One*. 2016;11:e0165475.

Roichman A, Kanfi Y, Glazz R, Naiman S, Amit U, Landa N, Tinman S, Stein I, Pikarsky E, **Leor J** and Cohen HY. SIRT6 Overexpression Improves Various Aspects of Mouse Healthspan. *J Gerontol A Biol Sci Med Sci*. 2016.

Madonna R, Van Laake LW, Davidson SM, Engel FB, Hausenloy DJ, Lecour S, **Leor J**, Perrino C, Schulz R, Ytrehus K, Landmesser U, Mummery CL, Janssens S, Willerson J, Eschenhagen T, Ferdinandy P and Sluijter JP. Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur Heart J*. 2016;37:1789-98.

Leor J, Palevski D, Amit U and Konfino T. Macrophages and regeneration: Lessons from the heart. *Semin Cell Dev Biol*. 2016;58:26-33.

Katz A, Maor E, **Leor J** and Klempfner R. Addition of beta-blockers to digoxin is associated with improved 1- and 10-year survival of patients hospitalized due to decompensated heart failure. *Int J Cardiol*. 2016;221:198-204.

Baabur-Cohen H, Vossen LI, Kruger HR, Eldar-Boock A, Yeini E, Landa-Rouben N, Tiram G, Wedepohl S, Markovsky E, **Leor J**, Calderon M and Satchi-Fainaro R. In vivo comparative study of distinct polymeric architectures bearing a combination of paclitaxel and doxorubicin at a synergistic ratio. *J Control Release*. 2016.

Roichman A, Kanfi Y, Glazz R, Naiman S, Amit U, Landa N, Tinman S, Stein I, Pikarsky E, **Leor J** and Cohen HY. SIRT6 Overexpression Improves Various Aspects of Mouse Healthspan. *J Gerontol A Biol Sci Med Sci*. 2016.

Madonna R, Van Laake LW, Davidson SM, Engel FB, Hausenloy DJ, Lecour S, **Leor J**, Perrino C, Schulz R, Ytrehus K, Landmesser U, Mummery CL, Janssens S, Willerson J, Eschenhagen T, Ferdinandy P and Sluijter JP. Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur Heart J*. 2016;37:1789-98.

Leor J, Palevski D, Amit U and Konfino T. Macrophages and regeneration: Lessons from the heart. *Semin Cell Dev Biol*. 2016.

Katz A, Maor E, **Leor J** and Klempfner R. Addition of beta-blockers to digoxin is associated with improved 1- and 10-year survival of patients hospitalized due to decompensated heart failure. *Int J Cardiol*. 2016;221:198-204.

Kain D, Amit U, Yagil C, Landa N, Naftali-Shani N, Molotski N, Aviv V, Feinberg MS, Goitein O, Kushnir T, Konen E, Epstein FH, Yagil Y and **Leor J**. Macrophages dictate the progression and manifestation of hypertensive heart disease. *Int J Cardiol*. 2016;203:381-95.

Baabur-Cohen H, Vossen LI, Kruger HR, Eldar-Boock A, Yeini E, Landa-Rouben N, Tiram G, Wedepohl S, Markovsky E, **Leor J**, Calderon M and Satchi-Fainaro R. In vivo comparative study of distinct polymeric architectures bearing a combination of paclitaxel and doxorubicin at a synergistic ratio. *J Control Release*. 2016.

Scomparin A, Salmaso S, Eldar-Boock A, Ben-Shushan D, Ferber S, Tiram G, Shmeeda H, Landa-Rouben N, **Leor J,** Caliceti P, Gabizon A and Satchi-Fainaro R. A comparative study of folate receptor-targeted doxorubicin delivery systems: dosing regimens and therapeutic index. *J Control Release*. 2015;208:106-20.

Konfino T, Landa N, Ben-Mordechai T and **Leor J**. The type of injury dictates the mode of repair in neonatal and adult heart. *J Am Heart Assoc*. 2015;4:e001320.

D'Uva G, Aharonov A, Lauriola M, Kain D, Yahalom-Ronen Y, Carvalho S, Weisinger K, Bassat E, Rajchman D, Yifa O, Lysenko M, Konfino T, Hegesh J, Brenner O, Neeman M, Yarden Y, **Leor J,** Sarig R, Harvey RP and Tzahor E. ERBB2 triggers mammalian heart regeneration by promoting cardiomyocyte dedifferentiation and proliferation. *Nat Cell Biol*. 2015;17:627-38.

Ben-Mordechai T, Palevski D, Glucksam-Galnoy Y, Elron-Gross I, Margalit R and **Leor J.** Targeting macrophage subsets for infarct repair. *J Cardiovasc Pharmacol Ther*. 2015;20:36-51.

Grants

2014-2019 Israel Science Foundations, Role of macrophages in myocardial regeneration

2018-2020 Ministry of Science, Polymer to treat heart failure of the 3rd age

2018-2021 Binational Science Foundation, A new method for imaging and treatment of heart failure (with Fred Epstein, Ayelet David)

2020-2022 Ministry of Science, Smart cells for heart repair

2020-2022 Ministry of Health, Targeting inflammation to treat cardiac fibrosis

Dr. Joseph Roitelman, Ph.D.

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Intracellular Regulation of Cholesterol Homeostasis

Positions

Senior Lecturer, Department of Human Genetics and Biochemistry, Sackler School of Medicine

Laboratory Director, Bert W. Strassburger Lipid Center, Sheba Medical Center

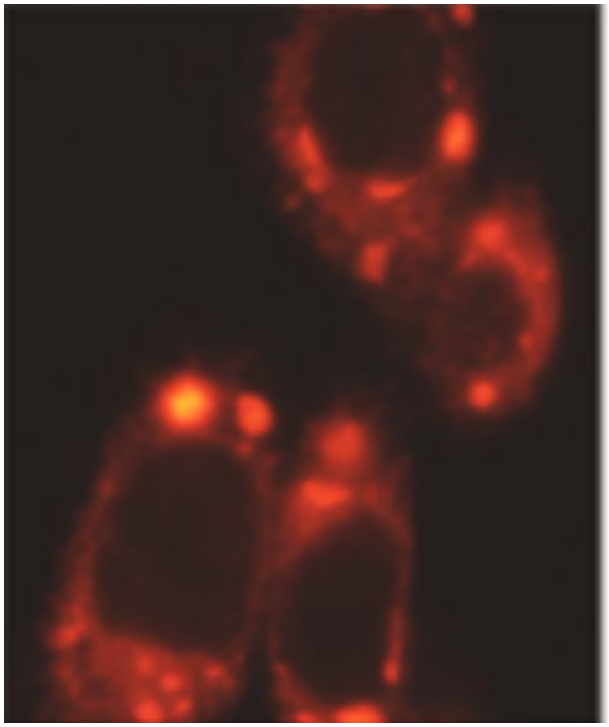
The levels of cholesterol in mammalian cells are tightly regulated by cholesterol itself via multitude of negative feedback mechanisms that coordinate its uptake from plasma lipoproteins and endogenous production in the mevalonate pathway. The major rate-limiting step in the mevalonate pathway is catalyzed by the enzyme HMG-CoA reductase, the target of statins class of cholesterol-lowering drugs.

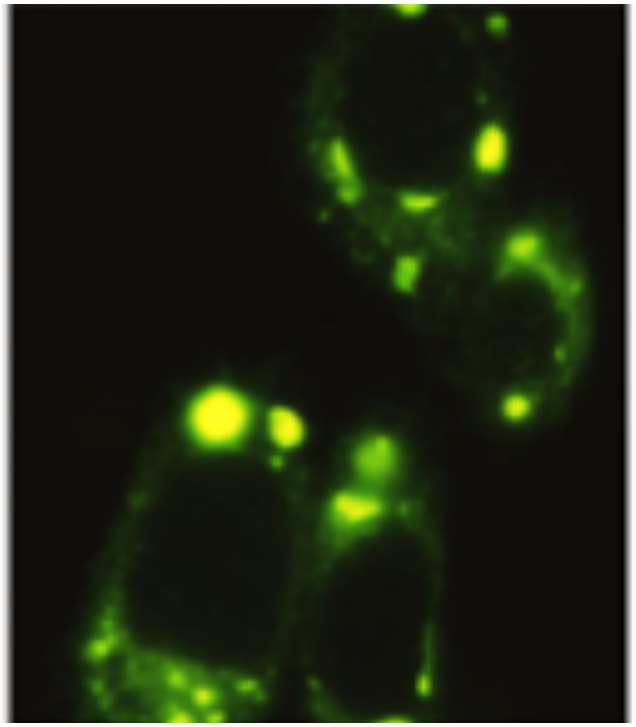
The intracellular abundance, hence activity, of HMG-CoA reductase is strictly controlled by cholesterol and intermediates of the mevalonate pathway, and the research in our laboratory is aimed to unravel the molecular events and cellular factors that operate in the degradation of HMG-CoA reductase protein.

Our studies have wider implications to our understanding of atherosclerosis and neoplastic processes, and afford new perspectives for devising novel therapeutic modalities to combat these diseases.

Publications

Loregger A, Raaben M, Tan J, Scheij S, Moeton M, van den Berg M, Gelberg-Etel H, Stickel E, **Roitelman J**, Brummelkamp T, Zelcer N. Haploid mammalian genetic screen identifies UBXD8 as a key determinant of HMGCR degradation and cholesterol biosynthesis. Arterioscler Thromb Vasc Biol. 2017;37(11):2064-2074.





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Stress and Inflammation in the Cardiovascular System

Positions (Prof. Shapira)

Deputy Director General and Director, Rehabilitation Hospital

Associate Dean, Tel Aviv Sourasky Medical Center

Full Clinical Professor

Research

- Cholinergic regulation of stress and inflammation.
- Exercise-induced urinary protein secretion as a risk for metabolic syndrome.
- Determination of new set of control limits for the identification of patients at risk.
- The influence of work characteristics (burnout and stress) on physical health.

The Tel Aviv Medical Center Inflammation Survey (TAMCIS) is a long-term, ongoing cardiovascular cohort study evaluating stress and inflammation in 22,000 apparently healthy working adults admitting to our medical center for routine annual medical check-ups. It is designed to evaluate the association between physiological and psychological measures of stress, inflammatory profile and their additive effect on cardiovascular risk.

Our database includes more than 50,000 visits with more than 600 parameters per visit; including medical history and medication, laboratory tests (Metabolic profile, Blood chemistry, blood count and Urine tests), ophthalmologist examination, exercise test and spirometry, psychological comprehensive questionnaire consisting of socio-demographic variables, personal and family medical history, health behaviors, among them dietary and sports habits, objective as well as subjective work conditions and various psychological scales such as depression, fear of terror, burnout, perceived control and social support. Research methods include basic molecular biology as well as sophisticated statistical models. The study team includes multidisciplinary researchers and physicians, from internal medicine, cardiology and neurology departments, biology and the School of Management.

Publications

Ben Assayag E, **Shenhar-Tsarfaty S**, Korczyn AD, Kliper E, Hallevi H, Shopin L, et al. Gait measures as predictors of poststroke cognitive function: evidence from the TABASCO study. Stroke. 46, 1077-1083, 2015.

S Shenhar-Tsarfaty, N Yayon, N Waiskopf, **I Shapira**, S Toker, D Zaltser, S Berliner, Y Ritov, H Soreq. Fear and C-reactive protein cosynergize annual pulse increases in healthy adults. P Natl Acad Sci USA (PNAS), 112, E467-471, 2015.

E Leshem-Rubinow, **S Shenhar-Tsarfaty**, A Milwidsky, S Toker, **I Shapira**, S Berliner, Y Benyamini, S Melamed, O Rogowski. Self-rated health is associated with elevated C-reactive protein even among apparently healthy individuals. IMAJ, 17, 213-217, 2015.

S Shenhar-Tsarfaty, **I Shapira**, S Toker, O Rogowski, S Berliner, Y Ritov, H Soreq.Weakened cholinergic blockade of inflammation associates with diabetes-related depression.Mol Med, 22, 156-161, 2016.

S Greenberg, **S Shenhar-Tsarfaty**, O Rogowski, **I Shapira**, D Zeltser, T Weinstein, D Lahav, J Vered, O Tovia-Brodie, Y Arbel, S Berliner, A Milwidsky. Exercise-induced albuminuria is related to the metabolic syndrome. Am J Physiol-Ren Physiol, 210, 1192-1196, 2016.

Shenhar-Tsarfaty S,Kliper E, Molad J, Berliner S, Shapira I, Ben-Bashat D, Shopin L, Tene O, Rosenberg GA, Bornstein NM, Ben Assayag E. Impaired renal function is associated with brain atrophy and poststroke cognitive decline. Neurology, 86, 1996-2005, 2016**.**

Lin T, Simchovitz A, **Shenhar-Tsarfaty S**, Vaisvaser S, Admon R, Hanin G, et al. Intensified vmPFC surveillance over PTSS under perturbed microRNA-608/AChE interaction. Translational Psychiatry. 6, e801, 2016.

Tene O, **Shenhar-Tsarfaty S**, Korczyn AD, Kliper E, Hallevi H, Shopin L, et al. Depressive symptoms following stroke and transient ischemic attack: is it time for a more intensive treatment approach? results from the TABASCO cohort study. Journal of Clinical Psychiatry. 77, 673-680, 2016.

Seyman E, Shaim H, **Shenhar-Tsarfaty S**, Jonash-Kimchi T, Bornstein NM, Hallevi H. The collateral circulation determines cortical infarct volume in anterior circulation ischemic stroke. BMC eurology. 16, 206, 2016.

Kliper E, Ben Assayag E, Korczyn AD, Auriel E, Shopin L, Hallevi H, **Shenhar-Tsarfaty S**, et al. Cognitive state following mild stroke: A matter of hippocampal mean diffusivity. Hippocampus. 26, 61-69, 2016.

Y Sofer, E Osher, R Limor, G Shefer, Y Marcus, **I Shapira**, K Tordjman, Y Greenman, S Berliner, N Stern. Gender determines serum free cortisol: higher levels in men. Endocr Pract, 22, 1415-1421, 2016.

Y Herishanu, A Polliack, **S Shenhar-Tsarfaty**, R Weinberger, R Gelman, T Ziv-Baran, D Zeltser, **I Shapira**, S Berliner, O Rogowski. Increased serum C-reactive protein levels are associated with shorter survival and development of second cancers in chronic lymphocytic leukemia. Ann Med, 2016.

Prof. Sami Viskin, M.D.

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samiviskin@gmail.com

Positions

Associate Professor, Senior Lecturer, Sackler Faculty of Medicine

Chair, Israel Working Group on Cardica Pacing and Electrophysiology, Israel heart Society

Associate Editor – Circulation

Past Associate Editor – *Heart Rhythm*

Past Associate Editor – *Europace*

Research

We perform clinical studies on cardiac arrhythmias, particularly related to long QT syndrome, Brugada syndrome and early repolarization. We have several ongoing studies on long QT syndrome caused by atrioventricular block, drug induced long QT syndrome, empiric quinidine therapy for Brugada syndrome.

Publications

Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm 2016;13:e50-86.

Wilkoff BL, Fauchier L, Stiles MK et al. Erratum to '2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-de fi brillator programming and testing' [Journal of Arrhythmia 32/1 (2016) 1-28]. J Arrhythm 2016;32:441-442.

Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace 2016;18:159-83.

Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. J Arrhythm 2016;32:1-28.

Viskin S, Havakuk O, Antzelevitch C, Rosso R. Malignant early repolarization: It's the T-wave, stupid. Heart Rhythm 2016;13:903-4.

Rosso R, Chorin E, Levi Y, Rogowski O, **Viskin S**. Radiofrequency Ablation of Atrial Fibrillation: Nonrandomized Comparison of Circular versus Point-by-Point "Smart" Ablation for Achieving Circumferential Pulmonary Vein Isolation and Curing Arrhythmic Symptoms. J Cardiovasc Electrophysiol 2016.

Patton KK, Ellinor PT, Ezekowitz M et al. Electrocardiographic Early Repolarization: A Scientific Statement From the American Heart Association. Circulation 2016;133:1520-9.

Mont L, Pelliccia A, Sharma S et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Europace 2016.

Mont L, Pelliccia A, Sharma S et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Eur J Prev Cardiol 2016.

Mizusawa Y, Morita H, Adler A et al. Prognostic significance of fever-induced Brugada syndrome. Heart Rhythm 2016;13:1515-20.

Michowitz Y, Viskin S, Rosso R. Exercise-induced Ventricular Tachycardia/Ventricular Fibrillation in the Normal Heart: Risk Stratification and Management. Card Electrophysiol Clin 2016;8:593-600.

Konigstein M, Rosso R, Topaz G et al. Drug-induced Brugada syndrome: Clinical characteristics and risk factors. Heart Rhythm 2016;13:108

Havakuk O, **Viskin S**. A Tale of 2 Diseases: The History of Long-QT Syndrome and Brugada Syndrome. J Am Coll Cardiol 2016;67:100-8.

Havakuk O, Viskin S. Reply: Long-QT Syndrome, Brugada Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia: A Tale of 3 Diseases : Ibutilide as a Torsade de Pointes Stress Test. J Am Coll Cardiol 2016;67:2806-7.

Chorin E, Rosso R, **Viskin S**. Electrocardiographic Manifestations of Calcium Abnormalities. Ann Noninvasive Electrocardiol 2016;21:7-9.

Chorin E, Hu D, Antzelevitch C et al. Ranolazine for Congenital Long-QT Syndrome Type III: Experimental and Long-Term Clinical Data. Circ Arrhythm Electrophysiol 2016;9.

Chorin E, Hochstadt A, **Viskin S** et al. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. Heart Rhythm 2016.

Antzelevitch C, Yan GX, Ackerman MJ et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latinoamericana de Estimulacifin Cardiaca y Electro fi siologia [SOLAECE]). Europace 2016.

Antzelevitch C, Yan GX, Ackerman MJ et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Heart Rhythm 2016;13:e295-324.

Antzelevitch C, Yan GX, Ackerman MJ et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. J Arrhythm 2016;32:315-339.

Adler A, Viskin S. Clinical Features of Genetic Cardiac Diseases Related to Potassium Channelopathies. Card Electrophysiol Clin 2016;8:361-72.

Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: Clinical characteristics, electrocardiographic parameters, and auxiliary testing. Heart Rhythm 2016;13:299-310.

Yankelson L, Steinvil A, Adler A, Viskin S. Reply: life-threatening events during endurance sports: is heat stroke more prevalent than arrhythmic death? J Am Coll Cardiol 2015;65:408-9.

Wilde AA, Viskin S. From whole exome sequencing to patient-specific therapy: another example of how basic research pays off in patient care. J Am Heart Assoc 2015;4.

Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AA. Everybody has Brugada syndrome until proven otherwise? Heart Rhythm 2015;12:1595-8.

Viskin S, Havakuk O, Schwaber MJ. Pro-Arrhythmic Effects of Noncardiac Medications: Lessons From Macrolide Antibiotics. J Am Coll Cardiol 2015;66:2185-8.

Shimiaie J, Sherez J, Aviram G et al. Determinants of Effort Intolerance in Patients With Heart Failure: Combined Echocardiography and Cardiopulmonary Stress Protocol. JACC Heart Fail 2015;3:803-14.

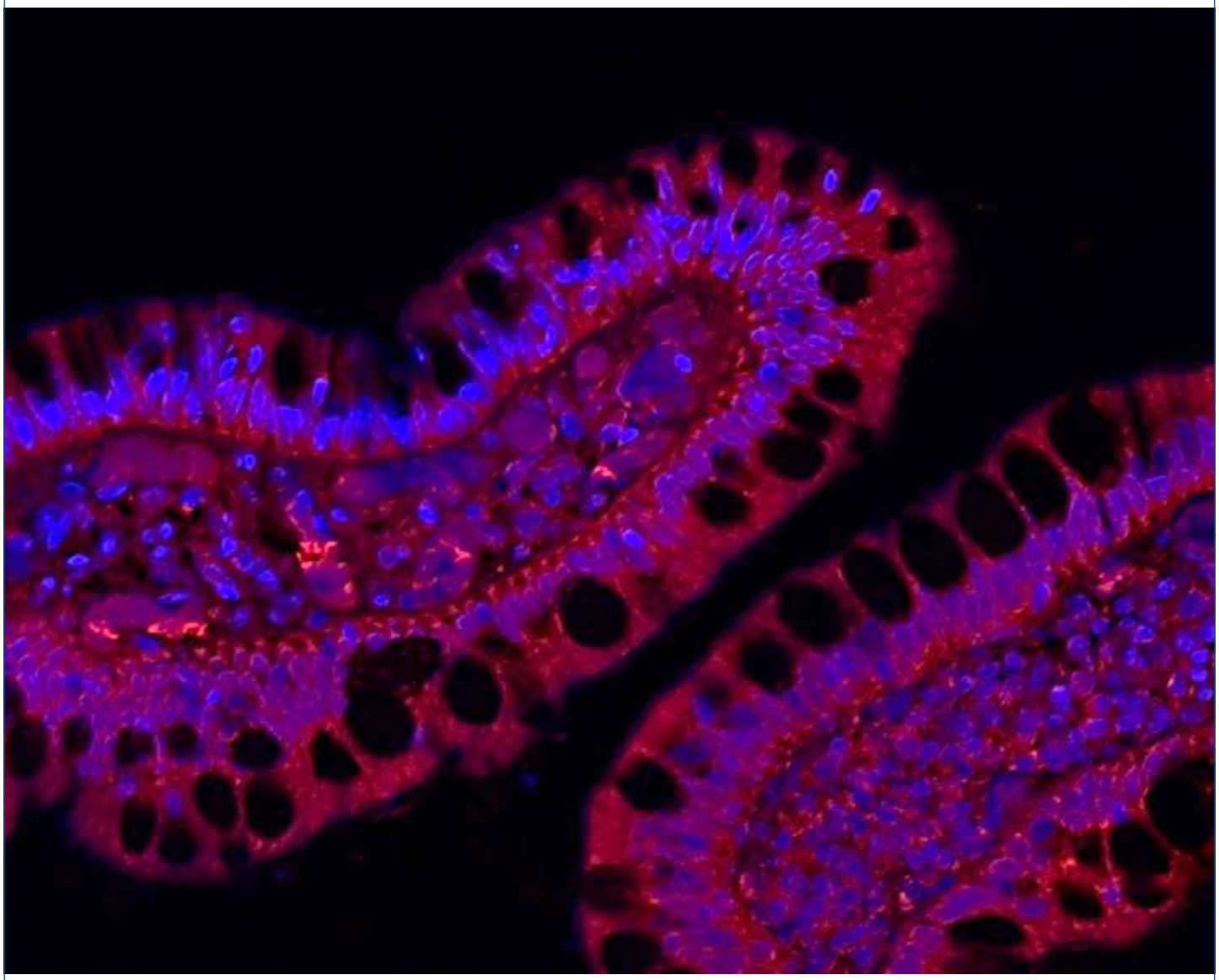
Rosso R, Viskin S. Early repolarization and arrhythmic death: six more years? Trends Cardiovasc Med 2015;25:31-2.

Chorin E, Havakuk O, Adler A et al. Diagnostic value of T-wave morphology changes during "QT stretching" in patients with long QT syndrome. Heart Rhythm 2015;12:2263-71.

Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada Syndrome: Thirty-Three-Year Experience Using Electrophysiologically Guided Therapy With Class 1A Antiarrhythmic Drugs. Circ Arrhythm Electrophysiol 2015;8:1393-402.

Adler A, Viskin S. Syncope in Hereditary Arrhythmogenic Syndromes. Cardiol Clin 2015;33:433-40.

Digestive System



Immunofluorescence of PAR-4 expression in human mucosal biopsy from normal pouch. Credit: Sarit Hoffman, Ilya Borovok, Iris Dotan, Nitsan Maharshak

Prof. Ziv Ben-Ari, M.D.

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Basic and Translational Research of Liver Diseases

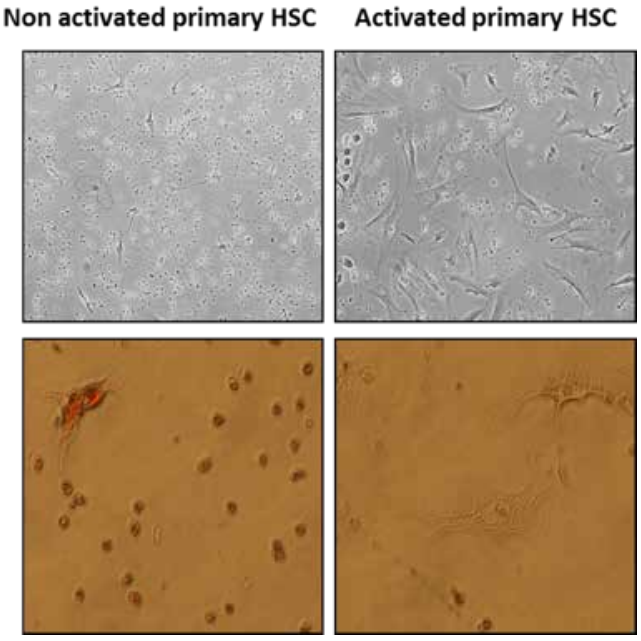
Positions

Director, Liver Disease Center

Research

Our lab is part of the Liver Disease Center at the Chaim Sheba Medical Center. We focus our studies on basic and applied liver disease research to better understand and improve the diagnosis and treatment of different liver diseases. We utilize various methods such as molecular biology, biochemistry, genetics, tissue culture and in-vitro and in-vivo models. The proximity between the Liver Disease Center and the lab creates a unique and highly successful dynamic relationship where the unsolved clinical needs are immediately translated into research for achieving better solutions.

The research in our lab is divided into two main projects:



Phenotypic alterations in HSCs after activation/differentiation to myoblast-like cells.

1. Molecular mechanisms in the development of liver fibrosis

Fibrosis is the excess accumulation of extracellular matrix (ECM), resulting from chronic, non-resolving inflammation. Multiple etiologies underlie development of liver fibrosis, such as chronic viral hepatitis B or C, autoimmune and biliary diseases, alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). Fibrosis progression toward cirrhosis is the major cause of liver-related morbidity and mortality. Patient with cirrhosis are more prone to develop liver failure, portal hypertension or infection and are at higher risk of developing hepatocellular carcinoma (HCC). In the normal liver, hepatic stellate cells (HSCs) constitute quiescent, vitamin A–storing cell. Following activation by specific stimuli released by an injured liver, HSCs undergo “activation”or transdifferentiation, yielding a myofibroblast-like cell. We are currently investigating the interactions between hepatocytes and HSCs in healthy and fibrotic livers in the different chronic liver diseases listed above. Our goal is to advance the research in this field and to establish resolution of liver fibrosis.

2. Microbiome and liver diseases

The human gastrointestinal tract hosts a large number of microbial cells, which exceeds their mammalian counterparts by approximately 3-fold. The genes expressed by these microorganisms constitute the gut microbiome and participate in diverse and essential functions, including digestion, regulation of energy metabolism and modulation of inflammation and immunity. The liver, due to its critical functional relationship with the gastrointestinal (GI) tract, is continually exposed to multiple harmful and beneficial microorganisms derived from the small and large intestines. We study the microbiota signature of patients with different liver diseases (Primary Sclerosing cholangitis (PSC), PSC-IBD, Hepatocellular carcinoma and cirrhosis) and compare

them to healthy control. Moreover, we investigate the correlation between environmental lifestyle and diet patterns, the host microbiome and disease etiologies.

Publications

Yanai H, Matalon S, Rosenblatt A, Awadie H, Berdichevski T, Snir Y, Kopylov U, Katz L, Stein A, Mlynarsky L, Tulchinsky H, Konikoff FM, Horin SB, Braun M, **Ben-Ari Z**, Chowers Y, Baruch Y, Shibolet O, Dotan I. Prognosis of primary sclerosing cholangitis in israel is independent of coexisting inflammatory bowel Disease. J Crohns Colitis. 2015;9(2):177-84.

Mor O, Bassal R, Michaeli M, Wax M, Ram D, Cohen-Ezra O, Cohen D, Mendelson E, **Ben-Ari Z**, Shohat T Prevalence of hepatitis E virus antibodies, Israel, 2009-2010. Emerg Infect Dis. 2015;21(4):692-4.

Ben-Ari Z, Weitzman E, Safran M. Oncogenic viruses and hepatocellular carcinoma. Clin Liver Dis. 2015;19(2):341-60.

Hochhauser E, Lahat E, Sultan M, Pappo O, Waldman M, Sarne Y, Shainberg A, Gutman M, Safran M*, **Ben-Ari Z** *. Ultra Low Dose Delta 9-Tetrahydrocannabinol Protects Mouse Liver from Ischemia Reperfusion Injury. Cell Physiol Biochem 2015; 36:1971-81.

Oren Ben-Shoshan S, Kagan P, Sultan M, Barabash Z, Dor C, Jacob-Hirsch J, Harmelin A, Pappo O, Marcu-Malina V, **Ben-Ari Z**, Amariglio N, Rechavi G, Goldstein I, Safran M. ADAR1 deletion induces NFκB and interferon signaling dependent liver inflammation and fibrosis. RNA Biology 2016.

Sultan M, **Ben-Ari Z**, Masoud R, Pappo O, Harats D, Kamari Y, Safran M. Interleukin-1α and Interleukin-1β play a central role in the pathogenesis of fulminant hepatic failure in mice. PLoS One. 2017;12(9):e0184084.

Gane EJ, Pianko S, Roberts SK, Thompson AJ, Zeuzem S, Zuckerman E, **Ben-Ari Z**, Foster GR, Agarwal K, Laursen AL, Gerstoft J, Gao W, Huang HC, Fitzgerald B, Fernsler D, Li JJ, Grandhi A, Liu H, Su FH, Wan S, Zeng Z, Chen HL, Dutko FJ, Nguyen BT, Wahl J, Robertson MN, Barr E, Yeh WW, Plank RM, Butterton JR, Esteban R. Safety and efficacy of an 8-week regimen of grazoprevir plus ruzasvir plus uprifosbuvir compared with grazoprevir plus elbasvir plus uprifosbuvir in participants without cirrhosis infected with hepatitis C virus genotypes 1, 2, or 3 (C-CREST-1 and C-CREST-2, part A): two randomised, phase 2, open-label trials. Lancet Gastroenterol Hepatol. 2017;2(11):805-813.

Wyles D, Wedemeyer H, **Ben-Ari Z,** Gane EJ, Hansen JB, Jacobson IM, Laursen AL, Luetkemeyer A, Nahass R, Pianko S, Zeuzem S, Jumes P, Huang HC, Butterton J, Robertson M, Wahl J, Barr E, Joeng HK, Martin E, Serfaty L; C-CREST Part C and C-SURGE Investigators. Grazoprevir, ruzasvir, and uprifosbuvir for hepatitis C virus after NS5A treatment failure. Hepatology. 2017;66(6):1794-1804.

Lotan E, Raskin SP, Amitai MM, Kleinbaum Y, Veitsman E, Weiss P, Cohen-Ezra O, Berdichevski T, **Ben-Ari Z**. The Role of Liver Segment-to-Spleen Volume Ratio in the Staging of Hepatic Fibrosis in Patients with Hepatitis C Virus Infection. Isr Med Assoc J. 2017;19(4):251-256.

Kagan P, Sultan M, Tachlytski I, Safran M, **Ben-Ari Z.** Both MAPK and STAT3 signal transduction pathways are necessary for IL-6-dependent hepatic stellate cells activation. PLoS One. 2017;12(5):e0176173.

Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(3):161-176.

Hézode C, Colombo M, Bourlière M, Spengler U, **Ben-Ari Z**, Strasser SI, Lee WM, Morgan L, Qiu J, Hwang P, Robertson M, Nguyen BY, Barr E, Wahl J, Haber B, Chase R, Talwani R, Marco VD; C-EDGE IBLD Study Investigators. Elbasvir/Grazoprevir for Patients With Hepatitis C Virus Infection and Inherited Blood Disorders: A Phase III Study. Hepatology. 2017

Gozlan Y, **Ben-Ari Z**, Moscona R, Shirazi R, Rakovsky A, Kabat A, Veizman E, Berdichevski T, Weiss P, Cohen-Ezra O, Lurie Y, Gafanovich I, Braun M, Cohen-Naftaly M, Shlomai A, Shibolet O, Zigmond E, Zuckerman E, Carmiel-Haggai M, Nimer A, Hazzan R, Maor Y, Kitay-Cohen Y, Shemer-Avni Y, Kra-Oz Z, Schreiber L, Peleg O, Sierra S, Harrigan PR, Mendelson E, Mor O. HCV genotype-1 subtypes and resistance-associated substitutions in drug-naive and in direct-acting antiviral treatment failure patients. Antivir Ther. 2017;22(5):431-441.

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Drug Mechanisms and Immunogenicity in IBD

Positions

Director, IBD Service, Gastroenterology Dept. Sheba Medical Center

Associate Professor of Medicine, Sackler Faculty of Medicine

Member, Organization Committee, European Crohn' & colitis Organziation (ECCO)

Research

We focus on translational science, aiming to study drug mechanisms in IBD. Specifically, we study mechanisms whereby immune-modulating and biologic drugs exert their cellular effects and/or cause unwanted adverse events, as well as immunogenicity of biologic drugs, i.e. the eliciting of immune hyper-responsiveness in the recipient towards the biologic drug. We are interested also in studying novel herbal compunds for possible synergistic effects with conventional immune-modulators.

Completed projects include:

1. A study to deciper the delay in onset of action of thiopurine related to gradual depletion of antigen-specific memory T-cells
2. Development of novel and one of the first available assays to measue anti-drug antibodies against infliximab, and later adalimumab and currently vedolizumab
3. Identifying the Fab fragment as the immune-dominant fragment of infliximab, responsible for eliciting anti-drug antibodies
4. Study of cross-immunogenicity of infliximab and its bio-similar drug, CT-P13

Ongoing projects include:

1. Studying cellular mecahnisms responsible for B-cell lymphoproliferation under immune-modulating drugs
2. Studing the decay in immune-suppression following azathioprine withdrawal
3. Studying herbal Chinese compounds effects on cells propogating inflammation

Publications

Ben-Horin S, Yavzori M, Benhar I, Picard O, Fudim E, Ungar B, Lee SY, Kim SH, Eliakim R, Chowers Y. Cross-immunogenicity: Antibodies to infliximab in Remicade-treated IBD patients similarly recognize the bio-similar Remsima. Gut 2016; 65(7):1132-8.

Ben-Horin S, Andrews JM, Katsanos KH, Rieder F, Steinwurz F, Karmiris K, Cheon JH, Moran GW, Cesarini M, Stone CD, Schwartz D, Protic M, Roblin X, Roda G, Chen MH, Har-Noy O, Bernstein CN. Combination of corticosteroids and 5-aminosalicylates or corticosteroids alone for patients with moderate-severe active ulcerative colitis: A global survey of physicians' practice. World J Gastroenterol. 2017;23(16):2995-3002.

Engel T, Ungar B, Ben-Haim G, Levhar N, Eliakim R, **Ben-Horin S**. Re-phrasing the question: A simple tool for evaluation of adherence to therapy in patients with inflammatory bowel disease. United European Gastroenterol J. 2017;5(6):880-886.

He Y, Mao R, Chen F, Xu PP, Chen BL, Wu Y, Qiu Y, Zhang SH, Feng R, Zeng ZR, **Ben-Horin S**, Chen MH. Thalidomide induces clinical remission and mucosal healing in adults with active Crohn's disease: a prospective open-label study. Therap Adv Gastroenterol. 2017;10(5):397-406

Lahat A*, Bar-Gil Shitrit A*, Naftali N, Milgrom Y, Elyakim R, Goldin E, Levhar N, Selinger L, Zuker T, Fudim E, Picard O,Yavzori M, Ben-**Horin S**. Vedolizumab levels in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2017; 12(1):120-123.

Ungar B, Kopylov U, Yavzori M, Fudim E, Picard O, Lahat A, Coscas D, Waterman M, Haj-Natour O,

Orbach-Zingboim N, Mao R, Chen M, Chowers Y, Eliakim R, **Ben-Horin S**. Association of Vedolizumab level, anti-drug antibodies, and α4β7 occupancy with response in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2017; pii: S1542-3565(17)31423-4.

Grants

2015–2020 Horizon 2020 Immungenicity of infliximab, within the SPARE trial (BioCycle consortium)

Dr. Sigal Fishman, M.D.

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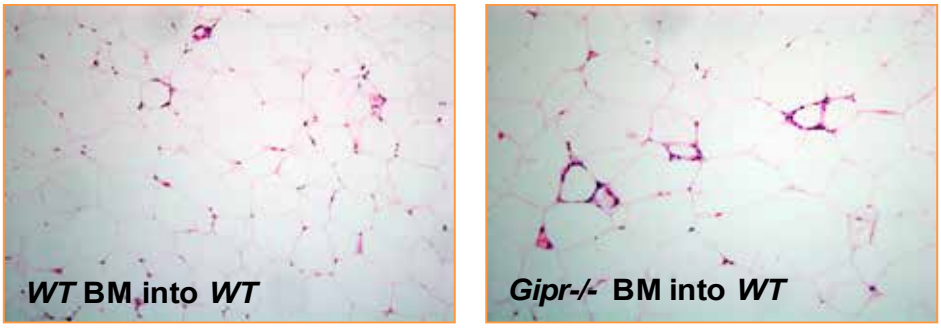
The Role of Incretin Hormones in Macrophage Regulation of Obesity, Inflammation and Insulin Resistance

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Recent studies have suggested that GIP participates in the dynamic and progressive crosstalk between the two fundamental systems of metabolism and immunity. Yet, whether GIP can directly act on immune cells and the resulting consequences on the development and progression of obesity remain elusive. We have previously demonstrated in a murine model of high fat diet (HFD) that a long-acting GIP analogue significantly reduces visceral fat infiltration of pro-inflammatory immune cells and improves insulin sensitivity, thus, highlighting a possible role for GIP as a linker between energy balance and immunologic responses. Our preliminary results clearly indicate that impairment of GIP-governed regulation of immune cells perturbs energy homeostasis, promotes insulin resistance (IR) and intensifies the inflammatory response under HFD. Therefore, we continue to investigate the direct immuno-regulatory role of GIP in immune cells and specifically in adipose tissue macrophages (ATM) and the resulting consequences on the inflammatory response and on the metabolic state in obese human and mice. Specifically, we hypothesize that GIP negatively regulates S100A8/9 in ATM and thereby affects myelopoiesis and energy homeostatasis by attenuating beiging in subcutaneous fat. In addition, we suggest that GIP positively mediates, at least in part, whole body energy homeostasis and adipose tissue metabolism through its direct effect on immune cell function. Here, we intend to utilize BM chimerism approach to target GIPR-deficiency to immune cells to explore the role of GIP in immune cells and specifically ATM. We are using chimeras reconstituted with GIP receptor (GIPR)-defficient bone marrow and determine the metabolic and immune phenotype of the mice. To specifically investigate the physiological role of GIP as regulator of ATM function, GIPR-deficiency has been targeted to ATM by using the cre-lox system and crossing the Gipr fl/fl mice with or Cx3cr1-cre mice. We are exploring the role of GIP-governed regulation of immune cell and specifically ATM function and the role of GIP-S100A8/9axis in dictating whole body energy balance, we will perform metabolic analyses that assess energy expenditure, fat versus glucose utilization, locomotor activity as well as insulin sensitivity. Bone marrow, blood and adipose



Visceral adipose tissue of chimeric mice reconstituted with WT or *Gipr*$^{-/-}$ bone marrow (BM) and exposed to a 14 weeks high fat diet regimen, showing increased infiltrating immune cells in the *Gipr*$^{-/-}$ BM reconstituted mice.

tissue myelopoiesis is assessed in the various mice exposed to a HFD regimen. We are also identifying target genes in visceral and subcutaneous fat of both chimeric mice and GIPR conditional knockout mice. Finally, we will study the ability of GIP to negatively regulate S100A8/9 in visceral fat explants and sorted ATM extracted from human obese patients.

Expected significance: Our integrative approach will allow significant progress towards revealing basic GIP governed immune-regulatory mechanisms operating at the interface between adipose tissue inflammation and metabolism and their involvement in the pathophysiology of obesity-induced IR. Insights gained in this study will uncover a yet unknown role for GIP in regulating the pathophysiological link between ATM and obesity and may lead to future identification of another class of incretin drugs, namely GIP analogs, with the potential to improve whole body insulin sensitivity via immune cell regulation.

Publications

Rabinowich L*, **Fishman S***, Hubel E, Thurm T, Park WJ, Pewzner-Jung Y, Futerman A, Halpern Z, Zvibel I. Sortilin deficiency improves the metabolic phenotype and reduces hepatic steatosis in a murine model of diet-induced obesity. *J Hepatol* 2015;62:175-81.* equal authors.

Shnell M, Gluck N, Abu-Abeid S, Santo E, **Fishman S**.Use of endoscopic septotomy for the treatment of late staple-line leaks after laparoscopic sleeve gastrectomy. *Endoscopy* 2017;49(1):59-63.

Fishman S, Shnell M, Gluck N, Meirsdorf S, Abu-Abeid S, Santo E. Use of sleeve-customized self-expandable metal stents for the treatment of staple-line leakage after laparoscopic sleeve gastrectomy. *Gastrointest Endosc.* 2015. pii: S0016-5107(14)02412-2.

Grants

2016–2019 Glucose-dependent insulinotropic polypeptide (GIP) improves adipose tissue inflammation and metabolism through direct regulation of adipose tissue macrophage function, Israel Science Foundation

Dr. Yael Haberman, M.D., Ph.D.

The Pediatric Gastroenterology Unit & Sheba Cancer Center
Sheba Medical Center

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Host: Microbial Interactions - Translational Research in Gastrointestinal Diseases

Positions

Physician-Scientist, Sheba Medical Center

Senior Lecturer, Tel Aviv University

Adjunct Assistant Professor, Division of Pediatric Gastroenterology, Hepatology, & Nutrition, Cincinnati Children's Hospital Medical Center, OH, USA.

Research

We are interested in integrating clinical questions, "big-data" approaches, basic science, and bioinformatics with a goal to improve personalized patients' diagnostic and therapeutic decision. Our interests include host-microbial interactions in health and pathologic conditions including Crohn's disease and ulcerative colitis. We use a high-throughput approach to detect the widest range of microbial shifts and host gene expression in the actual lining of the gut and feces to characterize disease phenotype and outcome to tailor personalized therapy.

Within our research we focus on characterizing the role of non-coding elements (non-coding RNAs) and and we try to elucidate if and how these non-coding regions take part in the host:microbial interactions.

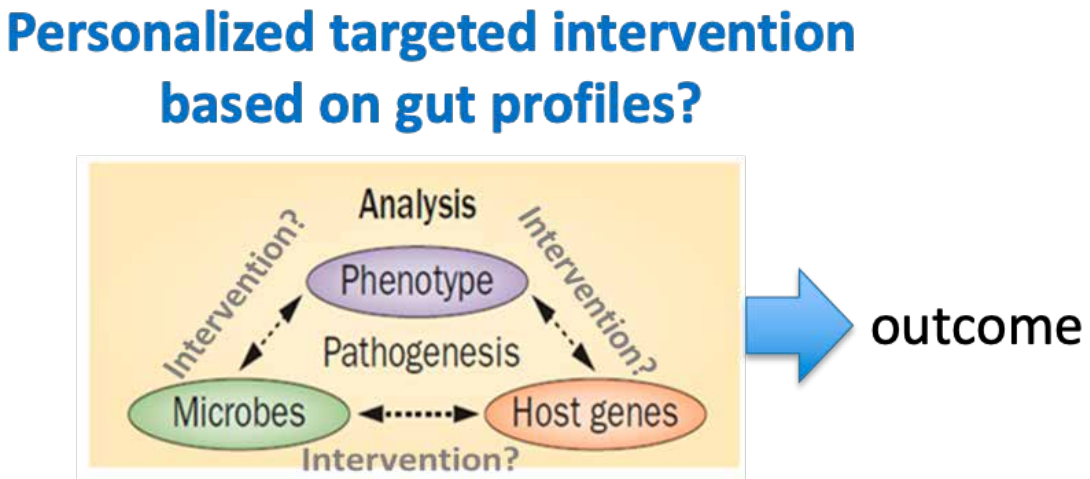
Publications

Bier A, Khasbab R, **Haberman Y**, Braun T, Hadar R, Sosnovski K, Amir A, Leibowitz A, Presenting dysbiosis after consuming a high fructose diet. Nutrients. 2020;12(1).

Loberman-Nachum N, Sosnovski K, Di Segni A, Efroni G, Braun T, BenShoshan M, Anafi L, Avivi C, Barshack I, Shouval DS, Denson LA, Amir A, Unger R, Weiss B, **Haberman Y**. Defining the Celiac disease transcriptome using clinical pathology specimens reveals biologic pathways and supports diagnosis. Sci Rep. 2019.

Levy-Shraga Y, Shenkar A, Modan-Moses D, Assa A, **Haberman Y**, Shouval D, Guz-Mark A, Lahad A, Weiss B. Longitudinal changes in bone mineral density in children with inflammatory bowel diseases. Acta Paediatr. 2019.

Iqbal NT, Syed S, Sadiq K, Khan MN, Iqbal J, Ma JZ, Umrani F, Ahmed S, Maier EA, Denson LA, **Haberman Y**, McNeal MM, Setchell KDR, Zhao X, Qureshi S, Shen L, Moskaluk CA, Liu TC, Yilmaz O, Brown DE, Barratt MJ, Kung VL, Gordon JI, Moore SR, Ali SA. Study of Environmental Enteropathy and Malnutrition (SEEM) in Pakistan: protocols for



biopsy based biomarker discovery and validation. BMC Pediatr. 2019;19(1):247.

Ben-Horin S, Lahat A, Amitai MM, Klang E, Yablecovitch D, Neuman S, Levhar N, Selinger L, Rozendorn N, Turner D, Chowers Y, Odes S, Schwartz D, Yanai H, Dotan I, Braun T, **Haberman Y**, Kopylov U, Eliakim R; Israeli IBD Research Nucleus (IIRN). Assessment of small bowel mucosal healing by video capsule endoscopy for the prediction of short-term and long-term risk of Crohn's disease flare: a prospective cohort study. Lancet Gastroenterol Hepatol. 2019.

Hyams JS, Davis Thomas S, Gotman N, **Haberman Y**, Karns R, Schirmer M, Mo A, Mack DR, Boyle B, Griffiths AM, LeLeiko NS, Sauer CG, Keljo DJ, Markowitz J, Baker SS, Rosh J, Baldassano RN, Patel A, Pfefferkorn M, Otley A, Heyman M, Noe J, Oliva-Hemker M, Rufo PA, Strople J, Ziring D, Guthery SL, Sudel B, Benkov K, Wali P, Moulton D, Evans J, Kappelman MD, Marquis MA, Sylvester FA, Collins MH, Venkateswaran S, Dubinsky M, Tangpricha V, Spada KL, Saul B, Wang J, Serrano J, Hommel K, Marigorta UM, Gibson G, Xavier RJ, Kugathasan S, Walters T, Denson LA. Clinical and biological predictors of response to standardised paediatric colitis therapy (PROTECT): a multicentre inception cohort study. Lancet. 2019;393(10182):1708-1720.

Braun T, Di Segni A, BenShoshan M, Neuman S, Levhar N, Bubis M, Picard O, Sosnovski K, Efroni G, Farage Barhom S, Glick Saar E, Lahad A, Weiss B, Yablecovitch D, Lahat A, Eliakim R, Kopylov U, Ben-Horin S, **Haberman Y**. Individualized dynamics in the gut microbiota precede Crohn's disease flares. Am J Gastroenterol. 2019.

Haberman Y, Karns R, Dexheimer PJ, Schirmer M, Somekh J, Jurickova I, Braun T, Novak E, Bauman L, Collins MH, Mo A, Rosen MJ, Bonkowski E, Gotman N, Marquis A, Nistel M, Rufo PA, Baker SS, Sauer CG, Markowitz J, Pfefferkorn MD, Rosh JR, Boyle BM, Mack DR, Baldassano RN, Shah S, Leleiko NS, Heyman MB, Grifiths AM, Patel AS, Noe JD, Aronow BJ, Kugathasan S, Walters TD, Gibson G, Thomas SD, Mollen K, Shen-Orr S, Huttenhower C, Xavier RJ, Hyams JS, Denson LA. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. Nat Commun. 2019;10(1):38.

Haberman Y, Schirmer M, Dexheimer PJ, Karns R, Braun T, Kim MO, Walters TD, Baldassano RN, Noe JD, Rosh J, Markowitz J, Crandall WV, Mack DR, Griffiths AM, Heyman MB, Baker SS, Kellermayer R, Moulton D, Patel AS, Gulati AS, Steiner SJ, LeLeiko N, Otley A, Oliva-Hemker M, Ziring D, Kirschner BS, Keljo DJ, Guthery SL, Cohen SA, Snapper S, Evans J, Dubinsky M, Aronow B, Hyams JS, Kugathasan S, Huttenhower C, Xavier RJ, Denson LA. Age-of-diagnosis dependent ileal immune intensification and reduced alpha-defensin in older versus younger pediatric Crohn Disease patients despite already established dysbiosis. Mucosal Immunol. 2019;12(2):491-502.

Werner L, Nunberg MY, Rechavi E, Lev A, Braun T, **Haberman Y**, Lahad A, Shteyer E, Schvimer M, Somech R, Weiss B, Lee YN, Shouval DS. Altered T cell receptor beta repertoire patterns in pediatric ulcerative colitis. Clin Exp Immunol. 2019 ;196(1):1-11.

Kelly D, Kotliar M, Woo V, Jagannathan S, Whitt J, Moncivaiz J, Aronow BJ, Dubinsky MC, Hyams JS, Markowitz JF, Baldassano RN, Stephens MC, Walters TD, Kugathasan S, **Haberman Y**, Sundaram N, Rosen MJ, Helmrath M, Karns R, Barski A, Denson LA, Alenghat T. Microbiota-sensitive epigenetic signature predicts inflammation in Crohn's disease. JCI Insight. 2018;3(18).

Denson LA, Jurickova I, Karns R, Shaw KA, Cutler DJ, Okou D, Alexander Valencia C, Dodd A, Mondal K, Aronow BJ, **Haberman Y**, Linn A, Price A, Bezold R, Lake K, Jackson K, Walters TD, Griffiths A, Baldassano RN, Noe JD, Hyams JS, Crandall WV, Kirschner BS, Heyman MB, Snapper S, Guthery SL, Dubinsky MC, Leleiko NS, Otley AR, Xavier RJ, Stevens C, Daly MJ, Zwick ME, Kugathasan S. Genetic and transcriptomic variation linked to neutrophil granulocyte-macrophage colony-stimulating factor signaling in pediatric Crohn's disease. Inflamm Bowel Dis. 2019.

Bier A, Braun T, Khasbab R, Di Segni A, Grossman E, **Haberman Y**, Leibowitz A. A High Salt Diet Modulates the Gut Microbiota and Short Chain Fatty Acids Production in a Salt-Sensitive Hypertension Rat Model. Nutrients. 2018 Aug 23;10(9). pii: E1154. doi: 10.3390/nu10091154. PMID: 30142973.

Ungar B, Glidai Y, Yavzori M, Picard O, Fudim E, Lahad A, **Haberman Y**, Shouval DS, Weintraub I, Eliakim R, Ben-Horin S, Weiss B. Association Between infliximab drug and antibody levels and therapy outcome in pediatric inflammatory bowel diseases. J Pediatr Gastroenterol Nutr. 2018.

Whitt J, Woo V, Lee P, Moncivaiz J, **Haberman Y**, Denson L, Tso P, Alenghat T. Disruption of epithelial HDAC3 in intestine prevents diet-induced obesity in mice. Gastroenterology. 2018. pii: S0016-5085(18)30478-5.

Di Segni A, Braun T, BenShoshan M, Farage Barhom S, Glick Saar E, Cesarkas K, Squires JE, Keller N, **Haberman Y**. Guided Protocol for Fecal Microbial Characterization by 16S rRNA-Amplicon Sequencing. J Vis Exp. 2018;(133).

Shaw KA, Cutler DJ, Okou D, Dodd A, Aronow BJ, **Haberman Y**, Stevens C, Walters TD, Griffiths A, Baldassano RN, Noe JD, Hyams JS, Crandall WV, Kirschner BS, Heyman MB, Snapper S, Guthery S, Dubinsky MC, Shapiro JM, Otley AR, Daly M, Denson LA, Kugathasan S, Zwick ME. Genetic variants and pathways implicated in a pediatric inflammatory bowel disease cohort. Genes Immun. 2018.

Haberman Y, BenShoshan M, Di Segni A, Dexheimer PJ, Braun T, Weiss B, Walters TD, Baldassano RN, Noe JD, Markowitz J, Rosh J, Heyman MB, Griffiths AM, Crandall WV, Mack DR, Baker SS, Kellermayer R, Patel A, Otley A, Steiner SJ, Gulati AS, Guthery SL, LeLeiko N, Moulton D, Kirschner BS, Snapper S, Avivi C, Barshack I, Oliva-Hemker M, Cohen SA, Keljo DJ, Ziring D, Anikster Y, Aronow B, Hyams JS, Kugathasan S, Denson LA. Long ncRNA landscape in the ileum of treatment-naive early-onset Crohn disease. Inflamm Bowel Dis. 2018;24(2):346-360.

Vardi I, Barel O, Sperber M, Schvimer M, Nunberg M, Field M, Ouahed J, Marek-Yagel D, Werner L, **Haberman Y**, Lahad A, Anikster Y, Rechavi G, Barshack I, McElwee JJ, Maranville J, Somech R, Snapper SB, Weiss B, Shouval DS. Genetic and structural analysis of a SKIV2L mutation causing Tricho-hepato-enteric syndrome. Dig Dis Sci. 2018.

Denson LA, Jurickova I, Karns R, Shaw KA, Cutler DJ, Okou D, Dodd A, Quinn K, Mondal K, Aronow BJ, **Haberman Y**, Linn A, Price A, Bezold R, Lake K, Jackson K, Walters TD, Griffiths A, Baldassano RN, Noe JD, Hyams JS, Crandall WV, Kirschner BS, Heyman MB, Snapper S, Guthery SL, Dubinsky MC, Leleiko NS, Otley AR, Xavier RJ, Stevens C, Daly MJ, Zwick ME, Kugathasan S. Clinical and genomic correlates of neutrophil reactive oxygen species production in pediatric patients with Crohn's disease. Gastroenterology. 2018. pii: S0016-5085(18)30210-5.

Nunberg MY, Werner L, Kopylov U, **Haberman Y**, Lahad A, Weiss B, Shouval DS. Impaired IL-10 receptor mediated suppression in monocyte from patients with Crohn's disease. J Pediatr Gastroenterol Nutr. 2018.

Dionisi-Vici C, Shteyer E, Niceta M, Rizzo C, Pode-Shakked B, Chillemi G, Bruselles A, Semeraro M, Barel O, Eyal E, Kol N, **Haberman Y**, Lahad A, Diomedi-Camassei F, Marek-Yagel D, Rechavi G, Tartaglia M, Anikster Y. Expanding the molecular diversity and phenotypic spectrum of glycerol 3-phosphate dehydrogenase 1 deficiency. J Inherit Metab Dis. 2016 Jul 1. [Epub ahead of print].

Moshkovits I, Reichman H, Karo-Atar D, Rozenberg P, Zigmond E, **Haberman Y**, Ben Baruch-Morgenstern N, Lampinen M, Carlson M, Itan M, Denson LA, Varol C, Munitz A. A key requirement for CD300f in innate immune responses of eosinophils in colitis. Mucosal Immunol. 2016. doi: 10.1038/mi.2016.37

Stephen J*, Vilboux T*, **Haberman Y***, Pri-Chen H, Pode-Shakked B, Marek-Yagel D, Barel O, Di Segni A, Eyal E, Hout-Siloni G, Lahad A, Shalem T, Rechavi G, Malicdan MCV, Weiss B, Gahl WA, and Anikster Y. Congenital Protein Losing Enteropathy: An inborn error of lipid metabolism due to *DGAT1* mutations. Eur J Hum Genet. 2016;24:1268-73. ***Equal contribution.**

Arora K, Sinha C, Zhang W, Moon CS, Ren A, Yarlagadda S, Dostmann WR, Adebiyi A, **Haberman Y**, Denson LA, Wang X, Naren AP. Altered cGMP Dynamics at the Plasma Membrane Contribute to Diarrhea in Ulcerative Colitis. Am J Pathol. 2015;185:2790-804.

Cutler DJ, Zwick ME, Okou DT, Prahalad S, Walters T, Guthery SL, Dubinsky M, Baldassano R, Crandall WV, Rosh J, Markowitz J, Stephens M, Kellermayer R, Pfefferkorn M, Heyman MB, LeLeiko N, Mack D, Moulton D, Kappelman MD, Kumar A, Prince J, Bose P, Mondal K, Ramachandran D, Bohnsack JF, Griffiths AM, **Haberman Y**, Essers J, Thompson SD, Aronow B, Keljo DJ, Hyams JS, Denson LA; PRO-KIIDS Research Group, Kugathasan S. Dissecting Allele Architecture of Early Onset IBD Using High-Density Genotyping. PLoS One. 2015;10(6).

Book chapters

Rothenberg ME, **Haberman Y**. 10th edition of Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Chapter 29: Eosinophilic Disorders of the Gastrointestinal Tract. January 2015.

Haberman Ziv Y, Collins M, Rothenberg ME. Chapter 50: Eosinophilic esophagitis. Yamada's Textbook of Gastroenterology. December 2015, Wiley-Blackwell.

Rothenberg ME, Collins M, **Haberman Ziv Y**. Chapter 11: Eosinophilic esophagitis. Yamada's Atlas of Gastroenterology. March 2016, Wiley-Blackwell.

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Positions

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Deputy Chief, Department of Gastroenterology and Liver Diseases ,Tel-Aviv Sourasky Medical Center

Research

We study the role of enteric bacteria in inflammatory and metabolic related disease conditions in humans and in-vitro. Specifically, we study how bacterial proteases impact the epithelial barrier function and how enteric microbial alterations are related to diseases. Clinically, we study the implication of fecal microbial transplantation in disease conditions.

Publications

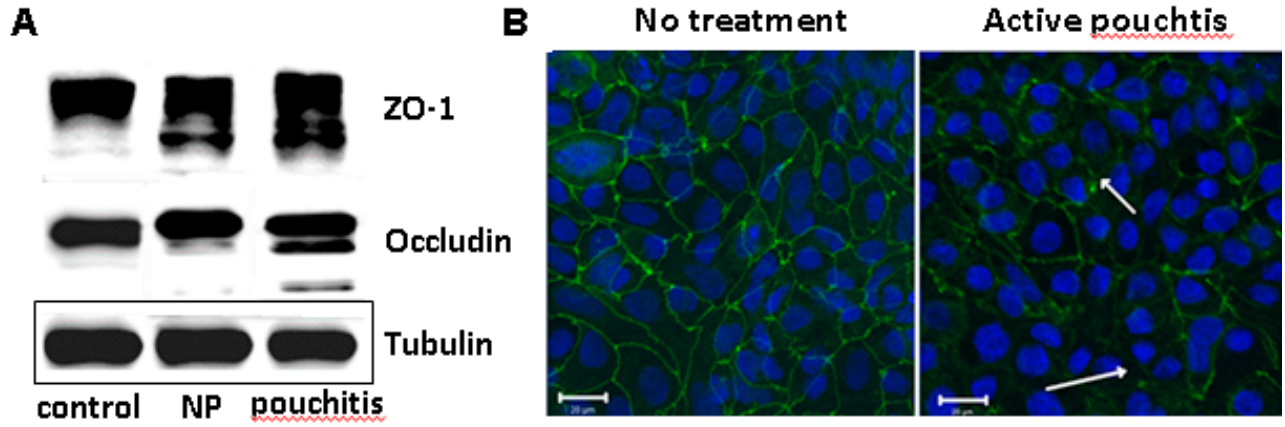
Reshef A, Kovacs A, Yahav L, Keren N, Ofer A, **Maharshak N**, Konikoff FM, Tulchinsky H, Gophna U, Dotan I. Pouch inflammation is associated with a decrease in key bacterial taxa. Gastroenterology. 2015; 149(3):718-27

Maharshak N, Huh E, Thurlow L, Herzog J, Djukic Z, Orlando R, Pawlinski R, Zang Y, Shanahan M, Ellermann M, Borst L, Patel S, Von Furstenberg R, Dotan, I, Henning S, Sartor RB, Carroll IM. Enterococcus faecalis serine protease mediates intestinal permeability and inflammation via Protease Activated Receptor 2. Infect Immun. 2015;83(7):2762-70

Maharshak N, Ryu HS, Jia FanT, Onyiah JC, Schulz S, Otterbein SL, Wong R, HansenJ, Otterbein EL, Carroll I, Plevy SE. Escherichia coli heme oxygenase modulates host innate immune responses. Microbiol Immunol. 2015. 59(8):452-65

Ringel Y*, **Maharshak N**, Ringel Kulka T, Lundqvist A, Sartor RB, Carroll, IM. High throughput sequencing reveals distinct microbial populations within the mucosal and luminal niches in healthy Individuals. Gut Microbes. 2015;6(3):173-81. Equal contribution.

Cohen NA, Livovsky DM, Yaakobovitch S, Ben Yehoyada M, Ben Ami R, Adler A, Guzner-Gur H, Goldin E, Santo ME, Halpern Z, Paz K, **Maharshak N**. Fecal microbiota transplantation for recurrent Clostridium difficile infection is highly effective- a retrospective study from two Israeli tertiary centers. IMAJ. 2016



Fecal supernatants from pouchitis patients have increased proteolytic activity, disrupt epithelial tight junctions and increase epithelial permeability. Fecal supernatants isolated from pouchitis patients compared to healthy controls and normal pouch (NP) patients caused: **(A)** disruption of tight junction proteins (ZO-1, occludin) as assessed by Western blot. **(B)** Decrease ZO-1 immunofluorescence (white arrows) of Caco-2 cells mononlayters. Alexa anti mouse 488 was used as the secondary antibody (green). Nuclei were counterstained with DAPI and are shown in blue.

Hod K, Ringel-KulkanT, Martin CF, **Maharshak N**, Ringel Y. High Sensitive C-Reactive Protein as a Marker for Inflammation in Irritable Bowel Syndrome. J Crohns Colitis. 2016. 50(3):227-32.

Maharshak N, Cohen NA, Reshef L, Tulchinsky H, Gophna U, Dotan I. Alterations of Enteric Microbiota in Patients with a Normal Ileal Pouch Are Predictive of Pouchitis. J Crohns Colitis. 2016; pii: jjw157.

Maharshak N, Cohen NA, Reshef L, Tulchinsky H, Gophna U, Dotan I. Enteric microbiota alterations in patients with a normal ileal pouch are predictive of pouchitis. JCC 2017. 11(3):314-320

Chen L, Wilson JE, Montgomery SA, Packey CD, Chou WC, **Maharshak N**, Plevy SE, Young VB, Sartor RB, Ting JPY. NLRP12 Attenuates Colon Inflammation by Maintaining Colonic Commensal Symbiosis and the Expansion of Lachnospiraceae Strains. Nat Immun 2017. 18(5):541-551.

Kopylov U, Ron Y, Avni-Biron I, Koslovsky B, Waterman M, Daher S, Ungar S, Yanai H, **Maharshak N**, Ben-Bassat O, Lichtenstein L, Bar Gil Shitrit A, Israeli E, Shwartz D, Zittan E, Eliakim R, Chowers Y, Ben-Horin S, Dotan I. Efficacy and safety of vedolizumab for induction of remission in inflammatory bowel disease-the Israeli real world experience. IBD Journal 2017. 23(3):404-408.

Hod K, Sperber AD, MSPH, Ron Y, Boaz M, Dickman R, Berliner S, Halpern Z, **Maharshak N**, Dekel R. A Double-Blind, Placebo-Controlled Study to Assess the Effect of the Probiotic Mixture Bio-25 on Symptoms and High-Sensitivity CRP (hs-CRP) in Women with Diarrhea-Predominant IBS. Neurogastroenterol 2017. 29(7). **Maharshak N** and Dekel R contributed equally

Iny O, Yanai H, Matalon S, Santo EM, Shibolet O, Dotan I, **Maharshak N**. Crohn's disease behavior and location is altered when associated with primary sclerosing cholangitis. Isr Med Assoc J 2016.

Friedman-Korn T, Livovsky DM, **Maharshak N**, Cohen NA, Paz K, Goldin E, Bar-Gil Shitrit A, Koslowsky B. Fecal transplantation for treatment of Clostridium difficile colitis in elderly and debilitated patients. Dig Dis Sci 2017

Cohen NA, Miller T, Na'aminh W, Hod K, Adler A, Cohen D, Guzner-Gur H, Santo E, Halpern Z, Carmeli Y, **Maharshak N**. Clostridium difficile fecal toxin level is associated with disease severity and prognosis. UEG 2017

Thurm T, Ablin JN, Buskila D, **Maharshak N**. Fecal Microbiota Transplantation for Fibromyalgia: A case report and review of the literature. OJG. 2017

Cohen NA, **Maharshak N**. Novel Indications for Fecal Microbial Transplantation: Update and Review of the Literature. Digestive Disease and Sciences. 2017. 62(5):1131-1145.

Mouhadeb O, Ben Shlomo S, Cohen K, Farkash I, Gruber S, **Maharshak N**, Halpern Z, Burstein E, Gluck N, Varol C. Impaired COMMD10-mediated regulation of Ly6Chi monocyte-driven inflammation disrupts gut barrier function. Front Immunol. 2018;9:2623.

Shapira S, Leshno A, Katz D, **Maharshak N**, Hevroni G, Jean-David M, Kraus S, Galazan L, Aroch I, Kazanov D, Hallack A, Becker S, Umanski M, Moshkowitz M, Dotan I, Arber N. Of mice and men: a novel dietary supplement for the treatment of ulcerative colitis. Therap Adv Gastroenterol. 2018;11:1756283X17741864.

Friedman-Korn T, Livovsky DM, **Maharshak** N, Cohen NA, Paz K, Bar-Gil Shitrit A, Goldin E, Koslowsky B. Fecal Transplantation for Treatment of Clostridium Difficile Infection in Elderly and Debilitated Patients. Dig Dis Sci. 2018;63(1):198-203.

Iny O, Yanai H, Matalon S, Santo E, Shibolet O, Dotan I, **Maharshak N**. Crohn's Disease behavior and location is altered when associated with Primary Sclerosing Cholangitis. Isr Med Assoc J. 2018;20(1):25-9.

Maharshak N, Barzilay I, Zinger H, Hod K, Dotan I. Clostridium difficile infection in hospitalized patients with inflammatory bowel disease: Prevalence, risk factors, and prognosis. Medicine (Baltimore). 2018;97(5):e9772.

Cohen NA, Miller T, Na'aminh W, Hod K, Adler A, Cohen D, Guzner-Gur H, Santo E, Halpern Z, Carmeli Y, **Maharshak N**. Clostridium difficile fecal toxin level is associated with disease severity and prognosis. United European Gastroenterol J. 2018;6(5):773-80.

Maharshak N, Ringel Y, Katibian D, Lundqvist A, Sartor RB, Carroll IM, Ringel-Kulka T. Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. Dig Dis Sci. 2018;63(7):1890-9.

Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S, Zur M, Regev-Lehavi D, Ben-Zeev Brik R, Federici S, Horn M, Cohen Y, Moor AE, Zeevi D, Korem T, Kotler E, Harmelin A, Itzkovitz S, **Maharshak N**, Shibolet O, Pevsner-Fischer M, Shapiro H, Sharon I, Halpern Z, Segal E, Elinav E. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell. 2018;174(6):1406-1423.e16.

Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, Kotler E, Zur M, Regev-Lehavi D, Brik RB-Z, Federici S, Cohen Y, Linevsky R, Rothschild D, Moor AE, Ben-Moshe S, Harmelin A, Itzkovitz S, **Maharshak N**, Shibolet O, Shapiro H, Pevsner-Fischer M, Sharon I, Halpern Z, Segal E, Elinav E. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell. 2018;174(6):1388-1405.e21.

Kopylov U, Verstockt B, Biedermann L, Sebastian S, Pugliese D, Sonnenberg E, Steinhagen P, Arebi N, Ron Y, Kucharzik T, Roblin X, Ungar B, Shitrit AB-G, Ardizzone S, Molander P, Coletta M, Peyrin-Biroulet L, Bossuyt P, Avni-Biron I, Tsoukali E, Allocca M, Katsanos K, Raine T, Sipponen T, Fiorino G, Ben-Horin S, Eliakim R, Armuzzi A, Siegmund B, Baumgart DC, Kamperidis N, **Maharshak N**, Maaser C, Mantzaris G, Yanai H, Christodoulou DK, Dotan I, Ferrante M. Effectiveness and safety of Vedolizumab in anti-TNF-naïve patients with inflammatory bowel disease-A multicenter retrospective European study. Inflamm Bowel Dis. 2018;24(11):2442-51.

Hod K, Dekel R, Cohen NA, Sperber A, Ron Y, Boaz M, Berliner S, **Maharshak N**. The effect of a multispecies probiotic on microbiota composition in a clinical trial of patients with diarrhea-predominant irritable bowel syndrome. Neurogastroenterol Motil. 2018;30(12):e13456.

Hod K, Sperber AD, **Maharshak N**, Ron Y, Shapira I, David Z, Rogowski O, Berliner S, Shenhar-Tsarfaty S, Dekel R. Serum cholinesterase activity is elevated in female diarrhea-predominant irritable bowel syndrome patients compared to matched controls. Neurogastroenterol Motil. 2018;30(12):e13464.

Greenberg SA, Youngster I, Cohen NA, Livovsky DM, Strahilevitz J, Israeli E, Melzer E, Paz K, Fliss-Isakov N, **Maharshak N**. Five years of fecal microbiota transplantation - an update of the Israeli experience. World J Gastroenterol. 2018;24(47):5403-14.

Kopylov U, Avni-Biron I, Ron Y, Koslowsky B, Waterman M, Daher S, Ungar B, Schwartz D, Zittan E, Openhaim M, Yanai H, Maharshak N, Bar Gil Shitrit A, Naftali T, Eliakim R, Chowers Y, Ben-Horin S, Dotan I. Effectiveness and safety of vedolizumab for maintenance treatment in inflammatory bowel disease-The Israeli real world experience. Dig Liver Dis. 2019;51(1):68-74.

Huttner BD, de Lastours V, Wassenberg M, **Maharshak N**, Mauris A, Galperine T, Zanichelli V, Kapel N, Bellanger A, Olearo F, Duval X, Armand-Lefevre L, Carmeli Y, Bonten M, Fantin B, Harbarth S; R-Gnosis WP3 study group. A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant Enterobacteriaceae: a randomized clinical trial. Clin Microbiol Infect. 2019; 25(7):830-8.

Godny L*, **Maharshak N***, Reshef L, Goren I, Yahav L, Fliss-Isakov N, Gophna U, Tulchinsky H, Dotan I. *Equal Contribution. Fruit consumption is associated with alterations in microbial composition and lower rates of pouchitis. J Crohns Colitis. 2019;13(10):1265-72.

Shapiro J, Cohen NA, Shalev V, Uzan A, Koren O, **Maharshak N**. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. J Dermatol 2019;46(7):595-603. Hoffman S, Aviv Cohen N, Carroll IM, Tulchinsky H, Borovok I, Dotan I, Maharshak N. Faecal Proteases from pouchitis patients activate protease activating receptor-2 to disrupt the epithelial barrier. J Crohn's Colitis 2019;13(12):1558-68.

Winder O, Fliss-Isakov N, Winder G, Scapa EF, Yanai H, Barnes S, Dekel R. Dotan, **Maharshak N**. Clinical outcomes of endoscopic balloon dilatation of intestinal strictures in patients with Crohn's disease. Medicine (Baltimore). 2019;98(35):e16864.

Ellermann M, Gharaibeh RZ, Maharshak N, Peréz-Chanona E, Jobin C, Carroll IM, Arthur JC, Plevy SE, Fodor AA, Brouwer CR, Sartor RB. Dietary iron variably modulates assembly of the intestinal microbiota in colitis-resistant and colitis-susceptible mice. Gut Microbes. 2020;11(1):32-50.

Bar-Gil Shitrit A, Ben Ya'acov A, Siterman M, Waterman M, Hirsh A, Schwartz, D, Zittan E, Adler Y, Koslowsky B, Avni-Biron I, Chowers Y, Ron Y, Israeli E, Ungar B, Yanai H, **Maharshak N**, Ben-Horin S, Eliakim R, Dotan I, Goldin E, Kopylov U. Effectiveness and safety of ustekinumab for induction of remission in patients with Crohn's disease- A multi-center Israeli study. United Eur Gastroenterology J 2020.

Sarbagili-Shabat C, Zelber-Sagi S, Fliss Isakov N, Ron Y, Hirsch A, **Maharshak N**. Development and validation of Processed Foods Questionnaire (PFQ) in adult inflammatory bowel diseases patients. Eur J Clin Nut. 2020

Hod K, Melamed S, Dekel R, **Maharshak N**, Sperber AD. Burnout, but not job strain, is associated with irritable bowel syndrome in working adults. J Psychosomatic Res. 2020.

Bar-Yoseph H, Carasso S, Shklar S, Korytny A, Even Dar R, Daud H, Nassar R, **Maharshak N**, Hussein K, Geffen Y, Koren O, Chowers Y, Geva-

Zatorsky N, Paul M. Oral capsulized Fecal microbiota transplantation for eradication of carbapenemase-producing Enterobacteriaceae colonization with a metagenomic perspective. Clin Infec Dis. 2020.

Grants

2017-2020 Fecal transplantation using a novel conditioning method for donor and recipient in moderate to severe treatment refractory ulcerative colitis. European Crohn's and Colitis Organization

2018-2020 The efficacy of non-absorbable antibiotics followed by fecal microbiota transplantation for eradication of carbapenem-resistant enterobacteriaceae colonization. Israel Ministry of Science and Technology

2018- 2020 Fecal Microbial Transplantation for the Optimization of Vedolizumab Treatment in Patients with Crohn's Disease. Takeda Ltd.

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Positions

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Waisbourd-Zinman - Attending Physician, Schneider Children's Medical Center of Israel

Research

Biliary atresia (BA) is a fibro-obliterative disease of the extrahepatic bile ducts affecting newborns, and is the leading indication for pediatric liver transplant. The etiology remains unknown and there is no effective treatment. We identified an isoflavonoid toxin, biliatresone, that causes BA outbreaks in Australian livestock and we showed that it causes lumen obstruction of neonatal mouse bile duct (NBD) explants. This is a novel tool for the study of BA and allows us to study the primary event in the disease, providing new potential for identifying therapeutic interventions. We found that biliatresone acts by inducing a rapid and transient decrease in reduced glutathione (GSH) and a decrease in SOX17

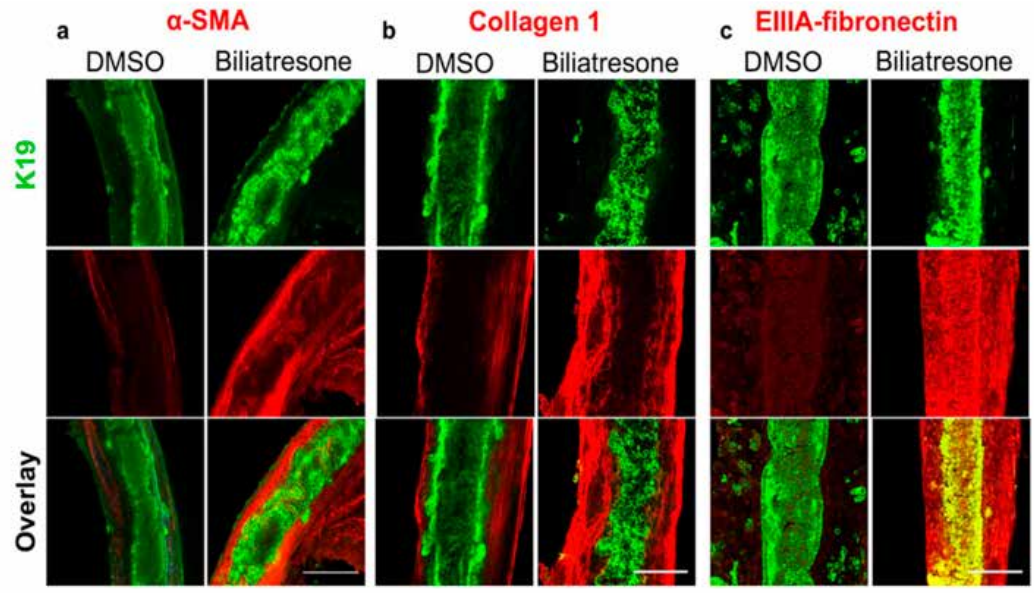

Figure: Biliatresone induces ductal fibrosis. Neonatal mouse bile duct explants were incubated with DMSO or biliatresone for 24 h and stained for the cholangiocyte marker K19 (green) or the myofibroblast marker smooth muscle actin (SMA) or collagen I or the EIIIA splice variant of fibronectin (all red). Scale bars 100 μm.

in cholangiocytes and that cholangiocyte injury can be mimicked using DL-buthionine sulfoximine (BSO) to reduce GSH or by knocking down *Sox17*. NBD cultured *ex vivo* and treated with either biliatresone or BSO showed disruption of the cholangiocyte monolayer, lumen obstruction, and subepithelial myofibroblast differentiation and fibrosis. Both obstruction and fibrosis could be prevented using GSH-protective agents, and were reversible with biliatresone wash out. In this proposal, we aim to define mechanistically the relationship between biliatresone, decreased GSH and downstream signaling molecules (Hey2, Hes1, RhoU, DAAM1 and other WNT signaling pathway genes) in the disruption of cholangiocytes and bile duct integrity. We will study the relationship between changes in cellular tubulin, loss of apical polarity, epithelial permeability and fibrosis and mechanism of repair of cholangiocyte damage and fibrosis. Understanding potential mechanisms of initial injury in BA may lead to new treatments.

Publications

Lorent K, Gong W, Koo K.A, **Waisbourd-Zinman O**, Karjoo S, Zhao X, Sealy I, Kettleborough R.N Stemple DL, Windsor PA, Whittaker SJ, Porter JR, Wells RG, Pack M. Identification of a plant isoflavonoid that causes biliary atresia. Science of Translational Medicine 2015; 6;7:286ra67.

Waisbourd-Zinman O, Koh H, Tsai S, Lavrut PM, Dang C, Zhao X, Pack M, Cave J Hawes M, Koo KA, Porter JR, Wells RG. Biliatresone, a toxin causing biliary atresia-like disease, acts via decreased glutathione and SOX17. Hepatology 2016; 64:880-93.

Zhao X, Lorent K, Wilkins B, Marchione D, Gillespie K, **Waisbourd-Zinman O**, So J, Koo KA, Shin D, Porter J, Wells RG, Blair I, Pack M. Glutathione Antioxidant Pathway Activity and Reserve Determine Toxicity and Specificity of the Biliary Toxin Biliatresone in Zebrafish. Hepatology 2016; 64:880-93.

Waisbourd-Zinman O, Mamula P, Piccoli DA. Chromosome 10q23 Deletion syndrome: An Overlap of Bannayan-Riley-Ruvalcaba Syndrome and Juvenile Polyposis Syndrome. J Paediatr Child Health 2016;52:852.

Waisbourd-Zinman O, Surrey LF, Schwartz AE, Russo PA, Wen J. A novel BSEP mutation causes a mild form of progressive familial cholestasis type 2. Annals of Hepatology.

Agostoni C, Moreno L, **Shamir R**. Palmitic acid and health: introduction. Crit Rev Food Sci Nutr 2016;56:1941-2.

Vandenplas Y, Alarcon P, Fleischer D, Hernell O, Kolacek S, Laignelet H, Lönnerdal B, Raman R, Rigo J, Salvatore S, **Shamir R**, Staiano A, Szajewska H, Van Goudoever J, von Berg A, Lee WS. Should partial hydrolysates be used as starter infant formula? A working group consensus. J Pediatr Gastroenterol Nutr 2016;62:22-35.

Assa A, Avni I, Ben-Bassat O, Niv Y, **Shamir R**. Practice variations in the management of inflammatory bowel disease between pediatric and adult gastroenterologists. J Pediatr Gastoenterol Nutr 2016;62:372-7.

Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, **Shamir R**, Vandenplas Y, van Goudoever JB, Weizman Z; ESPGHAN Working Group for Probiotics Prebiotics. Probiotics for the prevention of antibiotic-associated diarrhea in children. J Pediatr Gastroenterol Nutr 2016;62:495-506.

Hartman C, **Shamir R**. Nutrition and growth in chronic disease. World Rev Nutr Diet 2016;114:84-102.

Szajewska H, **Shamir R**, Mearin ML, Koninckx CR, Catassi C, Domellöf M, Fewtrell MS, Husby S, Papadopoulou A, Vandenplas Y, Castillejo G, Kolacek S, Koletzko S, Korponay-Szabó IR, Lionetti E, Polanco I, Troncone R. Gluten introduction and the risk of coeliac disease. A position paper by the European Society for Paediatric Gastroenterology, Hepatology & Nutrition. J Pediatr Gastroenterol Nutr 2016; 62:507-13.

Karas J, Ashkenazi S, Guarino A, Lo Vecchio A, **Shamir R**, Vandenplas Y, Szajewska H; Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT). Developing a core outcome measurement set for clinical trials in acute diarrhoea. Acta Paediatr 2016;105:e176-80.

Rinawi F, Rosenbach Y, Assa A, **Shamir R**. Ustekinumab for resistant pediatric Crohn's disease. J Pediatr Gastroenterol Nutr 2016;62:e34-5.

Eales J, Lenoir-Wijnkoop I, King S, Wood H, Kok FJ, **Shamir R**, Prentice A, Edwards M, Glanville J, Atkinson RL. Is consuming yoghurt associated with weight management outcomes? Results from a systematic review. Int J Obes 2016; 40(5):731-46.

Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Guarino A, Lifschitz C, Lionetti P, Orel R, Papadopoulou A, Ribes-Koninckx C, Ruemmele FM, Salvatore S, **Shamir R**, Schäppi M, Staiano A, Szajewska H, Thapar N, Wilschanski M. Functional gastro-intestinal disorder algorithms focus on early

recognition, parental reassurance and nutritional strategies. Acta Paediatr 2016;105:244-52.

Rub G, Marderfeld L, Poraz I, Hartman C, Amsel S, Rosenbaum I, Pergamentzev-Karpol S, Monsonego-Ornan E, **Shamir R**. Validation of a nutritional screening tool for ambulatory use in pediatrics. J Pediatr Gastroenterol Nutr 2016;62:771-5.

Koletzko B, **Shamir R**. Infant formula: Does one size fit all? Curr Opin Clin Nutr Metab Care 2016;19:205-7.

Chourdakis M, Hecht C, Gerasimidis K, Joosten KFM, Karagiozoglou-Lampoudi T, Koetse HA, Ksiazyk J, Lazea C, **Shamir R**, Szajewska H, Koletzko B, Hulst JM. Malnutrition risk in hospitalized children: Use of three screening tools in a large European population. Am J Clin Nutr 2016;103:1301-10.

Lo Vecchio A, Vandenplas Y, Benninga M, Broekaert I, Falconer J, Gottrand F, Lifschitz C, Lionetti P, Orel R, Papadopoulou A, Ribes-Koninckx C, Salvatore S, **Shamir R**, Schäppi M, Staiano A, Szajewska H, Thapar N, Wilschanski M, Guarino A. An international consensus report on a new algorithm for the management of infant diarrhoea. Acta Paediatr 2016;105:e384-9.

Ashkenazi-Hoffnung L, Mozer-Glassberg Y, Bilavsky E, Yassin R, **Shamir R**, Amir J. Children post liver transplantation hospitalized with fever are at a high risk for bacterial infections. Transpl Infect Dis 2016;18:333-40.

Ludvigsson JF, Agreus L, Ciacci C, Crowe SE, Geller MG, Green PHR, Hill I, Hungin AP, Koletzko S, Koltai T, Lundin KEA, Mearin ML, Murray JA, Reilly N, Walker MM, Sanders DS, **Shamir R**, Troncone R, Husby S. Guidelines: Transition from childhood to adulthood in coeliac disease: The Prague consensus report. Gut 2016;65:1242-51.

Masarwi M, Gaber Y, Dolkart O, Brosh T, **Shamir R**, Phillip M, Gat-Yablonski, G. Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats. Br J Nutr 2016;116:59-69.

Shamir R. The benefits of breast feeding, Nestle Nutr Inst Workshop Ser 2016;86:67-76.

Hartman C, Marderfeld L, Davidson K, Mozer-Glassberg Y, Poraz I, Silbermintz A, Zevit N, **Shamir R**. Food intake adequacy in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2016;63:437-44.

Pieścik-Lech M, Chmielewska A, **Shamir R**, Szajewska H. Systematic review: Early infant feeding and the risk of type 1 diabetes. J Pediatr Gastroenterol Nutr 2016.

Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Nachmias Friedler V, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. Evolution of disease phenotype in pediatric-onset Crohn's disease after more than 10 years follow up-Cohort study. Dig Liver Dis 2016.

Caubet JC, Szajewska H, **Shamir R**, Nowak-Węgrzyn A. Non IgE-mediated Gastrointestinal Food Allergies in children. Pediatr Allergy Immunol 2016.

Assa A, Frenkel-Nir Y, Leibovici-Weissman Y, Tzur D, Afek A, Katz LH, Levi Z, **Shamir R**. Anthropometric measures and prevalence trends in adolescents with coeliac disease: a population based study. Arch Dis Child 2016.

Yackobovitch-Gavan M, Lebenthal Y, Lazar L, Shalitin S, Demol S, Tenenbaum A, **Shamir R**, Phillip M. Effect of Nutritional Supplementation on Growth in Short and Lean Prepubertal Children after 1 Year of Intervention. J Pediatr 2016;179:154-9.

Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Friedler VN, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. Incidence of Bowel Surgery and Associated Risk Factors in Pediatric-Onset Crohn's Disease. Inflamm Bowel Dis 2016;22:2917-23.

Assa A, Frenkel-Nir Y, Tzur D, Katz LH, **Shamir R**. Cardiovascular risk factors in adolescents with celiac disease: a cross sectional population based study. J Pediatr Gastroenterol Nutr 2016.

Caubet JC, Szajewska H, **Shamir R**, Nowak-Węgrzyn A. Non IgE-mediated Gastrointestinal Food Allergies in children. Pediatr Allergy Immunol 2017;28:6-17.

Pieścik-Lech M, Chmielewska A, **Shamir R**, Szajewska H. Systematic review: Early infant feeding and the risk of type 1 diabetes. J Pediatr Gastroenterol Nutr 2017;64:454-9.

Assa A, Frenkel-Nir Y, Leibovici-Weissman Y, Tzur D, Afek A, Katz LH, Levi Z, **Shamir R**. Anthropometric measures and prevalence trends in adolescents with coeliac disease: a population based study. Arch Dis Child 2017;102:139-44.

Morgenstern S, Brook E, Rinawi F, **Shamir R**, Assa A. Tissue and peripheral eosinophilia as predictors for disease outcome in children with ulcerative colitis. Dig Liver Dis 2017;49:170-4.

Elli L, Branchi F, Sidhu R, Guandalini S, Assiri A, Rinawi F, **Shamir R**, Das P, Makharia GK. Small bowel villous atrophy: celiac disease and beyond. Expert Rev Gastroenterol Hepatol 2017;11:125-38.

Forbes A, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, **Shamir R**, Stardelova K, Wierdsma N, Wiskin A.E, Bischoff S.C. ESPEN Guideline: Clinical

Nutrition in inflammatory bowel disease. Clin Nutr 2017;36:321-47.

Matar M, Rinawi F, **Shamir R,** Assa A. Hypergammaglobulinemia is a marker of extraintestinal manifestations in pediatric inflammatory bowel disease. Turk J Gastroenterol 2017;28:131-4.

Rinawi F, Assa A, Eliakim R, Mozer-Glassberg Y, Nachmias Friedler V, Niv Y, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. The natural history of pediatric-onset IBD-unclassified and prediction of Crohn's disease reclassification: a 27-year study. Scand J Gastroenterol 2017;52:558-63.

Assa A, Bronsky J, Kolho KL, Zarubova K, de Meij T, Ledder O, Sladek M, van Biervliet S, Strisciuglio C, **Shamir R**. Anti-TNFα Treatment After Surgical Resection for Crohn's Disease Is Effective Despite Previous Pharmacodynamic Failure. Inflamm Bowel Dis 2017;23:791-7.

Crespo-Escobar P, Mearin ML, Hervás D, Auricchio R, Castillejo G, Gyimesi J, Martinez-Ojinaga E, Werkstetter K, Vriezinga SL, Korponay-Szabo IR, Polanco I, Troncone R, Stoopman E, Kolaček S, **Shamir R**, Szajewska H, Koletzko S, Ribes-Koninckx C. The role of gluten consumption at an early age in celiac disease development: a further analysis of the prospective PreventCD cohort study. Am J Clin Nutr 2017;105:890-6.

Koletzko B, Goulet O, Jochum F, **Shamir R**. Use of parenteral nutrition in the pediatric ICU: should we panic because of PEPaNIC? Curr Opin Clin Nutr Metab Care 2017;20:201-3.

Kolaček S, Hojsak I, Canani RB, Guarino A, Indrio F, Orel R, Pot B, **Shamir R**, Szajewska H, Vandenplas Y, van Goudoever J, Weizman Z. Commercial probiotic products: A call for improved quality control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr 2017;65:117-24.

Guz-Mark A, Rinawi F, Egotubov O, Shimon I, **Shamir R**, Assa A. Pediatric-onset inflammatory bowel disease poses risk for low bone mineral density at early adulthood. Dig Liver Dis 2017;49:639-42.

Assa A, Frenkel-Nir Y, Tzur D, Katz LH, **Shamir R**. Cardiovascular Risk Factors in Adolescents With Celiac Disease: A Cross Sectional Population Based Study. J Pediatr Gastroenterol Nutr 2017;65:190-4.

Assa A, Frenkel-Nir Y, Tzur D, Katz LH, **Shamir R**. Large population study shows that adolescents with celiac disease have an increased risk of multiple autoimmune and non-autoimmune comorbidities. Acta Paediatr 2017;106:967-72.

Vandenplas Y, Szajewska H, Benninga M, Di Lorenzo C, Dupont C, Faure C, Miqdadi M, Osatakul S, Ribes-Konickx C, Saps M, **Shamir R**, Annamaria Staiano A. Development of the Brussels Infant and Toddler Stool Scale ('BITSS'): protocol of the study. BMJ Open 2017;29:7.

Rothschild B, Rinawi F, Herman Y, Nir O, **Shamir R**, Assa A. Prognostic significance of granulomas in children with Crohn's disease. Scand J Gastroenterol 2017;52:716-21.

Grossman Z, Hadjipanayis A, Stiris T, Del Torso S, Mercier JC, Valiulis A, **Shamir R**. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). Eur J Pediatr 2017;176:829-31.

Scarpato E, Quitadamo P, Roman E, Jojkic-Pavkov D, Kolacek S, Papadopoulou A, Roma E, **Shamir R**, Lev MRB, Lutovac B, Djurisic V, Orel R, Koleilat A, Mneimneh S, Coppola V, Corazziari E, Staiano A. Functional Gastrointestinal Disorders in Children: A Survey on Clinical Approach in the Mediterranean Area. J Pediatr Gastroenterol Nutr 2017;64:e142-6.

Szajewska H, **Shamir R**. Editorial. Nutrition intervention in allergy prevention. Ann Nutr Metab 2017;70 Suppl 2:5.

Rinawi F, Ashkenazi S, Wilschanski M, Somekh E, **Shamir R**. Reccommendations for the Diagnosis and Management of Pediatric Acute Gastroenteritis in Israel - Update 2017. Harefuah 2017;3:189-93. Hebrew.

Bar-Maisels M, Gabet Y, **Shamir R**, Hiram-Bab S, Pasmanik-Chor M, Phillip M, Bar-Yoseph F, Gat-Yablonski G. Beta Palmitate Improves Bone Length and Quality during Catch-Up Growth in Young Rats. Nutrients 2017;18:9.

Magni P, Bier DM, Pecorelli S, Agostoni C, Astrup A, Brighenti F, Cook R, Folco E, Fontana L, Gibson RA, Guerra R, Guyatt GH, Ioannidis JP, Jackson AS, Klurfeld DM, Makrides M, Mathioudakis B, Monaco A, Patel CJ, Racagni G, Schünemann HJ, **Shamir R**, Zmora N, Peracino A. Perspective: Improving Nutritional Guidelines for Sustainable Health Policies: Current Status and Perspectives. Adv Nutr 2017;8:532-545.

Assa A, **Shamir R**. Exclusive enteral nutrition for inducing remission in inflammatory bowel disease in paediatric patients. Curr Opin Clin Nutr Metab Care 2017;20:384-9.

Rinawi F, Assa A, Eliakim R, Mozer Glassberg Y, Nachmias Friedler V, Niv Y, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. Predictors of pouchitis after ileal

pouch-anal anastomosis in pediatric-onset ulcerative colitis. Eur J Gastroenterol Hepatol 2017;29:1079-85.

Rinawi F, Assa A, Bashir H, Peleg S, **Shamir R**. Clinical and Phenotypic Differences in Inflammatory Bowel Disease Among Arab and Jewish Children in Israel. Dig Dis Sci 2017;62:2095-101.

Rzehak P, Oddy WH, Mearin ML, Grote V, Mori TA, Szajewska H, **Shamir R**, Koletzko S, Weber M, Beilin LJ, Huang RC, Koletzko B; WP10 working group of the Early Nutrition Project. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood. Am J Clin Nutr 2017;106:568-80.

Rinawi F, Assa A, Eliakim R, Glassberg YM, Friedler VN, Niv Y, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. Risk of Colectomy in Patients with pediatric-onset Ulcerative Colitis. J Pediatr Gastroenterol Nutr 2017;65:410-5.

Ari A, Morgenstern S, Chodick G, Matar M, Silbermintz A, Assa A, Mozer-Glassberg Y, Rinawi F, Nachmias-Friedler V, **Shamir R**, Zevit N. Oesophageal eosinophilia in children with coeliac disease. Arch Dis Child 2017;102:825-9.

Koletzko S, Auricchio R, Dolinsek J, Gillett P, Korponay-Szabo I, Kurppa K, Mearin L, Mäki M, Popp A, Ribes C, **Shamir R**, Stordal K, Troncone R, Werkstetter K, Wessels M, Zimmer KP, Husby S. No Need for Routine Endoscopy in Children With Celiac Disease on a Gluten-free diet. J Pediatr Gastroenterol Nutr 2017;65:267-9.

Chmielewska A, Pieścik-Lech M, **Shamir R**, Szajewska H. Systematic review: Early infant feeding practices and the risk of wheat allergy. J Paediatr Child Health 2017;53:889-96.

Herman Y, Rinawi F, Rothschild B, Nir O, **Shamir R**, Assa A. The Characteristics and Long-term Outcomes of Pediatric Crohn's Disease Patients with Perianal Disease. Inflamm Bowel Dis 2017;23:1659-65.

Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, Lillevang ST, Mearin ML, Ribes-Koninckx C, Thomas A, Troncone R, Filipiak B, Mäki M, Gyimesi J, Najafi M, Dolinšek J, Dydensborg Sander S, Auricchio R, Papadopoulou A, Vécsei A, Szitanyi P, Donat E, Nenna R, Alliet P, Penagini F, Garnier-Lengliné H, Castillejo G, Kurppa K, **Shamir R**, Hauer AC, Smets F, Corujeira S, van Winckel M, Buderus S, Chong S, Husby S, Koletzko S; ProCeDE study group. Accuracy of Tests for Antibodies Against Tissue-transglutaminase in Diagnosis of Celiac Disease, Without Biopsy. Gastroenterology 2017;153:924-35.

Werkstetter KJ, Korponay-Szabó IR, Popp A, Villanacci V, Salemme M, Heilig G, Lillevang ST, Mearin ML, Ribes-Koninckx C, Thomas A, Troncone R, Filipiak B, Mäki M, Gyimesi J, Najafi M, Dolinšek J, Dydensborg Sander S, Auricchio R, Papadopoulou A, Vécsei A, Szitanyi P, Donat E, Nenna R, Alliet P, Penagini F, Garnier-Lengliné H, Castillejo G, Kurppa K, **Shamir R**, Hauer AC, Smets F, Corujeira S, van Winckel M, Buderus S, Chong S, Husby S, Koletzko S; ProCeDE study group. Accuracy in Diagnosis of Celiac Disease Without Biopsies in Clinical Practice. Gastroenterology 2017; 153:924-35.

Interator H, Lebenthal Y, Hoshen M, Safra I, Balicer R, Leshno M, **Shamir R**. Distinct Lipoprotein Curves in Normal Weight, Overweight and Obese Children and Adolescents. J Pediatr Gastroenterol Nutr 2017; 65:673-80.

Shamir R. ESPGHAN Distinguished Service Award 2017 to Professor Olivier Goulet. J Pediatr Gastroenterol Nutr 2017; 65:487-8.

Nir O, Rinawi F, Amarilyo G, Harel L, **Shamir R**, Assa A. Phenotypic Features and Longterm Outcomes of Pediatric Inflammatory Bowel Disease Patients with Arthritis and Arthralgia. J Rheumatol 2017; 44:1636-43.

Rinawi F, Zevit N, Eliakim R, Niv Y, **Shamir R**, Assa A. Long-Term Outcomes After Primary Bowel Resection in Pediatric-Onset Crohn's Disease. Inflamm Bowel Dis 2017; 24:149-58.

Masarwi M, Isaac Solnik H, Phillip M, Yaron S, **Shamir R**, Pasmanic-Chor M. Food restriction followed by refeeding with a casein- or whey-based diet differentially affects the gut microbiota of pre-pubertal male rats. Journal of Nutritional Biochemistry 2018;51:27-39.

Hojsak I, Szajewska H, Canani RB, Guarino A, Indrio F, Kolacek S, Orel R, **Shamir R**, Vandenplas Y, van Goudoever JB, Weizman Z. Probiotics for the Prevention of Nosocomial Diarrhea in Children; ESPGHAN Working Group for Probiotics/Prebiotics. J Pediatr Gastroenterol Nutr 2018;66:3-9.

Rinawi F, Assa A, Hartman C, Mozer Glassberg Y, Nachmias Friedler V, Rosenbach Y, Silbermintz A, Zevit N, **Shamir R**. Long-term Extent Change of Pediatric-Onset Ulcerative Colitis. J Clin Gastroenterol 2017

Brandvayman Y, Rinawi F, **Shamir R**, Assa A. Associations of seasonal patterns and vitamin D levels with onset and flares of pediatric inflammatory bowel disease. Minerva Pediatr 2017

Assa A, Rinawi F, **Shamir R**. The long-term predictive properties of the Paris classification in pediatric inflammatory bowel disease patients. J Crohns Colitis 2017

Borrelli M, Maglio M, Korponay-Szabó IR, Vass V, Mearin ML, Meijer C, Niv-Drori H, Ribes-Koninckx C, Roca M, **Shamir R**, Troncone R, Auricchio R. Intestinal anti-transglutaminase 2 immunoglobulin A deposits in children at risk for coeliac disease (CD): data from the PreventCD study. Clin Exp Immunol 2017

Scarpato E, Kolacek S, Jojkic-Pavkov D, Konjik V, Živković N, Roman E, Kostovski A, Zdraveska N, Altamimi E, Papadopoulou A, Karagiozoglou-Lampoudi T, **Shamir R**, Bar Lev MR, Koleilat A, Mneimneh S, Bruzzese D, Leis R, Staiano A; MEAP Group. Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents in the Mediterranean Region of Europe. Clin Gastroenterol Hepatol 2017

Yackobovitch-Gavan M, Machtei A, Lazar L, **Shamir R**, Phillip M, Lebenthal Y. Randomised study found that improved nutritional intake was associated with better sleep patterns in prepubertal children who were both short and lean. Acta Paediatr 2017

Grants

	Personalizing Mediterranean diet in Children: the Ferrero Pilot Trial (RS)
2017-2020	ISF (OWZ)

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Elucidating Mechanisms of Endoplasmatic Reticulum (ER) Stress and mTOR Cross-Talk in Drug-Induced Liver Injury

Positions

Professor, Sackler Faculty of Medicine

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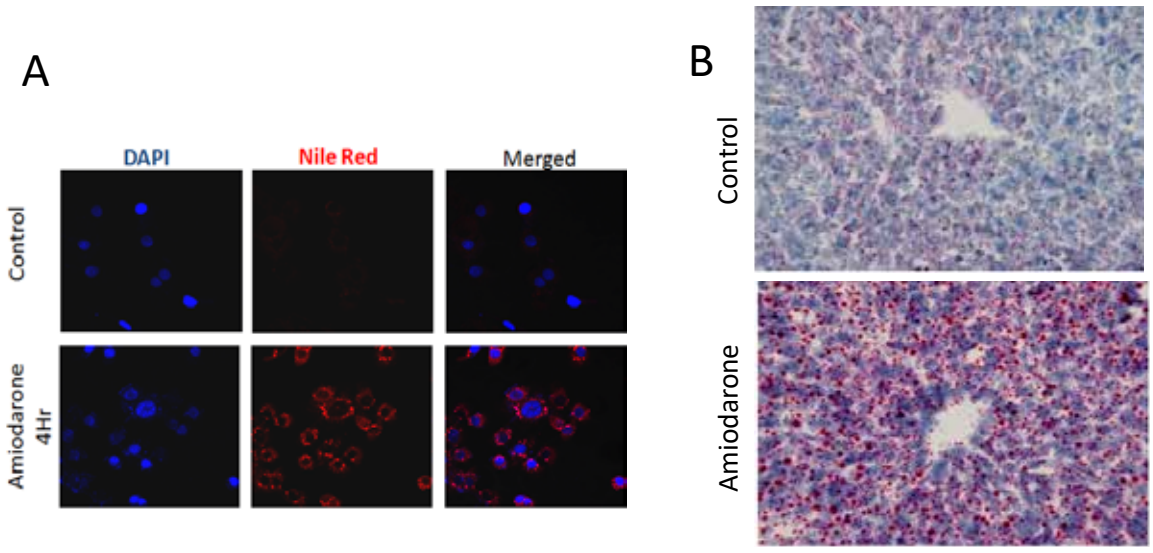
Research

The liver is a major site for drug metabolism and elimination, and is susceptible to drug toxicity. In fact, drug induced liver injury (DILI) has become the leading cause of acute liver failure in western countries, so DILI is a major clinical problem conferring significant health and financial burdens. The endoplasmic reticulum (ER) is the cellular site for protein folding. ER stress occurs when the amount of protein entering the ER exceeds its folding capacity. It induces a cyto-protective reaction collectively termed the unfolded protein response (UPR). We hypothesize that ER stress/UPR pathways are activated in response to hepatic drug metabolism survival-apoptosis-autophagy and together with mTOR signaling may mediate the hepatocyte damage and recovery associated with DILI. Our group is investigating the induction of ER stress/UPR by various hepatotoxic drugs, including acetaminophen (N-acetyl-p-aminophenol-APAP) and amiodarone. Our studies include DILI models in novel genetically modified mouse models with reduced ER stress. In addition, we are also exploring the therapeutic potential of chemical chaperones that relieve ER stress and may become therapies for DILI and improve liver regeneration following injury. In particular, we are focusing on the cross talk between ER stress and pathways of hepatic steatosis.



A. In vitro treatment with amiodarone induces lipid accumulation Lipid accumulation in immortalized hepatocytes assessed by Nile red staining. DAPI (blue) was used for nuclei staining. B. In vivo treatment with amiodarone leads to hepatic lipid accumulation. Oil Red O staining of liver from control or amiodarone treated mice.

Publications

Levy G, Bomze D, Heinz S, Ramachandran SD, Noerenberg A, Cohen M, **Shibolet O**, Sklan E, Braspenning J, Nahmias Y. Long-term culture and expansion of primary human hepatocytes. *Nat Biotechnol.* 2015 Dec;33(12):1264-1271.

Asman Y, Evenson AR, Even-Sapir E, **Shibolet O**. [18F]fludeoxyglucose positron emission tomography and computed tomography as a prognostic tool before liver transplantation, resection, and loco-ablative therapies for hepatocellular carcinoma. *Liver Transpl.* 2015;21(5):572-80.

Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, Kugelmas M, Murillo A, Weis N, Nahass R, **Shibolet O**, Serfaty L, Bourliere M, DeJesus E, Zuckerman E, Dutko F, Shaughnessy M, Hwang P, Howe AY, Wahl J, Robertson M, Barr E, Haber B.Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet*. 2015;385(9973):1087-97.

Webb M, Zimran A, Dinur T, **Shibolet O**, Levit S, Steinberg DM, Salomon O. Are transient and shear wave elastography useful tools in Gaucher disease? *Blood Cells Mol Dis*. 2016 Dec 23. pii: S1079-9796(16)30318-7.

Thaiss CA, Levy M, Korem T, Dohnalová L, Shapiro H, Jaitin DA, David E, Winter DR, Gury-BenAri M, Tatirovsky E, Tuganbaev T, Federici S, Zmora N, Zeevi D, Dori-Bachash M, Pevsner-Fischer M, Kartvelishvily E, Brandis A, Harmelin A,**Shibolet O**, Halpern Z, Honda K, Amit I, Segal E, Elinav E. Microbiota Diurnal Rhythmicity Programs Host Transcriptome Oscillations. *Cell.* 2016;167(6):1495-1510.e12.

Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, **Shibolet O**, Luetkemeyer A, Nahass R, Peng CY, Conway B, Grebely J, Howe AY, Gendrano IN, Chen E, Huang HC, Dutko FJ, Nickle DC, Nguyen BY, Wahl J, Barr E, Robertson MN, Platt HL; C-EDGE CO-STAR Study Group. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med*. 2016;165(9):625-634.

Levy G, Habib N, Guzzardi MA, Kitsberg D, Bomze D, Ezra E, Uygun BE, Uygun K, Trippler M, Schlaak JF, **Shibolet O**, Sklan EH, Cohen M, Timm J, Friedman N, Nahmias Y. Nuclear receptors control pro-viral and antiviral metabolic responses to hepatitis C virus infection. *Nat Chem Biol*. 2016;12(12):1037-1045.

Rabinowich L, Wendon J, Bernal W, **Shibolet O**. Clinical management of acute liver failure: Results of an international multi-center survey. *World J Gastroenterol*. 2016;22(33):7595-603.

Bashiardes S, Shapiro H, Rozin S, **Shibolet O**, Elinav E. Non-alcoholic fatty liver and the gut microbiota. *Mol Metab*. 2016;5(9):782-94.

Sherf Dagan S, Tovim TB, Keidar A, Raziel A, **Shibolet O**, Zelber-Sagi S. Inadequate protein intake after laparoscopic sleeve gastrectomy surgery is associated with a greater fat free mass loss. *Surg Obes Relat Dis*. 2017;13(1):101-109.

Mlynarsky L, Schlesinger D, Lotan R, Webb M, Halpern Z, Santo E, **Shibolet O**, Zelber-Sagi S. Non-alcoholic fatty liver disease is not associated with a lower health perception. *World J Gastroenterol.* 2016;22(17):4362-72.

Dagan SS, Zelber-Sagi S, Webb M, Keidar A, Raziel A, Sakran N, Goitein D,**Shibolet O**. Nutritional Status Prior to Laparoscopic Sleeve Gastrectomy Surgery. *Obes Surg*. 2016;26(9):2119-2126. Erratum in: Obes Surg. 2017 Jun 12.

Horsmans Y, Zhou J, Liudmila M, Golor G, **Shibolet O**, Quinlan M, Emotte C, Boss H, Castro H, Sellami D, Preston RA. Effects of Mild to Severe Hepatic Impairment on the Pharmacokinetics of Sonidegib: A Multicenter, Open-Label, Parallel-Group Study. *Clin Pharmacokinet*. 2017 Jun 2. doi: 10.1007/s40262-017-0560-2. [Epub ahead of print]

Zelber-Sagi S, Bord S, Dror-Lavi G, Smith ML, Towne SD Jr, Buch A, Webb M, Yeshua H, Nimer A, **Shibolet O**. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. *World J Gastroenterol*. 2017;23(10):1881-1890.

Sherf Dagan S, Keidar A, Raziel A, Sakran N, Goitein D, **Shibolet O**, Zelber-Sagi S. Do Bariatric Patients Follow Dietary and Lifestyle Recommendations during the First Postoperative Year? *Obes Surg.* 2017 Mar 16. doi: 10.1007/s11695-017-2633-6. [Epub ahead of print]

Zelber-Sagi S, Salomone F, Kolodkin-Gal I, Erez N, Buch A, Yeshua H, Webb M, Halpern Z, **Shibolet O**. Protective role of soluble receptor for advanced glycation end-products in patients with non-alcoholic fatty liver disease. *Dig Liver Dis.* 2017 May;49(5):523-529.

Zelber-Sagi S, Shoham D, Zvibel I, Abu-Abeid S, **Shibolet O**, Fishman S. Predictors for advanced fibrosis in morbidly obese non-alcoholic fatty liver patients. *World J Hepatol*. 2017;9(2):91-98.

Zelber-Sagi S, Azar S, Nemirovski A, Webb M, Halpern Z, **Shibolet O**, Tam J. Serum levels of endocannabinoids are independently associated with nonalcoholic fatty liver disease. *Obesity* (Silver Spring). 2017;25(1):94-101.

Hubel E, Saroha A, Park WJ, Pewzner-Jung Y, Lavoie EG, Futerman AH, Bruck R, Fishman S, Dranoff JA, **Shibolet O**, Zvibel I. Sortilin Deficiency Reduces Ductular Reaction, Hepatocyte Apoptosis, and Liver Fibrosis in Cholestatic-Induced Liver Injury. *Am J Pathol*. 2017;187(1):122-133.

Gozlan Y, Ben-Ari Z, Moscona R, Shirazi R, Rakovsky A, Kabat A, Veizman E, Berdichevski T, Weiss P, Cohen-Ezra O, Lurie Y, Gafanovich I, Braun M, Cohen-Naftaly M, Shlomai A, **Shibolet O**, Zigmond E, Zuckerman E, Carmiel-Haggai M, Nimer A, Hazzan R, Maor Y, Kitay-Cohen Y, Shemer-Avni Y, Kra-Oz Z, Schreiber L, Peleg O, Sierra S, Harrigan PR, Mendelson E, Mor O. HCV genotype-1 subtypes and resistance-associated substitutions in drug-naive and in direct-acting antiviral treatment failure patients. *Antivir Ther*. 2017 Jan 9. doi: 10.3851/IMP3123. [Epub ahead of print]

Reviews

Rabinowich L, **Shibolet O**. Drug Induced Steatohepatitis: An Uncommon Culprit of a Common Disease. *Biomed Res Int.* 2015; Article ID 168905.

Mlynarsky L, Menachem Y, **Shibolet O**. Treatment of hepatocellular carcinoma: Steps forward but still a long way to go. World J Hepatol. 2015;7(3):566-74.

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Mononuclear Phagocytes in Digestive Tract Diseases

Positions

Senior Lecturer, Sackler Faculty of Medicine, Department of Clinical Microbiology and Immunology

Director, Research Center for Digestive Tract & Liver Diseases

Research

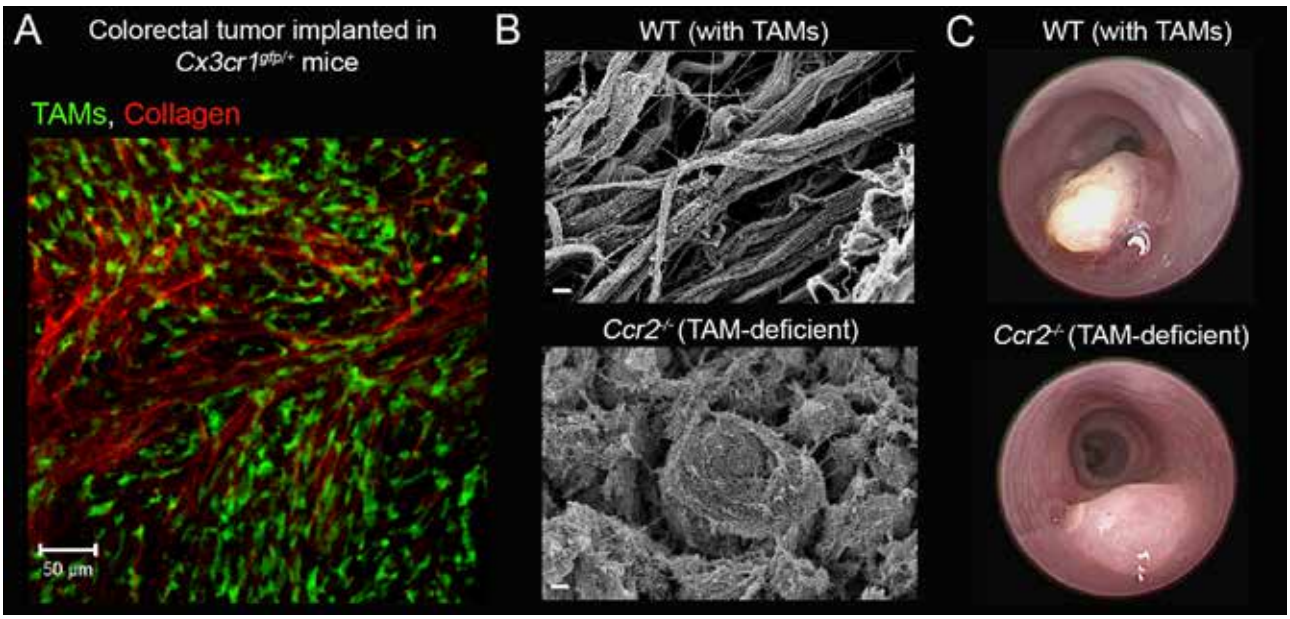
We are studying the role of mononuclear phagocytes in the pathogenesis of IBD, liver diseases, metabolic diseases and colorectal cancer. We utilize transgenic murine systems as well as human patient tissues to mechanistically unravel the involvement of these cells in the pathophysiology of these diseases. Among our main research topics:

- The interplay between immune cells and extracellular matrix (ECM) remodeling in the pathogenesis of IBD, colorectal cancer and liver fibrosis
- Monocytes and macrophage type of immune cells as pivotal drivers of inflammation and resolution during drug-induced liver injury, liver fibrosis and IBD
- The incretin hormone GIP as key linker between metabolism and immunity in type II diabetes

Publications

Chen Varol, Alexander Mildner and Steffen Jung. Macrophages: development and tissue specialization. 2015. *Annual Review in Immunology*. 33:643-75.

Itay Moshkovitz, Hadar reichman, Danielle Karo-Atar, Perri Rozenberg, Ehud Zigmond, Yael Ziv-Haberman, Netali Ben-Baruch-Morgenstern, Maria Lampinen, Marie Carlson, Michal Itan, Lee Denson, **Chen Varol** and Ariel Munitz. A key requirement for CD300f in



Tumor associated macrophages (TAMs) are pivotal constructors of the colorectal tumor collagenous matrix (Afik et al., JEM, 2016). (A) Confocal imaging showing the co-localization of TAMs (green) with collagen matrix (red). (B) Scanning electron microscopy (SEM) images of decellularized ECM scaffolds extracted from WT and TAM-deficient colorectal tumors. TAMs instruct collagen crosslinking and linearization processes, which are essential for tumor development, expansion and invasion. (C) Murine colonoscopy images showing the impaired colorectal tumor development in the absence of TAMs.

innate immune responses of eosinophils in colitis. 2017. *Mucosal Immunology.* 10:172-183.

Ran Afik*, Ehud Zigmond*, Milena Vugman, Mordehay Klepfish, Elee Shimshoni, Metsada Pasmanik Chor, Anjana Shenoy, Elad Bassat, Zamir Halpern, Tamar Geiger, Irit Sagi* and **Chen Varol***. Tumor macrophages are pivotal constructors of tumor collagenous matrix. 2016. *Journal of Experimental Medicine .* First co-authors equally contributed*

Fernanda Dana Mantelmacher, Sigal Fishman, Keren Cohen, Metsada Pasmanik Chor, Yuichiro Yamada, Isabel Zvibel, **Chen Varol**. Glucose-dependent insulinotropic polypeptide (GIP) receptor deficiency leads to impaired BM hematopoiesis. 2017. *Journal of Immunology*. 198: 000.

Helena Shifrin, Odelia Mouhadeb , Nathan Gluck, **Chen Varol**, Marta Weinstock. Cholinergic anti-inflammatory pathway does not contribute to prevention of ulcerative colitis by novel indoline carbamates. 2017. *The Journal of Neuroimmune Pharmacology. doi:10.1007/s11481-017-9735-8*

Shlomo Magdassi, Shoshi Bar-David, Yael Friedman-Levi, Ehud Zigmond, **Chen Varol**, Guy Lahat, Joseph Klausner, Sara Eyal, Eran Nizri. Intraoperative Localization of Rectal Tumors Using Liposomal Indocyanine Green. 2017. *Surg Innov*. 24:139-144

Grants

2016 – present Endogenous-like inhibitors for ADAM17 and ADAM8 –novel therapeutic agents for Inflammatory bowel diseases (IBD), Azrieli Foundation

2016 - 2019 Glucose-dependent insulinotropic polypeptide (GIP) improves adipose tissue inflammation and metabolism through direct regulation of adipose tissue macrophage function, Israel Science Foundation (ISF)

Dr. Isabel Zvibel, Ph.D.

Department of Internal Medicine; Sackler Faculty of Medicine; Research Center for Digestive Tract and Liver Diseases
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Investigating the Mechanisms of Liver Steatosis, Obesity and Cholestatic Injury

Positions

Principal investigator, Research Center for Digestive Tract and Liver Diseases

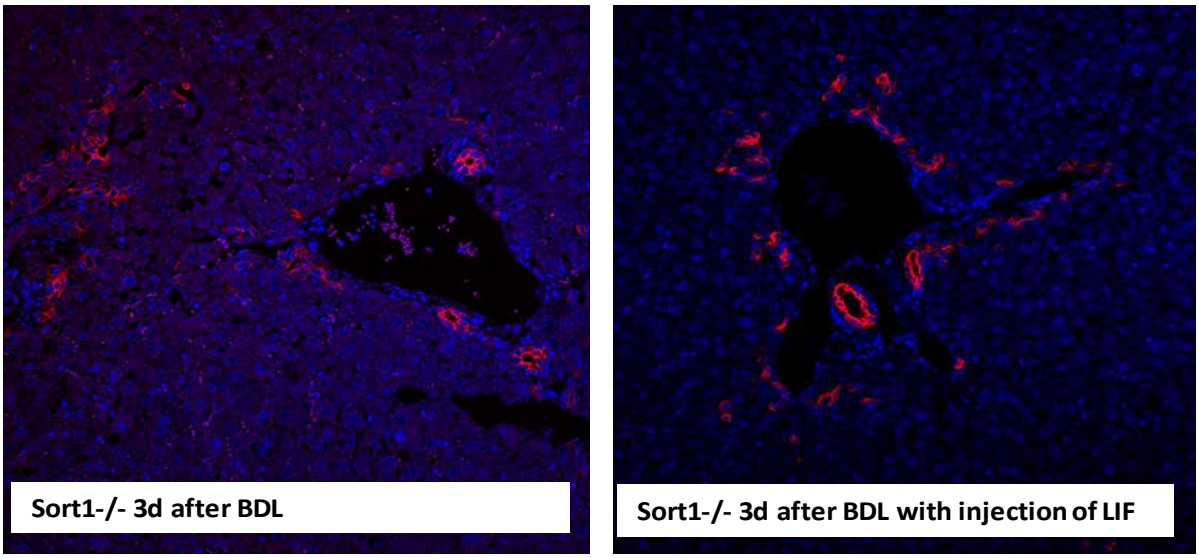
Tel Aviv Sourasky Medical Center

Senior Lecturer, Sackler Faculty of Medicine

Research

Our lab is investigating two main diseases, liver steatosis in models of diet-induced obesity and insulin resistance and cholestatic liver injury. Obesity and the metabolic syndrome accompanying it affect a large percentage of Western world population and the obesity epidemic is only expected to increase, therefore it's of the utmost importance to understand the mechanisms involved.

Cholestatic liver injury can be caused by various factors that impair bile flow and result in accumulation of bile in the liver, such as genetic defects, structural/mechanical obstruction of bile ducts impairing bile flow (e.g., common bile duct stones), toxins, and dysregulated function of the immune system. The two main cholestatic disorders in adult human patients are primary biliary cholangitis and primary sclerosing cholangitis for which liver transplantation is the only treatment as the disease progresses to liver failure. Specifically, we are investigating the roles played by sortilin, a trafficking molecule and a co-receptor, in both obesity and cholestatic liver damage, since we have found that sortilin deficiency has a protective role in diet-induced obesity and in murine models of primary sclerosing cholangitis. We are using both isolated liver cells (hepatocytes, cholangiocytes) as well as the cre-flox model where sortilin is deleted in various liver cells in order to further elucidate the mechanisms and signals regulating the protective roles of sortilin.



Staining for cytokeration 19 (red) shows formation of epithelial bile duct cells after cholestatic injury induced by bile duct ligation in *Sort1*$^{-/-}$ mice and inductionof proliferation of bile duct cells by administration of leukemia inhibitory factor (LIF).

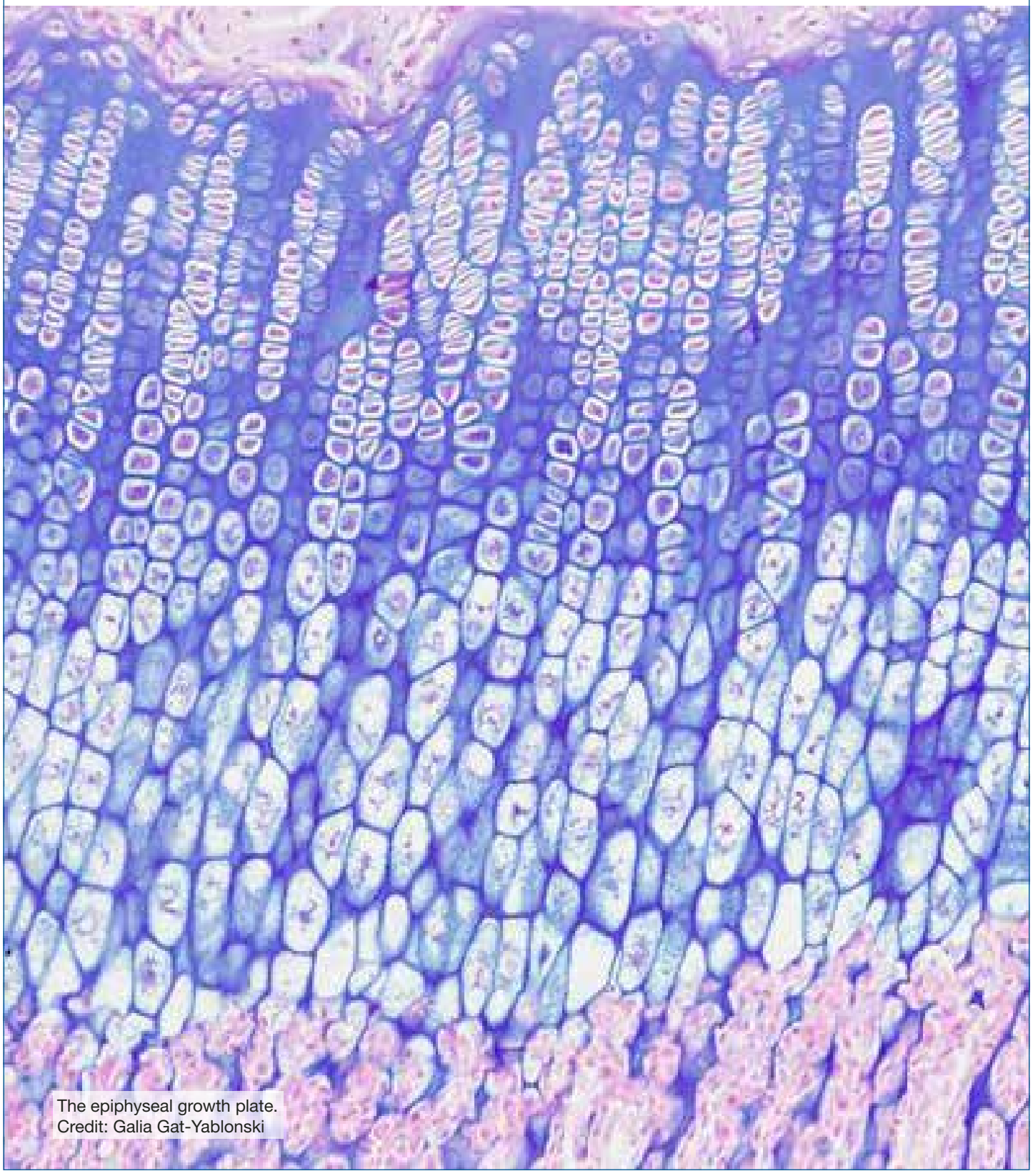
Publications

Rabinowich L*, Fishman S*, Hubel E, Thurm T, Park WJ, Pewzner-Jung Y, Futerman A, Halpern Z, **Zvibel I**.2015. Sortilin deficiency improves the metabolic phenotype and reduces hepatic steatosis in a murine model of diet-induced obesity. J Hepatol 62:175-81. *equal authors.

Hubel E, Saroha A, Park WJ, Pewzner-Jung Y, Lavoie EG, Futerman AH, Rafael Bruck, Sigal Fishman S, Dranoff JA, Shibolet O*, **Zvibel I***. 2016. Sortilin deficiency reduces ductular reaction, hepatocyte apoptosis and liver fibrosis in cholestatic-induced liver injury. Am.J. Pathol. 2017; 187:122-133. *equal senior authors.

Mantelmacher FD, Fishman S, Cohen K, Pasmanik Chor M, Yamada Y, **Zvibel I***, Varol C*. Glucose-Dependent Insulinotropic Polypeptide Receptor Deficiency Leads to Impaired Bone Marrow Hematopoiesis. *J Immunol*. 2017; 198:3089-3098. * equal senior authors.

Endocrine Disease



The epiphyseal growth plate.
Credit: Galia Gat-Yablonski

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Prof. Moshe Phillip, M.D.

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Investigating the Molecular Basis of Linear Growth in Children and Animal Models

Positions – Moshe Phillip, M.D.

Professor, Sackler Faculty of Medicine

Director, Institute for Endocrinology and Diabetes

National Center for Childhood Diabetes

Schneider Children's Medical Center of Israel

Vice Dean for Research and Development, Sackler Faculty of Medicine

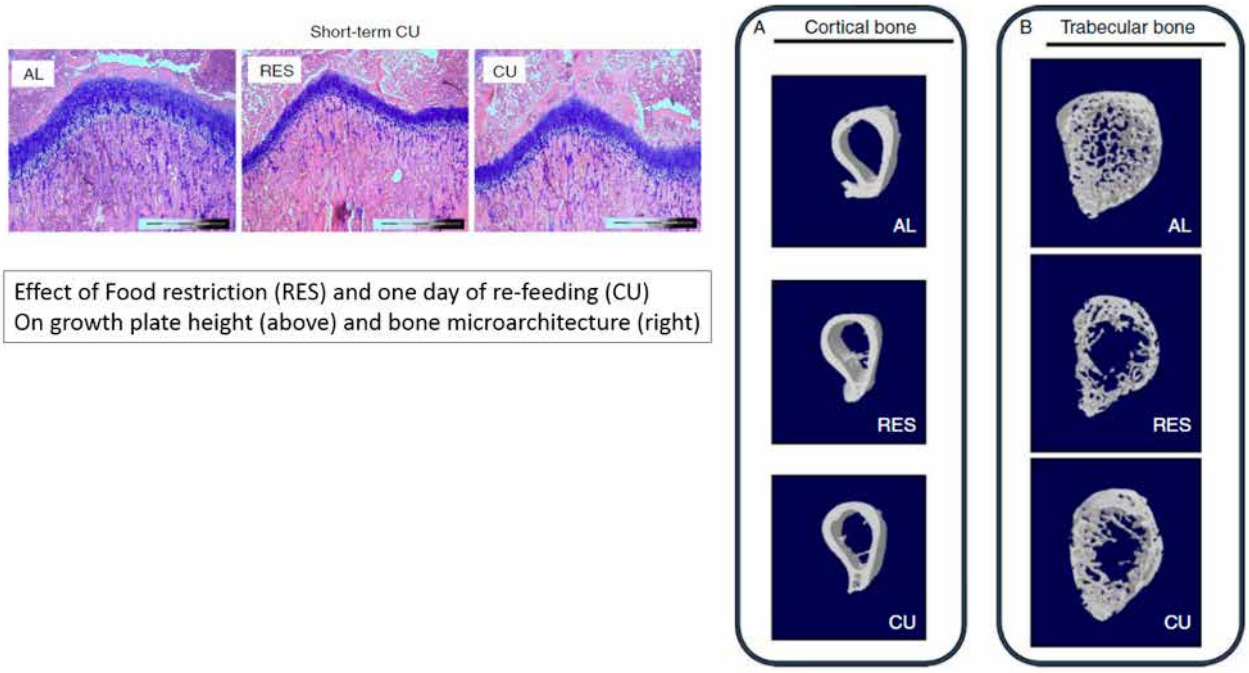
Positions – Galia Gat-Yablonski, Ph.D.

Senior Lecturer, Sackler Faculty of Medicine

Committee Member, Israel Endocrine Society

Research

Children's growth is regulated by both genetic and environmental factors. The most effective environmental factor is nutrition; however, the



Effect of Food restriction (RES) and one day of re-feeding (CU)
On growth plate height (above) and bone microarchitecture (right)

mechanisms connecting nutrition and longitudinal growth are still not fully understood. Deciphering theses mechanisms both in children and in animal models of rats and mice, has been the focus of our research, as currently means to improve growth in short statured children are very limited.

We have identified several novel and important factors that are involved in regulation of this process, including growth factors that are produced and secreted from adipocytes such as leptin and GDF5, transcription factors such as hypoxia inducible factor (HIF)-1, and epigenetic factors such microRNAs and histone deacetylases including SIRT1, HDAC10. We have also studies extensively the effect of nutritional manipulation on bone quality in young rats. We may now exploit these findings as targets of new treatment strategies for children with growth disorders as well as children with special nutritional needs like premature babies, infants and children with chronic diseases associated with nutritional problems.

Publications

Tal Ben-Ari, Yael Lebenthal, **Moshe Phillip**, Liora Lazar. Initiation of growth hormone therapy in idiopathic short stature: Do gender differences exist? Journal of Pediatric Endocrinology and Metabolism 2015;28(1-2):101-4

Shai Fuchs, **Galia Gat-Yablonski**, Biana Shtaif, Liora Lazar, **Moshe Phillip**, Yael Lebenthal. Vascular endothelial growth factor (VEGF) levels in short, GH treated children: A distinct pattern of VEGF-C in Noonan syndrome. J Endocrinol Invest. 2015;38:399-406.

G. Gat-Yablonski, **M. Phillip**. Nutritional Induced Catch-Up Growth. Nutrients 2015; 7:517-551

L Lazar, Y Lebenthal, M Yackobovitch-Gavan, S Shalitin, L de Vries, **M Phillip**, J Meyerovitch. Treated and untreated women with idiopathic precocious puberty: BMI evolution, metabolic outcome and general health between 3rd and 5th decades. J Clin Endocrinol Metab 2015; 100:1445-51.

Tadej Battelino and **Moshe Phillip**. Technologies in Diabetes–the Sixth ATTD Yearbook. Diabetes Technol Ther 2015; 17 Suppl1: S-2

Heneberg P, Malá M, Yorifuji T, **Gat-Yablonski G**, Lebenthal Y, Tajima T, Nogaroto V, Rypáčková B, Kocková L, Urbanová J, Anděl M. Low Frequencies of Autoimmunity-Associated PTPN22 Polymorphisms in MODY Patients, Including Those Transiently Expressing Islet Cell Autoantibodies. Int Arch Allergy Immunol. 2015;166:189-98.

Levy T, Bloch Y, Bar-Maisels M, **Gat-Yablonski G**, Djalovski A, Borodkin K, Apter A. Salivary oxytocin in adolescents with conduct problems and callous-unemotional traits. Eur Child Adolesc Psychiatry. 2015; 24: 1543-51

Liberman A, **Phillip M**, Buckingham B. Diabetes Technology and the Human Factor. Diabetes Technol Ther. 2015; 17 Suppl 1:S109-18

Tadej Battelino, Jasna Šuput Omladič, **Moshe Phillip**. Closed loop insulin delivery in diabetes. Best Practice & Research Clinical Endocrinology & Metabolism 2015; 29:315-325

Natasa Bratina, Shlomit Shalitin, **Moshe Phillip** and Tadej Battelino. Type 1 diabetes in the young: organization of two national centers in Israel and Slovenia. Zdrav Var 2015: 54: 139-

Onengut-Gumuscu S, Chen WM, Burren O, Cooper NJ, Quinlan AR, Mychaleckyj JC, Farber E, Bonnie JK, Szpak M, Schofield E, Achuthan P, Guo H, Fortune MD, Stevens H, Walker NM, Ward LD, Kundaje A, Kellis M, Daly MJ, Barrett JC, Cooper JD, Deloukas P; Type 1 Diabetes Genetics Consortium, Todd JA, Wallace C, Concannon P, Rich SS. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. Nature Genetics 47, 381–386 (2015)

Marianna Rachmiel, Pnina Strauss, Nitzan Dror, Hadassa Benzaquen, Orit Horesh, Nave Tova, Naomi Weintrob, Zohar Landau, Michal Ben-Ami, Alon Haim, **Moshe Phillip**, Tzvi Bistritzer, Eli C Lewis, Yael Lebenthal. Alpha1-Antitrypsin Therapy is Safe and Well Tolerated in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus. Pediatr Diabetes. 2016;17(5):351-9.

Biana Shtaif, Nitzan Dror, Meytal Bar-Maisels, **Moshe Phillip** & **Galia Gat-Yablonski**. Growth without Growth Hormone: Can growth and Differentiation Factor 5 be the mediator? Growth Factors 2015;33(4):309-18

Jeffrey Baron, Lars Sävendahl, Francesco De Luca, Andrew Dauber, **Moshe Phillip**, Jan M Wit, Ola Nilsson. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol. 2015; 11:735-46

Shalitin S, **Phillip M,** Krepel-Volsky S. Predictors of successful weight reduction and maintenance in obese children and adolescents**.** Acta Paediatr. 2016; 105:e42-6

Simranjeet Kaur, Aashiq H. Mirza, Caroline A. Brorsson, Tina Fløyel, Joachim Størling, Henrik B. Mortensen, Flemming Pociot, For the Hvidoere International Study Group. The genetic and regulatory

architecture of ERBB3-type 1 diabetes susceptibility locus. Mol Cell Endocrinol 2015.

Claudia Ziegler, Alon Liberman, Revital Nimri, Ido Muller, Simona Klemenčič, Nataša Bratina, Sarah Bläsig, Kerstin Remus**, Moshe Phillip**, Tadej Battelino, Olga Kordonouri, Thomas Danne, Karin Lange. Reduced Worries of Hypoglycaemia, High Satisfaction, and Increased Perceived Ease of Use after Experiencing Four Nights of MD-Logic Artificial Pancreas at Home (DREAM4). Journal of Diabetes Research. 2015 (2015), 590308.

Galit Pinto, Biana Shtaif, **Moshe Phillip, Galia Gat-Yablonski**. Growth attenuation is associated with histone deacetylase 10-induced authphagy in the liver. J Nutr Biochem. 2016;27:171-80.

Neu, A., Lange, K., Barrett, T., Cameron, F., Dorchy, H., Hoey, H., Jarosz-Chobot, P., Mortensen, H., Robert, J.-J., Robertson, K., de Beaufort, C. and on behalf of the Hvidoere Study Group (2015). Classifying insulin regimens – difficulties and proposal for comprehensive new definitions. Pediatric Diabetes (2015); 16: 402–406.

Nimri R, **Phillip M**. Toward Automation of Insulin Delivery - Management Solutions for Type 1 Diabetes. Endocr Dev. 2016; 30:1-13.

Liora Lazar, Yael Lebenthal, Karl Segal, Adam Steinmetz, Yulia Strenov, Maya Cohen, Isaac Yaniv, Michal Yackobovitch-Gavan, **Moshe Phillip**. Pediatric thyroid cancer: postoperative classifications and response-to-initial-therapy as prognostic factors. J Clin Endocrinol Metab. 2016;101(5):1970-9

Ahmed SF, **Phillip M**, Grimberg A. The Physiology and Mechanism of Growth. World Rev Nutr Diet. 2016;114:1-20.

Majdi Masarwi, Yankel Gabet, Oleg Dolkart, Tamar Brosh, Raanan Shamir, **Moshe Phillip, Galia Gat-Yablonski.** Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats. Br J Nutr. 2016; 116(1):59-69

Stacey M Anderson, Dan Raghinaru; Jordan E. Pinsker; Federico Boscari; Eric Renard; Bruce A. Buckingham; Revital Nimri; Francis J. Doyle III, Sue A. Brown; Patrick Keith-Hynes; Marc D Breton; Daniel Chernavvsky; Wendy C. Bevier, Paige K. Bradley; Daniela Bruttomesso, Simone Del Favero; Roberta Calore; Claudio Cobelli; Angelo Avogaro, Anne Farret; Jerome Place; Trang T. Ly; Satya Shanmugham; **Moshe Phillip**; Eyal Dassau; Isuru S. Dasanayake; Craig Kollman; John W. Lum; Roy W. Beck; Boris Kovatchev; for the Control to Range Study Group. Multinational Home Use of Closed-loop Control is Safe and Effective. Diabetes Care. 2016;39(7):1143-50.

Avital Adler, Michal-Yackobovitz Gavan, Riva Tauman, **Moshe Phillip**, Shlomit Shalitin. Do children, adolescents, and young adults with type 1 diabetes have increased prevalence of sleep disorders? Pediatr Diabetes. 2016 Aug 3. [Epub ahead of print]

Michal Yackobovitch-Gavan, Yael Lebenthal, Liora Lazar, Shlomit Shalitin, Sharon Demol, Ariel Tenenbaum, Raanan Shamir, **Moshe Phillip**. Effect of nutritional supplementation on growth in short and lean prepubertal children after one year of intervention. J Pediatr. 2016 Sep 30. pii: S0022-3476(16)30883-6.

Bello R, Lebenthal Y, Lazar L, Shalitin S, Tenenbaum A, **Phillip M**, de Vries L. Basal 17-hydroxyprogesterone cannot accurately predict non-classical congenital adrenal hyperplasia in children and adolescents**.** Acta Paediatr. 2016 [Epub ahead of print]

Shir Hadani, Yael Lebenthal, Liora Lazar, Raanan Shamir, **Moshe Phillip**. Lean healthy children with short stature have distinct eating patterns. Journal of Food Science and Engineering 6 (2016) 299-307.

Gat-Yablonski G, Finka A, Pinto G, Quadroni M, Shtaif B, Goloubinoff P. Quantitative proteomics of rat livers shows that unrestricted feeding is stressful for proteostasis with implications on life span. Aging (Albany NY). 2016;8(8):1735-58.

D.M. Maahs, B.A. Buckingham, J.R. Castle, A. Cinar, E.R. Damiano, E. Dassau, J.H. DeVries, F.J. Doyle III, S.C. Griffen, A. Haidar, L. Heinemann, R. Hovorka, T.W. Jones, C. Kollman, B. Kovatchev, B.L. Levy, R. Nimri, D. O'Neal, **M. Phillip,** E. Renard, S.J. Russell, S. A. Weinzimer, H. Zisser, J.W. Lum. Outcome Measures for Artificial Pancreas Clinical Trials: A Consensus Statement. Diabetes Care, accepted.

Avivit Brener, Eran Mel, Shlomit Shalitin, Liora Lazar, Liat de Vries, Ariel Tenenbaum, Tal Oron, **Moshe Phillip**, Yael Lebenthal. The effect of national service on metabolic control, weight status and incidence of acute diabetes complications in young adults with type 1 diabetes. IMAJ, accepted.

Dr. Yehuda Kamari, M.D, Ph.D.

Vascular Biology Research Unit; Bert W. Strassburger Lipid Center; Talpiot Sheba Medical Leadership Program; Sheba Medical Center, Tel Hashomer.

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Investigating Lipid Metabolism and Atherosclerosis

Positions

Senior Lecturer, Medicine, Sackler School of Medicine

Research

Our research interests are within the fields of metabolic inflammation that contributes to the derangements of fat accumulation in atherosclerosis, fatty liver disease and diabetes. Specifically, we study the role of the inflammatory cytokine IL-1α and the ubiquitin-like protein HLA-F Adjacent Transcript 10 (FAT10) in these diseases. We recently discovered that the inflammatory cytokine IL-1α has an important role in early and advanced stages of atherosclerosis and fatty liver disease. We also discovered an unexpected role of IL-1α in determining ovarian lifespan and fertility.

We apply advanced technologies including genetically modified mice (Cre/loxP), molecular and cellular biology and microarray analysis to identify and functionally characterize genes that regulate atherosclerosis with the ultimate aim to prevent and treat this deadly disease.

Publications

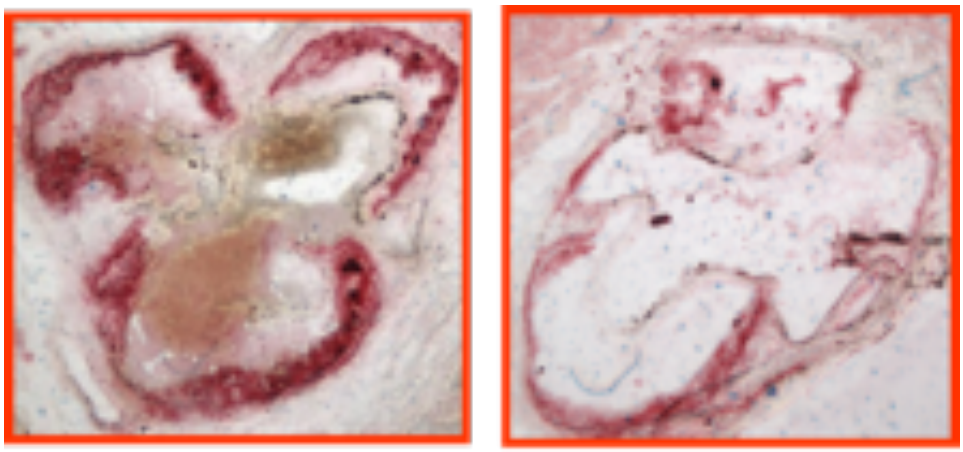
Zolberg Relevy N, Bechor S, Harari A, Ben-Amotz A, **Kamari Y**, Harats D and Shaish A. The Inhibition of Macrophage Foam Cell Formation by 9-cis β-beta-carotene is driven by BCMO1 Activity. PLoS One. 2015;10(1):e0115272.

Zolberg Relevy N, Rühl R, Harari A, Grosskopf I, Barshack I, Ben-Amotz A, Nir U, Gottlieb H, **Kamari Y**, Harats D and Shaish A. 9-cis -carotene Inhibits Atherosclerosis Development in Female LDLR-/- Mice. Functional Foods in Health and Disease. 2015;5(2): 67-79.

Almog T, Kandel-Kfir M, Shaish A, Dissen M, Shlomai G, Voronov E, Apte RN, D Harats, **Kamari Y.** Knockdown of interleukin-1alpha does not attenuate LPS-induced production of interleukin-1beta in mouse macrophages. Cytokine. 2015;73(1):138-43.

Kandel-Kfir M, Almog T, Shaish A, Shlomai G, Anafi L, Avivi C, Barshack I, Grosskopf I, Harats D, **Kamari Y**. Interleukin-1α deficiency attenuates endoplasmic reticulum stress-induced liver damage and CHOP expression in mice. J Hepatol. 2015;63(4):926-33.

Kamari Y, Fingrut O, Shaish A, Almog T, Kandel-Kfir M, Harats D, Rubinek T, Wolf I. The effect of klotho



IL-1α+/+ IL-1α-/-

Bone marrow-derived IL-1α deficiency reduces atherosclerosis.

treatment on atherogenesis, blood pressure and metabolic parameters in experimental rodent models. Hormone and Metabolic Research, 2016;48(3):196-200.

Grosskopf I, Shaish A, Charach G, Harats D, **Kamari Y.** Nifedipine Treatment for Hypertension Is Associated with Enhanced Lipolytic Activity and Accelerated Clearance of Post-prandial Lipemia. Hormone and Metabolic Research, 2016;48(4):257-62.

Bechor S, Zolberg Relevy N, Harari A, Almog T, **Kamari Y**, Ben-Amotz A, Harats D, Shaish A. 9-cis β-Carotene Increased Cholesterol Efflux to HDL in Macrophages. Nutrients. 2016;8(7).

Uri-Belapolsky S, Miller I, Shaish A, Levi M, Harats D, Ninio-Many L, **Kamari Y***, Shalgi R*. Interleukin 1-alpha deficiency increases the expression of follicle-stimulating hormone receptors in granulosa cells. Mol Reprod Dev. 2017;84(6):460-467. * Equal contribution

Gueta I, Loebstein R, Markovits N, **Kamari Y**, Halkin H, Livni G, Yarden-Bilavsky H. Voriconazole-induced QT prolongation among hemato-oncologic patients: clinical characteristics and risk factors. Eur J Clin Pharmacol. 2017;73(9):1181-1185.

Sultan M, Ben-Ari Z, Masoud R, Pappo O, Harats D, **Kamari Y***, Safran M*. Interleukin-1α and Interleukin-1β play a central role in the pathogenesis of fulminant hepatic failure in mice. PLoS One. 2017;12(9):e0184084. * Equal contribution.

Almog T, Kandel Kfir M, Levkovich H, Shlomai G, Barshack I, Stienstra R, Lustig Y, Leikin Frenkel A, Harari A, Bujanover Y, Apte R, Shaish A, Harats D, **Kamari Y**. Interleukin-1α deficiency reduces adiposity, glucose intolerance and hepatic de-novo lipogenesis in diet-induced obese mice. BMJ Open Diabetes Res Care. 2019;7(1):e000650.

Kandel-Kfir M, Garcia-Milan R, Gueta I, Lubitz I, Ben-Zvi I, Shaish A, Shir L, Harats D, Mahajan M, Canaan A, **Kamari Y**. IFNγ potentiates TNFα/TNFR1 signaling to induce FAT10 expression in macrophages. Mol Immunol. 2020;117:101-109.

A. Harari, A. Leikin Frenkel, A. Sagee, H. Cohen, **Kamari Y**, Kandel Kfir M., D. Harats, A. Shaish. Addition of fish oil to atherogenic high fat diet inhibited atherogenesis while olive oil did not, in ldl receptor KO mice. Nutr, Metab Cardiovasc Dis. 2020;30(4):709-716.

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Investigating the Impact of Maternal Fatty Acids Quality on the Fetal Gene Programming and Fingerprint of Health or Obesity Associated Disease

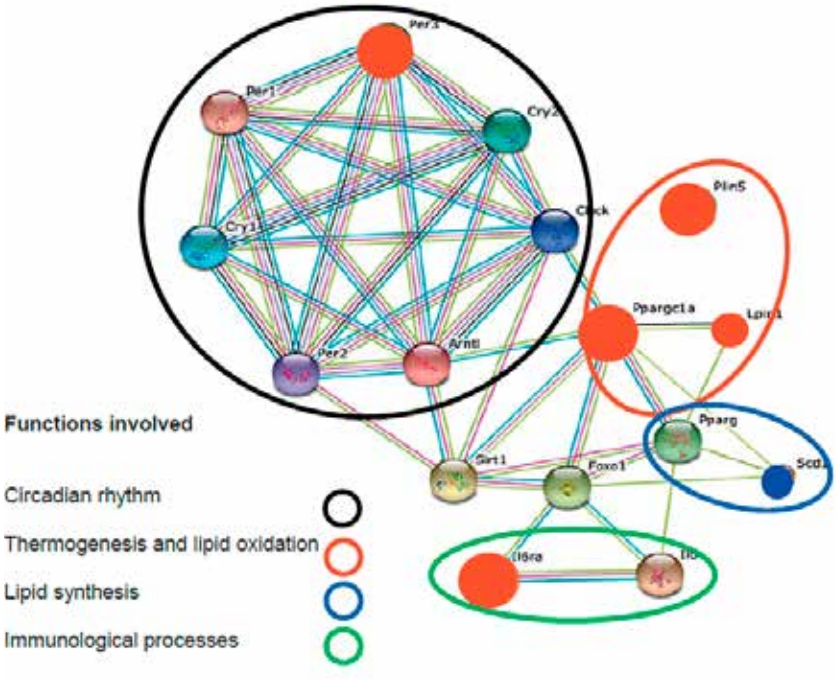
Positions

Associate Professor, CAMEA, Sackler Faculty of Medicine

Researcher at the Bert Strassburger Lipid Center, Sheba, Tel Hashomer

Research

We study the effect of maternal dietary fatty acids quality during pregnancy and lactation on the gene networks that are involved in lipogenesis and thermogenesis in the offspring. Obesity-associated chronic metabolic diseases such as Cardiovascular, Type 2 diabetes and Non-Alcoholic Steatohepatosis are purported to have an early in utero origin. The nutrigenetic impact of fatty acids quality in normcaloric diets and healthy mothers during development is almost unknown. We are exploring this question by studying the metabolic and genetic evolution of the offspring from birth to adult age in our animal nutritional model and in humans. We apply the latest methodologies including biochemistry, lipidomics, molecular biology, and microarray analysis to identify and functionally characterize genes that regulate the lipogenic and thermogenic processes that determine the energetic balance leading to obesity or its absence. Understanding the normal or obesity prone gene programming during development and characterizing the associated fingerprint in the offspring at birth is essential for the early diagnosis and design of treatments to prevent long-term metabolic obesity-associated disorders that are leading causes of disease in almost 40% of wold population and death.



Protein interaction between products of genes upregulated (red full) or down-regulated (blue full) by ω3 essential fatty acid (ALA) or saturated fatty acids (SFA). Enriched functions are marked using open colored circles.

Publications

Yehuda I, Madar A, **Leikin-Frenkel A**, Tamir S. 2015. Glabridin, an isoflavan from licorice root, down-regulates iNOS expression and activity under high glucose stress and inflammation. Molecular Nutrition & Food Research 59: 1041-1052.

L Shomonov Wagner, A Raz, **A Leikin-Frenkel**. 2015. Alpha linolenic acid in maternal diet halts the lipid disarray due to saturated fatty acids in the liver of mice offspring at weaning Lipids Health Dis. 26:14-14.

ML Kagan, AR Levy, **A Leikin-Frenkel**. 2015. Comparative study of tissue deposition of omega-3 fatty acids from polar-lipid rich oil of the microalgae *Nannochloropsis oculata* with krill oil in rats. Food Funct. 6:186-92.

Yehuda I, Madar Z, **Leikin-Frenkel A**, Szuchman-Sapir A, Magzal F, Markman G, Tamir S 2015. Glabridin, an isoflavan from licorice root, up-regulates paraoxonase 2 expression under hyperglycemia and protects it from oxidation. Molecular Nutrition & Food Research 10: 287-299.

Leikin-Frenkel A, Shomonov-Wagner L, Juknat A, Pasmanik-Chore M. 2015. Maternal Diet Enriched with Alpha Linolenic or Saturated Fatty Acids Differentially Regulates Gene Expression in Mice Offspring's liver. J Nutrigenet Nutrigenomics; 8:185-194.

Review

Leikin-Frenkel A. 2016. Is there A Role for Alpha-Linolenic Acid in the Fetal Programming of Health? Journal of Clinical Medicine 5:40.

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Reproductive Endocrinology and Infertility – From Basic Science to Clinical Application

Positions

Professor, Obstetrics and Gynecology, Sackler Faculty of Medicine.

Incumbent, Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Sackler Faculty of Medicine

Director, Division of Reproductive Endocrinology and Infertility, Sheba Medical Center

Co-Editor-in-Chief, Reproductive Biology and Endocrinology

Research

Our research includes:

- Various aspects of controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).
- The role of GnRH-analogues, and specifically GnRH agonist versus antagonist in COH for IVF.
- The different modes of triggering final follicular maturation.
- Endometrial preparation for frozen-thawed embryo transfer.
- Obesity and IVF outcome.
- Fragile X Associated Premature Ovarian Insufficiency (FXPOI) in FMR1 premutation carriers.
- Pre-implantation genetic screening (PGS) and diagnosis (PGD).
- Several aspects of ovarian hyperstimulation syndrome (OHSS): pathophysiology, prediction, prevention and its relation to the inflammatory response.

Publications

Manuscripts

Haas J, Zilberberg E, Machtinger R, Kedem A, Hourvitz A, **Orvieto R**. Do poor-responder patients benefit from increasing the daily gonadotropin dose during controlled ovarian hyperstimulation for IVF? Gyn Endocrinol 2015; 31(1): 79–82

Zilberberg E, Haas J, Dar S, Kedem A, Machtinger R, **Orvieto R**. Co-administration of GnRH-agonist and hCG for final oocyte maturation in patients with low proportion of mature oocytes.Gyn Endocrinol 2015;31(2):145-7.

Haas J, Mohr Sasson A, Barzilay E, Mazaki Tovi S, **Orvieto R**, Weizs B, Lipitz S, Yinon Y. Perinatal outcome following fetal reduction from twin-to-singleton, to reduce or not to reduce? Fertil Steril 2015;103:428–32

Haas J, Zilberberg E, Kedem A, Yerushalmi G, Dar S, Orvieto R. Do poor-responder patients benefit from increasing the daily gonadotropin dose from 300 to 450 IU during controlled ovarian hyperstimulation for IVF? Harefuah 2015;154(2):118-121

Governini L, Guerranti C, De Leo V, Boschi L, Luddi A, Gori M, **Orvieto R**, PiomboniP. Chromosomal aneuploidies and DNA fragmentation of human spermatozoa from patients exposed to perfluorinated compounds. Andrologia 2015;47(9):1012-9

Hourvitz A, Yerushalmi GM, Maman E, Raanani H, Elizur S, Brengauz M, **Orvieto R,** Dor J, Meirow D. Combination of ovarian tissue harvesting and immature oocyte collection for fertility preservation increases preservation yield Reprod Biomed Online 2015;31(4):497-505

Orvieto R, Dratviman-Storobinsky O, Cohen Y. Interleukin-2 production by cultured human granulosa cells. Am J Reprod Immunol 2015;74(5):392-7.

Haas J, Lantsberg D, Feldman N, Manela D, Machtinger R, Dar S, Rabinovici J, **Orvieto R**. Modifying the Luteal Phase Support in Natural Cycle Frozen-Thawed Embryo Transfer Improves Cycle Outcome. Gynecol Endocrinol 2015;31(11):891-3.

Elizur SE, Dratviman-Storobinsky O, Derech-Haim S, Leibovitz O, Dor J, **Orvieto R**, Cohen Y. FMR6 (a long non coding RNA) may play a role in the pathogenesis of fragile X associated premature ovarian insufficiency (FXPOI). Gynecol Endocrinol 2016;32(4):334-7.

Orvieto R, Shuly Y, Brengauz M, Feldman B. Should preimplantation genetic screening be implemented to routine clinical practice? Gynecol Endocrinol 2016;32(6):506-8.

Mansur A, Adir M, Yerushalmi G, Hourvitz A, Gitman H, Yung Y, **Orvieto R**, Machtinger R. Does BPA Alter Steroid Hormone Synthesis in Human Granulosa Cells In Vitro? Hum Reprod 2016;31:1562–1569

Haas J, Ophir L, Barzilay E, Machtinger R, Yung Y, **Orvieto R**, Hourvitz A. Standard hCG vs. double trigger for final follicular maturation results in different granulosa cells gene expressions Fertil Steril 2016;106(3):653-659

Cohen SB, Bouaziz J, Schiff E, Simon A, Nadgary M, Goldenberg M, **Orvieto R**, Revel A. In vitro fertilization outcomes following placement of Essure® micro-inserts in patients with hydrosalpinges who previously failed IVF treatment – a multicenter study J Minim Invasive Gynecol. 2016;23(6):939-43

Orvieto R, Feldman N, Lantsberg D, Manela D, Zilberberg E, Haas J. Natural cycle frozen-thawed embryo transfer-can we improve cycle outcome?J Assist Reprod Genet 2016;33(5):611-5.

Cohen SB, Bouaziz J, Jakobson-Setton A, Goldenberg M, Schiff E, **Orvieto R**, Shulman A. Hysteroscopically guided transvaginal ultrasound tubal catheterization - a novel office procedure. Eur J Obstet Gynecol Reprod Biol. 2016;204:113-116.

Orvieto R. Preimplantation genetic screening- the required RCT that has not yet been carried out. Reprod Biol & Endocrinol 2016;14:35

Lerner-Geva L, Boyko V Ehrlich S, Hourvitz A Haas J, Margalioth E, Levran D, Calderon I, **Orvieto R**, Ellenbogen A, Meyerovitch J Ron-El R, Farhi A. The possible risk for cancer among children born following assisted reproductive technology (ART) in Israel. Pediatric Blood & Cancer 2016;64:4

Adir M, Combelles CM, Mansur A, Ophir L, Hourvitz A, **Orvieto R**, Dor J, Machtinger R. Dibutyl phthalate impairs steroidogenesis and a subset of LH-dependent genes in cultured human mural granulosa cell in vitro. Reprod Toxicol 2017;69:13-18

Machtinger R, Duvdevani NR, Lebovitz O, Dor J, Hourvitz A, **Orvieto R**. Outcome of Gestational Surrogacy According to IVF Protocol. J Assist Reprod Genet 2017;34:445-449.

Abir R, Fisch B, Fisher N, Samara N, Lerer-Serfaty G, Ben-Haroush A, Stein A, **Orvieto R**. Attempts to improve human ovarian transplantation outcomes of needle immersed vitrification and slow-freezing by host and graft treatments. J Assist Reprod Genet 2017;34:663-644.

Lerner-Geva L, Boyko V Ehrlich S, Hourvitz A Haas J, Margalioth E, Levran D, Calderon I, **Orvieto R**, Ellenbogen A, Meyerovitch J Ron-El R, Farhi A. The possible risk for cancer among children born following assisted reproductive technology (ART) in Israel. Pediatric Blood & Cancer 2017;64(4).

Feldman B, Aizer A, Brengauz M, Dotan K, Levron J, Schiff E, **Orvieto R**. Preimplantation genetic diagnosis- Should we use ICSI for all? J Assist Reprod Genet 2017;34:1179–1183.

Cohen SB, Maschiah R, Bar On A, Goldenberg M, Schiff E, **Orvieto R**, Bouaziz J. Feasibility and Efficacy of Repeated Hysteroscopic Cesarean Niche Resection. Eur J Obstet Gynecol & Reprod Biol 2017;217:12–17

Vanni VS, Zilberberg E, Manela D, **Orvieto R**. Should corifollitropin alfa be offered to patients with "genuine" poor response to controlled ovarian hyperstimulation? Clin Exp Obstet Gynecol 2018;XLV(5):752-5.

Dar S, **Orvieto R**, Levron J, Haas J, Gat I, Raviv G. IVF outcome in azoospermic cancer survivors. Eur J Obstet Gynecol & Reprod Biol 2018;220:84-87.

Baum M, **Orvieto R**, Kon S. Machtinger R, Yerushalmi GM, Hourvitz A. Comparison of effects of thawing entire donor sperm vial vs. partial thawing (shaving) on on sperm quality. J Assist Reprod Genet 2018;35(4):645-648.

Kedem A Yerushalmi G, Brengauz M, Raanani H, **Orvieto R**, Hourvitz A, Meirow D. Outcome of immature oocytes collection of 119 cancer patients during ovarian tissue harvesting for fertility preservation. J Assist Reprod Genet 2018;35(5):851-856.

Bassil R, Casper R, Samara N, Hsieh TB, Barzilay E, **Orvieto** R, Haas J. Does the endometrial receptivity array really provide personalized embryo transfer? J Assist Reprod Genet 2018;35(7):1301-1305.

Kirshenbaum M, Ben-David A, Zilberberg E, Elkan Miller T, Haas J, **Orvieto R**. Influence of seasonal variation on in vitro fertilization success. PLoS ONE 2018; 13(7): e0199210.

Marom Haham L, Avrahami I, Domniz N, Ries-Levavi L, Berkenstadt M, **Orvieto R**, Cohen Y, Elizur SE. Preimplantation genetic diagnosis Versus Prenatal diagnosis - Reproductive decision making among FMR1 Premutation carriers wishing to conceive. J Assist Reprod Genet 2018.

Farhi A, Frankenthal D, Hirsh-Yechezkel G, Boyko V, **Orvieto R**, Ron-El R, Lerner-Geva L. The effect of body mass index (BMI) and gestational weight gain on adverse obstetrical outcomes in pregnancies following assisted reproductive technology as compared to spontaneously conceived pregnancies. Obesity Research & Clinical Practice 2018.

Samara N, Casper RF, Bassil R, Shere M, Barzilay E, **Orvieto R**, Haas J. Sub-endometrial contractility or computer-enhanced 3-D modeling scoring of the endometrium before embryo transfer: are they better than measuring endometrial thickness? J Assist Reprod Genet 2018.

Lantsberg D, Farhi A, Zaslavsky-Paltiel I, Silverman BG, Lerner-Geva L, **Orvieto R**. Deliveries following fertility preservation by ovarian tissue cryopreservation without autotransplantation – what should be expected? J Assist Reprod Genet 2018.

Friedman-Gohas M, Elizur SE, Dratviman-Storobinsky O, Aizer E, Haas J, Raanani H, **Orvieto R**, Cohen Y. FMRpolyG accumulates in FMR1 premutation granulosa cells. J Ov Res 2020;13(1):22.

Mohr Sasson A, **Orvieto R**, Blumenfeld S, Axelrod M, Mor-Hadar D, Grin L, Aizer A, Haas J. The association between follicle size and oocyte development as a function of final follicular maturation triggering. Reprod Biomed Online 2020;40:887-893.

Orvieto R, Kirshenbaum M, Galiano V, Elkan-Miller E, Zilberberg E, Haas J, Nahum N. Stop GnRH-agonist combined with multiple-dose GnRH-antagonist protocol for patients with "genuine" poor response undergoing controlled ovarian hyperstimulation for IVF. Front Endocrinol 2020; 11:182.

Shats M, Fenchel D, Katz G, Haas J, Machtinger R, Gat I, **Orvieto R**, Kedem A. Obstetric, neonatal and developmental delay outcomes following assisted hatching treatment: a retrospective cohort study. Gynecol Endocrinol 2020.

Haas J, Bassil R, Samara N, Zilberberg E, Mehta C, **Orvieto R**, Casper RF. Dual vs. hCG trigger for final follicular maturation. A prospective, double-blinded, randomized controlled study. Hum Reprod 2020.

Orvieto R, Mohr Sasson A, Aizer A, Nahum R, Blumenfeld S, Kirshenbaum M, Haas J. Do follicles of obese patients yield competent oocytes/ embryos? Gyn Obstet Invest Gynecol Obstet Invest 2020;85:290–293

Aizer A, Dratviman-Storobinsky O, Noach-Hirsh M, Konopnicki S, Raviv G, **Orvieto R**. Sperm retrieved by electro-ejaculation: Should we prefer fresh or cryopreserved sperm for ICSI? Andrologia 2020;00:e13671.

Alviggi C, Esteves S, **Orvieto R**, Conforti A, La Marca A, Fischer R; Andersen CY, Bühler K, Sunkara SK, Polyzos NP, Strina I, Carbone L, Bento FC, Galliano D, Yarali H, Vuong LN, Grynberg M, Drakopoulos P, Xavier P, Llacer J, Neuspiller F, Horton M, Roque M, Papanikolaou E, Banker M, Dahan MH, Foong S, Tournaye H, Blockeel C, Vaiarelli A, Humaidan P, Ubaldi FM. COVID-19 and Assisted Reproductive Technology Services: repercussions for patients and proposal for individualized clinical management. Reprod Biol & Endocrinol 2020;18(1):45.

Morgante G, Centini G, Troìa ML, **Orvieto R**, De Leo V. Ulipristal acetate before in vitro fertilization: efficacy in infertile women with submucous fibroids. Reprod Biol & Endocrinol 2020;18:50.

The International Do No Harm Group in IVF (IDNHG-IVF). Members of the IDNHG-IVF Gleicher N, Albertini DF, Barad DH, Homer H, Modi D, Murtinger M, Patrizio P, **Orvieto R**, Takahashi S, Weghofer A, Ziebe S, Noyes N. The 2019 PGDIS position statement on transfer of mosaic embryos within a context of new information on PGT-A. Reprod Biol & Endocrinol 2020;18:57

Orvieto R, Kirshenbaum M, Galiano V, Zilberberg E, Haas J, Nahum N. Stop GnRH-agonist combined with multiple-dose GnRH-antagonist for patients with elevated peak serum progesterone levels undergoing ovarian stimulation for IVF- a proof of concept. Gyn Obstet Invest 2020.

Shapira M, **Orvieto R**, Lebovitz O, Nahum R, Aizer A, Shegev-Zahav A, Haas J. Does daily co administration of gonadotropins and letrozole during the ovarian stimulation improve IVF outcome for poor and sub optimal responders? J Ovarian Res 2020;13:66.

Gat I, Barzilay E, Zemet R, Mohr-Sasson A, Kedem A, **Orvieto R**, Haas J. Do fertility treatments effect affect labor induction success rate? A retrospective cohort study. J Matern Fetal Neonatal Med 2020.

Aizer A, Noach-Hirsh M, Dratviman-Storobinsky O, Haas J, **Orvieto R**. Does the number of embryos loaded on a single cryo- carrier affect post-vitrification survival rate? Zygote 2020.

Meyer R, **Orvieto R**, Israel A, Sasson AM, Timerman Y, Gorodesky T, Toussia-Cohen S, Hendler I, Simchen

MJ, Machtinger R. Outcomes of singleton versus twin pregnancies in the fifth and sixth decades. Eur J Obstet Gynecol Reprod Biol. 2018;231:255-261

Cohen SB, Shapira M, Baron A, Bouaziz J, mashiach R, Goldenberg M, **Orvieto R**. Ultrasonography-guided hysteroscopic tubal catheterization of proximally occluded tubes- reproductive outcomes. Clin Exp Obstet Gynecol 2019;XLVI(6):872-5

Mohr-Sasson A, Spira M, Rahav R, Manela D, Schiff E, Mazaki-Tovi S, **Orvieto R**, Sivan E. Ovarian reserve after uterine artery embolization in women with morbidly adherent placenta: A cohort study. PLoS One. 2018;13(11):e0208139.

Lebovitz O, Haas J, James KE, Seidman DS, **Orvieto R**, Hourvitz A. The expected cumulative incidence of live birth of patients starting IVF treatment stage 41 years or older. Reprod Biomed Online 2018;37(5):533-541.

Kirshenbaum M, Feldman B, Aizer A, Haas J, **Orvieto R**. Preimplantation embryos sex ratios in couples with four or more children of same sex, what should be expected from a preimplantation genetic diagnosis cycle? Gynecol Endocrinol 2019:35(6):515–517

Farhi J, Elizur S, Yonish M, Seidman DS, Shulman A, Schiff E, **Orvieto R**. Assessment of a double freezing approach in the management of surplus embryos in IVF. Reprod Biomed Online 2019;38(4):517-519

Cohen SB, Schonmann R, Boaziz J, Seidman DS, **Orvieto R**, Mashiach R. Inhibin B level changes during the follicular phase in rats with unilateral ovarian torsion. Clin Exp Obstet Gynecol 2019; XLVI(5):797-9.

Haas J, Zilberberg E, Nahum R, Mor Sason A, Hourvitz A, Gat I, **Orvieto R**. Does double trigger (GnRH-agonist + hCG) improve outcome in poor responders undergoing IVF-ET cycle? A pilot study Gynecol Endocrinol. 2019 Jul;35(7):628-630

Farhi J, Cohen K, Mizrachi Y, Weissman A, Raziel A, **Orvieto R**. Should ICSI be implemented during IVF to all advanced-age patients with non-male factor subfertility? Reprod Biol & Endocrinol 2019;17:30

Ezra O, Haas J, Nahum R, Maman E, Cohen Y, Segev-Zahav A, **Orvieto R**. Do poor-responder patients undergoing IVF benefit from splitting and increasing the daily gonadotropin dose? Gynecol Endocrinol 2019;35(10):890–893

Lebovitz O, **Orvieto R**, James KE, Styer AK, Brown DN. Predictors of reproductive outcomes following myomectomy for intramural fibroids. Reprod Biomed Online 2019;39:484-91

Batsry L, **Orvieto R**, Mor-Hadar D, Yung Y, Gitman H, Shimon C, Zilberberg E, Haas J. Can we predict oocyte maturation prior to denudation for intracytoplasmic sperm injection? Gynecol Endocrinol 2020;36(3):265-267.

Friedman-Gohas M, Kirshenbaum M, Michaeli A, Domniz N, Elizur S, Raanani H, **Orvieto R**, Cohen Y. Does the presence of AGG interruptions within the CGG repeats tract have a protective effect on the fertility phenotype of female FMR1 premutation carriers? J Assist Reprod Genet 2020;37(4):849-854

Meyer R, **Orvieto R**, Timerman Y, Gorodesky T, Toussia-Cohen S, Kedem A, Simchen MJ, Machtinger R.Impact of the mode of conception on gestational hypertensive disorders at very advanced maternal age. Reprod Biomed Online 2020;40(2):281-6.

Cohen SB, Bouaziz J, Bar On A, **Orvieto R**. Fertility success rates in patients with secondary infertility and symptomatic cesarean scar niche undergoing hysteroscopic niche resection. Gynecol Endocrinol 2020

Reviews

Elizur SE, **Orvieto R**, Cohen Y. Are we Close to Solve the Mystery of Fragile X Associated Premature Ovarian Insufficiency (FXPOI) in FMR1 Premutation Carriers? Austin J In Vitro Fertili 2015;2(1): 1012.

Orvieto R. Triggering final follicular maturation-hCG, GnRH-agonist or both, when and to whom? J Ovarian Res 2015;8:60.

Orvieto R. A simplified universal approach to COH protocol for IVF: Ultrashort flare GnRH-agonist/ GnRH-antagonist protocol with tailored mode and timing of final follicular maturation. J Ovarian Res 2015;8:69.

Orvieto R, Seifer DB Biosimilar FSH preparations-are they identical twins or just siblings? Reprod Biol & Endocrinol 2016;14:32

Orvieto R, Gleicher N Should preimplantation genetic screening (PGS) be implemented to routine IVF practice? J Assist Reprod Genet. 2016

Palomba S, Homburg R, Santagni S, La Sala GB, **Orvieto R**. Risk of adverse pregnancy and perinatal outcomes after high technology infertility treatment: a comprehensive systematic review. Reprod Biol Endocrinol 2016;14(1):76.

Orvieto R. Triggering final follicular maturation for IVF cycles. Curr Pharm Biotechnol 2017

Elizur E, Berkenstadt M, Ries-Levavi L, Gruber N, Pinhas-Hamiel O, Hassin-Baer S, Raas-Rothschild

A, Raanani H, Cukierman-Yaffe T, **Orvieto R**, Cohen Y, Gabis L. premutation carriers. Are they really asymptomatic? Harefuah 2017

Gleicher N, **Orvieto R**. Is the hypothesis of preimplantation genetic screening (PGS) still supportable? A review. J Ovarian Res 2017;10:21.

Gat I, **Orvieto R**. "This is where it all started" – the pivotal role of PLCζ within the sophisticated process of mammalian reproduction: a systemic review. Basic and Clinical Andrology 2017; 27:9.

Orvieto R, Vanni VS, Gleicher N. The myths surrounding mild stimulation in vitro fertilization (IVF). Reprod Biol Endocrinol 2017;15:48.

Sanchez AM, Vanni VS, Bartiromo L, Papaleo E, Zilberberg E, Candiani M, **Orvieto R**, Vigano P. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res 2017;10:43.

Gat I, Raviv G, Baum M, Orvieto R. MSOME and IMSI: reasonable rationale, selective clinical value. Clin Exp Obstet Gynecol 2018

Reviews

Gat I, Raviv G, Baum M, **Orvieto R**. MSOME and IMSI: reasonable rationale, selective clinical value. Clin Exp Obstet Gynecol 2019;XLVI(5):679-689.

Agarwal A, Parekh N, Panner Selvam MK, Henkel R, Shah R, Homa ST, Ramasamy R, Ko E, Tremellen K, Esteves S, Majzoub A, Alvarez JG, Gardner DK, Jayasena CN, Ramsay JW, Cho CL, Saleh R, Sakkas D, Hotaling JM, Lundy SD, Vij S, Marmar J, Gosalvez J, Sabanegh E, Park HJ, Zini A, Kavoussi P, Micic S, Smith R, Busetto GM, Bakırcıoğlu ME, Haidl G, Balercia G, Puchalt NG, Ben-Khalifa M, Tadros N, Kirkman-Browne J, Moskovtsev S, Huang X, Borges E, Franken D, Bar-Chama N, Morimoto Y, Tomita K, Srini VS, Ombelet W, Baldi E, Muratori M, Yumura Y, La Vignera S, Kosgi R, Martinez MP, Evenson DP, Zylbersztejn DS, Roque M, Cocuzza M, Vieira M, Ben-Meir A, **Orvieto R**, Levitas E, Wiser A, Arafa M, Malhotra V, Parekattil SJ, Elbardisi H, Carvalho L, Dada R, Sifer C, Talwar P, Gudeloglu A, Mahmoud AMA, Terras K, Yazbeck C, Nebojsa B, Durairajanayagam D, Mounir A, Kahn LG, Baskaran S, Pai RD, Paoli D, Leisegang K, Moein MR, Malik S, Yaman O, Samanta L, Bayane F, Jindal SK, Kendirci M, Altay B, Perovic D, Harlev A. Male Oxidative Stress Infertility (MOSI): Proposed Terminology and clinical practice guidelines for management of idiopathic male infertility. World J Mens Health. 2019;37(3):296-312.

Kirshenbaum M, **Orvieto R**. Premature ovarian insufficiency and autoimmunity- an update appraisal. J Assist Reprod Genet. 2019;36(11):2207-2215.

Orvieto R. hMG versus recombinant FSH+ recombinant LH in controlled ovarian hyperstimulation for in vitro fertilization: Does the source of LH preparation matter? Reprod Biomed Online 2019;39(6):1001-5.

Kirshenbaum M, **Orvieto** R. Should we offer in vitro fertilization to couples with unexplained recurrent pregnancy loss? J Clin Med 2019, 8, 2001.

Orvieto R, Kirshenbaum M, Gleicher N. Is embryo cryopreservation causing macrosomia – and what else? Front. Endocrinol. 11:19.

Orvieto R, Gleicher N. Preimplantation genetic testing for aneuploidy (PGT-A)- finally revealed. J Assist Reprod Genet. 2020;37:669–672.

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Neuroendocrine Tumors

Positions

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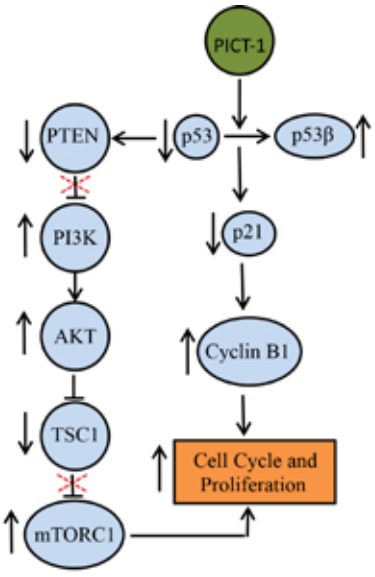
Sackler Faculty of Medicine, Tel Aviv University

Research

Our goal is to elucidate the molecular mechanisms that regulate the development of tumors called neuroendocrine tumors (NETs). In this heterogeneous family of tumors, we focus mainly on pituitary, medullary thyroid, lung and pancreatic NETs. We study the expression and function of genes that may affect cell proliferation and hormone secretion and we characterize the mechanisms of action of potential therapeutic compounds. In addition to various cell lines applied, cooperation with neurosurgeons and pathologists enable us access to multiple types of human tumors.



PICT-1 induces p53 splicing and resistance to mTOR inhibitor in Neuroendocrine Tumors

- The regulation of p53 splicing by PICT-1 and its effect on the sensitivity of neuroendocrine tumor cells to Everolimus, mTOR inhibitor
- The expression and function of Ephrins in non-functioning pituitary tumors
- Histone deacetylase inhibitors: their individual and combined effects with somatostatin analogs on PRL-secreting pituitary tumors
-

Publications

Masri-Iraqi H, Akirov A, **Shimon I**. Medical treatment landscape for active acromegaly in a pituitary center in Israel. Endocr Pract. 2020

Colao A, Bronstein MD, Brue T, De Marinis L, Fleseriu M, Guitelman M, Raverot G, **Shimon I**, Fleck J, Gupta P, Pedroncelli AM, Gadelha MR. Pasireotide for acromegaly: long-term outcomes from an extension

to the Phase III PAOLA study. Eur J Endocrinol. 2020; 182(6):583-594.

Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, Bolanowski M, Bonert V, Bronstein MD, Casanueva FF, Clemmons D, Colao A, Ferone D, Fleseriu M, Frara S, Gadelha MR, Ghigo E, Gurnell M, Heaney AP, Ho K, Ioachimescu A, Katznelson L, Kelestimur F, Kopchick J, Krsek M, Lamberts S, Losa M, Luger A, Maffei P, Marazuela M, Mazziotti G, Mercado M, Mortini P, Neggers S, Pereira AM, Petersenn S, Puig-Domingo M, Salvatori R, **Shimon I**, Strasburger C, Tsagarakis S, van der Lely AJ, Wass J, Zatelli MC, Melmed S. A consensus on the diagnosis and treatment of acromegaly comorbidities: An update. J Clin Endocrinol Metab. 2020;105(4).

Shimon I, Hirsch D, Tsvetov G, Robenshtok E, Akirov A, Fraenkel M, Eizenberg Y, Herzberg D, Barzilay-Yoseph L, Livner A, Friedrich I, Manisterski Y, Ishay A, Yoel U, Masri H. Hyperprolactinemia diagnosis in elderly men: a cohort of 28 patients over 65 years. Endocrine. 2019; 65(3):656-661.

Shimon I, Badiu C, Bossowski A, Doknic M, Dzivite-Krisane I, Hána V, Kollerova J, Natchev E, Pfeifer M, Szũcs N, Hey-Hadavi J, Gomez R. Adult growth hormone deficiency in CEE region: Heterogeneity of the patient pathway. Growth Horm IGF Res. 2019; 46-47:44-49.

Ozeri O, Cohen ZR, Hadani M, Nass D, **Shimon I**, **Rubinfeld H**. Antibody array strategy for human growth factor secretome profiling of GH-secreting adenomas. Pituitary. 2019; 22(4):344-352.

Akirov A, Greenman Y, Glaser B, S'chigol I, Mansiterski Y, Eizenberg Y, Shraga-Slutzky I, **Shimon I**. IGF-1 levels may increase paradoxically with dopamine agonist treatment for prolactinomas. Pituitary. 2018; 21(4):406-413.

Jallad RS, **Shimon I**, Fraenkel M, Medvedovsky V, Akirov A, Duarte FH, Bronstein MD. Outcome of pregnancies in a large cohort of women with acromegaly. Clin Endocrinol (Oxf). 2018; 88(6):896-907.

Shimon I, Adnan Z, Gorshtein A, Baraf L, Saba Khazen N, Gershinsky M, Pauker Y, Abid A, Niven MJ, Shechner C, Greenman Y. Efficacy and safety of long-acting pasireotide in patients with somatostatin-resistant acromegaly: a multicenter study. Endocrine. 2018; 62(2):448-455.

Hirsch D, **Shimon I**, Manisterski Y, Aviran-Barak N, Amitai O, Nadler V, Alboim S, Kopel V, Tsvetov G. Cushing's syndrome: comparison between Cushing's disease and adrenal Cushing's. Endocrine. 2018; 62(3):712-720.

Shimon I. Giant prolactinomas: Multi-modal approach to achieve tumor control. Endocrine. 2017; 56(2):227-228.

Akirov A, Gimbel H, Grossman A, Shochat T, **Shimon I**. Elevated TSH in adults treated for hypothyroidism is associated with increased mortality. Eur J Endocrinol. 2017; 176(1):57-66.

Shimon I, Sosa E, Mendoza V, Greenman Y, Tirosh A, Espinosa E, Popovic V, Glezer A, Bronstein MD, Mercado M. Giant prolactinomas larger than 60 mm in size: a cohort of massive and aggressive prolactin-secreting pituitary adenomas. Pituitary. 2016; 19(4):429-36.

Rubinfeld H, Cohen O, Kammer A, Yang G, Cohen ZR, Hadani M, **Shimon I**. Combination of mTOR inhibitors augments potency while activating PI3K signaling in pituitary tumors. Neuroendocrinology. 2016; 103(5):592-604.

Zornitzki T, **Rubinfeld H**, Lysyy L, Schiller T, Raverot V, **Shimon I**, Knobler H. pNET co-secreting GHRH and calcitonin: ex vivo hormonal studies in human pituitary cells. Endocrinol Diabetes Metab Case Rep. 2016; 150134.

Greenman Y, Cooper O, Yaish I, Robenshtok E, Sagiv N, Jonas-Kimchi T, Yuan X, Gertych A, **Shimon I**, Ram Z, Melmed S, Stern N. Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. Eur J Endocrinol. 2016; 175(1):63-72.

Tirosh A, Toledano Y, Masri-Iraqi H, Eizenberg Y, Tzvetov G, Hirsch D, Benbassat C, Robenshtok E, **Shimon I**. IGF-I levels reflect hypopituitarism severity in adults with pituitary dysfunction. Pituitary. 2016; 19(4):399-406.

Reviews

Shimon I. Metastatic spread to the pituitary. Neuroendocrinology. 2020

Duskin-Bitan H, **Shimon I.** Prolactinomas in males: any differences? Pituitary. 2020; 23 (1):52-57

Akirov A, Asa SL, Amer L, **Shimon I**, Ezzat S. The clinicopathological spectrum of acromegaly. J Clin Med. 2019; 8(11):1962.

Shimon I. Giant Prolactinomas. Neuroendocrinology. 2019; 109(1):51-56.

Tirosh A, **Shimon I**. Complications of acromegaly: thyroid and colon. Pituitary. 2017; 20(1):70-75.

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Mechanisms for the Development of Obesity and Diabetes – Molecular and Translational Aspects

Position

Associate Professor of Medicine, Sackler Faculty of Medicine

Research

With the worldwide epidemic proportions of obesity, its related morbidities such as cardiovascular disease and diabetes have become an emerging threat for public health. While the strong genetic predisposition for these conditions is a subject of intense research, less is known about the strong influence of various environmental factors on the pathophysiology of obesity and diabetes. We have recently established the Endocrinology and Diabetes Research Center at the Institute of Endocrinology at Sheba Medical Center with the vision to promote all aspects of research in the field of obesity, insulin resistance and diabetes.

Our group has focused on the following aspects of the pathophysiology of obesity and diabetes:

a. The role of food preservatives as 'metabolic disruptors': Some environmental and nutritional factors have been demonstrated to act as 'endocrine disruptors', with the ability to act as agonists or antagonists to certain receptors in a wide variety of biological systems. We have identified a common food preservative, with distinct metabolic effects. We were able to demonstrate that this food preservative results in an increase in hepatic glucose production as well as in changes in glucagon and insulin levels leading to liver insulin resistance. Chronic exposure results in weight gain, increase adiposity and systemic insulin resistance in mouse models. We are currently working on translating our pre-clinical results to humans in a series of randomized controlled trial. In addition, we continue to work using in-vitro and in-vivo animal models to assess the effects of micronutrients in modern nutrition on the development of obesity and diabetes.

b. Cellular mechanism linking over-nutrition with inflammation, insulin resistance and diabetes: Previous studies have clearly demonstrated that chronic inflammation and cellular stress is a central feature of obesity and its associated metabolic disease cluster. This inflammatory response is distinct, appears to respond to intrinsic cues, and does not resemble the classical inflammatory paradigm. Significant data have emerged in recent years on the molecular mechanisms leading to the development of these inflammatory and stress responses and how they are linked to metabolic homeostasis. Our research is focused on the regulation and adaptation to inflammation and stress within the tissue milieu in metabolically relevant tissues such as liver and adipose tissue. More specifically, we study cell-cell communication and the propagation of inflammatory and stress signals between cells within a tissue and the potential role of such communication in mediating insulin resistance and metabolic abnormalities.

c. In addition to utilizing basic research tools to promote our understanding on the mechanisms leading to insulin resistance and diabetes, we involve in clinical studies assessing novel risk factors and potential therapeutic approaches for these conditions. We are currently involved in several studies looking at the potential role of the novel adipokine FABP4 (fatty acid binding protein 4) in the insulin counter-regulatory response to hypoglycemia and as a potential contributor to the pathophysiology of gestational diabetes.

Publications

Tirosh A, de Souza RJ, Sacks F, Bray GA, Smith SR, LeBoff MS. Weight Loss and Dietary Macronutrient Content on Changes in BMD and Composition in Females and Males: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial. J Clin Endocrinol Metab. 2015; 100(6):2463-71.

Twig G, Shina A, Afek A, Derazne E, Tzur D, Cukierman-Yaffe T, Shechter-Amir D, Gerstein HC, **Tirosh A**. Sleep Quality and Risk of Diabetes and Coronary Artery Disease among Young Men. Acta Diabetol, 2015 Jun 16.

Twig G, Gerstein HC, Ben-Ami Shor D, Derazne E, Tzur D, Afek A, **Tirosh A**. Coronary Artery Disease Risk among Obese Metabolically Healthy Young Men. Eur J Endocrinol. 2015; 173(3):305-12.

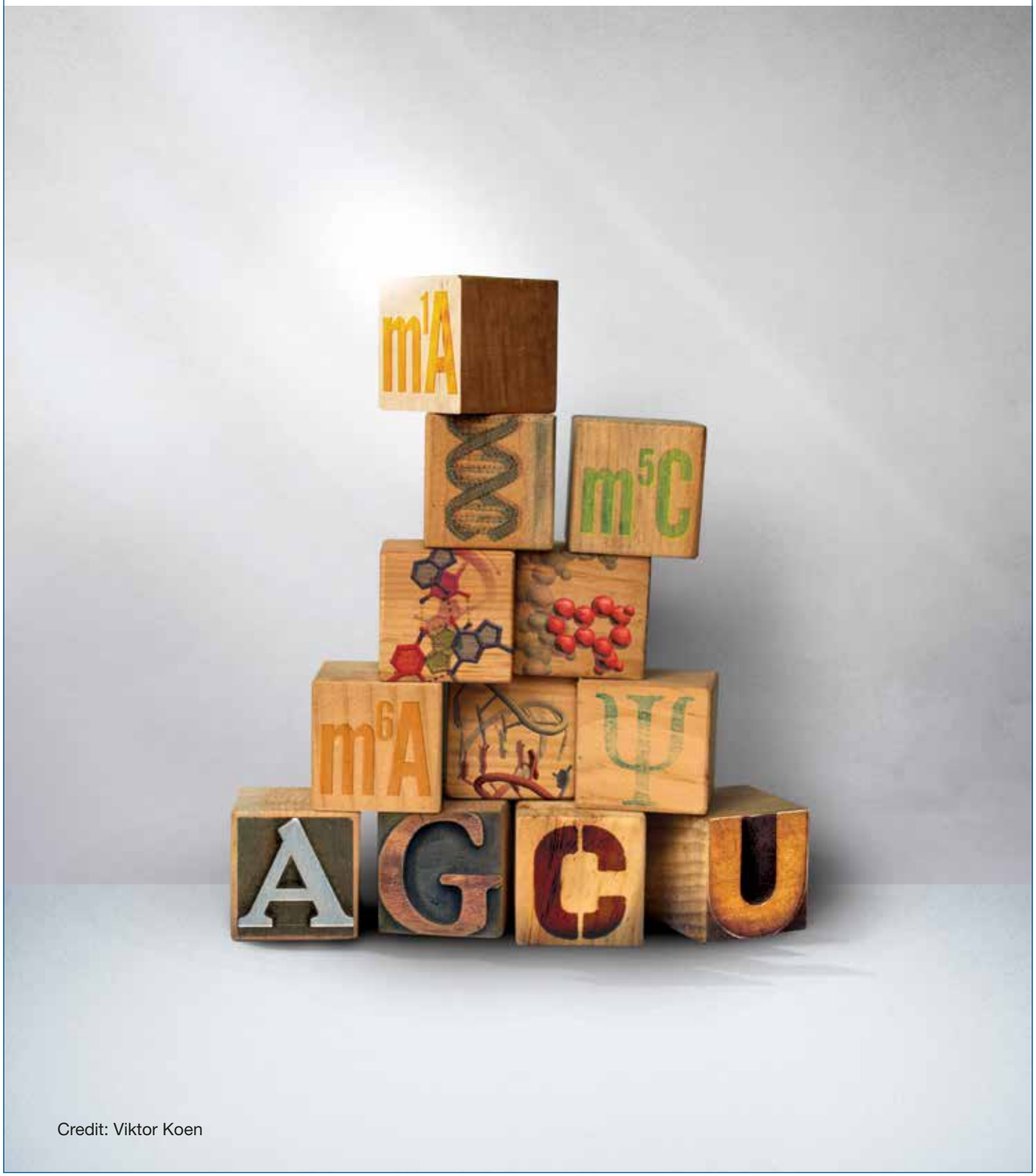
Burak MF, Inouye KE, White A, Lee A, Tuncman G, Calay ES, Sekiya M, **Tirosh A**, Eguchi K, Birrane G, Lightwood D, Howells L, Odede G, Hailu H, West S, Garlish R, Neale H, Doyle C, Moore A, Hotamisligil GS. Development of a therapeutic monoclonal antibody that targets secreted fatty acid-binding protein aP2 to treat type 2 diabetes. Sci Transl Med. 2015; 7(319):319ra205.

Twig G, Gerstein HC, Fruchter E, Shina A, Afek A, Derazne E, Tzur D, Cukierman-Yaffe T, Amital D, Amital H, **Tirosh A**. Self-Perceived Emotional Distress and Diabetes Risk Among Young Men. Am J Prev Med. 2016;50(6):737-45.

Grants

2017-2021	Principle Investigator Israeli Science Foundation (ISF) Connexin 43-mediated cell-cell communication and propagation of adipose tissue ER stress in obesity
2018-2020	Principle Investigator United States-Israel Binational Science Foundation (BSF) Impact of culinary coaching telemedicine program on body weight and metabolic outcomes
2019-2021	Principle Investigator European Foundation for the Study of Diabetes (EFSD) Patient reported outcomes and ambulatory glucose profiles in a virtual type 1 diabetes clinic
2016-2019	Innovative Clinical or Translational Science Award. The American Diabetes Association, Acute effects of the food preservative propionic acid on glucose metabolism in humans

Genetic Diseases & Genomics



Credit: Viktor Koen

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Deciphering the Molecular Basis of Inborn Errors of Metabolism and Rare Genetic Disorders

Positions

Professor, Sackler Faculty of Medicine

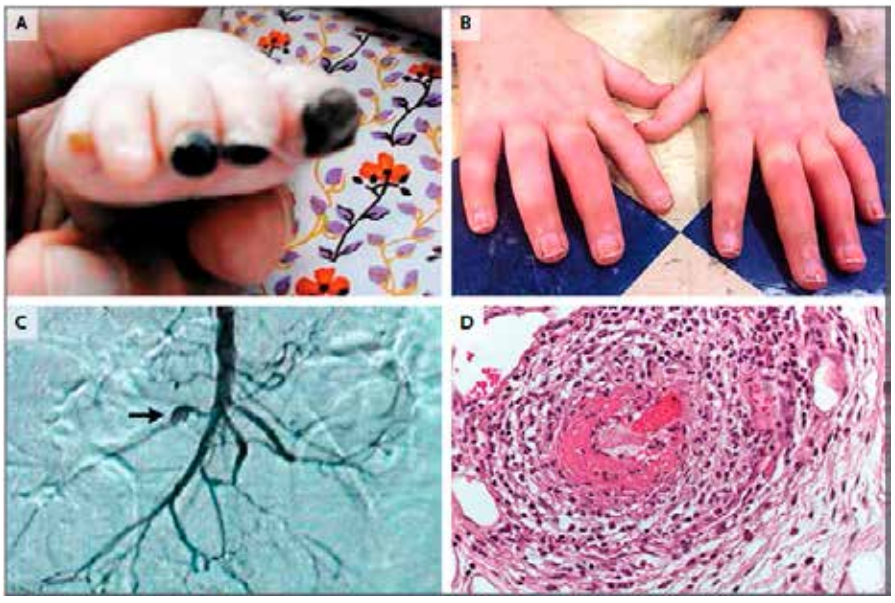
Director, Metabolic Disease Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer

Chairman, Israeli Society for Metabolic Diseases (ISMD)

Research

At the Metabolic Disease Unit and the Molecular Biochemistry laboratory at the Sheba Medical Center, we strive to identify and characterize the molecular basis of an array of inborn errors of metabolism (IEM) and other rare inherited disorders. As a referral center for patients with a wide array of IEMs, we take a "bedside to bench to bedside" approach, studying the biochemical pathways and genetic basis of their disease, delineating the functional effects of the disease-causing variants, and aiming our efforts at the exciting possibilities for novel therapeutic approaches.

In the past few years, we were the first to identify a causative association between variants in several genes and a number of new neurometabolic disorders, as published in the *New England Journal of Medicine*, *American Journal of Human Genetics*, *Brain*, *Journal of Biological Chemistry*, among others. This was the case, for instance, of an autosomal recessive subtype of Polyarteritis Nodosa vasculopathy, caused by



Clinical Features of Polyarteritis Nodosa Associated with Adenosine Deaminase 2 (ADA2) Mutations. Clinical manifestations of polyarteritis nodosa included digital necrosis of the toes in Patient B-III-3 (Panel A) and Raynaud's phenomenon and livedo reticularis in Patient B-III-6 (Panel B). Angiography of the celiac artery in Patient B-III-3 revealed an aneurysm (Panel C, arrow). Periarteritis, fibrinoid necrosis of the media, and destruction of the elastic laminae were revealed in a biopsy specimen of the superior mesenteric artery in Patient A-III-1 (Panel D, hematoxylin and eosin).

variants in the *CECR1* gene, encoding Adenosine Deaminase 2 (ADA2). Since the pucblication of our results [Navon Elkan P et al. *N Engl J Med* 2014], this disorder, manifesting with early-onset cerebral infarctions (among others), has been diagnosed in numerous families worldwide.

Most recently, we identified and characterized a newly recognized inherited neurotransmitter deficiency, caused by mutations in *DNAJC12* [soon to be published in the *American Journal of Human Genetics*]. This disorder was found to manifest in hyperphenylalaninemia, dystonia and intellectual disability. Interestingly, patients with the *DNAJC12*-associated phenotype showed dramatic clinical improvement following early treatment with BH4 and/or neurotransmitter precursors, and thus this unique disorder is a new treatable and preventable cause of intellectual disability.

Publications

Oz-Levi D, Weiss B, Lahad A, Greenberger S, Pode-Shakked B, Somech R, Olender T, Tatarsky P, Marek-Yagel D, Pras E, **Anikster Y**, Lancet D. Exome sequencing as a differential diagnosis tool: resolving mild trichohepatoenteric syndrome. Clin Genet. 2015 Jun;87(6):602-3.

Zhu X, Petrovski S, Xie P, Ruzzo EK, Lu YF, McSweeney KM, Ben-Zeev B, Nissenkorn A, **Anikster Y**, Oz-Levi D, Dhindsa RS, Hitomi Y, Schoch K, Spillmann RC, Heimer G, Marek-Yagel D, Tzadok M, Han Y, Worley G, Goldstein J, Jiang YH, Lancet D, Pras E, Shashi V, McHale D, Need AC, Goldstein DB. Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. Genet Med. 2015 Jan 15. doi: 10.1038/gim.2014.191.

Sofer S, Schweiger A, Blumkin L, Yahalom G, **Anikster Y**, Lev D, Ben-Zeev B, Lerman-Sagie T, Hassin-Baer S. The Neuropsychological profile of patients with 3-Methylglutaconic aciduria type III, Costeff syndrome. Am J Med Genet B Neuropsychiatr Genet. 2015 Apr;168(3):197-203.

Heimer G, Sadaka Y, Israelian L, Feiglin A, Ruggieri A, Marshall CR, Scherer SW, Ganelin-Cohen E, Marek-Yagel D, Tzadok M, Nissenkorn A, **Anikster Y**, Minassian BA, Zeev BB. CAOS-Episodic Cerebellar Ataxia, Areflexia, Optic Atrophy, and Sensorineural Hearing Loss: A third allelic disorder of the ATP1A3 gene. J Child Neurol. 2015 30(13):1749-56

Heimer G, Marek-Yagel D, Eyal E, Barel O, Oz Levi D, Hoffmann C, Ruzzo EK, Ganelin-Cohen E, Lancet D, Pras E, Rechavi G, Nissenkorn A, **Anikster Y**, Goldstein DB, Ben Zeev B. SLC1A4 mutations cause a novel disorder of intellectual disability, progressive microcephaly, spasticity and thin corpus callosum. Clin Genet. 2015;88(4):327-35.

Carmi N, Lev D, Leshinsky-Silver E, **Anikster Y**, Blumkin L, Kivity S, Lerman-Sagie T, Zerem A. Atypical presentation of Costeff syndrome-severe psychomotor involvement and electrical status epilepticus during slow wave sleep. Eur J Paediatr Neurol. 2015;19(6):733-6

Ben-Zeev B, Tabib A, Nissenkorn A, Garti BZ, Gomori JM, Nass D, Goldshmidt H, Fellig Y, **Anikster Y**, Nevo Y, Elpeleg O, Mevorach D. Devastating recurrent brain ischemic infarctions and retinal disease in pediatric patients with CD59 deficiency. Eur J Paediatr Neurol. 2015 19(6):688-93.

Nouriel A, Zisquit J, Helfand AM, **Anikster Y**, Greenberger S. Griscelli Syndrome Type 3: Two New Cases and Review of the Literature. Pediatr Dermatol. 2015 Nov;32(6):e245-8.

Stadel D, Millarte V, Tillmann KD, Huber J, Tamin-Yecheskel BC, Akutsu M, Demishtein A, Ben-Zeev B, **Anikster Y**, Perez F, Dötsch V, Elazar Z, Rogov V, Farhan H, Behrends C. TECPR2 Cooperates with LC3C to Regulate COPII-Dependent ER Export. Mol Cell. 2015 Oct 1;60(1):89-104.

Eisenkraft A, Pode-Shakked B, Goldstein N, Shpirer Z, van Bokhoven H, **Anikster Y**. Clinical Variability in a Family with an Ectodermal Dysplasia Syndrome and a Nonsense Mutation in the TP63 Gene. Fetal Pediatr Pathol. 2015 Nov 2;34(6):400-6

Pode-Shakked B, Marek-Yagel D, Greenberger S, Pode-Shakked N, Pras E, Barzilai A, Yassin S, Sidi Y, **Anikster Y**. A novel mutation in the C7orf11 gene causes nonphotosensitive trichothiodystrophy in a multiplex highly consanguineous kindred. Eur J Med Genet. 2015 Dec;58(12):685-8.

Heimer G, Oz-Levi D, Eyal E, Edvardson S, Nissenkorn A, Ruzzo EK, Szeinberg A, Maayan C, Mai-Zahav M, Efrati O, Pras E, Reznik-Wolf H, Lancet D, Goldstein DB, **Anikster Y**, Shalev SA, Elpeleg O, Ben Zeev B. TECPR2 mutations cause a new subtype of familial dysautonomia like hereditary sensory autonomic neuropathy with intellectual disability. Eur J Paediatr Neurol. 2016;20(1):69-79.

Rips J, Almashanu S, Mandel H, Josephsberg S, Lerman-Sagie T, Zerem A, Podeh B, **Anikster Y**, Shaag A, Luder A, Staretz Chacham O, Spiegel R. Primary and maternal 3-methylcrotonyl-CoA carboxylase deficiency: insights from the Israel

newborn screening program. J Inherit Metab Dis. 2015;39(2):211-7.

Stephen J, Vilboux T, Haberman Y, Pri-Chen H, Pode-Shakked B, Mazaheri S, Marek-Yagel D, Barel O, Di Segni A, Eyal E, Hout-Siloni G, Lahad A, Shalem T, Rechavi G, Malicdan MC, Weiss B, Gahl WA, **Anikster Y**. Congenital protein losing enteropathy: an inborn error of lipid metabolism due to DGAT1 mutations. Eur J Hum Genet. 2016;24(9):1268-73.

Dionisi-Vici C, Shteyer E, Niceta M, Rizzo C, Pode-Shakked B, Chillemi G, Bruselles A, Semeraro M, Barel O, Eyal E, Kol N, Haberman Y, Lahad A, Diomedi-Camassei F, Marek-Yagel D, Rechavi G, Tartaglia M, **Anikster Y**. Expanding the molecular diversity and phenotypic spectrum of glycerol 3-phosphate dehydrogenase 1 deficiency. J Inherit Metab Dis. 2016;39(5):689-95.

Ardon O, Procter M, Mao R, Longo N, Landau YE, Shilon-Hadass A, Gabis LV, Hoffmann C, Tzadok M, Heimer G, Sada S, Ben-Zeev B, **Anikster Y**. Creatine transporter deficiency: Novel mutations and functional studies. Mol Metab Genet Rep. 2016;8:20-3.

Shahrour MA, Staretz-Chacham O, Dayan D, Stephen J, Weech A, Damseh N, Pri Chen H, Edvardson S, Mazaheri S, Saada A; NISC Intramural Sequencing., Hershkovitz E, Shaag A, Huizing M, Abu-Libdeh B, Gahl WA, Azem A, **Anikster Y**, Vilboux T, Elpeleg O, Malicdan MC. Mitochondrial epileptic encephalopathy, 3-methylglutaconic aciduria and variable complex V deficiency associated with TIMM50 mutations. Clin Genet, 2016 [Epub ahead of print].

Rechavi E, Lev A, Eyal E, Barel O, Kol N, Barhom SF, Pode-Shakked B, **Anikster Y**, Somech R, Simon AJ. A Novel Mutation in a Critical Region for the Methyl Donor Binding in DNMT3B Causes Immunodeficiency, Centromeric Instability, and Facial Anomalies Syndrome (ICF). J Clin Immunol. 2016;36(8):801-809.

Haberman Y, Di Segni A, Loberman-Nachum N, Barel O, Kunik V, Eyal E, Kol N, Hout-Siloni G, Kochavi B, Avivi C, Schvimer M, Rechavi G, **Anikster Y**, Barshack I, Weiss B. Congenital Sucrase-isomaltase Deficiency: A Novel Compound Heterozygous Mutation Causing Aberrant Protein Localization. J Pediatr Gastroenterol Nutr. 2016 [Epub ahead of print].

Pode-Shakked B, Barash H, Ziv L, Gripp KW, Flex E, Barel O, Carvalho KS, Scavina M, Chillemi G, Niceta M, Eyal E, Kol N, Ben-Zeev B, Bar-Yosef O, Marek-Yagel D, Bertini E, Duker AL, **Anikster Y**, Tartaglia M, Raas-Rothschild A. Microcephaly, intractable seizures and developmental delay caused by biallelic variants in TBCD: Further delineation of a new chaperone-mediated tubulinopathy. Clin Genet. 2016 [Epub ahead of print].

Heimer G, Kerätär JM, Riley LG, Balasubramaniam S, Eyal E, Pietikäinen LP, Hiltunen JK, Marek-Yagel D, Hamada J, Gregory A, Rogers C, Hogarth P, Nance MA, Shalva N, Veber A, Tzadok M, Nissenkorn A, Tonduti D, Renaldo F; University of Washington Center for Mendelian Genomics., Kraoua I, Panteghini C, Valletta L, Garavaglia B, Cowley MJ, Gayevskiy V, Roscioli T, Silberstein JM, Hoffmann C, Raas-Rothschild A, Tiranti V, **Anikster Y**, Christodoulou J, Kastaniotis AJ, Ben-Zeev B, Hayflick SJ. MECR Mutations Cause Childhood-Onset Dystonia and Optic Atrophy, a Mitochondrial Fatty Acid Synthesis Disorder. Am J Hum Genet. 2016;99(6):1229-44.

Falik Zaccai TC, Savitzki D, Zivony-Elboum Y, Vilboux T, Fitts EC, Shoval Y, Kalfon L, Samra N, Keren Z, Gross B, Chasnyk N, Straussberg R, Mullikin JC, Teer JK, Geiger D, Kornitzer D, Bitterman-Deutsch O, Samson AO, Wakamiya M, Peterson JW, Kirtley ML, Pinchuk IV, Baze WB, Gahl WA, Kleta R, **Anikster Y**, Chopra AK. Phospholipase A2-activating protein is associated with a novel form of leukoencephalopathy. Brain. 2016 [Epub ahead of print].

Anikster Y, Haack TB, Vilboux T, Pode-Shakked B, Thöny B, Meissner T, Mayatepek E, Trefz FK, Marek-Yagel D, Berutti R, Benoist JF, Imbard A, Dorboz I, Heimer G, Landau Y, Ziv-Strasser L, Malicdan MCV, Gemperle-Britschgi C, Cremer K, Engels H, Meili D, Keller I, Brugmann R, Strom TM, Meitinger T, Mullikin JC, Schwartz G, Ben-Zeev B, Blau N, Hoffmann GF, Prokisch H, Opladen T, Schiff M. DNAJC12 mutations: a treatable cause of dystonia with hyperphenylalaninemia. Am J Hum Genet 2017 [Accepted for publication].

Barel O, Malicdan MC, Ben-Zeev B, Kandel J, Pri-Chen H, Stephen J, Castro IG, Metz J, Atawa O, Moshkovitz S, Ganelin E, Barshack I, Polak-Charcon S, Nass D, Marek-Yagel D, Amariglio N, Shalva N, Vilboux T, Ferreira C, Pode-Shakked B, Heimer G, Hoffmann C, Yardeni T, Nissenkorn A, Avivi C, Eyal E, Kol N, Glick Saar E, Wallace DC, Gahl WA, Rechavi G, Schrader M, Eckmann DM, **Anikster Y**. Deleterious variants in TRAK1 disrupt mitochondrial movement and cause fatal encephalopathy. Brain 2017 [Accepted for publication].

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Deciphering the Role of Novel Human Genes and the Pathophysiology Underlying Rare Monogenic Syndromes

Positions

Director, The Genetics Institute, Tel Aviv Sourasky Medical Center

Lecturer, Sackler Faculty of Medicine

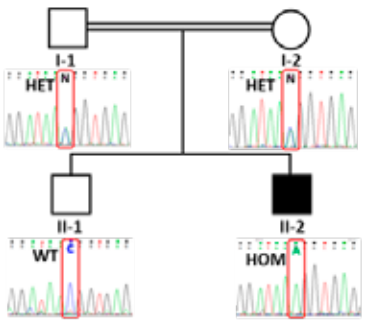
Chair, Israeli Society of Medical Geneticists

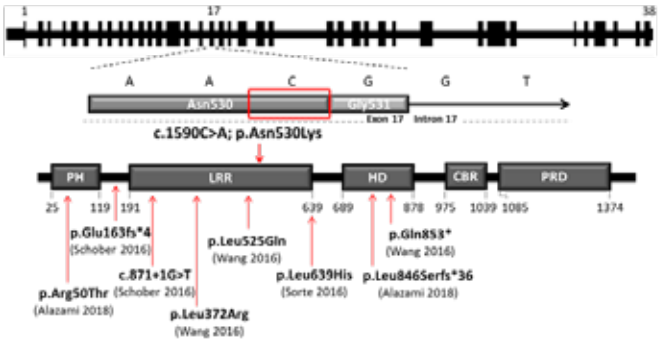
Research

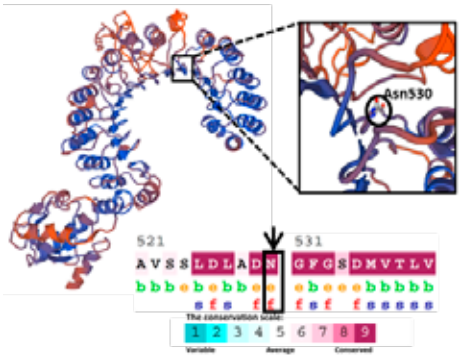
We study the the genetic basis of human Mendelian syndromes from various medical disciplines using next generation technologies, coupled with functional analyses to uncover novel disease pathways. Our laboratory combines genetic, computational and molecular biology methods to study rare diseases and investigate the pathophysiological mechanisms underlying these syndromes. In addition, we have collaborations with top experts in different medical and biological fields, both in Israel and worldwide.

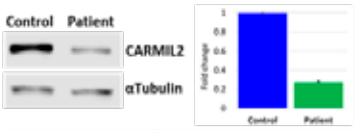
Over the last five years, we uncovered numerous novel human disease-causing genes using whole exome sequencing. These serve as a first step to better understanding human physiology in health and disease, followed by potential application of this knowledge to implement precision medicine and tailored treatments. Our discoveries provided personalized genetic counseling for families with rare genetic disorders and promoted the birth of healthy children through prenatal and preimplantation genetic diagnoses. Moreover, our findings paved the way to tailored medical treatment for some of the patients, which became the treatment of choice for similar patients worldwide. Our research is patient-driven with the aim of continued implementation of personalized medicine and disease prevention.

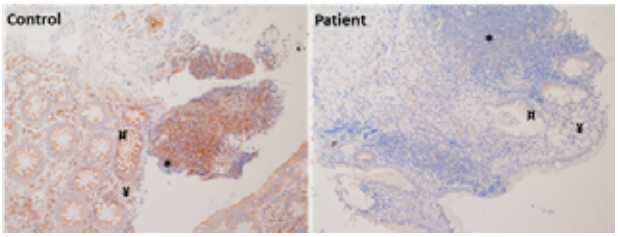
Recently, we embarked on a new project aimed at identify risk and protective variants in genes











involved in COVID-19 morbidity and disease severity in the hope of identifying in-risk patients and new treatment target targets. We are also taking part in an international consortium aimed at understanding the genetic predisposition to SARS-CoV-2 infection https://www.covidhge.com/

Publications

Mistry PK, Lukina E, Ben Turkia H, Amato D, **Baris Feldman H (Baris H)**, Dasouki M, Ghosn M, Mehta A, Packman S, Pastores G, Petakov M, Assouline S, Balwani M, Danda S, Hadjiev E, Ortega A, Shankar S, Solano MH, Ross L, Angell J, Peterschmitt MJ. Effect of oral eliglustat vs placebo on spleen volume in patients with splenomegaly and Gaucher disease type 1: the ENGAGE randomized clinical trial. *JAMA*. 2015;313(7):695-706.

Goldberg Y, Barnes-Kedar I, Lerer I, Halpern N, Plesser M, Hubert A, Kadouri L, Goldshmidt H, Solar I, Strul H, Rosner G, **Baris Feldman H (Baris H)**, Peretz T, Levi Z, Kariv R. Genetic features of Lynch syndrome in the Israeli population. *Clin Genet*. 2015;87(6):549-53.

Haer-Wigman L, Newman H, Leibu R, Bax NM, **Baris Feldman H (Baris H)**, Rizel L, Banin E, Massarweh A, Roosing S, Lefeber DJ, Zonneveld-Vrieling MN, Isakov O, Shomron N, Sharon D, Den Hollander AI, Hoyng CB, Cremers FPM, Ben-Yosef T. Non-syndromic retinitis pigmentosa due to mutations in the mucopolysaccharidosis type IIIC gene, heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT). *Hum Mol Genet*. 2015;24(13):3742-51.

Levi Z, Kariv R, Barnes-Kedar I, Goldberg Y, Half E, Morgentern S, Eli B, **Baris Feldman H (Baris H)**, Vilkin A, Belfer RG, Niv Y, Elhasid R, Dvir R, Abu-Freha N, Cohen S. The gastrointestinal manifestation of constitutional mismatch repair deficiency syndrome: from a single adenoma to polyposis-like phenotype and early onset cancer. *Clin Genet*. 2015;88(5):474-8.

Elstein D, Abrahamov A, Oz A, Arbel N, **Baris Feldman H (Baris H)**, Zimran A. 13,845 home therapy infusions with velaglucerase alfa exemplify safety of velaglucerase alfa and increased compliance to every-other-week intravenous enzyme replacement therapy for Gaucher disease. *Blood Cells Mol Dis*. 2015;55(4):415-8.

Stelzer G, Plaschkes I, Oz-Levi D, Alkelai A, Olender T, Zimmerman S, Twik M, Belinky F, Fishilevich S, Nudel R, Guan-Golan Y, Warshawsky D, Dahary D, Kohn A, Mazor Y, Kaplan S, Iny Stein T, **Baris Feldman H (Baris H)**, Rappaport N, Safran M, Lancet D. VarElect: the phenotype-based variation prioritizer of the GeneCards Suite. *BMC Genomics*. 2016;17 Suppl 2:444.

Ekhilevitch N, Kurolap A, Oz-Levi D, Mory A, Hershkovitz T, Ast G, Mandel H, **Baris Feldman H (Baris H)**. Expanding the MYBPC1 phenotypic spectrum: a novel homozygous mutation causes arthrogryposis multiplex congenita. *Clin Genet*. 2016;90(1):84-9.

Baris Feldman H (Baris H), Weisz Hubshman M, Bar-Sever Z, Kornreich L, Shkalim Zemer V, Cohen IJ. Re-evaluation of bone pain in patients with type 1 Gaucher disease suggests that bone crises occur in small bones as well as long bones. *Blood Cells Mol Dis*. 2016;60:65-72.

Kurolap A, Orenstein N, Kedar I, Weisz Hubshman M, Tiosano D, Mory A, Levi Z, Marom D, Cohen L, Ekhilevich N, Douglas J, Nowak CB, Tan W-H, **Baris Feldman H (Baris H)**. Is one diagnosis the whole story? patients with double diagnoses. *Am J Med Genet A*. 2016;170(9):2338-48.

Aronson M, Gallinger S, Cohen Z, Cohen S, Dvir R, Elhasid R, **Baris Feldman H (Baris H)**, Kariv R, Druker H, Chan H, Ling SC, Kortan P, Holter S, Semotiuk K, Malkin D, Farah R, Sayad A, Heald B, Kalady MF, Penney LS, Rideout AL, Rashid M, Hasadsri L, Pichurin P, Riegert-Johnson D, Campbell B, Bakry D, Al-Rimawi H, Alharbi QK, Alharbi M, Shamvil A, Tabori U, Durno C. Gastrointestinal findings in the largest series of patients with Hereditary Biallelic Mismatch Repair Deficiency Syndrome: Report from the international consortium. *Am J Gastroenterol*. 2016;111(2):275-84.

Baris Feldman H (Baris H), Barnes-Kedar I, Toledano H, Halpern M, Hershkovitz D, Lossos A, Lerer I, Peretz T, Kariv R, Cohen S, Half EE, Magal N, Drasinover V, Wimmer K, Goldberg Y, Bercovich D, Levi Z. Constitutional mismatch repair deficiency in Israel: High proportion of founder mutations in MMR genes and consanguinity. *Pediatr Blood Cancer*. 2016;63(3):418-27.

Agranat S, **Baris Feldman H (Baris H)**, Kedar I, Shochat M, Rizel S, Perry S, Margel D, Sulkes A, Yerushalmi R. Earlier age of breast cancer onset in Israeli BRCA carriers-Is it a real phenomenon? *Breast J*. 2016;22(6):662-6.

Kurolap A, Armbruster A, Hershkovitz T, Hauf K, Mory A, Paperna T, Hannappel E, Tal G, Nijem Y, Sella E, Mahajnah M, Ilivitzki A, Hershkovitz D, Ekhilevitch N, Mandel H, Eulenburg V, **Baris Feldman H (Baris H)**. Loss of Glycine Transporter 1 causes a subtype of Glycine Encephalopathy with Arthrogryposis and

mildly elevated cerebrospinal fluid glycine. *Am J Hum Genet*. 2016;99(5):1172-80.

Yokote K, Chanprasert S, Lee L, Eirich K, Takemoto M, Watanabe A, Koizumi N, Lessel D, Mori T, Hisama FM, Ladd PD, Angle B, **Baris Feldman H (Baris H)**, Cefle K, Palanduz S, Ozturk S, Chateau A, Deguchi K, Easwar TKM, Federico A, Fox A, Grebe TA, Hay B, Nampoothiri S, Seiter K, Streeten E, Piña-Aguilar RE, Poke G, Poot M, Posmyk R, Martin GM, Kubisch C, Schindler D, Oshima J. WRN mutation update: Mutation spectrum, patient registries, and translational prospects. *Hum Mutat*. 2017;38(1):7-15.

Kurolap A, Eshach-Adiv O, Hershkovitz T, Paperna T, Mory A, Oz-Levi D, Zohar Y, Mandel H, Chezar J, Azoulay D, Peleg S, Half EE, Yahalom V, Finkel L, Weissbrod O, Geiger D, Tabib A, Shaoul R, Magen D, Bonstein L, Mevorach D, **Baris Feldman H (Baris H)**. Loss of CD55 in eculizumab-responsive protein-losing enteropathy. *N Engl J Med*. 2017;377(1):87-9.

Lieberman S, Walsh T, Schechter M, Adar T, Goldin E, Beeri R, Sharon N, **Baris Feldman H (Baris H)**, Ben Avi L, Half E, Lerer I, Shirts BH, Pritchard CC, Tomlinson I, King M-C, Levy-Lahad E, Peretz T, Goldberg Y. Features of patients with hereditary mixed polyposis syndrome caused by duplication of GREM1 and implications for screening and surveillance. *Gastroenterology*. 2017;152(8):1876-1880.e1.

Mistry PK, Lukina E, Ben Turkia H, Shankar SP, **Baris Feldman H (Baris H)**, Ghosn M, Mehta A, Packman S, Pastores G, Petakov M, Assouline S, Balwani M, Danda S, Hadjiev E, Ortega A, Gaemers SJM, Tayag R, Peterschmitt MJ. Outcomes after 18 months of eliglustat therapy in treatment-naïve adults with Gaucher disease type 1: The phase 3 ENGAGE trial. *Am J Hematol*. 2017;92(11):1170-6.

Tesch VK, IJspeert H, Raicht A, Rueda D, Dominguez-Pinilla N, Allende LM, Colas C, Rosenbaum T, Ilencikova D, **Baris Feldman H (Baris H)**, Nathrath MHM, Suerink M, Januszkiewicz-Lewandowska D, Ragab I, Azizi AA, Wenzel SS, Zschocke J, Schwinger W, Kloor M, Blattmann C, Brugieres L, van der Burg M, Wimmer K, Seidel MG. No overt clinical immunodeficiency despite immune biological abnormalities in patients with constitutional mismatch repair deficiency. *Front Immunol*. 2018;9:1506.

Abu Freha N, Leibovici Weissman Y, Fich A, Barnes Kedar I, Halpern M, Sztarkier I, Behar DM, Arbib Sneh O, Vilkin A, **Baris Feldman H (Baris H)**, Gingold R, Lejbkowicz F, Niv Y, Goldberg Y, Levi Z. Constitutional mismatch repair deficiency and Lynch syndrome among consecutive Arab Bedouins with colorectal cancer in Israel. *Fam Cancer*. 2018;17(1):79-86.

Arkadir D, Dinur T, Mullin S, Mehta A, **Baris Feldman H (Baris H)**, Alcalay RN, Zimran A. Trio approach reveals higher risk of PD in carriers of severe vs. mild GBA mutations. *Blood Cells Mol Dis*. 2018;68:115-6.

Sagi-Dain L, Maya I, Peleg A, Reches A, Banne E, **Baris Feldman H (Baris H)**, Tenne T, Singer A, Ben-Shachar S. Microarray analysis in pregnancies with isolated unilateral kidney agenesis. *Pediatr Res*. 2018;83(4):825-8.

Singer A, Maya I, Koifman A, Nasser Samra N, **Baris Feldman H (Baris H)**, Falik-Zaccai T, Ben Shachar S, Sagi-Dain L. Microarray analysis in pregnancies with isolated echogenic bowel. *Early Hum Dev*. 2018;119:25-8.

Chen A*, Tiosano D*, Guran T*, **Baris Feldman H (Baris H)***, Bayram Y, Mory A, Shapiro-Kulnane L, Hodges CA, Akdemir ZC, Turan S, Jhangiani SN, van den Akker F, Hoppel CL, Salz HK, Lupski JR, Buchner DA. *Equal contribution. Mutations in the mitochondrial ribosomal protein MRPS22 lead to primary ovarian insufficiency. *Hum Mol Genet*. 2018;27(11):1913-26.

Friederich MW, Timal S, Powell CA, Dallabona C, Kurolap A, Palacios-Zambrano S, Bratkovic D, Derks TGJ, Bick D, Bouman K, Chatfield KC, Damouny-Naoum N, Dishop MK, Falik-Zaccai TC, Fares F, Fedida A, Ferrero I, Gallagher RC, Garesse R, Gilberti M, González C, Gowan K, Habib C, Halligan RK, Kalfon L, Knight K, Lefeber D, Mamblona L, Mandel H, Mory A, Ottoson J, Paperna T, Pruijn GJM, Rebelo-Guiomar PF, Saada A, Sainz B, Salvemini H, Schoots MH, Smeitink JA, Szukszto MJ, Ter Horst HJ, van den Brandt F, van Spronsen FJ, Veltman JA, Wartchow E, Wintjes LT, Zohar Y, Fernández-Moreno MA*, **Baris Feldman H (Baris H)***, Donnini C*, Minczuk M*, Rodenburg RJ*, Van Hove JLK*. *Equal Supervision. Pathogenic variants in glutamyl-tRNAGln amidotransferase subunits cause a lethal mitochondrial cardiomyopathy disorder. *Nat Commun*. 2018;9(1):4065.

Maya I, Singer A, **Baris Feldman H (Baris H)**, Goldberg Y, Shalata A, Khayat M, Ben-Shachar S, Sagi-Dain L. Prenatal microarray analysis in right aortic arch-a retrospective cohort study and review of the literature. *J Perinatol*. 2018;38(5):468-73.

Kurolap A, Eshach-Adiv O, Gonzaga-Jauregui C, Dolnikov K, Mory A, Paperna T, Hershkovitz T, Overton JD, Kaplan M, Glaser F, Zohar Y, Shuldiner AR, Berger G, **Baris Feldman H (Baris H)**. Establishing the role of PLVAP in protein-losing enteropathy: a homozygous

missense variant leads to an attenuated phenotype. *J Med Genet*. 2018;55(11):779-84.

Hershkovitz T, Kurolap A, Ruhrman-Shahar N, Monakier D, DeChene ET, Peretz-Amit G, Funke B, Zucker N, Hirsch R, Tan W-H, **Baris Feldman H**. Clinical diversity of MYH7-related cardiomyopathies: Insights into genotype-phenotype correlations. *Am J Med Genet A*. 2019;179(3):365-72.

Kurolap A, Eshach Adiv O, Hershkovitz T, Tabib A, Karbian N, Paperna T, Mory A, Vachyan A, Slijper N, Steinberg R, Zohar Y, Mevorach D, **Baris Feldman H**. Eculizumab Is safe and effective as a long-term treatment for protein-losing enteropathy due to CD55 deficiency. *J Pediatr Gastroenterol Nutr*. 2019;68(3):325-33.

Paperna T, Sharon-Shwartzman N, Kurolap A, Goldberg Y, Moustafa N, Carasso Y, Feinstien M, Mory A, Reznick-Levi G, Gonzaga-Jauregui C, Shuldiner AR, Basel-Salmon L, Ofran Y, Half EE, **Baris Feldman H**. Homozygosity for CHEK2 p.Gly167Arg leads to a unique cancer syndrome with multiple complex chromosomal translocations in peripheral blood karyotype. *J Med Genet*. 2019; 57(7):500-504.

Weiss K, Ekhilevitch N, Cohen L, Bratman-Morag S, Bello R, Martinez AF, Hadid Y, Shlush LI, Kurolap A, Paperna T, Mory A, **Baris Feldman H (Baris H)**, Muenke M. Identification of a novel PCNT founder pathogenic variant in the Israeli Druze population. *Eur J Med Genet*. 2019; 63(2):103643.

Tiosano D*, **Baris Feldman H (Baris H)***, Chen A*, Hitzert MM*, Schueler M*, Gulluni F*, Wiesener A, Bergua A, Mory A, Copeland B, Gleeson JG, Rump P, van Meer H, Sival DA, Haucke V, Kriwinsky J, Knaup KX, Reis A, Hauer NN, Hirsch E, Roepman R, Pfundt R, Thiel CT, Wiesener MS, Aslanyan MG, Buchner DA.*Equal contribution. Mutations in PIK3C2A cause syndromic short stature, skeletal abnormalities, and cataracts associated with ciliary dysfunction. *PLoS Genet*. 2019;15(4):e1008088.

Gallon R, Mühlegger B, Wenzel S-S, Sheth H, Hayes C, Aretz S, Dahan K, Foulkes W, Kratz CP, Ripperger T, Azizi AA, **Baris Feldman H**, Chong A-L, Demirsoy U, Florkin B, Imschweiler T, Januszkiewicz-Lewandowska D, Lobitz S, Nathrath M, Pander H-J, Perez-Alonso V, Perne C, Ragab I, Rosenbaum T, Rueda D, Seidel MG, Suerink M, Taeubner J, Zimmermann S-Y, Zschocke J, Borthwick GM, Burn J, Jackson MS, Santibanez-Koref M, Wimmer K. A sensitive and scalable microsatellite instability assay to diagnose constitutional mismatch repair deficiency by sequencing of peripheral blood leukocytes. *Hum Mutat*. 2019;40(5):649-55.

Kurolap A, Eshach Adiv O, Konnikova L, Werner L, Gonzaga-Jauregui C, Steinberg M, Mitsialis V, Mory A, Nunberg MY, Wall S, Shaoul R, Overton JD, Regeneron Genetics Center, Shuldiner AR, Zohar Y, Paperna T, Snapper SB, Shouval DS, **Baris Feldman H**. A unique presentation of infantile-onset colitis and eosinophilic disease without recurrent infections resulting from a novel homozygous CARMIL2 variant. *J Clin Immunol* 39(4):430-439.

Hershkovitz T, Kurolap A, Gonzaga-Jauregui C, Paperna T, Mory A, Wolf SE, Regeneron Genetics Center, Overton JD, Shuldiner AR, Saada A, Mandel H, **Baris Feldman H**. A novel TUFM homozygous variant in a child with mitochondrial cardiomyopathy expands the phenotype of combined oxidative phosphorylation deficiency 4. *J Hum Genet*. 2019;64(6):589-95.

Kurolap A, del Toro M, Spiegel R, Gutstein A, Shafir G, Cohen IJ, Barrabés JA, **Baris Feldman H (Feldman HB)**. Gaucher disease type 3c: New patients with unique presentations and review of the literature. *Mol Genet Metab.* 2019;127(2):138-46.

Weiss K, Lazar HP, Kurolap A, Martinez A, Paperna T, Cohen L, Smelan MF, Wallen S, Solveig H, Keren B, Terhal P, Irving M, Takaku M, Roberts JD, Petrovich RM, Vergano S, Kenney A, Hove H, Dechene E, Quinonez S, Colin E, Rumple M, Jain M, Monteil D, Roeder E, van Haeringen A, Gambello M, Santani A, Medne L, Krock B, Skraba CM, Zackai EH, Dubbs HA, Smol T, Ghoumid J, Parker M, Wright M, Turnpenny P, Clayton-Smith J, Metcalfe K, Kurumizaka H, Gelb B, **Baris Feldman H**, Campeau PM, Muenke M, Wade PA, Lachlan K. The CHD4-related syndrome: A comprehensive investigation of the clinical spectrum, genotype-phenotype correlations and molecular basis. *Genet Med*. 2019; 22(2):389-397.

Bernstein-Molho R, Barnes-Kedar I, Ludman MD, Reznik G, **Baris Feldman H (Feldman HB)**, Samra NN, Eilat A, Peretz T, Peretz LP, Shapira T, Magal N, Kalis ML, Yerushalmi R, Vinkler C, Liberman S, Basel-Salmon L, Shohat M, Levy-Lahad E, Friedman E, Bazak L, Goldberg Y. The yield of full BRCA1/2 genotyping in Israeli Arab high-risk breast/ovarian cancer patients. *Breast Cancer Res Treat*. 2019; 178(1):231-237.

Grants

2019-2020	Israel Innovation Authority
2020-2021	Israel Innovation Authority

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Identification of Novel Gene-Phenotype Associations in Rare Diseases

Positions

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Research

Approximately 80 percent of rare diseases are caused by altered functions of proteins encoded by single genes. Diagnostic success leading to personalized treatments and prevention of complications for individuals with rare diseases depends on progress in the discovery of genes underlying these conditions. Our goal at the Raphael Recanati Genetics Institute at the Rabin Medical Center is to decipher the etiology of rare diseases in humans. Main areas of our research include: 1) identification of new syndromes and new gene-disease associations for neurodevelopmental disorders, eye disorders, skin disorders and other phenotypes; 2) investigation of the role of artificial intelligence-based platforms in the interpretation of broad genomic sequencing results, and 3) definition of the role of clinical geneticists in connecting phenotype to genotype during genomic variant interpretation process. To date, we have identified more than 20 new gene-disease associations. As a result of these discoveries, population-based preventive carrier screening programs in at-risk populations have been established.

Publications

Masotti A, Uva P, Davis-Keppen L, **Basel-Vanagaite L**, Cohen L, Pisaneschi E, Celluzzi A, Bencivenga P, Fang M, Tian M, Xu X, Cappa M, Dallapiccola B. Keppen-Lubinsky Syndrome Is caused by mutations in the inwardly rectifying K(+) channel encoded by KCNJ6. Am J Hum Genet. 2015;96:295-300.

Basel-Vanagaite L, Smirin-Yosef P, Essakow JL, Tzur S, Lagovsky I, Maya I, Pasmanik-Chor M, Yeheskel A, Konen O, Orenstein N, Weisz Hubshman M, Drasinover V, Magal N, Peretz Amit G, Zalzstein Y, Zeharia A, Shohat M, Straussberg R, Monté D, Salmon-Divon M, Behar DM. Homozygous MED25 mutation implicated in eye-intellectual disability syndrome. Hum Genet. 2015;34:577-87.

Rojnueangnit K, Xie J, Gomes A, Sharp A, Callens T, Chen Y, Liu Y, Cochran M, Abbott MA, Atkin J, Babovic-Vuksanovic D, Barnett CP, Crenshaw M, Bartholomew DW, **Basel L**, Bellus G, Ben-Shachar S, Bialer MG, Bick D, Blumberg B, Cortes F, David KL, Destree A, Duat-Rodriguez A, Earl D, Escobar L, Eswara M, Ezquieta B, Frayling IM, Frydman M, Gardner K, Gripp KW, Hernández-Chico C, Heyrman K, Ibrahim J, Janssens S, Keena BA, Llano-Rivas I, Leppig K, McDonald M, Misra VK, Mulbury J, Narayanan V, Orenstein N, Galvin-Parton P, Pedro H, Pivnick EK, Powell CM, Randolph L, Raskin S, Rosell J, Rubin K, Seashore M, Schaaf CP, Scheuerle A, Schultz M, Schorry E, Schnur R, Siqveland E, Tkachuk A, Tonsgard J, Upadhyaya M, Verma IC, Wallace S, Williams C, Zackai E, Zonana J, Lazaro C, Claes K, Korf B, Martin Y, Legius E, Messiaen L. High incidence of Noonan Syndrome features including short stature and pulmonic stenosis in patients carrying NF1 missense mutations affecting p.Arg1809: Genotype-phenotype correlation. Hum Mutat. 2015;36:1052-63.

Kumar R, Corbett MA, Van Bon BW, Gardner A, Woenig JA, Jolly LA, Douglas E, Friend K, Tan C, Van Esch H, Holvoet M, Raynaud M, Field M, Leffler M, Budny B, Wisniewska M, Badura-Stronka M, Latos-Bieleńska A, Batanian J, Rosenfeld JA, **Basel-Vanagaite L**, Jensen C, Bienek M, Froyen G, Ullmann R, Hu H, Love MI, Haas SA, Stankiewicz P, Cheung SW, Baxendale A, Nicholl J, Thompson EM, Haan E, Kalscheuer VM, Gecz J. Increased STAG2 dosage defines a novel cohesinopathy with

intellectual disability and behavioral problems. Hum Mol Genet. 2015;24:7171-81.

Mimouni-Bloch A, Yeshaya J, Kahana S, Maya I, **Basel-Vanagaite L**. A de-novo interstitial microduplication involving 2p16.1-p15 and mirroring 2p16.1-p15 microdeletion syndrome: clinical and molecular analysis. Eur J Paediatr Neurol. 2015;19:711-5.

Shkalim-Zemer V, Davidovits M, Konen O, **Basel-Vanagaite L**. Sotos syndrome with co-morbid polycystic kidney disease: a case report. J Clin Case Rep. 2015;5:612.

Reinstein E, Smirin-Yosef, P, Lagovsky I, Davidov B, Peretz Amit G, Neumann D, Orr-Urtreger A, Ben-Shachat S, **Basel-Vanagaite L**. A founder mutation in ADAMTSL4 causes early-onset bilateral ectopia lentis among Jews of Bukharian origin. Mol Gent Metab. 2016;117:38-41.

Cohen R, Halevy A, Aharoni S, Kraus D, Konen O, **Basel-Vanagaite L**, Goldberg-Stern H, Straussberg R. Polymicrogyria and myoclonic epilepsy in autosomal recessive cutis laxa type 2A. Neurogenetics. 2016;17:251-257.

Basel-Vanagaite L, Wolf L, Orin M, Larizza L, Gervasini , Krantz ID, Deardoff MA. Recognition of the Cornelia de Lange syndrome phenotype with facial dysmorphology novel analysis. Clin Genet. 2016;89:557-63.

Eskin-Schwartz M*, **Basel-Vanagaite L***, David M, Lagovsky I, Ben-Amitai D, Smirin-Yosef P, Atzmony L, Hodak E. Intra-familial variation in clinical phenotype of CARD14-related psoriasis. Acta Derm Venereol. 2016;96:885-7. [*Shared first coauthorship]

Maya I, Kahana S, Yeshaya J, Tenne T, Yacobson S, Agmon-Fishman I, Cohen-Vig L, Levi A, Reinstein E, **Basel-Vanagaite L**, Sharony R. Chromosomal microarray analysis in fetuses with aberrant right subclavian artery. Ultrasound Obstet Gynecol. 49;337-341.

Weiss K, Terhal PA, Cohen L, Bruccoleri M, Irving M, Martinez AF, Rosenfeld JA, Machol K, Yang Y, Liu P, Walkiewicz M, Beuten J, Gomez-Ospina N, Haude K, Fong CT, Enns GM, Bernstein JA, Fan J, Gotway G, Ghorbani M; DDD Study., van Gassen K, Monroe GR, van Haaften G, **Basel-Vanagaite L**, Yang XJ, Campeau PM, Muenke M. De Novo mutations in CHD4, an ATP-dependent chromatin remodeler gene, cause an intellectual disability syndrome with distinctive dysmorphisms. Am J Hum Genet. 2016;99:934-941.

Weisz Hubshman M*, **Basel-Vanagaite L***, Krauss A, Konen O, Levy Y, Garty BZ, Smirin-Yosef P, Maya I, Lagovsky I, Taub E, Marom D, Gaash D, Shichrur K, Avigad S, Hayman Manzur L, Villa A, Sobacchi C, Shohat M, Yaniv I, Stein J. Homozygous deletion of RAG1, RAG2 and 5' region TRAF6 causes severe immune suppression and atypical osteopetrosis. Clin Genet. 2017;91:902-907. [*Shared first coauthorship]

Orenstein N, Weiss K, Oprescu SN, Shapira R, Kidron D, **Vanagaite-Basel L**, Antonellis A, Muenke M. Bi-allelic IARS mutations in a child with intra-uterine growth retardation, neonatal cholestasis, and mild developmental delay. Clin Genet. 2016;91:913-917

Smirin-Yosef P*, Zuckerman-Levin N*, Tzur S, Granot Y, Cohen L, Sachsenweger J, Borck G, Lagovsky I, Salmon-Divon M, Wiesmüller L, **Basel-Vanagaite L**. A biallelic mutation in the homologous recombination repair gene SPIDR is associated with human gonadal dysgenesis. J Clin Endocrinol Metab. 2016;102:681-688 [*Shared first coauthorship]

Basel-Vanagaite L, Pillar N, Isakov O, Smirin-Yosef P, Lagovsky I, Orenstein N, Salmon-Divon M, Tamary H, Bazak L, Meyerovitch, Pelli, Botchan S, Farberov L, Weissglas D, Shomron N. X-linked Elliptocytosis with impaired growth is related to mutated AMMECR1. Gene. 606;47-52

Lee JYW, Hsu C, Michael M, Nanda A, Liu L, McMillan JR, Pourreyron C, Takeichi T, Tolar J, Reid E, Hayday T, Blumen SC, Abu-Mouch S, Straussberg R, **Basel-Vanagaite L,** Barhum Y, Zouabi Y, Al-Ajmi H, Huang H, Lin T, Akiyama M, Lee JYY, McLean WHI, Simpson MA, Parsons M, McGrath JA. Large intragenic deletion in DSTYK underlies autosomal recessive complicated spastic paraparesis (SPG23). Am J Hum Genet. 2017;100:364-370.

Cohen L, Orenstein N, Weisz-Hubshman M, Bazak L, Davidov B, Reinstein E, Tzur S, Behar D, Smirin-Yosef P, Salmon-Divon M, Gross A, Shohat M, **Basel-Vanagaite L**. Utilization of whole exome sequencing in diagnostics of genetic disease: Rabin Medical Center's experience. Harefuah. 2017;156:212-216.

Salpietro V, Lin W, Delle Vedove A, Storbeck M, Liu Y, Efthymiou S, Manole A, Wiethoff S, Ye Q, Saggar A, McElreavey K, Krishnakumar SS; SYNAPS Study Group, Pitt M, Bello OD, Rothman JE, **Basel-Vanagaite L**, Hubshman MW, Aharoni S, Manzur AY, Wirth B, Houlden H. Homozygous mutations in VAMP1 cause a presynaptic congenital myasthenic syndrome. Ann Neurol. 2017;81:597-603.

Solomon-Zemler R, **Basel-Vanagaite L**, Steier D, Yakar S, Mel E, Phillip M, Bazak L, Bercovich D, Werner H, de Vries L. A novel heterozygous IGF-1 receptor mutation associated with hypoglycemia. Endocr Connect. 2017;6:395-403.

Bardin R, Hadar E, Haizler-Cohen L, Gabbay-Benziv R, Meizner I, Kahana S, Yeshaya J, Yacobson S, Cohen-Vig L, Agmon-Fishman I, **Basel-Vanagaite L**, Maya I. Cytogenetic analysis in fetuses with late onset abnormal sonographic findings. J Perinat Med. 2018;46:975-982.

Yilmaz R, Szakszon K, Altmann A, Altunoglu U, Senturk L, McGuire M, Calabrese O, Madan-Khetarpal S, **Basel-Vanagaite L**, Borck G. Kaufman oculocerebrofacial syndrome: Novel UBE3B mutations and clinical features in four unrelated patients. Am J Med Genet A. 2018;176:187-193.

Abbott JA, Meyer-Schuman R, Lupo V, Feely S, Mademan I, Oprescu SN, Griffin LB, Alberti MA, Casasnovas C, Aharoni S, **Basel-Vanagaite L**, Züchner S, De Jonghe P, Baets J, Shy ME, Espinós C, Demeler B, Antonellis A, Francklyn C. Substrate interaction defects in histidyl-tRNA synthetase linked to dominant axonal peripheral neuropathy. Hum Mutat. 2018;39:415-432.

Weisz Hubshman M, Broekman S, van Wijk E, Cremers F, Abu-Diab A, Khateb S, Tzur S, Lagovsky I, Smirin-Yosef P, Sharon D, Haer-Wigman L, Banin E, **Basel-Vanagaite L**, de Vrieze E. Whole-exome sequencing reveals POC5 as a novel gene associated with autosomal recessive retinitis pigmentosa. Hum Mol Genet. 2018;27:614-624.

Hemati P, Revah-Politi A, Bassan H, Petrovski S, Bilancia CG, Ramsey K, Griffin NG, Bier L, Cho MT, Rosello M, Lynch SA, Colombo S, Weber A, Haug M, Heinzen EL, Sands TT, Narayanan V, Primiano M, Aggarwal VS, Millan F, Sattler-Holtrop SG, Caro-Llopis A, Pillar N, Baker J, Freedman R, Kroes HY, Sacharow S, Stong N, Lapunzina P, Schneider MC, Mendelsohn NJ, Singleton A, Loik Ramey V, Wou K, Kuzminsky A, Monfort S, Weiss M, Doyle S, Iglesias A, Martinez F, Mckenzie F, Orellana C, van Gassen KLI, Palomares M, Bazak L, Lee A, Bircher A, **Basel-Vanagaite L**, Hafström M, Houge G; C4RCD Research Group; DDD study, Goldstein DB, Anyane-Yeboa K. Refining the phenotype associated with GNB1 mutations: Clinical data on 18 newly identified patients and review of the literature. Am J Med Genet A. 2018;176:2259-2275

Barnes-Kedar I, Bernstein-Molho R, Ginzach N, Hartmajer S, Shapira T, Magal N, Kalis ML, Peretz T, Shohat M, **Basel-Salmon L**, Friedman E, Bazak L, Goldberg Y. The yield of full BRCA1/2 genotyping in Israeli high-risk breast/ovarian cancer patients who do not carry the predominant mutations. Breast Cancer Res Treat. 2018;172:151-157.

Orenstein N, Goldberg-Stern H, Straussberg R, Bazak L, Weisz Hubshman M, Kropach N, Gilad O, Scheuerman O, Dory Y, Kraus D, Tzur S, Magal N, Kilim Y, Shkalim Zemer V, **Basel-Salmon L**. A de novo GABRA2 missense mutation in severe early-onset epileptic encephalopathy with a choreiform movement disorder. Eur J Paediatr Neurol. 2018;22:516-524.

Maya I, Sharony R, Yacobson S, Kahana S, Yeshaya J, Tenne T, Agmon-Fishman I, Cohen-Vig L, Goldberg Y, Berger R, **Basel-Salmon L**, Shohat M. When genotype is not predictive of phenotype: implications for genetic counseling based on 21,594 chromosomal microarray analysis examinations. Genet Med. 2018;20:128-131.

Basel-Salmon L, Orenstein N, Markus-Bustani K, Ruhrman-Shahar N, Kilim Y, Magal N, Hubshman MW, Bazak L. Improved diagnostics by exome sequencing following raw data reevaluation by clinical geneticists involved in the medical care of the individuals tested. Genet Med. 2019;21:1443–1451

Gurovich Y, Hanani Y, Bar O, Nadav G, Fleischer N, Gelbman D, **Basel-Salmon** L, Krawitz PM, Kamphausen SB, Zenker M, Bird LM, Gripp KW. Identifying facial phenotypes of genetic disorders using deep learning. Nat Med. 2019;1:60-64.

Shohet A, Cohen L, Haguel D, Mozer Y, Shomron N, Tzur S, Bazak L, **Basel-Salmon L**, Krause I. Variant in SCYL1 gene causes aberrant splicing in a family with cerebellar ataxia, recurrent episodes of liver failure, and growth retardation. Eur J Hum Genet. 2019;27:263-268

Rabinowitz T, Polsky A, Golan D, Danilevsky A, Shapira G, Raff C, **Basel- Salmon L**, Matar RT, Shomron N. Bayesian-based noninvasive prenatal diagnosis of single-gene disorders. Genome Res. 2019;29:428-438.

Horn S, Au M, **Basel-Salmon L**, Bayrak-Toydemir P, Chapin A, Cohen L, Elting MW, Graham JM, Gonzaga-Jauregui C, Konen O, Holzer M, Lemke J, Miller CE, Rey LK, Wolf NI, Weiss MM, Waisfisz Q, Mirzaa GM, Wieczorek D, Sticht H, Abou Jamra R. De novo variants in PAK1 lead to intellectual disability with macrocephaly and seizures. Brain. 2019;142:3351-3359.

Bernstein-Molho R, Barnes-Kedar I, Ludman MD, Reznik G, Feldman HB, Samra NN, Eilat A, Peretz T, Peretz LP, Shapira T, Magal N, Kalis ML, Yerushalmi R, Vinkler C, Liberman S, **Basel-Salmon L**, Shohat M, Levy-Lahad E, Friedman E, Bazak L, Goldberg Y. The yield of full BRCA1/2 genotyping in Israeli Arab high-risk breast/ovarian cancer patients. Breast Cancer Res Treat. 2019;178:231-237.

Shen J, Oza AM, Del Castillo I, Duzkale H, Matsunaga T, Pandya A, Kang HP, Mar-Heyming R, Guha S, Moyer K, Lo C, Kenna M, Alexander JJ, Zhang Y, Hirsch Y, Luo M, Cao Y, Wai Choy K, Cheng YF, Avraham KB, Hu X, Garrido G, Moreno-Pelayo MA, Greinwald J, Zhang K, Zeng Y, Brownstein Z, **Basel-Salmon L**, Davidov B, Frydman M, Weiden T, Nagan N, Willis A, Hemphill SE, Grant AR, Siegert RK, DiStefano MT, Amr SS, Rehm HL, Abou Tayoun AN; ClinGen Hearing Loss Working Group. Consensus interpretation of the p.Met34Thr and p.Val37Ile variants in GJB2 by the ClinGen Hearing Loss Expert Panel. Genet Med. 2019;21:2442-2452.

Sagi-Dain L, Cohen Vig L, Kahana S, Yacobson S, Tenne T, Agmon-Fishman I, Klein C, Matar R, **Basel-Salmon L**, Maya I. Chromosomal microarray vs. NIPS: analysis of 5541 low-risk pregnancies. Genet Med. 2019;21:2462-2467.

Magini P, Smits DJ, Vandervore L, Schot R, Columbaro M, Kasteleijn E, van der Ent M, Palombo F, Lequin MH, Dremmen M, de Wit MCY, Severino M, Divizia MT, Striano P, Ordonez-Herrera N, Alhashem A, Al Fares A, Al Ghamdi M, Rolfs A, Bauer P, Demmers J, Verheijen FW, Wilke M, van Slegtenhorst M, van der Spek PJ, Seri M, Jansen AC, Stottmann RW, Hufnagel RB, Hopkin RJ, Aljeaid D, Wiszniewski W,Gawlinski P, Laure-Kamionowska M, Alkuraya FS, Akleh H, Stanley V, Musaev D, Gleeson JG, Zaki MS, Brunetti-Pierri N, Cappuccio G, Davidov B, **Basel-Salmon L,** Bazak L, Shahar NR, Bertoli-Avella A, Mirzaa GM, Dobyns WB, Pippucci T, Fornerod M, Mancini GMS. Loss of SMPD4 causes a developmental disorder characterized by microcephaly and congenital arthrogryposis. Am J Hum Genet. 2019;105:689-705.

Sagi-Dain L, Goldberg Y, Peleg A, Sukenik-Halevy R, Sofrin-Drucker E, Appelman Z, Josefsberg BYS, Ben-Shachar S, Vinkler C, **Basel-Salmon L**, Maya I. The rare 13q33-q34 microdeletions: eight new patients and review of the literature. Hum Genet. 2019;138:1145-1153.

Toledano H, Orenstein N, Sofrin E, Ruhrman-Shahar N, Amarilyo G, **Basel-Salmon L**, Shuldiner AR, Smirin-Yosef P, Aronson M, Al-Tarrah H, Bazak L, Gonzaga-Jauregui C, Tabori U, Wimmer K, Goldberg Y. Paediatric systemic lupus erythematosus as a manifestation of constitutional mismatch repair deficiency. J Med Genet. 201.

Bend R, Cohen L, Carter MT, Lyons MJ, Niyazov D, Mikati MA, Rojas SK, Person RE, Si Y, Wentzensen IM; Regeneron Genetics Center, Torti E, Lee JA, Boycott KM, **Basel-Salmon L**, Ferreira CR, Gonzaga-Jauregui C. Phenotype and mutation expansion of the PTPN23 associated disorder characterized by neurodevelopmental delay and structural brain abnormalities. Eur J Hum Genet. 2019;28:76-87.

Lieberman S, Beeri R, Walsh T, Schechter M, Keret D, Half E, Gulsuner S, Tomer A, Jacob H, Cohen S, **Basel-Salmon L**, Mansur M, Berger R, Katz LH, Golomb E, Peretz T, Levy Z, Kedar I, King MC, Levy-Lahad E, Goldberg Y. Variable features of juvenile polyposis syndrome with gastric involvement among patients with a large genomic deletion of BMPR1A. Clin Transl Gastroenterol. 2019;10:e00054.

Basel-Salmon L, Orenstein N, Markus-Bustani K, Ruhrman-Shahar N, Kilim Y, Magal N, Hubshman MW, Bazak L. Improved diagnostics by exome sequencing following raw data reevaluation by clinical geneticists involved in the medical care of the individuals tested. Genet Med. 2019;21:1443-1451.

Weisz-Hubshman M, Meirson H, Michaelson-Cohen R, Beeri R, Tzur S, Bormans C, Modai S, Shomron N, Shilon Y, Banne E, Orenstein N, Konen O, Marek-Yagel D, Veber A, Shalva N, Imagawa E, Matsumoto N, Lev D, Lerman Sagie T, Raas-Rothschild A, Ben-Zeev B, **Basel-Salmon L**, Behar DM, Heimer G. Novel WWOX deleterious variants cause early infantile epileptic encephalopathy, severe developmental delay and dysmorphism among Yemenite Jews. Eur J Paediatr Neurol. 2019;23:418-426.

Paperna T, Sharon-Shwartzman N, Kurolap A, Goldberg Y, Moustafa N, Carasso Y, Feinstien M, Mory A, Reznick-Levi G, Gonzaga-Jauregui C, Shuldiner AR, **Basel-Salmon L**, Ofran Y, Half EE, Baris Feldman H. Homozygosity for CHEK2 p.Gly167Arg leads to a unique cancer syndrome with multiple complex chromosomal translocations in peripheral blood karyotype. J Med Genet. 2019;57:500-504.

Li L, Ghorbani M, Weisz-Hubshman M, Rousseau J, Thiffault I, Schnur RE, Breen C, Oegema R, Weiss MM, Waisfisz Q, Welner S, Kingston H, Hills JA, Boon EM, **Basel-Salmon L**, Konen O, Goldberg-Stern H, Bazak L, Tzur S, Jin J, Bi X, Bruccoleri M, McWalter K, Cho MT, Scarano M, Schaefer GB, Brooks SS, Hughes SS, van Gassen KLI, van Hagen JM, Pandita TK, Agrawal PB, Campeau PM, Yang XJ. Lysine acetyltransferase 8 is involved in cerebral development and syndromic intellectual disability. J Clin Invest. 2020;130:1431-1445

Mak CCY, Doherty D, Lin AE, Vegas N, Cho MT, Viot G, Dimartino C, Weisfeld-Adams JD, Lessel D, Joss S, Li C, Gonzaga-Jauregui C, Zarate YA, Ehmke N, Horn D, Troyer C, Kant SG, Lee Y, Ishak GE, Leung G, Barone Pritchard A, Yang S, Bend EG, Filippini F, Roadhouse C, Lebrun N, Mehaffey MG, Martin PM, Apple B, Millan F, Puk O, Hoffer

MJV, Henderson LB, McGowan R, Wentzensen IM, Pei S, Zahir FR, Yu M, Gibson WT, Seman A, Steeves M, Murrell JR, Luettgen S, Francisco E, Strom TM, Amlie-Wolf L, Kaindl AM, Wilson WG, Halbach S, **Basel-Salmon L**, Lev-El N, Denecke J, Vissers LELM, Radtke K, Chelly J, Zackai E, Friedman JM, Bamshad MJ, Nickerson DA; University of Washington Center for Mendelian Genomics, Reid RR, Devriendt K, Chae JH, Stolerman E, McDougall C, Powis Z, Bienvenu T, Tan TY, Orenstein N, Dobyns WB, Shieh JT, Choi M, Waggoner D, Gripp KW, Parker MJ, Stoler J, Lyonnet S, Cormier-Daire V, Viskochil D, Hoffman TL, Amiel J, Chung BHY, Gordon CT. MN1 C-terminal truncation syndrome is a novel neurodevelopmental and craniofacial disorder with partial rhombencephalosynapsis. Brain. 2020;143:55-68.

Tan TY, Sedmík J, Fitzgerald MP, Halevy RS, Keegan LP, Helbig I, **Basel-Salmon L**, Cohen L, Straussberg R, Chung WK, Helal M, Maroofian R, Houlden H, Juusola J, Sadedin S, Pais L, Howell KB, White SM, Christodoulou J, & O'Connell MA. Bi-allelic ADARB1 variants associated with microcephaly, intellectual disability, and seizures. Am J Hum Genet. 2020;106:467-483.

Maya I, **Basel-Salmon L**, Singer A, Sagi-Dain L. High-frequency low-penetrance copy-number variant classification: should we revise the existing guidelines? Genet Med. 2020;22:1276-1277.

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Genomics and Epitranscriptomics

Positions

Professor, Sackler Faculty of Medicine

Djerassi Chair in Oncology, Tel Aviv University

Head - Cancer Research Center, Sheba Medical Center, Tel Hashomer

Head- The Wohl Institute of Translational Medicine, Sheba Medical Center, Tel Hashomer

Research

Our main interest lies in the deciphering of novel genetic and epigenetic mechanisms affecting global gene expression and their implication in cancer and neuronal disorders.

Our research interests are:

- The deciphering of the role of RNA epigenetics, including RNA editing and RNA methylation in the regulation of gene expression and cell fate.
- The study of transposable genetic elements in cancer and development
- Genetic and genomic studies relevant to cancer and genetic diseases
- Genetically non-identical tumors

Publications

Manuscripts

Simon AJ, Lev A, Zhang Y, et al Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects. J Exp Med. 2016; 8:1429-1440.

Dominissini D, Nachtergaele S, Moshitch-Moshkovitz S et al, The dynamic N1-methyladenosine methylome in eukaryotic messenger RNA. Nature, 2016; 530(7591):441-6.

Choi J, Leong K et al. N6-methyladenosine in mRNA disrupts tRNA selection and translation-elongation dynamics. Nature Struct Mol Biol. 2016; 23(2):110-5.

Geula S, Moshitch-Moshkovitz S, Dominissini D et al. m6A mRNA methylation facilitates resolution of naïve pluripotency toward differentiation. Science 2015;347(6225):1002-6

Reviews

Frye M, Jaffrey SR, Pan T, **Rechavi G,** Suzuki T. RNA modifications: what have we learned and where are we headed? Nat Rev Genet. 2016;17(6):365-72.

Grants

2013-2017	Israel Centers of Research Excellence (I-CORE)
2014-2019	Flight Attendants Medical Research Institute FAMRI

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Rare Diseases Diagnosis and Research

Positions

Pediatrician - Medical Geneticist, Sheba Medical Center

Director, Institute for Rare Diseases

Associate Professor, Sackler Faculty of Medicine

National Coordinator, Orphanet Israel

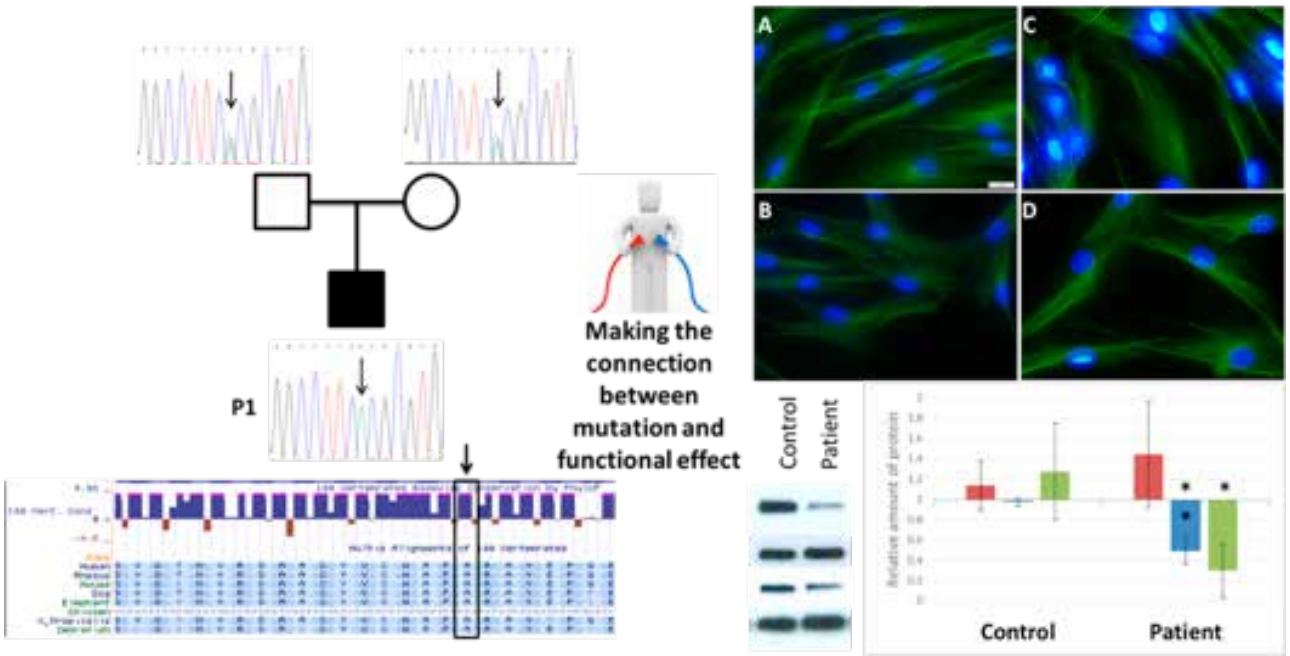
National Coordinator, Rare Diseases National Registry

Research

There are more than 6000 rare diseases affecting more than 60 million people in Europe and the US alone. Most of these diseases are affecting children , are chronic and are of genetic etiology.

Advances in rare disease research are very quickly changing the pediatric care for children affected with these non identified diseases which are very often complex. Research is one of the basics stones for building an accurate care of patients and families. Here, we wish to incorporate research to awareness, diagnosis, treatment and health policy. Our goals include identification of rare diseases causing genes, study the function of the abnormal protein , and finally deciphering new protein pathways in order to establish new therapies. Since the laboratory is in a clinical setting the results of the work is translated into genetic counseling and clinical care and sometimes treatment (MPS II-MPS IV-Fabry disease). With this in mind we are performing cellular studies and drug screens targeted to rare diseases in collaboration with other laboratories, aiming to better understand pathways such as the one linked to mucolipin 1 involved in the mucolipidosis IV clinical symptoms with the goal to provide a specific therapy.

In the field of clinical research, we focus on different subjects that include different topics such as: Natural history of MPS III (Hetz project; Understanding of the practical aspects of the medical genetics (Genet Med. 2016;18(4):372-7); Ongoing project on how the patients are dealing with the information linked to the results of the use of new technologies such as CNV and Exome sequencing.



Publications

Heimer G, Kerätär JM, Riley LG, Balasubramaniam S, Eyal E, Pietikäinen LP, Hiltunen JK, Marek-Yagel D, Hamada J, Gregory A, Rogers C, Hogarth P, Nance MA, Shalva N, Veber A, Tzadok M, Nissenkorn A, Tonduti D, Renaldo F; University of Washington Center for Mendelian Genomics., Kraoua I, Panteghini C, Valletta L, Garavaglia B, Cowley MJ, Gayevskiy V, Roscioli T, Silberstein JM, Hoffmann C, **Raas-Rothschild A**, Tiranti V, Anikster Y, Christodoulou J, Kastaniotis AJ, Ben-Zeev B, Hayflick SJ. MECR Mutations Cause Childhood-Onset Dystonia and Optic Atrophy, a Mitochondrial Fatty Acid Synthesis Disorder. Am J Hum Genet. 2016.

Pode-Shakked B, Barash H, Ziv L, Gripp KW, Flex E, Barel O, Carvalho KS, Scavina M, Chillemi G, Niceta M, Eyal E, Kol N, Ben-Zeev B, Bar-Yosef O, Marek-Yagel D, Bertini E, Duker AL, Anikster Y, Tartaglia M, **Raas-Rothschild A.** Microcephaly, intractable seizures and developmental delay caused by biallelic variants in TBCD: Further delineation of a new chaperone-mediated tubulinopathy. Clin Genet. 2016.

Reinstein E, Gutierrez-Fernandez A, Tzur S, Bormans C, Marcu S, Tayeb-Fligelman E, Vinkler C, **Raas-Rothschild A,** Irge D, Landau M, Shohat M, Puente XS, Behar DM, Lopez-Otın C. Congenital dilated cardiomyopathy caused by biallelic mutations in Filamin C. Eur J Hum Genet. 2016;24(12):1792-1796.

Scott EM, Halees A, Itan Y, Spencer EG, He Y, Azab MA, Gabriel SB, Belkadi A, Boisson B, Abel L, Clark AG; **Greater Middle East Variome Consortium**., Alkuraya FS, Casanova JL, Gleeson JG. Characterization of Greater Middle Eastern genetic variation for enhanced disease gene discovery. Characterization of Greater Middle Eastern genetic variation for enhanced disease gene discovery. Nat Genet. 2016;48(9):1071-6.

Rechavi E, Levy-Mendelovich S, Stauber T, Shamash J, Reinstein S, Vernitsky H, Adam D, Simon AJ, Lev A, **Raas-Rothschild A,** Somech R. Combined immunodeficiency in a patient with mosaic monosomy 21. Immunol Res. 2016;64(4):841-7.

Byrne S, Jansen L, U-King-Im JM, Siddiqui A, Lidov HG, Bodi I, Smith L, Mein R, Cullup T, Dionisi-Vici C, Al-Gazali L, Al-Owain M, Bruwer Z, Al Thihli K, El-Garhy R, Flanigan KM, Manickam K, Zmuda E, Banks W, Gershoni-Baruch R, Mandel H, Dagan E, **Raas-Rothschild A**, Barash H, Filloux F, Creel D, Harris M, Hamosh A, Kölker S, Ebrahimi-Fakhari D, Hoffmann GF, Manchester D, Boyer PJ, Manzur AY, Lourenco CM, Pilz DT, Kamath A, Prabhakar P, Rao VK, Rogers RC, Ryan MM, Brown NJ, McLean CA, Said E, Schara U, Stein A, Sewry C, Travan L, Wijburg FA, Zenker M, Mohammed S, Fanto M, Gautel M, Jungbluth H. EPG5-related Vici syndrome: a paradigm of neurodevelopmental disorders with defective autophagy. Brain. 2016;139(Pt 3):765-81.

Mimouni-Bloch A, Finezilber Y, Rothschild M, **Raas-Rothschild A.** Extensive Mongolian Spots and Lysosomal Storage Diseases. J Pediatr. 2016;170:333-e1.

Eventov-Friedman S, Frumkin A, Bar-Oz B, **Raas-Rothschild A**. Mosaic Trisomy 14 in a Newborn with Multiple Malformations: When Chromosomal Microarray is a Clue to Diagnosis. Isr Med Assoc J. 2015;17(7):459-60.

Sukenik-Halevy R, Ludman MD, Ben-Shachar S, **Raas-Rothschild A.** The time-consuming demands of the practice of medical genetics in the era of advanced genomic testing. Genet Med. 2016;18(4):372-7.

Terhal PA, Nievelstein RJ, Verver EJ, Topsakal V, van Dommelen P, Hoornaert K, Le Merrer M, Zankl A, Simon ME, Smithson SF, Marcelis C, Kerr B, Clayton-Smith J, Kinning E, Mansour S, Elmslie F, Goodwin L, van der Hout AH, Veenstra-Knol HE, Herkert JC, Lund AM, Hennekam RC, Mégarbané A, Lees MM, Wilson LC, Male A, Hurst J, Alanay Y, Annerén G, Betz RC, Bongers EM, Cormier-Daire V, Dieux A, David A, Elting MW, van den Ende J, Green A, van Hagen JM, Hertel NT, Holder-Espinasse M, den Hollander N, Homfray T, Hove HD, Price S, **Raas-Rothschild A**, Rohrbach M, Schroeter B, Suri M, Thompson EM, Tobias ES, Toutain A, Vreeburg M, Wakeling E, Knoers NV, Coucke P, Mortier GR. A study of the clinical and radiological features in a cohort of 93 patients with a COL2A1 mutation causing spondyloepiphyseal dysplasia congenita or a related phenotype. Am J Med Genet A. 2015;167A(3):461-75.

Reviews

Mendlovic J, Barash H, Yardeni H, Banet-Levi Y, Yonath H, **Raas-Rothschild A.** [RARE DISEASES DTC: DIAGNOSIS, TREATMENT AND CARE]. Harefuah. 2016 Apr;155(4):241-4, 253. Hebrew.

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New Gene Identification and Genotype-Phenotype Correlation

Positions

Associate Professor of Pediatrics and Human Molecular Genetics and Biochemistry, Sackler School of Medicine

Committee Member, Israel Medical Association, Israeli Board of Medical Genetics, American Society of Human Genetics, American Board of Medical Genetics, Institutional Review Board (Helsinki) Assaf Harofeh

Member, Research and Development Committee, Tel Aviv University

Research

We study genetically undefined families using homozygosity mapping and EXOME analyses, in collaboration with other leading centers, to define disease causing genes. Once a causative mutation is defined, further functional studies are carried out. We identified at least five new genes in the last decade that enabled counseling patients and prenatal diagnosis.

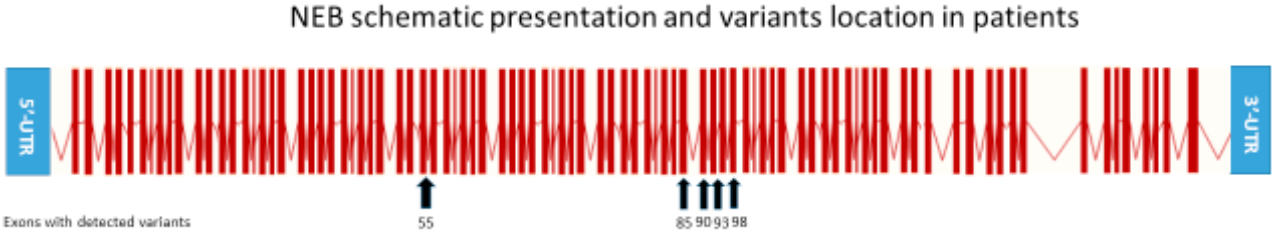
We investigate the genotype-phenotype correlation of newly defined mutations to expand the disease spectrum and impact of genetic disorders.

Publications

Yablonski-Peretz T, Paluch Shimon S, Soussan Gutman L, Kaplan Y, Dvir A, Barnes-Kedar I, Kadury L, Semenysty V, Noa Efrat (Ben Baruch) N, Victoria Neiman V, Yafit Glasser Y, Michaelson-Cohen R, Katz L, Kaufman B, Talia Golan T, **Reish O**, Ayala Hubert A, Safra T, Yaron Y, Friedman E. Screening for germline mutations in breast/ovarian cancer susceptibility genes in high-risk families in Israel. Breast Cancer Res and Treat, 2016, 155(1):133-8

Reish O*, Liam A*, Zouella A., Roth Y, Polack-Charcon S., Baboushkin T., Benyamini L., Mussaffi H., Sheffield V., Parvari R. A homozygous *NME7* mutation is associated with *situs inversus totalis* . Hum Mut, 2016, 37(8):727-31. Equal contribution*

Feingold-Zadok M, Chitayat D, Chong K, Injeyan M, Shannon P, Chapmann D, Maymon R, Pillar N, **Reish O**. Mutations in the NEB gene cause fetal akinesia/arthrogryposis multiplex congenita. *Prenat Diagn*. 2016 Dec 9 [Epub ahead of print]



NEB gene schematic presentation. The gene contains several transcripts ranging from 149-183 exons. The arrows point at specific exons where variants were detected in patients with prenatal AMC.

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Investigating the Molecular Genetics of Skin Diseases

Positions

Chair, Department of Dermatology, Tel Aviv Medical Center

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Research

Our laboratory has been investigating the genetic basis of skin disorders for the past 15 years. Monogenic skin disorders are known to be prevalent among Middle Eastern populations, and at this regard, our laboratory is ideally situated to carry research in that field. These efforts have led to the deciphering of the molecular basis of more than 20 genetic diseases by members of our group. The deciphering of the molecular basis of a monogenic disorder invariably reveals a novel pathway whose importance is exemplified by the disease resulting from its malfunction. We systematically explore the mechanistic aspects of these new pathways using almost exclusively humanized models such as three-dimensional skin equivalents, hair organ cultures and chimeric mouse models. Once the function of a novel gene product is established, this new knowledge can be translated in the form of new treatments for rare and more common diseases alike. For example, we have found that defective expression of P-cadherin causes hair loss due to disrupted Wnt signaling. We are now developing small inhibitors for this new pathway as a new treatment for conditions associated with excessive hair growth. Based on a similar paradigm we are now also investigating the genetic basis of complex skin traits including psoriasis and pemphigus, a dreadful autoimmune disorder associated with 90% mortality if left untreated.

Artificial human skin grown in vitro

Ex vivo culture of human hair follicles

Publications

Samuelov L, Sarig O, Gat A, **Sprecher E**. Extensive lentigo simplex, linear epidermolytic nevus and epidermolytic nevus comedonicus caused by a somatic mutation in KRT10. Br J Dermatol, 173, 293-296, 2015.

van der Velden J, van Geel M, Nellen R, Jonkman M, McGrath J, Nanda A, **Sprecher E**, van Steensel M; McLean I, Cassidy A. Novel TGM5 mutations in acral peeling skin syndrome. Exp Dermatol, 24, 285-289, 2015.

Li Q, Chung HJ, Ross N, Keller M, Andrews J, Kingman J, Sarig O, Fuchs-Telem D, **Sprecher E,** Uitto J. Analysis of CARD14 Polymorphisms in Pityriasis Rubra Pilaris: Activation of NF-κB. J Invest Dermatol, 135, 1905-1908, 2015.

Zeeli T, Padalon-Brauch G, Ellenbogen E, Gat A, Sarig O, **Sprecher E.** Pyoderma gangrenosum, acne and ulcerative colitis in a patient with a novel mutation in the PSTPIP1 gene. Clin Exp Dermatol, 40, 367-372, 2015.

Warshauer E, Samuelov L, Sarig O, Vodo D, Bindereif A, Kanaan M, Gat U, Fuchs-Telem D, Shomron N, Farberov L, Pasmanik-Chor M, Nardini G, Winkler E, Meilik B, Petit I, Paus R, **Sprecher E**, Nousbeck J. RBM28, a protein deficient in ANE syndrome, regulates hair follicle growth via miR-203 and p63. Exp Dermatol, 24, 618-22, 2015.

McAleer MA, Pohler E, Smith FJ, Wilson NJ, Cole C, MacGowan S, Koetsier JL, Godsel LM, Harmon RM, Gruber R, Crumrine D, Elias PM, McDermott M, Butler K, Broderick A, Sarig O, **Sprecher E**, Green KJ, McLean WH, Irvine AD. Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin. J Allergy Clin Immunol, 136, 1268-1276, 2015.

Mashiah J, Harel A, Bitterman O, Sagi L, Gat A, Fellig Y, Ben-Shachar S, **Sprecher E**. Isotretinoin treatment of autosomal recessive congenital ichthyosis complicated by co-existing dysferlinopathy. Clin Exp Dermatol, 41, 390-393, 2016.

Vodo D, Sarig O, Peled A, Frydman M, Greenberger S, **Sprecher E**. Autosomal dominant cutis laxa resulting from an intronic mutation in *ELN.* Exp Dermatol, 24, 885-887, 2016.

Schiller S, Seebode C, Wieser G, Goebbels S, Ruhwedel T, Horowitz M, Rapaport D, Sarig O, **Sprecher E**, Emmert S. Non-keratinocyte SNAP29 influences epidermal differentiation and hair follicle formation in mice. Exp Dermatol, 25, 647-9, 2016.

Pavlovsky M, Samuelov L, **Sprecher E**, Matz H. NB-UVB phototherapy for generalized granuloma annulare. Dermatol Ther, 29, 152-154, 2016.

Tekin B, Yucelten D, Beleggia F, Sarig O, **Sprecher E**. Papillon–Lefèvre syndrome: Case series of 6 patients and identification of a novel mutation. Int J Dermatol, 55, 898-902, 2016.

Geller S, Gat A, Harel A, Mashiah J, Zeeli T, Eming R, Ishii N, Hertl M, Hashimoto T, Sprecher E. Childhood pemphigus foliaceus with exclusive immunoglobulin G autoantibodies to desmocollins. Pediatr Dermatol, 33, e10-3, 2016.

Schiller SA, Seebode C, Wieser GL, Goebbels S, Möbius W, Horowitz M, Sarig O, Sprecher E, Emmert S. Establishment of two mouse models for CEDNIK syndrome reveals the pivotal role of SNAP29 in epidermal differentiation. J Invest Dermatol, 136, 672-679, 2016.

Khamaysi Z, Bochner R, Indelman M, Magal L, Avitan-Hersh E, Sarig O, Sprecher E, Bergman R. Segmental basal cell nevus syndrome caused by an activating mutation in Smoothened. Br J Dermatol, 175, 178-181, 2016.

Eskin-Schwartz M, Metzger Y, Peled A, Weissglas-Volkov D, Malchin N, Gat A, Vodo D, Mevorah B, Shomron N, Sprecher E, Sarig O. Somatic mosaicism for a “lethal” GJB2 mutation results in a patterned form of spiny hyperkeratosis without eccrine involvement. Ped Dermatol, 33, 322-326, 2016.

Mashiah Y, Kutz A, Ben Ami R, Savion M, Goldberg I, Gan Or T, Zidan O, Sprecher E, Harel A. Tinea capitis outbreak among pediatric refugee population, an evolving health care challenge. Mycoses, 59, 553-537, 2016.

Vodo D, Sarig O, Geller S, Ben-Asher E, Olender T, Bochner R, Goldberg I, Nosgorodsky J, Alkelai A, Tatarskyy P, Peled A, Baum S, Barzilai A, Ibrahim SM, Zillikens D Lancet D, **Sprecher E**. Identification of a functional risk variant for pemphigus vulgaris in the *ST18* gene. PLoS Genetics, 12:e1006008, 2016.

Pigors M, Sarig O, Heinz L, Plagnol V, Fischer J, Mohamad J, Malchin N, Rajpopat S, Kharfi M, Lestringant GG, **Sprecher E**, Kelsell DP, Blaydon DC. Loss-of-function mutations in *SERPINB8* linked to exfoliative ichthyosis with impaired mechanical stability of intercellular adhesions. Am J Hum Genet, 99, 430-436, 2016.

Malchin N, Sarig O, Grafi-Cohen M, Geller S, Goldberg I, Shani A, Gat A, **Sprecher E**, Mashiah JA novel homozygous deletion in *EXPH5* causes a

skin fragility phenotype: case report and literature review. Clin Exp Dermatol, in press, 2016.

Eskin-Schwartz M, Drozhdina M, Sarig O, Gat A, Jackman T, Isakov O, Shomron N, Samuelov L, Malchin N, Peled A, Vodo D, Hovnanian A, Ruzicka T, Koshkin S, Harmon B, Koetsier JL, Green K, Paller A, **Sprecher E**. Epidermolytic ichthyosis sine epidermolysis. Am J Dermatopathol, in press, 2016.

Lin Z, Li S, Feng C, Yang S, Wang H, Ma D, Zhang J, Gou M, Bu D, Zhang T, Kong X, Wang X, Sarig O, Ren Y, Dai L, Liu H, Zhang J, Li F, Hu Y, Padalon-Brauch G, Vodo D, F Zhou, Chen T, Deng H, **Sprecher E**, Yang Y, Tan X. Stabilizing mutations of KLHL24 ubiquitin 1ligase cause loss of keratin 14 and human skin fragility. Nat Genet, in press, 2016.

Bochner R, Samuelov L, Sarig O, Li Q, Adase CA, Isakov O, Malchin N, Vodo D, Shayevitch R, Peled A, Yu BD, Fainberg G, Warshauer E, Adir N, Erez N, Gat A, Gottlieb Y, Rogers T, Pavlovsky M, Goldberg I, Shomron N, Sandilands A, Campbell LE, MacCallum S, McLean WHI, Ast G, Gallo RL, Uitto J, **Sprecher E**. Calpain 12 function revealed through the study of an atypical case of autosomal recessive congenital ichthyosis. J Invest Dermatol, in press, 2016.

Peled A, Sarig O, Samuelov L, Bertolini M, Ziv L, Weissglas-Volkov D, Eskin-Schwartz M, Adase CA, Malchin N, Bochner R, Fainberg G, Goldberg I, Sugawara K, Baniel A, Tsuruta D, Luxenburg C, Adir N, Duverger O, Morasso M, Shalev S, Gallo RL, Shomron N, Paus R, **Sprecher E**. Mutations in *TSPEAR*, Encoding a Regulator of Notch Signaling, Affect Tooth and Hair Follicle Morphogenesis. PLoS Genetics, in press, 2016.

Ü Basmanav FB, Cau L, Tafazzoli A, Méchin MC, Wolf S, Romano MT, Valentin F, Wiegmann H, Huchenq A, Kandil R, Garcia Bartels N, Kilic A, George S, Ralser DJ, Bergner S, Ferguson DJ, Oprisoreanu AM, Wehner M, Thiele H, Altmüller J, Nürnberg P, Swan D, Houniet D, Büchner A, Weibel L, Wagner N, Grimalt R, Bygum A, Serre G, Blume-Peytavi U, **Sprecher E,** Schoch S, Oji V, Hamm H, Farrant P, Simon M, Betz RC. Mutations in Three Genes Encoding Proteins Involved in Hair Shaft Formation Cause Uncombable Hair Syndrome. Am J Hum Genet, in press, 2017

Samuelov L, Li Q, Bochner R, Najor N, AlbrechtL, Malchin N, Goldsmith T, Grafi-Cohen M, Vodo D, Fainberg G, Meilik B, Goldberg I, Warshauer E, Rogers T, Edie S, Ishida-Yamamoto A, Burzenski L, Erez N, Murray SA, Irvine AD, Shultz LD, Green K, Uitto J, **Sprecher E**, Sarig O. SVEP1 plays a crucial role in epidermal differentiation, Exp Dermatol, in press, 2017

Mohamed J, Malchin N, Shalev S, Sarig O, **Sprecher E**. ARCI7 revisited and re-positioned. J Invest Dermatol, in press, 2017

Peled A, Sarig O, Samuelov L, Bertolini M, Ziv L, Weissglas-Volkov D, Eskin-Schwartz M, Adase CA, Malchin N, Bochner R, Fainberg G, Goldberg I, Sugawara K, Baniel A, Tsuruta D, Luxenburg C, Adir N, Duverger O, Morasso M, Shalev S, Gallo RL, Shomron N, Paus R, **Sprecher E**. Mutations in *TSPEAR*, Encoding a Regulator of Notch Signaling, Affect Tooth and Hair Follicle Morphogenesis. PLoS Genetics, in press, 2017

Review

Grants

2017-2020	COST: “A European Network for Connective Tissue Calcifying Diseases”. Investigators: PI Ludovic Martin (PI); Eli Sprecher et al (co-PIs)
2017-2019	Kamin Fund, Israel Ministry of Economy: “SAMD9 as a molecular target for the treatment of skin inflammatory diseases” PI: Eli Sprecher, Co-PI: Ofer Sarig

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The Lab for microRNA Research

microRNAs in human disorders: Psoriasis

One of the main research subjects in the lab is the involvement of miRNAs in the psoriasis. We found that the miRNAs' expression differs between psoriatic and normal skin. Some of these miRNAs are involved in biochemical cycles which regulate skin development and others regulate the interplay between immunocytes and keratinocytes. We are exploring how the expression of these miRNAs is regulated and how they affect the pathogenesis of the disease.

Skin cancer squamous cell carcinoma (SCC)

Skin carcinogenesis, as in most other cancer types, is believed to be a multi-step process with several steps along its malignant evolution: Solar elastosis (SE), actinic keratosis (AK or KIN1-2), a more advanced stage of AK; (KIN3) and CSCC. Using high-throughput deep sequence analysis of five stages along the malignant evolution we clearly see that miRNAs expression is distinct in each of the predefined five stages of malignant progression, a typical signature characterizes each stage. Currently we are investigating the biochemical pathways regulated by these miRNAs and their role in the malignant transformation of keratinocytes.

Parasites exosomal miRNAs as diagnostic tool and their effect on host immune cells

Parasitic infections are responsible for considerable human suffering. Currently, diagnosis and management of parasitic infections is challenging in many settings. We hypothesize that pathogen-specific miRNA can be utilized to understand, diagnose and manage parasitic infections. We have undertaken a pilot study of schistosomiasis as preliminary proof-of-concept for need and feasibility of miRNA-based diagnosis for parasitic infections. Schistosomiasis is a parasitic disease caused by helminthes (blood-flukes) of the genus Schistosoma that affects more than 200 million people, mostly in the developing world. Infection in returning travelers

The lab researchers and students

has received increasing attention, including among Israeli travelers. We were able to detect the presence of schistosomal miRNAs in the micro-vesicles fraction harvested from the patient sera. The Schistosoma parasites have developed multiple mechanisms for modulating or suppressing host immunity. We hypothesize that the adult Schistosoma utilizes secreted exosomes as a mechanism to manipulate and escape the immune system. Currently, we have data suggesting this hypothesize.

The lab researchers and students. PhD students: Mizrahi Adi, Masalha Moamen (MD/PhD student); Postdoc fellow: Dr Layani Adi; Former lab members - PhD students: Dr Lerman Galya, Dr Zehavi Liron, Dr Bonen Hamutal; M.Sc students: Vestin Assaf, Volman Ella, Weinstein Jonathan; Scientist: Dr Elharrar Einat. Location: Sheba Medical Center.

Publications

Meningher T., Lerman G., Regev-Rudzki, N., Gold D., Ben-Dov I., Sidi., Avni D., Schwartz, E. Schistosomal miRNAs isolated from Extracellular Vesicles in sera of infected patients; a new tool for diagnosis and follow-up of human schistosomiasis. The Journal of Infectious Diseases (accepted for publication), doi:10.1093/infdis/jiw539.

Elharrar E.+, Moamen M.+, Lerman G., Leibowitz-Amit R., Kassem R., Moti Harats M., Sidi Y., Avni D. Positive-negative feedback loop between miR-197 and IL-17A signaling in human keratinocytes. Immunome Research 2016 125:1.

Zehavi L., Hagit Schayek H., Jacob-Hirsch J., Sidi Y., Leibowitz-Amit L., and Avni D. MiR-377 targets E2F3 and alters the NF-kB signaling pathway through MAP3K7 in malignant melanoma Mol Cancer. 2015 (14):68.

Mizrahi A, Barzilai A, Gur-Wahnon D, Ben-Dov IZ, Glassberg S, Meningher T, Elharar E, Masalha M, Jacob-Hirsch J, Tabibian-Keissar H, Barshack I, Roszik J, Leibowitz-Amit R, Sidi Y*, Avni D*. (* Equal contribution). Alterations of microRNAs throughout the malignant evolution of cutaneous squamous cell carcinoma: the role of miR-497 in epithelial to mesenchymal transition of keratinocytes. Oncogene. 2018;37(2):218-230.

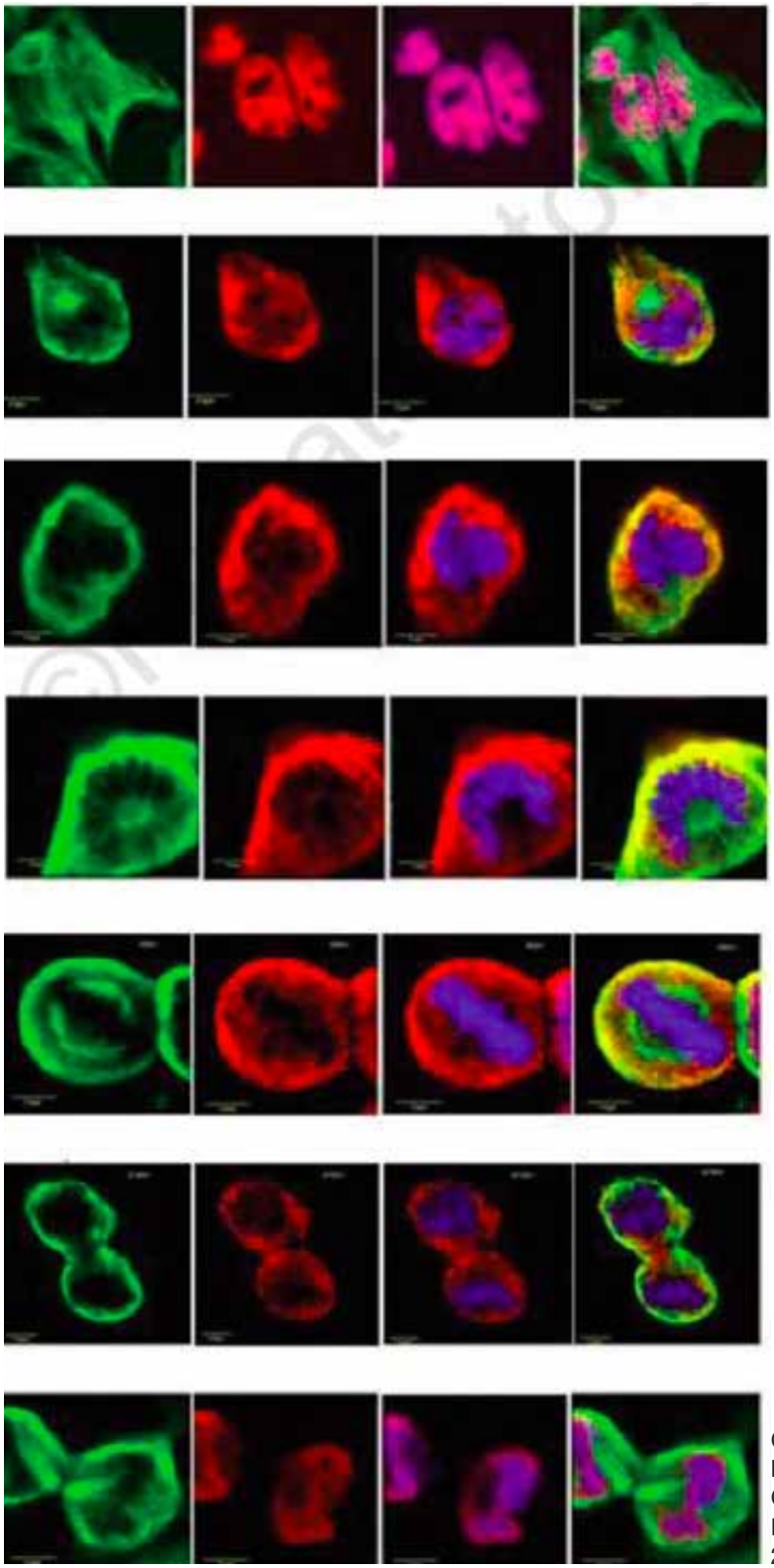
Lifshiz Zimon R, Lerman G, Elharrar E., Meningher T, Barzilai A, Masalha M, Chintakunta R, Hollander E, Goldbart R, Traitel T, Harats M, Sidi Y*, Avni D*, Kost J*. (* Equal contribution and corresponding authors). Ultrasound targeting of Q-starch/miR-197 complexes for topical treatment of psoriasis. J Control Release. 2018;284:103-111.

Meningher T, Boleslavsky D, Barshack I, Tabibian-Keissar H, Kohen R, Gur-Wahnon D, Ben-Dov IZ, Sidi Y, Avni D*, Schwartz E.* (* Equal contribution and corresponding authors). Giardia lamblia miRNAs as a new diagnostic tool for human giardiasis. PLoS Negl Trop Dis. 2019;13(6):e0007398.

Meningher T, Barsheshet Y, Ofir-Birin Y, Gold D, Dekel E, Sidi Y, Schwartz, E, Regev-Rudzki N, Avni O, Avni D. Schistosomes exosomal miRNAs: modulators of host T helper cell differentiation. EMBO Rep. 2019; 21:e47882

Masalha M, Sidi Y, Avni D. The contribution of feedback loops between miRNAs, cytokines and growth factors to the pathogenesis of psoriasis. Exp Dermatol. 2018;27(6):603-610.

Immunology & Hematology



Cell cycle-dependent localization of codanin-1. Credit: Noy-Lotan et al. Haematologica 94:629-37, 2009

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Improving the Management of Inflammatory/ Autoimmune and Rheumatic Diseases Using Tissue-homing Extracellular Vesicles and Medical Cannabinoids

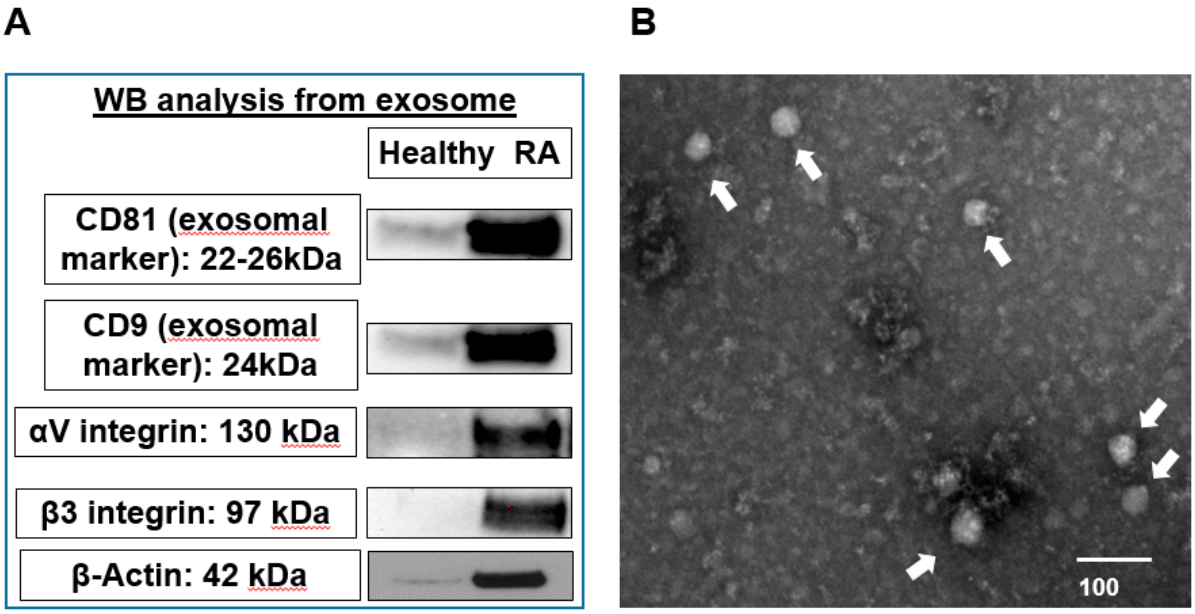
Positions

Head of research laboratory, Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center (affiliated to Tel Aviv University).

Research

Our focus and goals at the lab are to establish innovative solutions and better ways to improve the current treatment for inflammatory/autoimmune and rheumatic diseases using the following research strategies:

1. Improved drug delivery using specific tissue-homing small exctracellular vedicles ('exosomes') in inflammatory/autoimmune and rheumatic diseases: We hypothesized that isolation of tissue-specific homing exosomes derived from autologous blood sample (serum, plasma and/ or activated peripheral blood mononuclear cells) may improve the delivery of FDA-approved anti-inflammatory drugs which will be encapsulated into these exosomes and will be injected back to the patient. Tissue-specific homing receptors (such as: integrins or chemokine receptors) being expressed on the surface of exosomes will be used to enrich these tissue-specific homing exosomes using commercially available techniques (immunomagentic separation). The drug-loaded exosomes can be injected back to the diseased



The specific synovial-homing receptor αvβ3 integrin is expressed on serum-derived exosomes ($CD9^+/CD81^+$) from rheumatoid arthritis (RA) mice. A. Total exosomes were isolated from pool of serum samples of RA mice (Collagen-induced arthritis model) (n=5) and Sham (n=5) mice. Exosomes homogenates were separated using SDS-PAGE and subjected to immunoblotting with antibodies against CD9, CD81, αv, β3 (Santa Cruz Biotechnology) and β-actin (R&D system). Total 7 µgr protein were loaded into each well. B. Transmissiion Electro Microscopy (TEM) analysis shows a nano-size vesicle (~40nm) of exosomes derived from sera of RA mice.

subjects and will naturally find their way to the inflamed tissue. We believe that this approach will increase the specificity and efficiency of the current treatment, therefore it will reduce side effects as compare to the delivery of free drugs and will improve the quality of life of patients with inflammatory/autoimmune/rheumatic diseases.

2. Exploring the effect of novel therapeutic candidates: anti-inflammatory small molecules and/or natural compounds (such as plant-derived cannabinoids) in experimental inflammatory/autoimmune diseasese (Animal models of Collagen-induced arthritis, DSS-induced Coltis, Bleomycin-induced systemic sclerosis etc.). Moreover, our lab exploring the effect of these therapeutic candidates on inflammatory mediators - *in vitro* (using relevant primary cells and/or cell lines) and *ex vivo*, in patients-derived blood components (such as PBMCs) and/or in their relevant inflamed tissue biopsies.
3. Our lab has expertise also in the field of autoantibodies, through the measurement of patient-derived panel of autoantibodies, isolation of autoantibodies (total IgG/IgM or specific IgGs) from blood samples of patients and through exploring their potential pathogenic role using passive transfer of these antibodies into naïve animals following evaluation of clinical manifestations (reported by the patients) in the animals.
4. We are focusing also in exploring the potential immune-related pathomechanism of fibromyalgia sundrome – through examination of the effect of varios conventional and unconventional treatments (Neurofeedback, cannabinoids etc.) on patient-derived immune system components and neuroinflammatory mediators.
5. Our lab is also focusing on the effect of dangerous adjuvants (such as silicone, metal implants etc) on human health in general and more specifically on the immune system.

Publications

Halpert, G., Amital, H., and Shoenfeld, Y. (2020) [Silicone Breast Implants - Historical Medical Error], *Harefuah 159*, 697-702.

Borodina, E., Katz, I., Antonelly, A., Gzgzyan, A. M., Dzhemlikhanova, L. K., Ostriski, Y., Niauri, D., Jamilya, K., Bitsadze, V., Makatsariya, A., Tincani, A., Nalli, C., Churilov, L. P., Shovman, O., **Halpert, G**., Blank, M., Shoenfeld, Y., and Amital, H. (2020) The pathogenic role of circulating Hashimoto's Thyroiditis-derived TPO positive IgG on fetal loss in naive mice, *American Journal of Reproductive Immunology*, e13331.

Kagan, P., **Halpert, G.**, Amital, H., Shapira, R., and Shoenfeld, Y. (2020) Autoimmune/Inflammatory Syndrome Induced by Adjuvant Associated with a Metal Implant in the Mouth; Explantation Was Followed by Recovery, *Isr Med Assoc J 9*, 516-517.

Ben-Ami Shor, D., Lachnish, J., Bashi, T., Dahan, S., Shemer, A., Segal, Y., Shovman, O., **Halpert, G.**, Volkov, A., Barshack, I., Amital, H., Blank, M., and Shoenfeld, Y. (2019) Immunomodulation of Murine Chronic DSS-Induced Colitis by Tuftsin-Phosphorylcholine, *Journal of Clinical Medicine 9*.

Huang, X., Zhuang, J., Chung, S. W., Huang, B., **Halpert, G.**, Negron, K., Sun, X., Yang, J., Oh, Y., Hwang, P. M., Hanes, J., and Suk, J. S. (2019) Hypoxia-tropic Protein Nanocages for Modulation of Tumor- and Chemotherapy-Associated Hypoxia, *ACS Nano 13*, 236-247.

Date, A. A.*, Halpert, G.*, Babu, T., Ortiz, J., Kanvinde, P., Dimitrion, P., Narayan, J., Zierden, H., Betageri, K., Musmanno, O., Wiegand, H., Huang, X., Gumber, S., Hanes, J., and Ensign, L. M. (2018) Mucus-penetrating budesonide nanosuspension enema for local treatment of inflammatory bowel disease, *Biomaterials 185*, 97-105.

Date, A. A., Rais, R., Babu, T., Ortiz, J., Kanvinde, P., Thomas, A. G., Zimmermann, S. C., Gadiano, A. J., **Halpert, G.**, Slusher, B. S., and Ensign, L. M. (2017) Local enema treatment to inhibit FOLH1/GCPII as a novel therapy for inflammatory bowel disease, *Journal of Controlled Release 263*, 132-138.

Dardik, R.*, Livnat, T.*, Halpert, G.*, Jawad, S., Nisgav, Y., Azar-Avivi, S., Liu, B., Nussenblatt, R. B., Weinberger, D., and Sredni, B. (2016) The small tellurium-based compound SAS suppresses inflammation in human retinal pigment epithelium, *Molecular Vision 22*, 548-562.

Halpert G, Katz I, Shovman O, Tarasov S, Ganina KK, Petrova N, Tocut M, Volkov A, Barshack I, Blank M, Amital H. (2020) IVIG ameliorate inflammation in collagen induced arthritis- projection for IVIG therapy in rheumatoid arthritis, *Clin Exp Immunol*, 2020.

Reviews

Halpert, G., and Sredni, B. (2014) The effect of the novel tellurium compound AS101 on autoimmune diseases, *Autoimmunity Reviews 13*, 1230-1235.

Grants

2021-2023 Reducing networking gaps between Rīga Stradiņš University (RSU) and internationally – leading counterparts in viral infection-induced autoimmunity research, Educational Grant of EU; Role: Collaborator

2020-2021 Laboratory of Mosaic of Autoimmunity (LMA); Saint Petersburg State University; Role: Collaborator

2020-2022 Sheba Medical Center: Second chance: Improved drug delivery using gut-specific homing small extracellular vesicles for the treatment of inflammatory bowel diseases, Role: PI

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Primary Immunodeficiencies (PIDs) – From Bed to Bench and Back

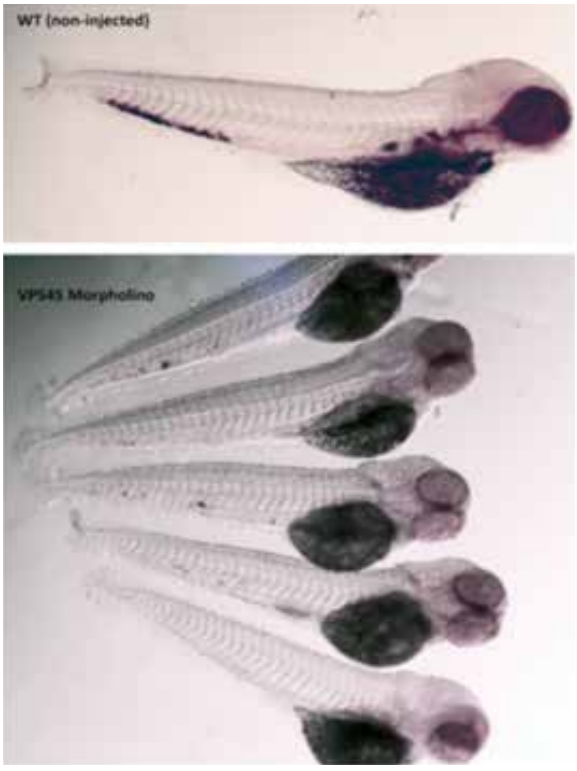
Positions

Head, Pediatric Department, Immunology Services

Research

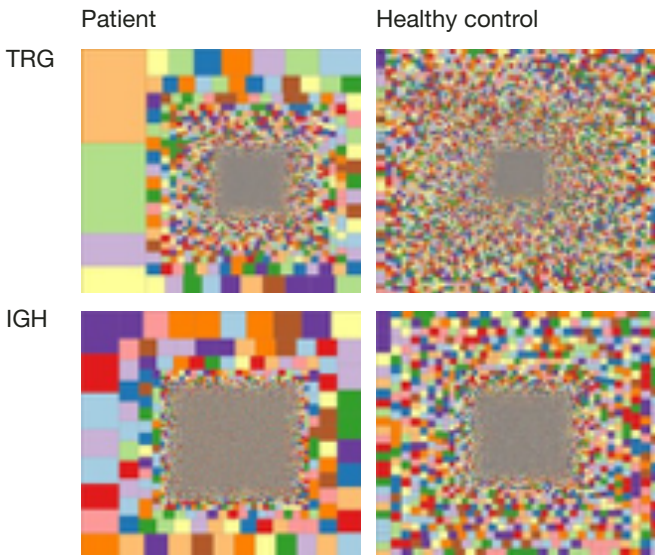
Our research focuses on:

1. Primary immunodeficiencies - finding and characterizing novel diseases
2. Newborn screening for immunodeficiency
3. Investigating fetal immunity in health and diseases
4. Next generation sequencing to illustrate and understand for T and B cell receptor repertoires



Myeloperoxidase signals in wild-type and Vps45 knockdown zebrafish embryos. In situ hybridization of WT non-injected embryo and five VPS45 deficient morpholino injected embryos 5 days after fertilization. Results of whole-mount in situ hybridization with the use of a digoxigenin-labeled RNA probe against zebrafish myeloperoxidase are shown. The myeloperoxidase detects neutrophils in the caudal hematopoietic tissue.

Our pediatric immunology clinic and laboratory are dedicated to the diagnostic evaluation, treatment, monitoring and research of patients with disorders of the immune system, including congenital immunodeficiencies and autoimmune diseases. In addition, we are leading Israel in the field of newborn screening for severe immunodeficiency and recently became the national laboratory for validating results obtained from this program. We are acknowledged as a "Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiency" (www.jmfworld.org) – which is the "gold standard" benchmark for excellence in this field. Part of our service is in-house laboratory which is well-experienced in the most advanced immunological and molecular assays that are used world-wide to assess immune function. We are interested in thymus functions in health (embryonic development and neonates) and in PIDs, as reflected by V(D)J rearrangement and thymic output of T cells, as well as B cell development, using advanced molecular methods, such as TREC and , KREC analyses and next generation sequencing (NGS). We use whole exome sequencing (WES) to discover new PIDs. This approach led us to identify to date several novel mutations that cause inherited PIDs. We found that mutations in two of these mutated novel genes, *VPS45* (*New England Journal of Medicine,* 2013) and *STN1* (*Journal of Experimental Medicine*, 2016) cause syndromic PIDs, i.e. severe congenital neutropenia (SCN5) and Coats plus, respectively. In our large PID cohort of patients some mutations were found in genes that have not been known until now to be involved in the development of the immune system. We continue to find such mutations in novel genes that cause PIDs



Immune repertoire determined by NGS for Ataxia Telangiectasia (AT) patient. Tree map representation of T cell receptor Gamma (TRG) and B cell Immunoglobulin heavy chain (IGH) repertoires in PBMCs samples from patient with AT deficiency and healthy control. Each dot represents a unique V to J joining and the size of the dot represents relative frequency within that sample. The dominant and expanded clones in TRG and IGH repertoires of a patient with AT deficiency can be noted.

with atypical clinical characteristics and study their pathophysiology mechanisms, using also a zebra fish model. Characterization of proteins encoded by the activity of these genes in immune cells of patients compared with those of healthy individuals enable us a better understanding of the development and function of the immune system, as well as designing new targeted drugs or gene therapy to the immune deficiency the patients suffer from. Another interest in our lab is to investigate T and B cell development and repertoire productions in health and disease including the development of the immune system in fetal life (*Science Translational Medicine*, 2015). We have used traditional methodologies (e.g. flow cytometry or PCR analysis) to illustrate cell repertoire in patients with immunodeficiency, autoimmunity and in developing human embryos. Yet the recent development of next generation sequencing (NGS) techniques enabled analysis of these immune repertoires to a depth that was unreached before. This was already used by us in various pathologic conditions including immunodeficiencies, autoimmune disorders and infections. One of the advantages of the NGS technology over the traditional methodologies for investigation of the expanded clones and for clinical follow-up is that it ensures finding of the clonal receptor rearrangements in every patient due to the enormous depth of sequencing. It allows for the detection of multiple sub-clones, specific preferential usage of V, D and J gene segments and complementarity determining region 3 (CDR3) characteristics and to look for clonotypic sharing in patients with a similar disease. In addition, with the use of the CRISPR-Cas9 genome editing platform, we are modeling relevant primary immunodeficiency causing genes, such as RAG1/2, DCLRE1C (artemis) and ATM in wild type human lymphocytic cell-lines, and are using this 'bed to bench and back' approach to correct these mutated genes as a strategy to develop innovative curative gene correction therapy in patients' cells.

Publications

Simon, A. J., Lev, A., Zhang, Y., Weiss, B., Rylova, A., Eyal, E., Kol, N., Barel, O., Cesarkas, K., Soudack, M., Greenberg-Kushnir, N., Rhodes, M., Wiest, D. L., Schiby, G., Barshack, I., Katz, S., Pras, E., Poran, H., Reznik-Wolf, H., Ribakovsky, E., Simon, C., Hazou, W., Sidi, Y., Lahad, A., Katzir, H., Sagie, S., Aqeilan, H. A., Glousker, G., Amariglio, N., Tzfati, Y., Selig, S., Rechavi, G. & **Somech, R.** (2016) Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects, *The Journal of Experimental Medicine*.

Rechavi, E., Levy-Mendelovich, S., Stauber, T., Shamash, J., Reinstein, S., Vernitsky, H., Adam, D., Simon, A. J., Lev, A., Raas-Rothschild, A. & **Somech, R**. (2016) Combined immunodeficiency in a patient with mosaic monosomy 21, *Immunologic Research.* 64, 841-7.

Rechavi, E., Lev, A., Eyal, E., Barel, O., Kol, N., Barhom, S. F., Pode-Shakked, B., Anikster, Y., **Somech, R**. & Simon, A. J. (2016) A Novel Mutation in a Critical Region for the Methyl Donor Binding in DNMT3B Causes Immunodeficiency, Centromeric Instability, and Facial Anomalies Syndrome (ICF), *Journal of Clinical Immunology*.

4. Levy-Mendelovich, S., Rechavi, E., Abuzaitoun, O., Vernitsky, H., Simon, A. J., Lev, A. & **Somech, R**. (2016) Highlighting the problematic reliance on CD18 for diagnosing leukocyte adhesion deficiency type 1, *Immunologic Research.* 64, 476-82.

5. Rechavi, E., Lev, A., Lee, Y. N., Simon, A. J., Yinon, Y., Lipitz, S., Amariglio, N., Weisz, B., Notarangelo, L. D. & **Somech, R**. (2015) Timely and spatially regulated maturation of B and T cell repertoire during human fetal development, *Science Translational Medicine.* 7, 276ra25.

6. Meerschaut, I., Bordon, V., Dhooge, C., Delbeke, P., Vanlander, A. V., Simon, A., Klein, C., Kooy, R. F., **Somech, R**. & Callewaert, B. (2015) Severe congenital neutropenia with neurological impairment due to

a homozygous VPS45 p.E238K mutation: A case report suggesting a genotype-phenotype correlation. *American Journal of Medical Genetics Part A*.

Machnes-Maayan, D., Lev, A., Katz, U., Mishali, D., Vardi, A., Simon, A. J. & **Somech, R.** (2015) Insight into normal thymic activity by assessment of peripheral blood samples, *Immunologic Research.* 61, 198-205.

Dar, N., Gothelf, D., Korn, D., Frisch, A., Weizman, A., Michaelovsky, E., Carmel, M., Yeshayahu, Y., Dubnov-Raz, G., Pessach, I. M., Simon, A. J., Lev, A. & **Somech, R.** (2015) Thymic and bone marrow output in individuals with 22q11.2 deletion syndrome, *Pediatric Research.* 77, 579-85.

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Novel Pathways Involved in Normal Hematopoiesis and Congenital Hematological Disorders

Positions

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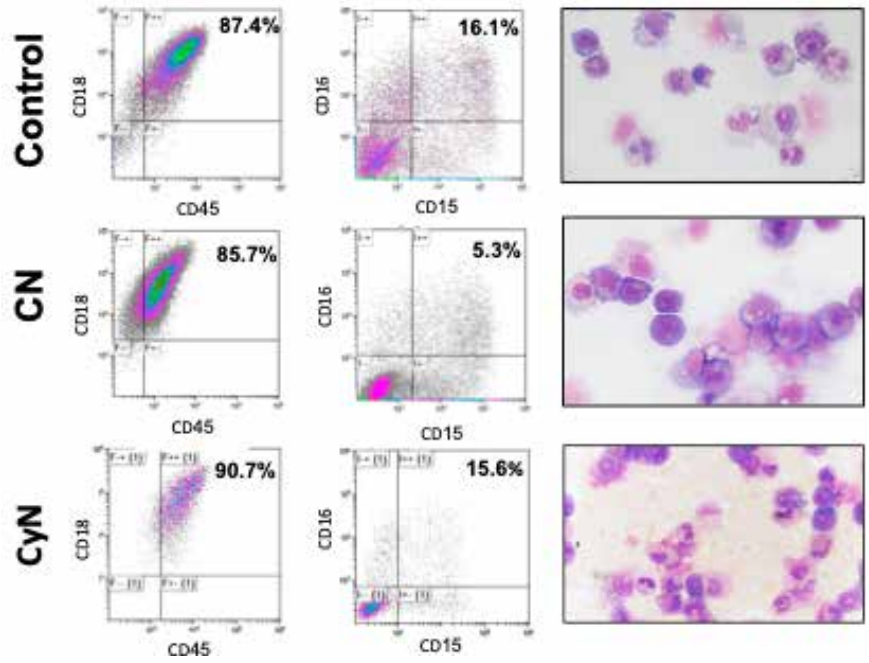
Research

We study pathways involved in normal and diseased hematopoiesis. All our research aims emerge from clinical dillemas.

Our research is divided into:

1. The study of severe congenital neutropenia and cyclic neutropenia. Severe congenital neutropenia (SCN) is a mono-lineage bone marrow failure syndrome, characterized by early onset of neutropenia accompanied by severe infections. Bone marrow examination demonstrates promyelocytic maturation arrest. Cyclic neutropenia (CyN) is a congenital syndrome characterized by oscillations of the neutrophil counts with a nadir occurring every 21 days. Mutations in the *ELANE* gene can cause both diseases. We aim to identify key signaling pathways underlying SCN and CyN and their phenotypic differences, in order to establish better diagnostic criteria and novel therapeutic approaches. We use induced pluripotent stem cells (iPSCs) generated from patients with congenital neutropenias. Our iPSC system recapitulates the myeloid differentiation arrest found in bone marrows of patients with SCN and shows a difference in the myeloid differentiation potential between SCN and CyN (Figure).
2. Elucidating the myeloid transformation processes in patients with congenital neutropenia. One severe complication of SCN is the development of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). An early event in



this process involves acquisition of truncating mutations in the receptor of the granulocyte-colony stimulating factor (G-CSF), which are unique to patients with SCN. We aim to understand the signal transduction pathways triggered by the mutated G-CSF receptor in patients with congenital neutropenia in order to improve the diagnostic, preventive and therapeutic approaches for leukemia development. This study is performed on patients-derived iPSCs using the CRISPR/Cas9 gene editing system for the introduction of somatic mutations that are similar to those found in patients.

3. Understanding the molecular processes involved in rare congenital anemia syndromes. The regulation of erythroid gene expression and erythroid differentiation is governed by the interplay between GATA1 and GATA2, that share a common DNA binding motif, and a key event in normal erythropoiesis is a "switch" in the expression of the two transcription factors. We aim to study the roles of GATA1 and GATA2 in initiating and driving red blood cell differentiation and their contribution to a rare anemia syndorme caused by mutations in GATA1. This study is preformed in immortalized human CD34+ cells in combination with gene editing methods.

Publications

Giani FC, Fiorini C, Wakabayashi A, Ludwig LS, Salem RM, Jobaliya CD, Regan SN, Ulirsch JC, Liang G, **Steinberg-Shemer O**, Guo MH, Esko T, Tong W, Brugnara C, Hirschhorn JN, Weiss MJ, Zon LI, Chou ST, French DL, Musunuru K, Sankaran VG. Targeted application of human genetic variation can improve red blood cell production from stem cells. *Cell Stem Cell*. 2016;7;18(1):73-78.

Steinberg-Shemer O, Keel S, Dgany O, Walsh T, Noy-Lotan S, Krasnov T, Yacobovich J, Quarello P, Ramenghi U, King MC, Shimamura A, Tamary H. Diamond Blackfan Anemia: A nonclassical patient with diagnosis assisted by genomic analysis. *J Pediatr Hematol Oncol*. 2016;38(7):e260-2.

Yacobovich J, Abu-Ahmed S, **Steinberg-Shemer O**, Goldberg T, Cohen M, Tamary H. Anti-D treatment for pediatric immune thrombocytopenia: Is the bad reputation justified? *Semin Hematol*. 2016;53 Suppl 1:S64-6.

Gilad O, **Shemer OS**, Dgany O, Krasnov T, Nevo M, Noy-Lotan S, Rabinowicz R, Amitai N, Ben-Dor S, Yaniv I, Yacobovich J, Tamary H. Molecular diagnosis of α-thalassemia in a multiethnic population. *Eur J Haematol*. 2017;98(6):553-562.

Steinberg-Shemer O, Ulirsch JC, Noy-Lotan S, Krasnov T, Attias D, Dgany O, Laor R, Sankaran VG, Tamary H. Whole-exome sequencing identifies an α-globin cluster triplication resulting in increased clinical severity of β-thalassemia. *Cold Spring Harb Mol Case Stud.* 2017;3(6).

Tanous O, **Steinberg Shemer O**, Yacobovich J, Zoldan M, Horovitz Y, Yaniv I, Rabizadeh E, Tamary H, Nakav S, Lahav J. Evaluating platelet function disorders in children with bleeding tendency - A single center study. *Platelets.* 2017;28(7):676-681.

Seo A, **Steinberg-Shemer O**, Unal S, Casadei S, Walsh T, Gumruk F, Shalev S, Shimamura A, Akarsu NA, Tamary H, King MC. Mechanism for survival of homozygous nonsense mutations in the tumor suppressor gene BRCA1. *Proc Natl Acad Sci U S A*. 2018;115(20):5241-5246.

Shefer Averbuch N, **Steinberg-Shemer O**, Dgany O, Krasnov T, Noy-Lotan S, Yacobovich J, Kuperman AA, Kattamis A, Ben Barak A, Roth-Jelinek B, Chubar E, Shabad E, Dufort G, Ellis M, Wolach O, Pazgal I, Abu Quider A, Miskin H, Tamary H. Targeted next generation sequencing for the diagnosis of patients with rare congenital anemias. *Eur J Haematol*. 2018;101(3):297-304.

Steinberg-Shemer O, Tamary H. Gray platelet syndrome mimicking atypical autoimmune lymphoproliferative syndrome: the key is in the blood smear. *Blood*. 2018;131(24):2737.

Steinberg-Shemer O, Yacobovich J, Cohen M, Cabantchik IZ, Tamary H. Labile plasma iron as an indicator of patient adherence to iron chelation treatment. *Blood Cells Mol Dis*. 2018;71:1-4.

Steinberg-Shemer O, Goldberg TA, Yacobovich J, Levin C, Koren A, Revel-Vilk S, Ben-Ami T, Kuperman AA, Shkalim Zemer V, Toren A, Kapelushnik J, Ben-Barak A, Miskin H, Krasnov T, Noy-Lotan S, Dgany O, Tamary H. Characterization and genotype-phenotype correlation of patients with Fanconi anemia in a multi-ethnic population. *Haematologica*. 2019.

Barg AA, Toren A, Tamary H, Yacobovich J, **Steinberg-Shemer O**, Gilad O, Goldstein G, Miskin H, Revel-Vilk S, Rosenbeg N, Kenet G, Zemer VS. Essential thrombocythemia A retrospective case series. *Pediatr Blood Cancer*. 2020;67(5):e28183.

Gilad O, **Steinberg-Shemer O**, Dgany O, Krasnov T, Noy-Lotan S, Tamary H, Yacobovich J. Alpha-Thalassemia carrier due to -α3.7 deletion: Not so silent. *Acta Haematol*. 2020:1-6.

Goldberg L, Simon AJ, Rechavi G, Lev A, Barel O, Kunik V, Toren A, Schiby G, Tamary H, **Steinberg-Shemer O**, Somech R. Congenital neutropenia with variable clinical presentation in novel mutation of the SRP54 gene. *Pediatr Blood Cancer*. 2020;67(6).

Steinberg-Shemer O, Tamary H. Impact of next-generation sequencing on the diagnosis and treatment of congenital anemias. *Mol Diagn Ther*. 2020.

Yacobovich J, Barzilai-Birenboim S, **Steinberg-Shemer O**, Stark P, Pazgal I, Tamary H. Splenectomy in childhood for non-malignant haematologic disorders - long-term follow-up shows minimal adverse effects. *Br J Haematol*. 2020.

Grants

2020-2023 Israel Innovation Authority. *The CRISPR-IL Consortium - AI technologies for improving the efficiency and accuracy of genome editing*, with Dr. Yehudit Birger and Prof. Shai Izraeli.

2020-2023 Varda and Boaz Dotan Research Center in Hemato-Oncology. *Novel method for selection of CD34+cells after editing Runx1 gene mutations*, with Prof. Dani Offen.

2019-2021 Physician-Scientist Grant. European Hematology Association. *Elucidating the pathophysiology of severe congenital neutropenia and the pathways involved in malignant transformation*.

2019-2022 Physician-Scientist Grant. Israel Science Foundation. *Elucidating the mechanisms of congenital anemia caused by germline GATA1s mutation: The roles of GATA2.*

2018-2020 Israel Cancer Association. *Elucidating the pathways involved in malignant transformation in severe congenital neutropenia patients.*

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Molecular and Cellular Studies of Rare Disorders of Hematopoiesis

Positions

Professor of Pediatrics, Sackler Faculty of Medicine

Director, Hematology Unit, Schneider Children's Medical Center of Israel

Research

We study rare hematological disorders, using different cellular model systems. The roles of codanin-1 in normal hematopoiesis and in the pathogenesis of congenital dyserythropoietic anemia type I (CDA I). CDA I is a rare disorder causing anemia and bone abnormalities. We have identified CDAN1, the gene causing CDA I, in 2002, by linkage analysis. Codanin-1, encoded by CDAN1, is ubiquitously expressed and necessary for early embryonic development. However, its roles in hematopoiesis are not known. We generated erythroid tissue specific KO mice, and identified early anemia and embryonic lethality caused by a complete lack of codanin-1. We are also utilizing other model systems for the disease, including K562 cell line, murine fetal liver erythroid differentiation system, and primary human erythroid cultures. Understanding the roles of codanin-1 in red blood cells development may shed light on specialized processes involved in erythropoiesis. Even more significant, elucidating the role of codanin-1 in CDA I may help develop novel therapeutic approaches to alleviate the anemia in these patients.

Cdan1 erythroid conditional mice embryo are small and pale, with no visible erythropoiesis in the fetal liver.

The pathomechanisms of severe congenital neutropenia and cyclic neutropenia through patients will be understandood by using derived induced pluripotent stem cells. We use the cutting edge technology of induced pluripotent stem cells generated from patients with congenital neutropenia as a model system for severe congenital neutropenia and cyclic neutropenia, caused by ELANE mutations. We aim to define the granulopoietic defects caused by these mutations, establish a genotype-phenotype correlation of iPSC lines carrying ELANE mutations causing both diseases, and study novel potential therapies by pharmacological correction of the granulopoietic defects detected.

Publications

Lebel A, Yacobovich J, Krasnov T, Koren A, Levin C, Kaplinsky C, Ravel-Vilk S, Laor R, Attias D, Ben Barak A, Shtager D, Stein J, Kuperman A, Miskin H, Dgany O, Giri N, Alter BP, **Tamary H**. Genetic analysis and clinical picture of severe congenital neutropenia in Israel. Pediatr Blood Cancer. 62(1):103-8, 2015.

Shalev H, Al-Athamen K, Levi I, Levitas A, **Tamary H**. Morbidity and mortality of adult patients with congenital dyserythropoietic anemia type I. Eur J Haematol. 2016.

Steinberg Shemer O, Keel S, Dgany O, Walsh T, Noy-Lotan S, Krasnov T, Yacobovich J, Quarello P,

Ramenghi U, King MC, Shimamura A, **Tamary H**. Diamond Blackfan Anemia – an Evasive Diagnosis in a Non-Classical Patient. J Pediatr Hematol Oncol. 2016;38(7):e260-2.

Amir AZ, Horev G, Yacobovich J, Bennett M, **Tamary H**. Distal limb anomalies in patients with congenital dyserythropoietic anemia. Am J Med Genet A. 2016.

Shalev H, Al-Athamen K, Levi I, Levitas A, **Tamary H**. Morbidity and mortality of adult patients with congenital dyserythropoietic anemia type IEur J Haematol. 2017;98(1):13-18

Tanous O, Steinberg Shemer O, Yacobovich J, Zoldan M, Horovitz Y, Yaniv I, Rabizadeh E, **Tamary H**, Nakav S, Lahav J. Evaluating platelet function disorders in children with bleeding tendency - A single center study Platelets. 2017;6:1-6

Gilad O, Shemer OS, Dgany O, Krasnov T, Nevo M, Noy-Lotan S, Rabinowicz R, Amitai N, Ben-Dor S, Yaniv I, Yacobovich J, **Tamary H** Molecular diagnosis of α-thalassemia in a multiethnic population Eur J Haematol. 2017;98(6):553-562

Iolascon A, Andolfo I, Barcellini W, Corcione F, Garçon L, Franceschi LD, Pignata C, Graziadei G, Pospisilova D, Rees DC, de Montalembert M, Rivella S, Gambale A, Russo R, Ribeiro L, Vives-Corrons J, Aguilar Martinez P, Kattamis A, Gulbis B, Cappellini MD, Roberts I, **Tamary H**. Recommendations regarding splenectomy in hereditary hemolytic anemias Haematologica. 2017;102(8):1304-1313.

Seo A, Ben-Harosh M, Sirin M, Stein J, Dgany O, Kaplelushnik J, Hoenig M, Pannicke U, Lorenzm M, Schwarz K, Stockklausner C, Walsh T, Gulsuner S, Lee MK, Sendamarai A, Sanchez-Bonilla M, King MC, Cario H, Kulozik AE, Debatin KM, Schulz A, **Tamary H**, Shimamura A Bone marrow failure unresponsive to bone marrow transplant is caused by mutations in thrombopoietin Blood. 2017;130(7):875-880

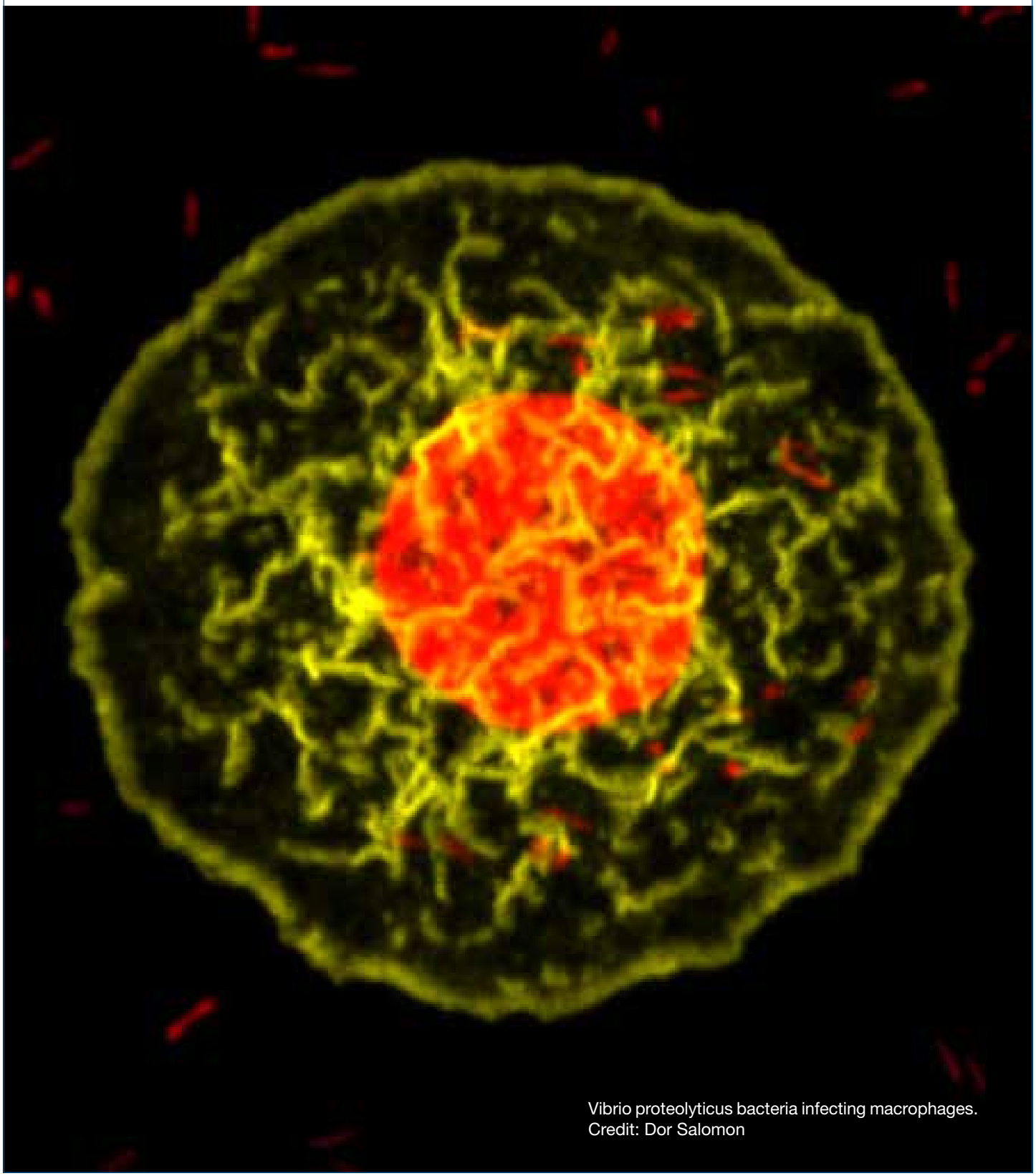
Resnitzky P, Shaft D, Shalev H, Kapelushnik J, Dgany O, Krasnov T, **Tamary H**. Morphological features of congenital dyserythropoietic anemia type I: The role of electron microscopy in diagnosis Eur J Haematol. 2017;99(4):366-371.

Da Costa L, O'Donohue MF, van Dooijeweert B, Albrecht K, Unal S, Ramenghi U, Leblanc T, Dianzani I, **Tamary H**, Bartels M, Gleizes PE, Wlodarski M, MacInnes AW Molecular approaches to diagnose Diamond-Blackfan anemia: The EuroDBA experience. Eur J Med Genet. 2017;S1769-7212(17)

Grants

2016-2019 The European Diamond-Blackfan Anemia Consortium. E-Rare

Infectious Diseases



Vibrio proteolyticus bacteria infecting macrophages.
Credit: Dor Salomon

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Mechanisms of Virulence and Drug Resistance in Pathogenic Fungi

Positions

Senior Lecturer, Sackler School of Medicine

Head, Infectious Diseases Unit, Tel Aviv Sourasky Medical Center

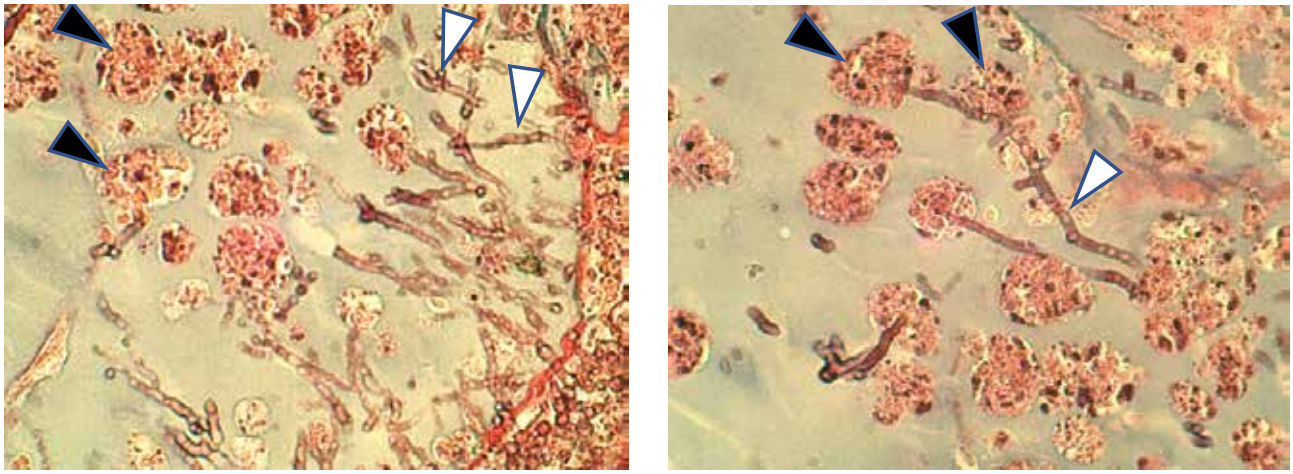
Director, Molecular Mycology Laboratory, Tel Aviv Sourasky Medical Center

Research

We study the pathobiology and epidemiology of medically important fungi. Fungal infections are encountered with increasing frequency in advanced medical settings, and are associated with high mortality rates. Specifically, *Candida* species are frequent causes of hospital-acquired bloodstream infection, particularly in the intensive care setting, whereas *Aspergillus* species and other pathogenic filamentous fungi cause sinopulmonary and disseminated infections in immunocompromised patients.

Our work has outlined the incidence, drug resistance patterns, geographic distribution, risk factors and outcomes of *Candida* bloodstream infections in Israeli hospitals. A multicenter effort is currently underway to study the epidemiology of invasive mold infections in Israel.

We are specifically interested in *Candida glabrata*, an opportunistic pathogen notable for its limited susceptibility to antifungal agents and its tendency to rapidly evolve resistance following exposure to antifungal azole drugs. Using population analysis techniques, we showed that clinical strains of *C. glabrata* are often heterogenous at the cell-population level with respect drug resistance. This phenomenon, termed heteroresistance, facilitates the expansion of drug-resistant subpopulations during antifungal treatment. We discovered that heteroresistance is associated with over-expression of efflux transporters, and that heteroresistant strains can persist *in vivo* despite high-dose azole treatment. Heteroresistance is not captured by standard susceptibility tests performed at clinical laboratories, and may explain the mismatch between susceptibility data and treatment outcomes.



In vivo assay for angiotropism and angioinvasion: Matrigel plugs implanted subcutaneously induce the formation of endothelial cell networks (black arrowheads). *A. fumigatus* forms hyphae (white arrowheads) that invade neovessels. Genetic manipulation is used to dissect *A. fumigatus* genes responsible for angiotropism and angioinvasion.

Additional work has focused on the emerging species *Candida auris*. Unknown until recently, *C. auris* is a multidrug resistant organism that has caused simultaneous outbreaks of invasive infections in multiple countries in Europe, North and South America, Africa and Asia. We characterized the drug resistance and pathogenicity traits of *C. auris* isolates. Ongoing work at our lab aims to define optimal treatment strategies for *C. auris* infection using in vitro and animal models.

Invasion of host blood vessels is characteristic of invasive Aspergillus fumigatus infection. We have previously shown that angioinvasive *A. fumigatus* produces gliotoxin, a secondary metabolite which down-regulates host angiogenesis. We hypothesized that angioinvasion is essential for *A. fumigates* virulence. Research conducted at the Tel Aviv Medical Center Mycology laboratory and at the laboratory of Prof. Nir Osherov at the Sackler School of Medicine aims to understand the genetic underpinnings of angiotropism and angioinvasion. We predict that this line of research will uncover novel targets for the treatment and prevention of invasive aspergillosis.

Publications

Brosh-Nissimov T, **Ben-Ami R**. Differential association of fluconazole dose and dose/MIC ratio with mortality in patients with *Candida albicans* and non-*albicans* bloodstream infection. Clin Microbiol Infect 2015;21: 1011-1017.

Ben-Ami R, Denning D. Estimating the Burden of Fungal Diseases in Israel. Isr Med Assoc J 2015;17:374-379.

Cohen NA, **Ben-Ami R**, Guzner-Gur H, Santo ME, Halpern Z, Maharshak N. Fecal Microbiota Transplantation for *Clostridium difficile*-associated diarrhea. Isr Med Assoc J 2015;17:510-4.

Cohen NA, Livovsky DM, Yaakobovitch S, Ben Yehoyada M, **Ben-Ami R**, Adler A, Guzner-Gur H, Goldin E, Santo ME, Halpern Z, Paz K, Maharshak N. A retrospective comparison of fecal microbial transplantation methods for recurrent Clostridium difficile infection. Isr Med Assoc J 2016; 18:594-599.

Ben-Ami R, Zimmerman O, Finn T, Amit S, Novikov A, Wertheimer N, Lurie-Weinberger M, Berman J. Heteroresistance to fluconazole is a continuously distributed phenotype among *Candida glabrata* clinical strains associated with *in vivo* persistence. mBio 2016; 7: e00655-16.

Vitenshtein A, Bauman Y, Gur C, Glasner A, **Ben-Ami R**, Osherov N, Cormack BP, and Mandelboim O. NK cell recognition of *Candida glabrata* through novel binding of NKp46 and NCR1 to fungal ligands Epa1, Epa6, and Epa7. Cell Host Microb 2016; 20:527-34.

Osherov N, **Ben-Ami R**. Modulation of host angiogenesis as a microbial survival strategy and therapeutic target. PLoS Pathogen 2016;12:e1005479.

Ben-Ami R, Berman J, Novikov A, Bash E, Shachor-Meyouhas Y, Zakin S, Maor Y, Tarabia J, Schechner V, Adler A, Finn T. Multidrug-resistant *Candida haemulonii* and *C. auris*, Tel Aviv, Israel. Emerg Infect Dis. 2017; 23:195-203

Katchman E, **Ben-Ami R**, Savyon M, Chemtob D, Avidor B, Wasserman A, Zeldis I, Girshengorn S, Amitai Z, Sheffer R, Turner D. Successful control of a large outbreak of HIV infection associated with injection of cathinone derivatives in Tel Aviv, Israel. Clin Microbiol Infect, In Press.

Cohen R, Babushkin F, Cohen S, Marina A, Shapiro M, Uda M, Khabra E, Adler A, **Ben-Ami R**, Paikin S. A prospective survey of *Pseudomonas aeruginosa* colonization and infection in the intensive care unit. Antimicrob Resist Infect Control 2017; 6:7.

Mandelblat M, Frenkel M, Abbey D, **Ben-Ami R**, Berman J, Segal E. Phenotypic and Genotypic Characteristics of Bloodstream and Mucosal Isolates of *Candida albicans*. Mycoses, In Press.

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Investigating Infectious Diseases

Positions

Head of Department, Medicine E, Rabin Medical Center, Beilinson Hospital

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Editor-in-Chief, Clinical Microbiology and Infection

Director, Infectious Diseases University Research Center, Rabin Medical Center, Beilinson Hospital

Research

Our research focuses on improving the treatment and management of patients with severe infections and at the same time, focusing on interventions that will reduce the rise of resistance to antibiotics in micro-organisms. Our main goal is to reduce mortality and suffering caused to patients by these infections.

Together with partners in Denmark, we have developed a computerized decision support system for antibiotic treatment in patients with moderate to severe infections. It was tested in a multi-center trial in three countries, and was shown to improve the outcome of patients, while at the same time reducing unnecessary use of antibiotics and hospital stay.

Our studies, systematic reviews and meta-analyses and clinical studies, served to change international guidelines and improve patient's management. For example:

- Study that stopped the use of single-dose antibiotics for urinary tract infection.
- A clear evidence on the benefit of appropriate empirical antibiotic treatment
- Antibiotic prophylaxis for neutropenic patients.
- Discontinuing the use of beta-lactam/aminoglycoside combinations.
- Proof that some antibiotics (tigecycline and cefipime) are less effective than others.
- Current projects
- Optimizing diagnosis, treatment and outcome definitions in elderly patients with bacterial infections (Ministry of Science, Technology and Space).
- The impact of a decision support system for antibiotic decisions on appropriateness of treatment, morbidity and mortality, consumption of antibiotics and resistance to antibiotic drugs (The Israeli national institute for health policy research).
- AIDA: Investigator-driven clinical trials of off-patent antibiotics. Preserving old antibiotics for the future (EU- FP7-HEALTH-2011-two-stage).
- Combatting Bacterial Resistance in Europe – Molecules against Gram Negative Infections (IMI – COMBACTE-MAGNET).
- Transnational Research Projects on the Transmission Dynamics of Antibacterial Resistance (ERA-NET/JPI-EC-AMR).

Publications

Eliakim-Raz N, Bates DW, **Leibovici L**. Predicting bacteraemia in validated models - A Systematic Review. Clin Microbiol Infect. 2015, pii:S1198-743X(15)00249-9.

Zusman O, Farbman L, Tredler Z, Daitch V, Lador A, **Leibovici L**, Paul M. Association between hypoalbuminemia and mortality among subjects treated with ertapenem versus other carbapenems: prospective cohort study. Clin Microbiol Infect. 2015

Eliakim-Raz N, Lador A, Leibovici-Weissman Y, Elbaz M, Paul M, **Leibovici L**. Efficacy and safety of chloramphenicol: joining the revival of old antibiotics? Systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2015

Paul M, Bronstein E, Yahav D, Goldberg E, Bishara J, **Leibovici L**. External validity of a randomised controlled trial on the treatment of severe

infections caused by MRSA. BMJ Open. 2015 Sep 11;5(9):e008838.

Andreassen S, Zalounina A, Paul M, Sanden L, **Leibovici L**. Interpretative reading of the antibiogram--a semi-naïve Bayesian approach. Artif Intell Med. 2015 Nov;65(3):209-17.

Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, Dickstein Y, Nseir W, Dan M, **Leibovici L**. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial. BMJ. 2015 May 14;350:h2219.

Avni T, Grossman A, **Leibovici L**, Gafter-Gvili A. In reply--Continued Caution Recommended in Use of Intravenous Iron Preparations. Mayo Clin Proc. 2015 May;90(5):696.

Gafter-Gvili A, Cohen E, Avni T, Grossman A, Vidal L, Garty M, **Leibovici L**, Krause I. Predicting the emergence of anemia--A large cohort study. Eur J Intern Med. 2015 Jun;26(5):338-43.

Yahav D, Schlesinger A, Daitch V, Akayzen Y, Farbman L, Abu-Ghanem Y, Paul M, **Leibovici L**. Presentation of infection in older patients--a prospective study. Ann Med. 2015 Jun;47(4):354-8.

Steinmetz T, Eliakim-Raz N, Goldberg E, **Leibovici L**, Yahav D. Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clin Microbiol Infect. 2015 Jul;21(7):665-73.

Zalmanovici Trestioreanu A, Lador A, Sauerbrun-Cutler MT, **Leibovici L**. Antibiotics for asymptomatic bacteriuria. Cochrane Database Syst Rev. 2015 Apr 8;4:CD009534.

Paul M, **Leibovici L**. On neuraminidase inhibitors and evidence-based medicine. Clin Microbiol Infect. 2015 Mar;21(3):214-6.

Eliakim-Raz N, **Leibovici L**. ACP Journal Club: some antimicrobials increased admissions and ED visits for hypoglycemia in older users of glipizide or glyburide. Ann Intern Med. 2015 Feb 17;162(4):JC13.

Taha A, Vinograd I, Sakhnini A, Eliakim-Raz N, Farbman L, Baslo R, Stemmer SM, Gafter-Gvili A, **Leibovici L**, Paul M. The association between infections and chemotherapy interruptions among cancer patients: Prospective cohort study. J Infect. 2015 Mar;70(3):223-9.

Avni T, Shiver-Ofer S, **Leibovici L**, Tacconelli E, DeAngelis G, Cookson B, Pagani L, Paul M. Participation of elderly adults in randomized controlled trials addressing antibiotic treatment of pneumonia. J Am Geriatr Soc. 2015 Feb;63(2):233-43.

Harris PN, McNamara JF, Lye DC, Davis JS, Bernard L, Cheng AC, Doi Y, Fowler VG Jr, Kaye KS, **Leibovici L**, Lipman J, Llewelyn MJ, Munoz-Price S, Paul M, Peleg AY, Rodríguez-Baño J, Rogers BA, Seifert H, Thamlikitkul V, Thwaites G, Tong SY, Turnidge J, Utili R, Webb SA, Paterson DL. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect. 2016 Nov 1. pii: S1198-743X(16)30512-2.

Benattar YD, Omar M, Zusman O, Yahav D, Zak-Doron Y, Altunin S, Elbaz M, Daitch V, Granot M, **Leibovici L**, Paul M. The Effectiveness and Safety of High-Dose Colistin: Prospective Cohort Study. Clin Infect Dis. 2016 Oct 6. pii: ciw684.

Paul M, **Leibovici L**. Observational studies examining patient management in infectious diseases. Clin Microbiol Infect. 2016 May 13. pii: S1198-743X(16)30129-X.

Pulcini C, **Leibovici L**; CMI Editorial Office. CMI guidance for authors of surveys. Clin Microbiol Infect. 2016 Nov;22(11):901-902.

Sanden L, Paul M, **Leibovici L**, Andreassen S. Quantifying the associations between antibiotic exposure and resistance - a step towards personalised antibiograms. Eur J Clin Microbiol Infect Dis. 2016 Dec;35(12):1989-1996.

Green H, Tobar A, Gafter-Gvili A, **Leibovici L**, Klein T, Rahamimov R, Mor E, Grossman A. Serum Lactate Dehydrogenase is Elevated in Ischemic Acute Tubular Necrosis but Not in Acute Rejection in Kidney Transplant Patients. Prog Transplant. 2016

Huttner A, **Leibovici L**, Theuretzbacher U, Huttner B, Paul M. Closing the evidence gap in infectious disease: point-of-care randomization and informed consent. Clin Microbiol Infect. 2016 Aug 3. pii: S1198-743X(16)30267-1.

Shaw E, Addy I, Stoddart M, Vank C, Grier S, Wiegand I, **Leibovici L**, Eliakim-Raz N, Vallejo-Torres L, Morris S, MacGowan A, Carratalà J, Pujol M; COMBACTE-MAGNET Consortium. Retrospective observational study to assess the clinical management and outcomes of hospitalised patients with complicated urinary tract infection in countries with high prevalence of multidrug resistant Gram-negative bacteria (RESCUING). BMJ Open. 2016 Jul 29;6(7):e011500.

Yahav D, Shaked H, Goldberg E, Yassin S, Eliakim-Raz N, Paul M, Bishara J, **Leibovici L**. Time trends

in Staphylococcus aureus bacteremia, 1988-2010, in a tertiary center with high methicillin resistance rates. Infection. 2016

Paul M, Yahav D, **Leibovici L**. Management of Community-Acquired Pneumonia. JAMA. 2016 Jul 12;316(2):220-1.

Dickstein Y, Nir-Paz R, Pulcini C, Cookson B, Beović B, Tacconelli E, Nathwani D, Vatcheva-Dobrevska R, Rodríguez-Baño J, Hell M, Saenz H, **Leibovici L**, Paul M. Staffing for infectious diseases, clinical microbiology and infection control in hospitals in 2015: results of an ESCMID member survey. Clin Microbiol Infect. 2016 Sep;22(9):812.e9-812.e17.

Dickstein Y, Geffen Y, Andreassen S, **Leibovici L**, Paul M. Predicting Antibiotic Resistance in Urinary Tract Infection Patients with Prior Urine Cultures. Antimicrob Agents Chemother. 2016 Jul 22;60(8):4717-21.

Dickstein Y, **Leibovici L**, Yahav D, Eliakim-Raz N, Daikos GL, Skiada A, Antoniadou A, Carmeli Y, Nutman A, Levi I, Adler A, Durante-Mangoni E, Andini R, Cavezza G, Mouton JW, Wijma RA, Theuretzbacher U, Friberg LE, Kristoffersson AN, Zusman O, Koppel F, Dishon Benattar Y, Altunin S, Paul M; AIDA consortium. Multicentre open-label randomised controlled trial to compare colistin alone with colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative infections (AIDA): a study protocol. BMJ Open. 2016 Apr 20;6(4):e009956.

Bitterman R, Hussein K, **Leibovici L**, Carmeli Y, Paul M. Systematic review of antibiotic consumption in acute care hospitals. Clin Microbiol Infect. 2016 Jun;22(6):561.e7-561.e19.

Daitch V, Babich T, Singer P, **Leibovici L**. Quality of Reporting Nutritional Randomized Controlled Trials in Patients With Cystic Fibrosis. J Pediatr Gastroenterol Nutr. 2016 Aug;63(2):265-9.

Yahav D, Schlesinger A, Shaked H, Goldberg E, Paul M, Bishara J, **Leibovici L**. Clinical presentation, management and outcomes of Staph aureus bacteremia (SAB) in older adults. Aging Clin Exp Res. 2016 Feb 12.

Yahav D, Yassin S, Shaked H, Goldberg E, Bishara J, Paul M, **Leibovici L**. Risk factors for long-term mortality of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2016 May;35(5):785-90.

Yahav D, Eliakim-Raz N, **Leibovici L**, Paul M. Bloodstream infections in older patients. Virulence. 2016 Apr 2;7(3):341-52.

Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Lim WS, Al Mamun A, Anovadiya AP, Araújo WN, Azziz-Baumgartner E, Báez C, Bantar C, Barhoush MM, Bassetti M, Beovic B, Bingisser R, Bonmarin I, Borja-Aburto VH, Cao B, Carratala J, Cuezzo MR, Denholm JT, Dominguez SR, Duarte PA, Dubnov-Raz G, Echavarria M, Fanella S, Fraser J, Gao Z, Gérardin P, Giannella M, Gubbels S, Herberg J, Higuera Iglesias AL, Hoeger PH, Hoffmann M, Hu X, Islam QT, Jiménez MF, Kandeel A, Keijzers G, Khalili H, Khandaker G, Knight M, Kusznierz G, Kuzman I, Kwan AM, Lahlou Amine I, Langenegger E, Lankarani KB, Leo YS, Linko R, Liu P, Madanat F, Manabe T, Mayo-Montero E, McGeer A, Memish ZA, Metan G, Mikić D, Mohn KG, Moradi A, Nymadawa P, Ozbay B, Ozkan M, Parekh D, Paul M, Poeppl W, Polack FP, Rath BA, Rodríguez AH, Siqueira MM, Skręt-Magierło J, Talarek E, Tang JW, Torres A, Törün SH, Tran D, Uyeki TM, van Zwol A, Vaudry W, Velyvyte D, Vidmar T, Zarogoulidis P; PRIDE Consortium Investigators., Nguyen-Van-Tam JS. Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an individual participant data meta-analysis. Influenza Other Respir Viruses. 2016 May;10(3):192-204.

Dickstein Y, Geffen Y, **Leibovici L**, Paul M. Comparison of Antibiotic Susceptibility Patterns of Bacterial Isolates Based on Time From Hospitalization and Culture Source: Implications for Hospital Antibiograms. Infect Control Hosp Epidemiol. 2016 Feb;37(2):212-4.

Carrara E, Pfeffer I, Zusman O, **Leibovici L**, Paul M. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. Int J Antimicrob Agents. 2017

Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N; WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2017

Paul M, **Leibovici L**. Drug Development for Multidrug-Resistant Bacteria: Why Compromise? J Infect Dis. 2017

Stern A, Skalsky K, Avni T, Carrara E, **Leibovici L**, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2017

Drozdinsky G, Ben-Zvi H, Kushnir S, **Leibovici L**, Yahav D. Colistin exposure as a risk factor for

infections caused by inherently colistin resistant Enterobacteriaceae - a case control study. Clin Microbiol Infect. 2017

Leibovici L, Xu JF. CMI workshop in Shanghai, China. Clin Microbiol Infect. 2017

Zusman O, Farbman L, Elbaz M, Daitch V, Cohen M, Eliakim-Raz N, Babich T, Paul M, **Leibovici L**, Yahav D. A decision support model to predict the presence of an acute infiltrate on chest radiograph. Eur J Clin Microbiol Infect Dis. 2017

Babich T, Zusman O, Elbaz M, Ben-Zvi H, Paul M, **Leibovici L**, Avni T. Empirical Antibiotic Treatment Does Not Improve Outcomes in Catheter-Associated Urinary Tract Infection: Prospective Cohort Study. Clin Infect Dis. 2017

Leibovici L. Are we making an impact? Clin Microbiol Infect. 2017

Dalal A, Eskin-Schwartz M, Mimouni D, Ray S, Days W, Hodak E, **Leibovici L**, Paul M. Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database Syst Rev. 2017

Leibovici L. A new series of reviews in CMI: 'How to … '. Clin Microbiol Infect. 2017

Beyar-Katz O, Dickstein Y, Borok S, Vidal L, **Leibovici L**, Paul M. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. Cochrane Database Syst Rev. 2017

Leibovici L, Macnab F, Pereira-Moreira R. CMI readers' survey. Clin Microbiol. Infect. 2017;23(9):587-589.

Zayyad H, Eliakim-Raz N, **Leibovici L**, Paul M. Revival of old antibiotics: needs, the state of evidence and expectations. Int J Antimicrob Agents. 2017;49(5):536-541.

Leibovici L. Immediate rejection of manuscripts without peer review at the CMI. Clin Microbiol Infect. 2017;23(8):499.

Leibovici L, Friedman J. CMI Theme Issues: Invitation to submit papers. Clin Microbiol Infect. 2017;23(2):57.

Paul M, Yahav D, Dishon Benattar Y, **Leibovici L**. Reply to Zavascki and Nation. Clin Infect Dis. 2017;64(5):696.

Leibovici L. The nuts and bolts of doing science. Clin Microbiol Infect. 2017;23(5):275.

Harris PNA, McNamara JF, Lye DC, Davis JS, Bernard L, Cheng AC, Doi Y, Fowler VG Jr, Kaye KS, **Leibovici L**, Lipman J, Llewelyn MJ, Munoz-Price S, Paul M, Peleg AY, Rodríguez-Baño J, Rogers BA, Seifert H, Thamlikitkul V, Thwaites G, Tong SYC, Turnidge J, Utili R, Webb SAR, Paterson DL. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect. 2017;23(8):533-541.

Paul M, **Leibovici L**. Observational studies examining patient management in infectious diseases. Clin Microbiol Infect. 2017;23(3):127-128.

Green H, Tobar A, Gafter-Gvili A, **Leibovici L**, Klein T, Rahamimov R, Mor E, Grossman A. Serum Lactate Dehydrogenase is Elevated in Ischemic Acute Tubular Necrosis but Not in Acute Rejection in Kidney Transplant Patients. Prog Transplant. 2017;27(1):53-57.

Huttner A, **Leibovici L**, Theuretzbacher U, Huttner B, Paul M. Closing the evidence gap in infectious disease: point-of-care randomization and informed consent. Clin Microbiol Infect. 2017;23(2):73-77.

Yahav D, Shaked H, Goldberg E, Yassin S, Eliakim-Raz N, Paul M, Bishara J, **Leibovici L**. Time trends in Staphylococcus aureus bacteremia, 1988-2010, in a tertiary center with high methicillin resistance rates. Infection. 2017;45(1):51-57.

Yahav D, Schlesinger A, Shaked H, Goldberg E, Paul M, Bishara J, **Leibovici L**. Clinical presentation, management and outcomes of Staph aureus bacteremia (SAB) in older adults. Aging Clin Exp Res. 2017;29(2):127-133.

Reviews

Leibovici L. Ethical considerations in research published in the CMI. Clin Microbiol Infect. 2016 Dec;22(12):957.

Leibovici L. Structured abstracts for narrative reviews. Clin Microbiol Infect. 2016 Nov 7. pii: S1198-743X(16)30548-1.

Tacconelli E, Cataldo MA, Paul M, **Leibovici L**, Kluytmans J, Schröder W, Foschi F, De Angelis G, De Waure C, Cadeddu C, Mutters NT, Gastmeier P, Cookson B. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. BMJ Open. 2016 Feb 19;6(2):e010134.

Leibovici L. Message from the new CMI Editor-in-Chief. Clin Microbiol Infect. 2016 Apr;22(4):293.

Leibovici L, Paul M. Antibiotic treatment: balancing patients' rights. Lancet Respir Med. 2016 Jan;4(1):10-1

Leibovici L, Paul M, Garner P, Sinclair DJ, Afshari A, Pace NL, Cullum N, Williams HC, Smyth A, Skoetz N, Del Mar C, Schilder AG, Yahav D, Tovey D. Addressing resistance to antibiotics in systematic reviews of antibiotic interventions. J Antimicrob Chemother. 2016 Sep;71(9):2367-9. Leibovici L, Paul M. The CMI welcomes systematic reviews. Clin Microbiol Infect. 2016 May;22(5):397.

Avni T, Bieber A, Green H, Steinmetz T, **Leibovici L**, Paul M. Diagnostic Accuracy of PCR Alone and Compared to Urinary Antigen Testing for Detection of Legionella spp.: a Systematic Review. J Clin Microbiol. 2016 Feb;54(2):401-11.

Avni T, Lador A, Lev S, **Leibovici L**, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PLoS One. 2015 Aug 3;10(8):e0129305.

Eliakim-Raz N, Bates DW, **Leibovici L**. Predicting bacteraemia in validated models – a systematic review. Clin Microbiol Infect. 2015 Apr;21(4):295-301.

Leibovici L, Paul M. Ethical dilemmas in antibiotic treatment: focus on the elderly. Clin Microbiol Infect. 2015 Jan;21(1):27-9.

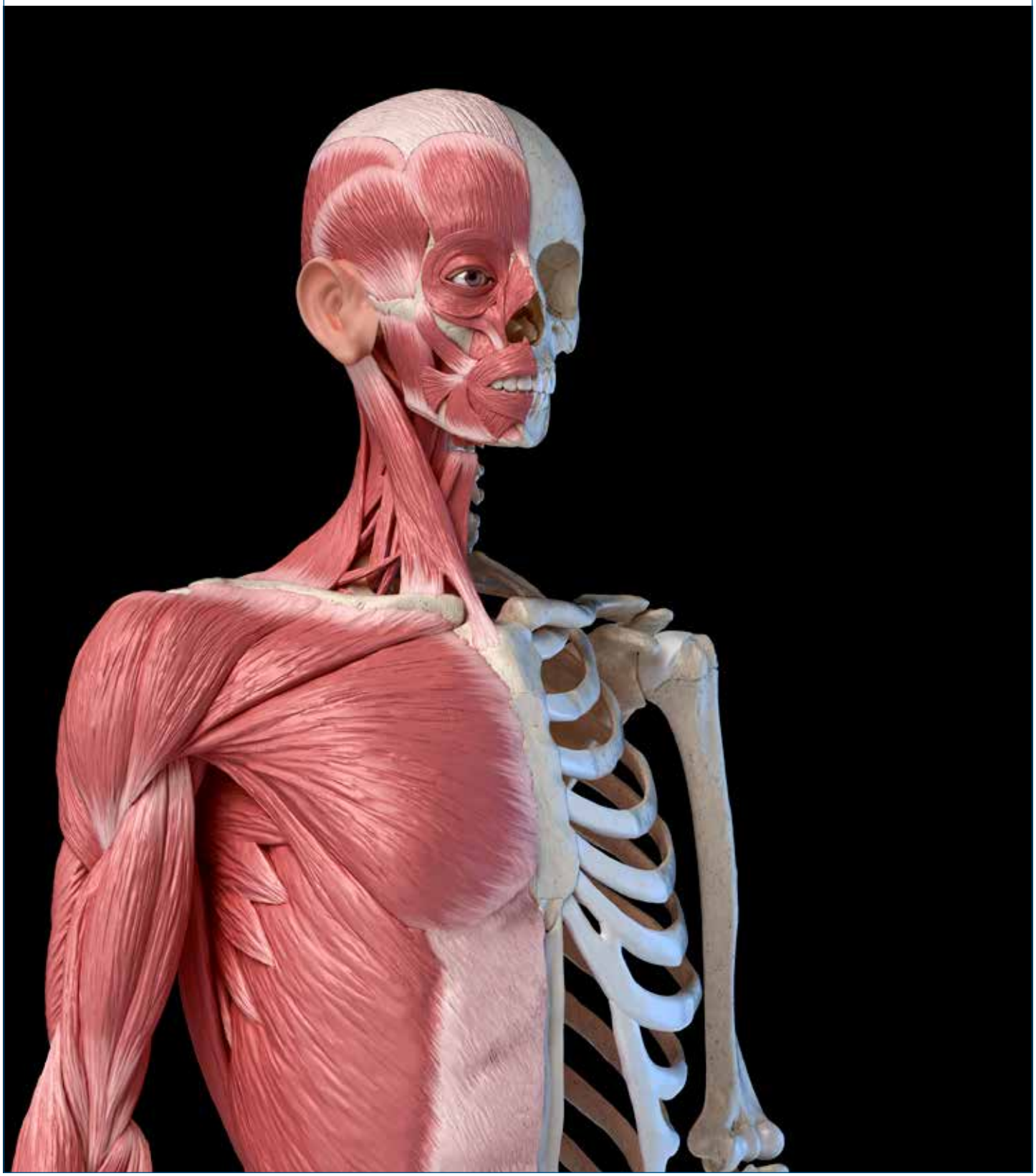
Avni T, Bieber A, Grossman A, Green H, **Leibovici** L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015 Jan;90(1):12-23.

Grants

2016-2021 IMI – COMBACTE-MAGNET: Combatting Bacterial Resistance in Europe – Molecules Against Gram Negative Infections

2016-2019 ERA-NET/ JPI-EC-AMR: Transnational Research Projects on the Transmission Dynamics of Antibacterial Resistance

Musculoskeletal Disorders



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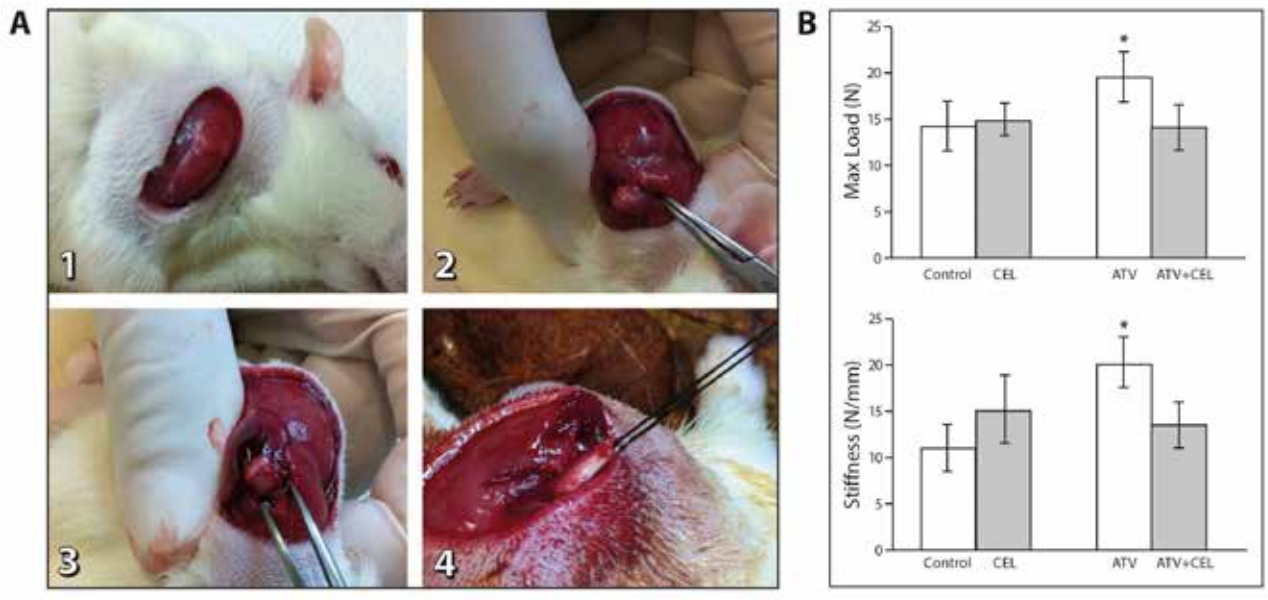
Investigating the Biomechanical Properties and Healing of Rotator Cuff Tendons



COX2-dependent stimulation of tendon healing by Atorvastatin (ATV). A. Rotator cuff repair model in rats. Under anesthesia, skin incision over the deltoid muscle (1); the deltoid is gently split (2) to uncover the supraspinatus tendon. The tendon is then cut adjacent to its footprint on the humeral head (3) and repositioned by suturing to the humerus (4). **B.** After 3 weeks, biomechanical testing in tension shows higher loads to failure and stiffness values in the ATV group compared with control, Celecoxib (CEL) and CEL+ATV groups.

Positions

Senior Lecturer, Sackler Faculty of Medicine

Committee Member, Tel Aviv Medical Center Institutional Review Board

Research

We study the biomechanical properties of rotator cuff tendons in various scenarios. Rotator cuff tears are a leading cause of shoulder pain and dysfunction in elderly as well as young population. Tendon healing is often impaired and requires surgical intervention. While technology and surgical techniques developed enormously during the last decades, biologic factors are still the limiting factor in tendon healing and re-tear. Studies are performed using a rat model imitating tendon tears and surgical repairs. Tendon healing is studied under various conditions including pharmacoligical agents and magnetic fields. The effect of pharmacologic agents on bone density and bone-tendon interface is also studied.

Publications

Maman E, Yehuda C, Pritsch T, Morag G, Brosh T, Sharfman Z, **Dolkart O**. Detrimental effect of repeated and single subacromial corticosteroids injections on intact and injured rotator cuff: biomechanical and imaging studies in rats. Am J Sports Med. 2016;44(1):177-82.

Gigi R, **Dolkart O**, Sharfman T Z, Goldstein Y, Brosh T, Rath E, **Maman E**, **Chechik O**. Biomechanical evaluation of two arthroscopic techniques for biceps tenodesis: Triple loop suture versus simple suture. J Shoulder Elbow Surg. 2017;26(1):165-169.

O Dolkart, **O Chechik**, A Bivas, T Brosh, M Drexler, Z Weinerman, **E Maman.** Subacromial corticosteroid injections transiently decrease suture anchor pullout strength: biomechanical studies in rats. J Shoulder Elbow Surg, In press.

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Investigating Gait, Balance, Falls and Motor-Cognitive Interactions in Aging and Disease

Positions

Professor, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University

Director, The Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center

Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center

Movement Disorders Society Task Force on Technology

Gait Advisory Committee for the Michael J. Fox Foundation for Parkinson's Research

International Society of Posture and Gait Research Strategic Planning Committee

Board of Directors, International Society for the Measurement of Physical Behaviour

Assocaite Editor, Journal of NeuroEngineering & Rehabilitation

Associate Editor, Journals of Gerontology: Medical Sciences

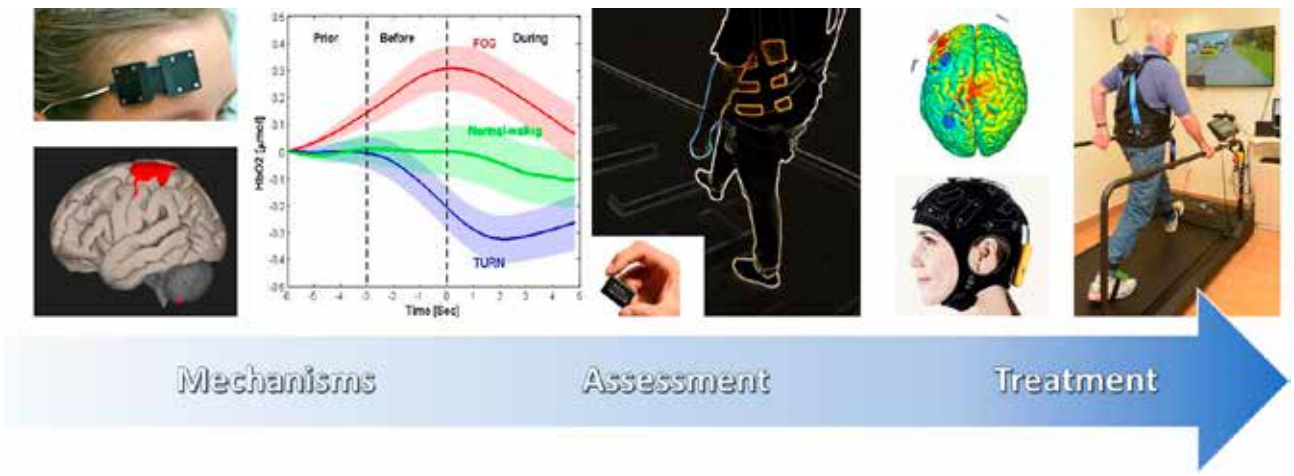
Editorial Board, Gait & Posture

Review Editor in Movement Disorders, Frontiers in Neurology

American Federation of Aging Research's National Scientific Advisory Council

Research

At the Center for the Study of Movement, Cognition, and Mobility, we investigate balance, walking, and falls as well as the prevention and restoration of loss of mobility, motor function, and cognition associated with aging and neurological disease (e.g., Parkinson's, multiple sclerosis, Alzheimer's, post-stroke, children with ADHD). Our research team leverages a combination of clinical, engineering and neuroscience expertise to achive three main objectives: 1) acquire new understandings of the *mechanisms* that contribute to cognitive and motor function and their changes with aging and disease; 2) construct and validate new methods and tools for early *detection* and *tracking* of cognitive and motor decline associated with aging and neuro-degeneration. This includes the development of new "bio-markers" that can be used for early



Examples of the modalities that we use to study, assess and treat gait, balance, falls and motor-cognitive interactions.

diagnosis, prognosis, and for quantitative tracking of disease progression, aging, and the response to therapeutic interventions (e.g., at-home monitoring using wearable devices and machine learning) and 3) develop novel methods for *prevention* and *treatment* (e.g., using virtual reality, pharmacologic therapy, motor learning, non-invasive brain stimulation).

Examples of ongoing projects in the lab include a) fMRI, EEG, and fNIRS imaging of balance and gait in Parkinson's disease and aging during usual walking and during challenging conditions such as when negotiationg obstacles; b) virtual-reality based intervention for gait and cognitive function in older adults and patients with multiple sclerosis; c) transcranial direct current stimulation to study the mechanisms and to ameliorate freezing of gait in patients with Parkinson's disease; d) Smartphone-based intervention to improve gait and cognition and to reduce fall risk in older adults; e) transcranial direct current stimulation to study the mechanisms and to reduce fall risk and the effects of dual tasking in older adults; f) investigation of genetic contributions to gait and mobility; g) 24/7 monitoring of gait and mobility using body-fixed sensors to study the effects of osteoarthritis on mobility and to identify early markers of Parkinson's disease. h) neural network studies of cognitive aging and mobility; i) effects of high intensity exercise on cognition, gait and mobility in older adults with mild cognitive impairment.

Publications

Manuscripts

Weiss A, Herman T, Giladi N, **Hausdorff JM**. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS One* 9:e96675; 2014.

Ben AE, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Hallevi H, Shopin L, Auriel E, Giladi N, Mike A, Halevy A, Weiss A, Mirelman A, Bornstein NM, **Hausdorff JM**. Gait measures as predictors of poststroke cognitive function: evidence from the TABASCO study. *Stroke* 46:1077-1083; 2015.

Herman T, Weiss A, Brozgol M, Wilf-Yarkoni A, Giladi N, **Hausdorff JM**. Cognitive function and other non-motor features in non-demented Parkinson's disease motor subtypes. *J Neural Transm (Vienna)* 122:1115-1124; 2015.

Ihlen EA, Weiss A, Helbostad JL, **Hausdorff JM**. The Discriminant Value of Phase-Dependent Local Dynamic Stability of Daily Life Walking in Older Adult Community-Dwelling Fallers and Nonfallers. *Biomed Res Int* 2015:402596; 2015.

Klucken J, Friedl KE, Eskofier BM, **Hausdorff JM**. Guest Editorial: Enabling Technologies for Parkinson's Disease Management. *IEEE J Biomed Health Inform* 19:1775-1776; 2015.

Maidan I, Bernad-Elazari H, Gazit E, Giladi N, **Hausdorff JM**, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. *J Neurol* 262:899-908; 2015.

Mazilu S, Calatroni A, Gazit E, Mirelman A, **Hausdorff JM**, Troster G. Prediction of Freezing of Gait in Parkinson's From Physiological Wearables: An Exploratory Study. *IEEE J Biomed Health Inform* 19:1843-1854; 2015.

Mirelman A, Bernad-Elazari H, Nobel T, Thaler A, Peruzzi A, Plotnik M, Giladi N, **Hausdorff JM**. Effects of Aging on Arm Swing during Gait: The Role of Gait Speed and Dual Tasking. *PLoS One* 10:e0136043; 2015.

Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, Giladi N, Hendler T, **Hausdorff JM**. Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. *J Neurol* 262:2448-2456; 2015.

Trojaniello D, Ravaschio A, **Hausdorff JM**, Cereatti A. Comparative assessment of different methods for the estimation of gait temporal parameters using a single inertial sensor: application to elderly, post-stroke, Parkinson's disease and Huntington's disease subjects. *Gait Posture* 42:310-316; 2015.

Walsh JN, Manor B, **Hausdorff JM**, Novak V, Lipsitz L, Gow B, Macklin EA, Peng CK, Wayne PM. Impact of Short- and Long-term Tai Chi Mind-Body Exercise Training on Cognitive Function in Healthy Adults: Results From a Hybrid Observational Study and Randomized Trial. *Glob Adv Health Med* 4:38-48; 2015.

Wayne PM, **Hausdorff JM**, Lough M, Gow BJ, Lipsitz L, Novak V, Macklin EA, Peng CK, Manor B. Tai Chi Training may Reduce Dual Task Gait Variability, a Potential Mediator of Fall Risk, in Healthy Older Adults: Cross-Sectional and Randomized Trial Studies. *Front Hum Neurosci* 9:332; 2015.

Weiss A, Herman T, Giladi N, **Hausdorff JM**. Association between Community Ambulation Walking Patterns and Cognitive Function in Patients with Parkinson's Disease: Further Insights into Motor-Cognitive Links. *Parkinsons Dis* 2015:547065; 2015.

Weiss A, Herman T, Giladi N, **Hausdorff JM**. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait:

insights using a body-fixed sensor worn for 3 days. *J Neural Transm (Vienna)* 122:403-410; 2015.

Bernad-Elazari H, Herman T, Mirelman A, Gazit E, Giladi N, **Hausdorff JM**. Objective characterization of daily living transitions in patients with Parkinson's disease using a single body-fixed sensor. *J Neurol* 263:1544-1551; 2016.

Dockx K, Bekkers EM, Van dB, V, Ginis P, Rochester L, **Hausdorff JM**, Mirelman A, Nieuwboer A. Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst Rev* 12:CD010760; 2016.

Ginis P, Nieuwboer A, Dorfman M, Ferrari A, Gazit E, Canning CG, Rocchi L, Chiari L, **Hausdorff JM**, Mirelman A. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinson's disease: A pilot randomized controlled trial. *Parkinsonism Relat Disord* 22:28-34; 2016.

Ihlen EAF, Weiss A, Beck Y, Helbostad JL, **Hausdorff JM**. A comparison study of local dynamic stability measures of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech* 49:1498-1503; 2016.

Ihlen EAF, Weiss A, Bourke A, Helbostad JL, **Hausdorff JM**. The complexity of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech* 49:1420-1428; 2016.

Iluz T, Weiss A, Gazit E, Tankus A, Brozgol M, Dorfman M, Mirelman A, Giladi N, **Hausdorff JM**. Can a Body-Fixed Sensor Reduce Heisenberg's Uncertainty When It Comes to the Evaluation of Mobility? Effects of Aging and Fall Risk on Transitions in Daily Living. *J Gerontol A Biol Sci Med Sci* 71:1459-1465; 2016.

James EG, Leveille SG, You T, **Hausdorff JM**, Travison T, Manor B, McLean R, Bean JF. Gait coordination impairment is associated with mobility in older adults. *Exp Gerontol* 80:12-16; 2016.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, **Hausdorff JM**, Mirelman A. Altered brain activation in complex walking conditions in patients with Parkinson's disease. *Parkinsonism Relat Disord* 25:91-96; 2016.

Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, Deutsch JE, **Hausdorff JM**, Claassen JA, Mirelman A. The role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: An fNIRS study. *Neurorehabil Neural Repair* 30:963-971; 2016.

Mirelman A, Rochester L, Maidan I, Del DS, Alcock L, Nieuwhof F, Rikkert MO, Bloem BR, Pelosin E, Avanzino L, Abbruzzese G, Dockx K, Bekkers E, Giladi N, Nieuwboer A, **Hausdorff JM**. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet* 388:1170-1182; 2016.

Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, Saunders-Pullman R, Raymond D, Doan N, Bressman SB, Marder KS, Alcalay RN, Rao AK, Berg D, Brockmann K, Aasly J, Waro BJ, Tolosa E, Vilas D, Pont-Sunyer C, Orr-Urtreger A, **Hausdorff JM**, Giladi N. Arm swing as a potential new prodromal marker of Parkinson's disease. *Mov Disord* 31:1527-1534; 2016.

Nieuwhof F, Reelick MF, Maidan I, Mirelman A, **Hausdorff JM**, Olde Rikkert MG, Bloem BR, Muthalib M, Claassen JA. Measuring prefrontal cortical activity during dual task walking in patients with Parkinson's disease: feasibility of using a new portable fNIRS device. *Pilot Feasibility Stud* 2:59; 2016.

Pelosin E, Ogliastro C, Lagravinese G, Bonassi G, Mirelman A, **Hausdorff JM**, Abbruzzese G, Avanzino L. Attentional Control of Gait and Falls: Is Cholinergic Dysfunction a Common Substrate in the Elderly and Parkinson's Disease? *Front Aging Neurosci* 8:104; 2016.

Rosenberg-Katz K, Maidan I, Jacob Y, Giladi N, Mirelman A, **Hausdorff JM**. Alterations in conflict monitoring are related to functional connectivity in Parkinson's disease. *Cortex* 82:277-286; 2016.

Rosenberg-Katz K, Herman T, Jacob Y, Kliper E, Giladi N, **Hausdorff JM**. Subcortical Volumes Differ in Parkinson's Disease Motor Subtypes: New Insights into the Pathophysiology of Disparate Symptoms. *Front Hum Neurosci* 10:356; 2016.

van der Leeuw G, Eggermont LH, Shi L, Milberg WP, Gross AL, **Hausdorff JM**, Bean JF, Leveille SG. Pain and cognitive function among older adults living in the community. *J Gerontol A Biol Sci Med Sci* 71:398-405; 2016.

Weiss A, Brozgol M, Giladi N, **Hausdorff JM**. Can a single lower trunk body-fixed sensor differentiate between level-walking and stair descent and ascent in older adults? Preliminary findings. *Med Eng Phys* 38:1146-1151; 2016.

Weiss A, Mirelman A, Giladi N, Barnes LL, Bennett DA, Buchman AS, **Hausdorff JM**. Transition between the timed up and go turn to sit subtasks: is timing everything? *J Am Med Dir Assoc* 17:864; 2016.

Arie L, Herman T, Shema-Shiratzky S, Giladi N, **Hausdorff JM**. Do cognition and other non-motor symptoms decline similarly among patients with

Parkinson's disease motor subtypes? Findings from a 5-year prospective study. *J Neurol* 264:2149-2157; 2017.

Arndt H, Burkard S, Talavera G, Garcia J, Castells D, Codina M, **Hausdorff JM**, Mirelman A, Harte R, Casey M, Glynn L, Di RM, Rossi L, Stara V, Rosevall J, Rusu C, Carenas C, Breuil F, Reixach E, Carrabina J. Real-Time Constant Monitoring of Fall Risk Index by Means of Fully-Wireless Insoles. *Stud Health Technol Inform* 237:193-197; 2017.

Broom L, Ellison BA, Worley A, Wagenaar L, Sorberg E, Ashton C, Bennett DA, Buchman AS, Saper CB, Shih LC, **Hausdorff JM**, VanderHorst VG. A translational approach to capture gait signatures of neurological disorders in mice and humans. *Sci Rep* 7:3225; 2017.

Brozgol M, Arbiv M, Mirelman A, Herman T, **Hausdorff JM**, Vaisman N. Vertical ground reaction force during standing and walking: Are they related to bone mineral density left-right asymmetries? *Gait Posture* 54:174-177; 2017.

Dagan M, Herman T, Mirelman A, Giladi N, **Hausdorff JM**. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. *Exp Brain Res* 235:2463-2472; 2017.

Dawe RJ, Leurgans SE, Yang J, Bennett JM, **Hausdorff JM**, Lim AS, Gaiteri C, Bennett DA, Buchman AS. Association between quantitative gait and balance measures and total daily physical activity in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* ; 2017.

Di RM, **Hausdorff JM**, Stara V, Rossi L, Glynn L, Casey M, Burkard S, Cherubini A. Concurrent validation of an index to estimate fall risk in community dwelling seniors through a wireless sensor insole system: A pilot study. *Gait Posture* 55:6-11; 2017.

Dockx K, Alcock L, Bekkers E, Ginis P, Reelick M, Pelosin E, Lagravinese G, **Hausdorff JM**, Mirelman A, Rochester L, Nieuwboer A. Fall-prone older people's attitudes towards the use of virtual reality technology for fall prevention. *Gerontology* 63:590-598; 2017.

Gow BJ, **Hausdorff JM**, Manor B, Lipsitz LA, Macklin EA, Bonato P, Novak V, Peng CK, Ahn AC, Wayne PM. Can Tai Chi training impact fractal stride time dynamics, an index of gait health, in older adults? Cross-sectional and randomized trial studies. *PLoS One* 12:e0186212; 2017.

James EG, Leveille SG, **Hausdorff JM**, Barton B, Cote S, Karabulut M, Conatser P, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Coordination impairments are associated with falling among older adults. *Exp Aging Res* 43:430-439; 2017.

James EG, Conatser P, Karabulut M, Leveille SG, **Hausdorff JM**, Cote S, Tucker KL, Barton B, Bean JF, Al SS, Markides KS. Mobility limitations and fear of falling in non-English speaking older Mexican-Americans. *Ethn Health* 22:480-489; 2017.

James EG, Leveille SG, **Hausdorff JM**, Travison T, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Rhythmic Interlimb Coordination Impairments and the Risk for Developing Mobility Limitations. *J Gerontol A Biol Sci Med Sci* 72:1143-1148; 2017.

James EG, Leveille SG, **Hausdorff JM**, Travison T, Cote S, Conatser P, Karabulut M, Mendes AC, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Rhythmic interlimb coordination impairments are associated with mobility limitations among older adults. *Exp Aging Res* 43:337-345; 2017.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, **Hausdorff JM**, Mirelman A. Disparate effects of training on brain activation in Parkinson disease. *Neurology* 89:1804-1810; 2017.

Maidan I, Bernad-Elazari H, Giladi N, **Hausdorff JM**, Mirelman A. When is higher level cognitive control needed for locomotor tasks among patients with Parkinson's Disease? *Brain Topogr* 30:531-538; 2017.

Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, **Hausdorff JM**. Effects of aging on prefrontal brain activation during challenging walking conditions. *Brain Cogn* 115:41-46; 2017.

Nieuwhof F, Bloem BR, Reelick MF, Aarts E, Maidan I, Mirelman A, **Hausdorff JM**, Toni I, Helmich RC. Impaired dual tasking in Parkinson's disease is associated with reduced focusing of cortico-striatal activity. *Brain* 140:1384-1398; 2017.

Palmerini L, Rocchi L, Mazilu S, Gazit E, **Hausdorff JM**, Chiari L. Identification of characteristic motor patterns preceding freezing of gait in Parkinson's Disease using wearable sensors. *Front Neurol* 8:394; 2017.

Stuart S, Hunt D, Nell J, Godfrey A, **Hausdorff JM**, Rochester L, Alcock L. Do you see what I see? Mobile eye-tracker contextual analysis and inter-rater reliability. *Med Biol Eng Comput*; 2017.

Tankus A, Strauss I, Gurevich T, Mirelman A, Giladi N, Fried I, **Hausdorff JM**. Subthalamic neurons encode both single- and multi-limb movements in Parkinson's Disease patients. *Sci Rep* 7:42467; 2017.

van der Leeuw G, Leveille SG, Jones RN, **Hausdorff JM**, McLean R, Kiely DK, Gagnon M, Milberg WP. Measuring attention in very old adults using the Test

of Everyday Attention. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 24:543-554; 2017.

Hausdorff JM, Hillel I, Shustak S, Del Din S, Bekkers E MJ, Pelosin E, Nieuwhof F, Rochester L Mirelman A. Everyday stepping quantity and quality among older adult fallers with and without mild cognitive impairment: Initial evidence for new motor markers of cognitive deficits? *J Gerontol Med Sci* ePub ahead of print, 2017.

Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, Giladi N, Mirelman A, **Hausdorff JM**. Age-associated changes in obstacle negotiation strategies: Does size and timing matter? *Gait Posture* 59:242-247; 2018.

Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, Manor B, **Hausdorff JM**. Multi-target transcranial direct current stimulation for freezing of gait in Parkinson's disease: A step forward? *Mov Disord,* in press 2018.

Reviews

Mirelman A, Giladi N, **Hausdorff JM**. Body-fixed sensors for Parkinson Disease. *JAMA* 314:873-874; 2015.

Sorond FA, Cruz-Almeida Y, Clark DJ, Viswanathan A, Scherzer CR, De JP, Csiszar A, Laurienti PJ, **Hausdorff JM**, Chen WG, Ferrucci L, Rosano C, Studenski SA, Black SE, Lipsitz LA. Aging, the central nervous system, and mobility in older adults: Neural mechanisms of mobility impairment. *J Gerontol A Biol Sci Med Sci* 70:1526-1532; 2015.

Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, Eskofier BM, Merola A, Horak F, Lang AE, Reilmann R, Giuffrida J, Nieuwboer A, Horne M, Little MA, Litvan I, Simuni T, Dorsey ER, Burack MA, Kubota K, Kamondi A, Godinho C, Daneault JF, Mitsi G, Krinke L, **Hausdorff JM**, Bloem BR, Papapetropoulos S. Technology in Parkinson's disease: Challenges and opportunities. *Mov Disord* 31:1272-1282; 2016.

Varma VR, **Hausdorff JM**, Studenski SA, Rosano C, Camicioli R, Alexander NB, Chen WG, Lipsitz LA, Carlson MC. Aging, the Central nervous system, and mobility in older adults: Interventions. *J Gerontol A Biol Sci Med Sci* 71:1451-1458; 2016.

Fasano A, Canning CG, **Hausdorff JM**, Lord S, Rochester L. Falls in Parkinson's disease: A complex and evolving picture. *Mov Disord* 32:1524-1536; 2017.

Song R, Grabowska W, Park M, Osypiuk K, Vergara-Diaz GP, Bonato P, **Hausdorff JM**, Fox M, Sudarsky LR, Macklin E, Wayne PM. The impact of Tai Chi and Qigong mind-body exercises on motor and non-motor function and quality of life in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism Relat Disord* 41:3-13; 2017.

Wajda DA, Mirelman A, **Hausdorff JM**, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: A systematic review. *Expert Rev Neurother* 17:251-261; 2017.

Grants

2016-2020 Michael J Fox Foundation for Parkinson's Research, The Effects of Multi-focal Transcranial Direct Current Stimulation on Freezing of Gait in Patients with Parkinson's Disease: A Randomized Controlled Trial (JM Hausdorff, PI)

2016-2019 National Multiple Sclerosis Society, Virtual Reality-treadmill combined intervention for enhancing mobility and cognitive function in patients with Relapsing-Remitting Multiple Sclerosis (JM Hausdorff, PI)

2016-2019 Ministry of Science, Technology and Space, Development and validation a Smartphone-based system for improving gait, cognition and socialization in elderly (A Mirelman PI)

2016-2021 National Institutes of Health, Racial Differences in Late-Life Cognitive decline and risk of Alzheimer's Disease (L Barnes, PI; JM Hausdorff Israeli PI)

2016-2019 US-Israel Bi-National Science Foundation, Enhancing brain activity to improve dual task walking in older adult fallers: a functional near-infrared spectroscopy and transcranial direct current stimulation study (JM Hausdorff Israeli PI, L Lipsitz US PI).

2017-2019 Israel Science Foundation, The role of the frontal lobe in obstacle negotiation in patients with Parkinson's disease (JM Hausdorff, PI)

2017-2022 National Institutes of Health, Impaired Gait in Older Adults: Pathologies of Alzheimer's disease and Related Disorders (A Buchman, PI; JM Hausdorff Israeli PI)

2017-2021 National Institutes of Health, Exploring Cognitive Aging Using Refernce Ability Neural Networks (Y Stern PI; JM Hausdorff Israeli PI)

2017-2021 National Health Medical Research Council (Australia) BRAIN Training Trial: Balance, Resistance, or INterval Training Trial: A Randomised Controlled Trial of Three Exercise Modalities in Mild Cognitive Impairment (M Fiatarone-Singh PI; JM Hausdorff Israeli PI)

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Investigating the Pathophysiology and Therapeutic Option for Muscular Dystrophy

Positions

Director, Institute of Neurology

Scneider Children'S Medical Center of Israel

Professor, Sackler Faculty of Medicine

Chair, Israeli Child Neurologist Association

Research

The main goal of our research is to develop new therapies for Duchenne and Becker muscular dystrophy (DMD and BMD) and other neuromuscular dystrophies which currently have no cure. DMD is the most common muscular dystrophy in children. DMD patients suffer from progressive muscle atrophy and weakness**,** lose independent ambulation by the age of 13 years and often die in their third decade.

Our laboratory focuses on understanding biochemical and molecular mechanisms leading to muscle dystrophy and the significant processes contributing to its secondary effects and disease progression, such as chronic inflammation and fibrosis. We are using diverse anti-inflammatory and anti-fibrotic agents and also combination therapies, to tackle the massive inflammation and fibrosis to improve outcomes in mouse models of DMD and of congenital muscular

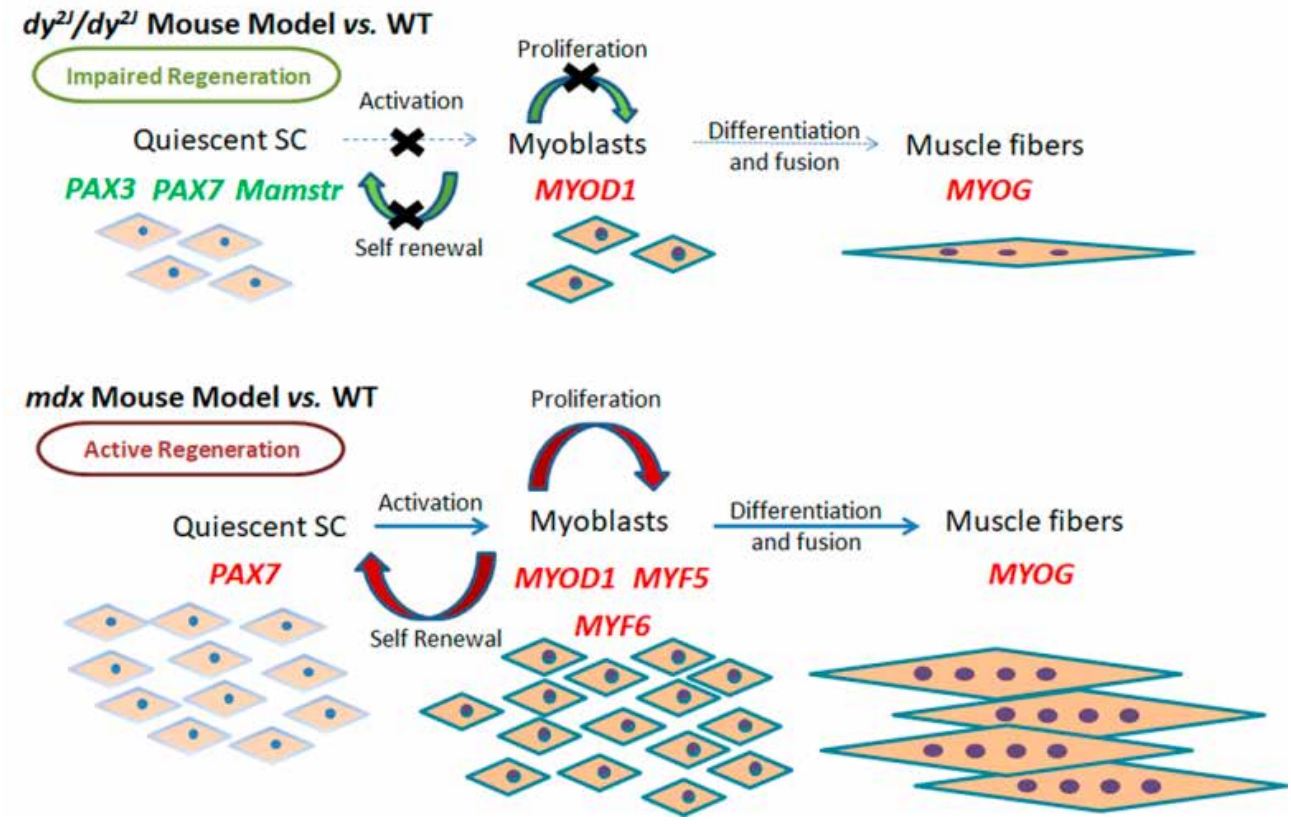


Figure 1. Model for the impaired regeneration mechanism in dy^{2J}/dy^{2J} mouse skeletal muscle (Yanay et al 2019).

dystrophy (CMD). We also combined different novel strategies of gene therapy, small molecules and nanotechnology such as liposomes, exosomes and other nanoparticles to deliver drugs specifically to muscles. Diverse methodologies, including mouse models, human muscle biopsies, primary muscle satellite cells, and bioinformatics techniques are employed. We use novel high throughput sequencing (RNA-Seq) platform enabling us to identify novel genes that promote muscle regeneration and seek to extend the animal findings to humans. In addition to pure translational studies, biomarkers in our laboratory are evaluated as an aid to study Duchenne and Becker muscular dystrophy patients' physical activity and performance.

Publications

Elbaz M, Yanay N, Laban S, Rabie M, Mitrani-Rosenbaum S, **Nevo Y**. Life or death by NFkB, Losartan promotes muscle survival in dy2j/dy2j mouse. Cell Death Dis. 2015;6:e1690. _

Rokach O, Sekulic-Jablanovic M, Voermans N, Wilmshurst J, Pillay K, Heytens L, Zhou H, Muntoni F, Gautel M, **Nevo Y**, Rosenbaum S, Attali R, Finotti A, Gambari R, Jungbluth H, Zorzato F & Treves S. Epigenetic changes as a common trigger of muscle weakness in congenital myopathies. Hum Mol Genet. 2015;24(16):4636-47.

Haziza S, Magnani R, Lan D, Keinan O, Saada Reisch A, Eli Hershkovitz E, Nurit Yanai N, **Nevo Y**, Houtz RL, Sheffield VC, Golan H, Parvari R. Calmodulin methyltransferase is required for growth, muscle strength, somatosensory development and brain function. PloS Genet 2015;11(8):e1005388.

Ben-Zeev B, Tabib A, Nissenkorn A, Garti BZ, Gomori JM, Nass D, Goldshmidt H, Fellig Y, Anikster Y **Nevo Y**, Elpeleg O, Mevorach D. Devastating recurrent brain ischemic infarctions and retinal disease in pediatric patients with CD59 deficiency. Eur J Paediatr Neurol. 2015;19(6):688-93.

Aharoni S. Barwick KEC, Straussberg R, Harlalka GV, **Nevo Y**, Chioza BA, Meriel M. McEntagart MM, Mimouni-Bloch A, Weedon M, Crosby AH. Novel homozygous missense mutation in *GAN* causes Charcot-Marie-Tooth disease type 2 in a large consanguineous family from Israel. BMC Medical Genet 2016;17(1):82.

Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S; CINRG investigators. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. Neurology, 2016;87(4):401-9.

Bello L, Flanigan KM, Weiss RB; United Dystrophinopathy Project, Spitali P, Aartsma-Rus A, Muntoni F, Zaharieva I, Ferlini A, Mercuri E, Tuffery-Giraud S, Claustres M, Straub V, Lochmüller H, Barp A, Vianello S, Pegoraro E, Punetha J, Gordish-Dressman H, Giri M, McDonald CM, Hoffman EP;Cooperative International Neuromuscular Research Group. Association study of exon variants in the NF-κB and TGFβ pathways identifies CD40 as a modifier of duchenne muscular dystrophy. Am J Hum Genet. 2016; 99, 1163–1171.

Hogarth MW, Houweling PJ, Thomas KC, Gordish-Dressman H, Bello L; Cooperative International Neuromuscular Research Group (CINRG), Pegoraro E, Hoffman EP, Head SI, North KN. Evidence for ACTN3 as a genetic modifier of Duchenne muscular dystrophy. Nat Commun. 2017;8:14143.

McDonald CM, Campbell C, Torricelli RE, Finkel RS, Flanigan KM, Goemans N, Heydemann P, Kaminska A, Kirschner J, Muntoni F, Osorio AN, Schara U, Sejersen T, Shieh PB, Sweeney HL, Topaloglu H, Tulinius M, Vilchez JJ, Voit T, Wong B, Elfring G, Kroger H, Luo X, McIntosh J, Ong T, Riebling P, Souza M, Spiegel RJ, Peltz SW, Mercuri E; Clinical Evaluator Training Group; ACT DMD Study Group. Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 390(10101):1489-1498.

Anderson J, Seol H, Gordish-Dressman H, Hathout Y, Spurney CF; CINRG Investigators. Interleukin 1 Receptor-Like 1 Protein (ST2) is a potential biomarker for cardiomyopathy in Duchenne Muscular Dystrophy. Pediatr Cardiol. 2017;38(8):1606-1612.

McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, Clemens PR, Hoffman EP, Cnaan A, Gordish-Dressman H; CINRG Investigators. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018;391(10119):451-46.

Thangarajh M1, Elfring GL2, Trifillis P2, McIntosh J2, Peltz SW2. Ataluren Phase 2b Study Group. The relationship between deficit in digit span and genotype in nonsense mutation Duchenne muscular dystrophy. Neurology. 2018; 91(13):e1215-e1219.

McDonald CM, Gordish-Dressman H, Henricson EK, Duong T, Joyce NC, Jhawar S, Leinonen M, Hsu F, Connolly AM, Cnaan A, Abresch RT; CINRG investigators. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and

without glucocorticoids. Neuromuscul Disord. 2018;28(11):897-909.

Aharoni S., Sadeh M, Shapira Y, Edvardson S, Daana M, Dor-Wollman T, Mimouni-Bloch A, Halevy A, Cohen R, Sagie L, Argov Z, Rabie R , Spiegel R, Chervinsky R, Engel AG, **Nevo Y**. Congenital myasthenic syndrome in Israel: Genetic and clinical characterization. Neuromuscul Disord, 2017;27(2):136-140.

Mizrachi T, Brill L, Rabie M, **Nevo Y**, Fellig Y, Maayan Zur M, Karussis D, Abramsky O, Brenner T and Vaknin-Dembinsky A. NMO IgG and AQP4 peptide can induce aggravation of EAMG and immune mediated muscle weakness. J. Immunol Res, 2018;2018:5389282

Conklin LS , Damsker JM, Jusko WJ, Schwartz B, Mengle-Gaw L, Smith EC, Mah J, Guglieri M, **Nevo Y**, Kuntz N, McDonald C, Tulinius M, Ryan M, Webster R, Castro D, Finkel RS, Smith A, Morgenroth LP, Arrieta A, Shimony M, Jaros M, Shale P, McCall JM, Nagaraju K, van den Anker J, Ward L, Ahmet A, Cornish MR, Hoffman EP, Clemens PR. Phase IIa trial in Duchenne muscular dystrophy shows vamorolone is a First-in-class dissociative steroidal anti-inflammatory drug. Pharmacological Res, 2018;136; 140-150.

McDonald CM, **Gordish-Dressman H**, **Henricson EK**, **Duong T**, **Joyce NC**, **Jhawar S**, **Leinonen M**, **Hsu F**, **Connolly AM**, **Cnaan A**, **Abresch RT**; **CINRG investigators for PubMed**. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: Long-term natural history with and without glucocorticoids. **Neuromuscul Disord.** 2018;28(11):897-909.

Turjeman K, Yanay N, Elbaz M, Bavli Y, Gross M, Rabie M, Barenholz Y, and **Nevo Y**. Liposomal steroid nano-drug is superior to steroids as-is in mdx mouse model of Duchenne muscular dystrophy. Nanomedicine. 2019; 16:34-44.

Yosha-Orpaz N, Aharoni S, Rabie M, and **Nevo Y**, Atypical clinical presentations of pediatric acute immune- mediated polyneuropathy. J Child Neurol, 2019;34(5):268-276.

Sheffer R, Gur M, Brooks R, Salah S, Daana M, Fraenkel N, Eisenstein E, Rabie M, **Nevo Y**, Jalas C, Elpeleg O, Edvardson S, Harel T. Biallelic variants in AGTPBP1, involved in tubulin deglutamylation, are associated with cerebellar degeneration and motor neuropathy. Eur J Hum Genet. 2019; 27(9):1419-1426.

Conrado DJ, Larkindale J, Berg A, Hill M, Burton J, Abrams KR, Abresch RT, Bronson A, Chapman D, Crowther M, Duong T, Gordish-Dressman H, Harnisch L, Henricson E, Kim S, McDonald CM, Schmidt S, Vong C, Wang X, Wong BL, Yong F, Romero K. Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC). Towards regulatory endorsement of drug development tools to promote the application of model-informed drug development in Duchenne muscular dystrophy. J Pharmacokinet Pharmacodyn. 2019; 46(5):441-455.

Yanay N, Elbaz M, Konikov-Rozenman J, Elgavish S, Nevo Y, Fellig Y, Rabie M, Mitrani-Rosenbaum S, **Nevo Y**. Pax7, Pax3 and Mamstr genes are involved in skeletal muscle impaired regeneration of dy2J/dy2J mouse model of Lama2-CMD. Hum Mol Genet. 2019; 28(20):3369-3390.

Hoffman EP, Schwartz BD, Mengle-Gaw LJ, Smith EC, Castro D, Mah JK, McDonald CM, Kuntz NL, Finkel RS, Guglieri M, Bushby K, Tulinius M, **Nevo Y**, Ryan MM, Webster R, Smith AL, Morgenroth LP, Arrieta A, Shimony M, Siener C, Jaros M, Shale P, McCall JM, Nagaraju K, van den Anker J, Conklin LS, Cnaan A, Gordish-Dressman H, Damsker JM, Clemens PR; and the Cooperative International Neuromuscular Research Group. Vamorolone trial in Duchenne muscular dystrophy shows dose-related improvement of muscle function. Neurology. 2019 24;93(13):e1312-e1323

Rabie M, Yanay N, Fellig Y, Konikov-Rozenman J, **Nevo Y.** Improvement of motor conduction velocity in hereditary neuropathy of LAMA2-CMD *dy^{2J}*/*dy^{2J}* mouse model by glatiramer acetate. Clinical Neurophysiology, 2019; **130 (10)**,1988-1994.

McDonald CM, Sajeev G....,; ACT DMD Study Group; Tadalafil DMD Study Group. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: a meta-analysis of disease progression rates in recent multicenter clinical trials. Muscle Nerve. 2019; 61(1):26-35.

Spitali P, Zaharieva I, Bohringer S et al. TCTEX1D1 Is a genetic modifier of disease progression in Duchenne Muscular Dystrophy. Eur J Hum Genet 2020 28(6):815-825.

Shinkarevsky Fleitman I, **Nevo Y**, **Harel** L, **Amarilyo** G, **Dori A**, **Agmon-Levin** A, **Kachko** L, **Zaks Hoffer** A, **Dabby** R, **Rabie** M, **Aharoni** S. Small fiber neuropathy associated with autoinflammatory syndromes in children. Muscle Nerve, 2020; 61(6):791-796.

Greer K, Johnsen R, **Nevo Y**, Fellig Y, Fletcher S, Wilton S. Single exon skipping can address a multi-exon duplication in the dystrophin gene. Int J Mol Sci 2020

Yanay N, Rabie M, **Nevo Y**. Impaired Regeneration in dystrophic muscle-new target for therapy. Front Mol Neurosci 2020;13:69.

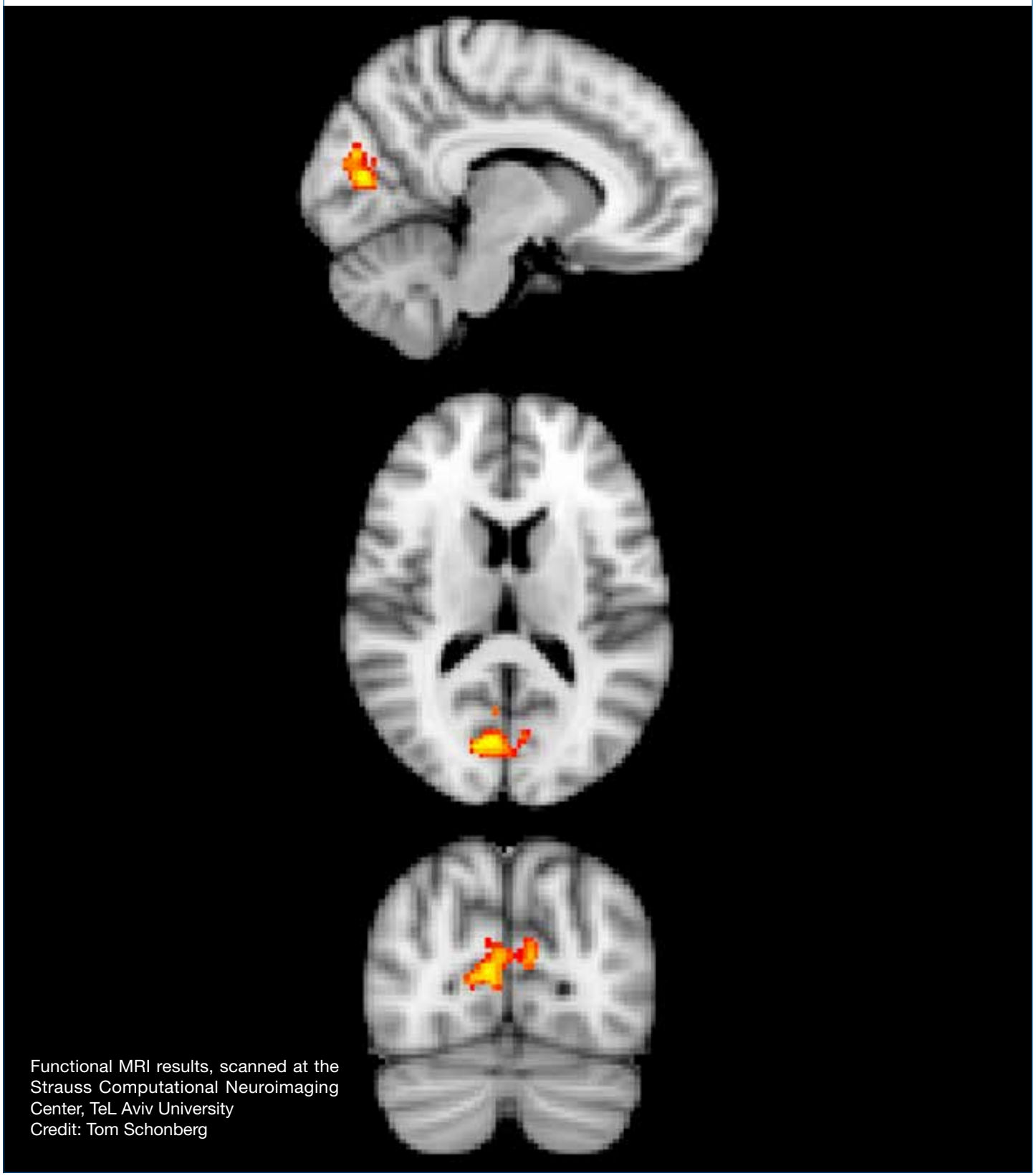
Chapters and Editorials

Rabie M, **Nevo Y**. Emery Dreifuss and laminopathies (Invited Chapter). In: International Neurology: A Clinical Approach, 2ND edition. Editor(s): Robert P. Lisak, Daniel D. Truong, William M. Carroll, Roongroj Bhidayasiri. Wiley Blackwell Publishing, Chichester, UK, 2016

Rabie M, Ashwal S, **Nevo Y**. Inflammatory neuropathy. In: Swaiman Textbook of Pediatric Neurology. 6th edition. Editors: By Kenneth F. Swaiman, MD, Stephen Ashwal, MD, Donna M Ferriero, MD and Nina F Schor, MD, PhD. Saunders Elsevier – 2018.

Nevo Y, Wang, C. Editorial: Spinal Muscular Atrophy – a preliminary result toward a new therapy. Neurology, 2016, 86(10):884-5.

Neurological & Psychiatric Diseases



Functional MRI results, scanned at the Strauss Computational Neuroimaging Center, TeL Aviv University
Credit: Tom Schonberg

Dr. Felix Benninger, M.D.

Felsenstein Medical Research Center, Beilinson Hospital
Department of Neurology, Rabin Medical Center

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Laboratory of Clinical Neuroscience

Positions

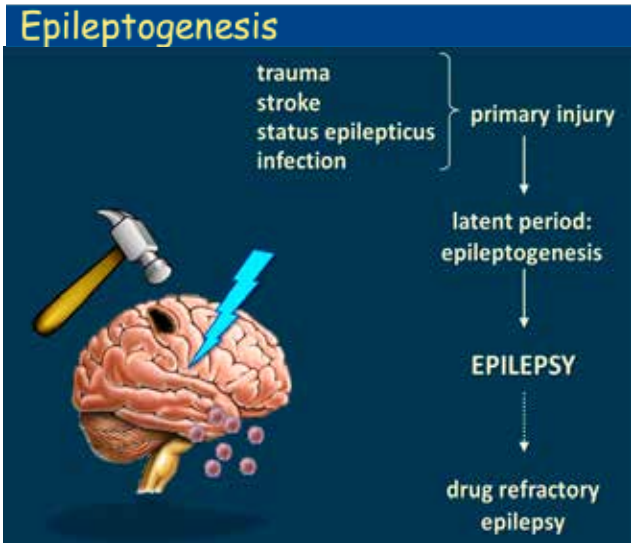
Head of Laboratory, Felsenstein Medical Research Center

Senior Lecturer, Sackler Faculty of Medicine

Research

Our laboratory is interested in the development (genesis) and the patho-physiology of neurological disorders. We are highly translational and are trying to find solutions starting with real-life clinical problems with our methodology in the laboratory. Besides general neurology, we are focusing on the development of epilepsy (epileptogenesis) and the possibility to find a preventive treatment for patients about to develop epilepsy instead of treating, as today, the symptoms: epileptic seizures.

Our methods in the laboratory include electroencephalogram EEG in living and freely moving rodents as well as video-EEG recordings. Hereby, seizures can be detected, and quantified, and possible preventive treatment assessed. Furthermore, we are using human EEG in a highly computational analysis developed by Dr. Oded Shor to separate patient groups (dementia, depression, schizophrenia and patients with epilepsy) by using a short EEG recording. Our goal here is to predict diseases using brain signature of the EEG even before symptom onset. In collaboration with the genetics department at Rabin Medical Center, we are using protein modelling and normal-mode-analysis (NMA) to re-classify possible single nucleotide mutations previously not known to have a physiological impact. This is done by a method created by our post-doc Dr. Oded Shor and includes the use of in-silico protein dynamics with entropy quantification to compare different proteins. We are a very fluid group and open for new projects and very much appreciate our close collaboration with the team of Prof. Daniel Offen at the same institute. Our strengths lies in the ability to be close to patients problems through clinics and ward rounds as well as having highly qualified mathematical and computational knowledge.



Publications

Benninger F, Khlebtovsky A, Roditi Y, Keret O, Steiner I, Melamed E, Djaldetti R. Beneficial effect of levodopa therapy on stooped posture in Parkinson's disease. Gait Posture. 2015. 42(3):263-8.

Honig A, Chen S, Bar-Yossef R, **Benninger F**, Blatt I, Neufeld M, Kipervasser S, Eichel R and Ekstein D. Asystole in the epilepsy unit. BMC Neurol. 2015 14;15:80.

Benninger F, Glat MJ, Barhum Y, Ben-Zur T, Kogan E, Steiner I, Yaffe D, Offen D. Ectopic muscle expression of neurotrophic factors improves recovery after nerve injury. J Mol Neurosci. 2016;58(1):39-45.

Benninger F, Glat M, Offen D, Steiner I. Glial fibrillary acidic protein as marker of astrocytic activation in cerebrospinal fluid of patients with amyotrophic lateral sclerosis. J Clin Neurosci. 2016;26:75-8.

Benninger F, Afawi Z, Korczyn AD, Oliver KL, Pendziwiat M, Nakamura M, Sano A, Helbig I, Berkovic SF, Blatt I. Seizures as presenting and prominent symptom in Chorea-Acanthocytosis

with c.2343del VPS13A gene mutation. Epilepsia. 2016;57(4):549-56.

Lotan I, Fireman L, **Benninger F**, Weizman A, Steiner I. Psychiatric side effects of acute high-dose corticosteroids therapy in neurological conditions. Int Clin Psychopharmacol. 2016 Jul;31(4):224-31.

Khlebtovsky A, Djaldetti R, Rodity Y, Keret O, Tsvetov G, Slutzcki-Shraga I, **Benninger F**. Progression of postural changes in Parkinson's disease: quantitative assessment. J Neurol. 2017;264:675-683.

Benninger F, Gross A, Madar R, Illouz T, Griffioen K, Steiner I, Offen D, Okun E. Toll-like receptor 3 deficiency decreases epileptogenesis in a pilocarpine model of SE-induced epilepsy in mice. Epilepsia. 2017;58(4):586-596

Benninger F, Holtkamp M. [Epilepsie beim Schlaganfall: Methodik und die Empfehlungen]. [German] Der Nervenarzt.

Oliver, K; Franceschetti, S; Milligan, Carol Muona, M; Mandelstam, S; Canafoglia, L; Boguszewska-Chachulska, A; Korczyn, A; Bisulli, F; Di Bonaventura, C; Ragona, F; Michelucci, R; Ben-Zeev, B; Straussberg, R; Panzica, F; Massano, J; Friedman, D; Crespel, A; Engelsen, B; Andermann, F; Andermann, E; Spodar, K; Lasek-Bal, A; Riguzzi, P; Pasini, E; Tinuper, P; Licchetta, L; Gardella, E; Lindenau, M; Wulf, A; Møller, R; **Benninger, F**; Afawi, Z; Rubboli, G; Reid, C; Maljevic, S; Lerche, H; Lehesjoki, A-E; Petrou, S; Berkovic, S. Myoclonus epilepsy and ataxia due to KCNC1 mutation: Analysis of 20 cases and and K+ channel properties. Annals of Neurology 2017;81(5):677-689.

Offen D, Guy R, Ben-Zur T, **Benninger F**, Glat MJ, Panski A, Lamdan R, Danon U, Yaffe D, Grynspan F; Human muscle progenitor cells ectopically expressing neurotrophic factors enhance intrinsic neuronal regeneration in a sciatic nerve injury mouse model. Cytotherapy 2018;20(5):S94.

Goldstein L, Shihman B, Amiel N, **Benninger F**. Termination of pregnancy in women with epilepsy - A retrospective single center study. Epilepsy Behav. 2018; 87:89-91.

Lotan I, Hellmann MA, **Benninger F**, Stiebel-Kalish H, Steiner I. Recurrent optic neuritis - Different patterns in multiple sclerosis, neuromyelitis optica spectrum disorders and MOG-antibody diseases. J Neuroimmunol. 2018;324:115-118.

Steiner I, Khlebtovsky A, **Benninger F**. A Hypothesis for mechanisms of weakness distribution in muscular dystrophies. J Neurol Disord 2018;6: 389.

Shihman B, Goldstein L, Amiel N, **Benninger F**. Antiepileptic drug treatment during pregnancy and delivery in women with epilepsy – a retrospective single center study. Epilepsy Research 2019; 149:66-69.

Helbig I, Lopez-Hernandez T, Shor O, Galer P, Ganesan S, Pendziwiat M, Rademacher A, Ellis CA, Hümpfer N, Schwarz N, Seiffert S, Peeden J, Shen J, **Štěrbová** K, Hammer TB, Møller RS, Shinde DN, Tang S, Smith L, Poduri A, Krause R, **Benninger F**, Helbig KL, Haucke V, Weber YG; EuroEPINOMICS-RES Consortium. A recurrent missense variant in AP2M1 impairs clathrin-mediated endocytosis and causes developmental and epileptic encephalopathy; GRIN Consortium. Am J Hum Genet. 2019;104(6):1060-1072.

Lotan I, **Benninger F**, Mendel R, Hellmann M, Steiner I. Does CSF pleocytosis have a predictive value for disease course in MS? Neurology, Neuroimmunology & Neuroinflammatio; 2019; 6(5): e584.

Lenz M, Ben Shimon M, Benninger F, Neufeld MY, Shavit-Stein E, Vlachos A, Maggio N. Systemic thrombin inhibition ameliorates seizures in a mouse model of pilocarpine-induced status epilepticus. J Mol Med 2019;97:1567–1574.

Milikovsky D, Ofer J, Senatorov V, Friedman A, Prager O, Scheintuch L, Elazari N, Veksler R, Bar-Klein G, Swissa E, Hanael E, Ben-Arie G, Shefenbauer O, Kamisntrky L, Saar-Ashkenazy R, Shelef I, Shamir M, Goldberg I, Glik A, **Benninger F**, Kaufer, D, Friedman A. Paroxysmal slow cortical activity in Alzheimer's disease and epilepsy is associated with blood-brain barrier dysfunction. Science Trans Med 2019; 11(521):eaaw8954.

Lotan I, **Benninger F**, Hellmann MA, Sicsic C, Brenner T, Kahana E, Steiner I. Incidence of AChR-Ab positive myasthenia gravis in Israel: A population-based study. Acta Neurologica Scandinavia 2020;142(1):66-73.

Grants

2016-2019 Israel Science Foundation

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Cognitive and Emotion Research Lab
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Investigating Cognitive and Emotional Difficulties that Typify Different Psychopathologies in Life Span: Therapeutic Brain Stimulation

Positions

Co-Cordinator, Course of Continuing Medical Education in Psychiatry, TAU

Head, Child and Adolescent Outpatient Clinic "Shalvata"

Head, Cognitive and Emotion Research Lab

Research

Our research work is embedded in our clinical dielemas and difficulties. Our studies have focused on: Cognitive and emotional domains in the course and development of different pathologies, especially depression and ADHD. We are interested in the interplay between anxiety and ADHD and a differential effect of Methylphenidate on state anxiety. We were able to show effects of depression on cognition in depressed adolescents with some cognitive domains related to state the depressive episode and others to the the trait. In recent years, our studies have focused on brain stimulation, especially deep transcranial magnetic stimulation (rTMS), effects of pharmaco and psychotherapy and placebo on emotions and cognition.

Publications

Gvirts HZ, Mayseless N, Segev A, Lewis DY, Feffer K, Barnea Y, **Bloch Y**, Shamay-Tsoory SG. Novelty-seeking trait predicts the effect of methylphenidate on creativity. J Psychopharmacol. 2016.

Segev A, Rovner M, Appel DI, Abrams AW, Rotem M, **Bloch Y**. Possible Biases of Researchers' Attitudes Toward Video Games: Publication Trends Analysis of the Medical Literature (1980-2013). J Med Internet Res. 2016;18(7):e196.

Feffer K, Lichtenberg P, Becker G, **Bloch Y**, Netzer R, Nitzan U. A comparative study with depressed patients on the acceptability of placebo use. Gen Hosp Psychiatry. 2016;41:53-6.

Segev A, Gvirts HZ, Strouse K, Mayseless N, Gelbard H, Lewis YD, Barnea Y, Feffer K, Shamay-Tsoory SG, **Bloch Y**. A possible effect of methylphenidate on state anxiety: A single dose, placebo controlled, crossover study in a control group. Psychiatry Res. 2016;241:232-5.

Nitzan U, Bekerman T, Becker G, Lichtenberg P, Lev-Ran S, Walter G, Maoz H, **Bloch Y**. Physician perception regarding side-effect profile at the onset of antidepressant treatment: a survey of Israeli psychiatrists and primary care physicians. Ann Gen Psychiatry. 2016;15:5.

Gvirts HZ, Braw Y, Harari H, Lozin M, **Bloch Y**, Fefer K, Levkovitz Y. Executive dysfunction in bipolar disorder and borderline personality disorder. Eur Psychiatry. 2015;30(8):959-64.

Segev A, Mimouni-Bloch A, Ross S, Silman Z, Maoz H, **Bloch Y**. Evaluating Computer Screen Time and Its Possible Link to Psychopathology in the Context of Age: A Cross-Sectional Study of Parents and Children. PLoS One. 2015;10(11):e0140542.

Bloch Y, Aviram S, Neeman R, Braw Y, Nitzan U, Maoz H, Mimouni-Bloch A. Methylphenidate mediated change in prosody is specific to the performance of a cognitive task in female adult ADHD patients. World J Biol Psychiatry. 2015;16(8):635-9.

Maoz H, Aviram S, Nitzan U, Segev A, **Bloch Y**. Association Between Continuous Performance and Response Inhibition Tests in Adults With ADHD. J Atten Disord. 2015.

Bloch Y, Arad S, Levkovitz Y. Deep TMS add-on treatment for intractable Tourette syndrome:

A feasibility study. World J Biol Psychiatry. 2016;17(7):557-61.

Bloch Y, Aviram S, Braw Y, Gvirts HZ, Rabany L, Walter G. Attention improves after clinical improvement in acutely depressed adolescents. J Neuropsychiatry Clin Neurosci. 2015;27(2):153-6.

Grants

The Israel National Health Policy (NIHP) grant "Collecting routine outcome measures" in the mental health system". 2014-present

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Investigating Chronic and Acute Pain Mechanisms and New Ways for Pain Modulation and Relief

Positions

Head, Institute for Pain Medicine, Sourasky Medical Center

Research

Chronic pain is a complex physiological condition affecting around 17% of the population. While acute pain, following noxious stimuli or tissue damage, is useful as a warning sign and usually disappears when the trauma is over, chronic pain persists even though the tissue has been healed. Moreover, chronic pain often triggers an array of neurologic, immunologic, physical and psychological changes that worsen the patient's situation and are not related to the original cause of the pain.

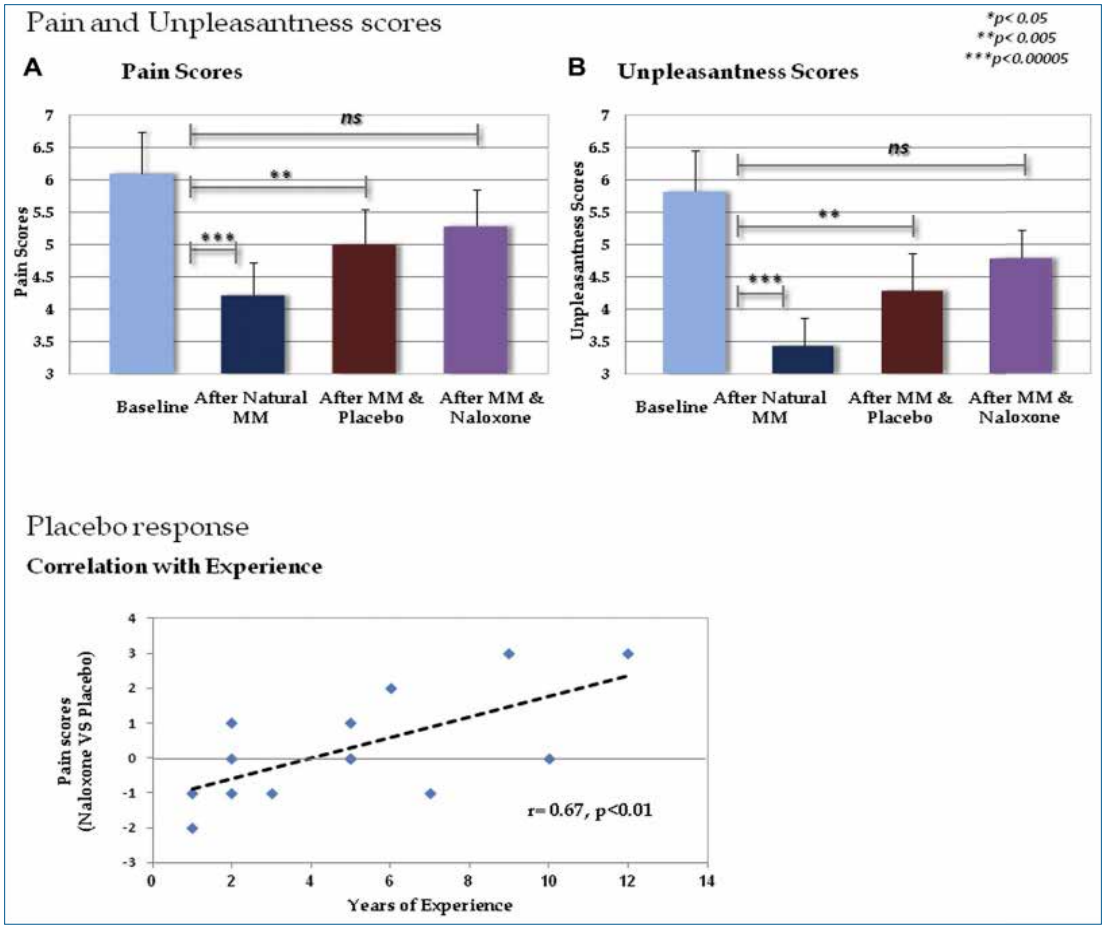

Figure: (Top panel) Mean pain and unpleasantness scores. Mean pain (A, left panel) and unpleasantness scores (B, right panel) following: a painful cold stimulus (baseline); natural meditation; meditation after placebo administration; and meditation after naloxone administration, respectively. Bars represent standard error. (Bottom panel) The differences in pain scores following naloxone vs placebo and participants' mindfulness meditation (MM) experience. The positive correlation of the response to intervention with years of experience suggests reduced response to placebo with increasing experience.

At the Institute for Pain Medicine, we focus on the biochemical basis of pain transmission and pain relieving treatments. For example, in a recent study we showed, for the first time, that meditation involves endogenous opioid pathways, mediating its analgesic effect. In another study, we investigated gender effect on the relationships between parasympathetic activity and pain modulation. We found that women demonstrated higher parasympathetic activity compared to men, which resulted in a subsequent lower pain perception. In a third study, we showed that many patients suffering from complex regional pain syndrome (CRPS), are diagnosed with alexithymia which can be regarded as an outcome of CRPS, highlighting the importance of early CRPS diagnosis and support. These and additional research findings hold promising therapeutic implications and further elucidate the fine mechanisms involved in human pain modulation.

Future research/programs: TMS TDCS Biofeedback, Pain rehabilitation programs, Cannabis database

Publications

Shlaifer A, Sharfman ZT, Martin HD, Amar E, Kazum E, Warschawski Y, Paret M, **Brill S**, Drexler M, Rath E. Preemptive Analgesia in Hip Arthroscopy: A Randomized Controlled Trial of Preemptive Periacetabular or Intra-articular Bupivacaine in Addition to Postoperative Intra-articular Bupivacaine. *Arthroscopy*. 2017;33(1):118-124.

Feingold D, Goor-Aryeh I, **Brill S**, Delayahu Y, Lev-Ran S. Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain.*Pain Med.* 2017;18(2):294-306.

Sharon H, Maron-Katz A, Ben Simon E, Flusser Y, Hendler T, Tarrasch R, **Brill S.** Mindfulness Meditation Modulates Pain Through Endogenous Opioids.*Am J Med.* 2016;129(7):755-8.

Hadas Nahman-Averbuch, Lior Dayan, Elliot Sprecher, Uri Hochberg, **Silviu Brill**, David Yarnitsky, Giris Jacob. Pain Modulation and Autonomic Function: The Effect of Clonidine. *Pain Med* (2016) 17 (7): 1292-1301.

Dayan L, **Brill S**, Hochberg U, Jacob G. Is adenosine a modulator of peripheral vasoconstrictor responses ?*Clin Auton Res.* 2016;26(2):141-7.

Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, **Brill S**, Yarnitsky D, Jacob G. Sex differences in the relationships between parasympathetic activity and pain modulation. *Physiol Behav.* 2016;154:40-8.

Rokach A, **Brill S**, Goor Aryeh I. Caregivers of chronic pain patients: Their loneliness and burden. Nurs Palliat Care 1: doi: 10.15761/NPC.1000128

Lerman SF, Rudich Z, **Brill S**, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. *Psychosom Med.* 2015;77(3):333-41.

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The Pathophysiology and Development of Movement Disorders and Specifically Parkinson's Disease

Positions

Research

We have been leading a large-scale research endeavor to clinically and epidemiologically characterize the Ashkenazi Jewish Parkinson's Disease (PD) population in Israel and to identify genes that influence the risk of developing the disease in this population. In recent years our group has conducted groundbreaking research on the influence of mutations in two major genes - LRRK2 and GBA. The research was first aimed at identifying the prevalence of mutations in these genes in patients with PD and explores differences in phenotype. Our research then evolved to include first degree relatives of these patients to explore early markers of disease in healthy asymptomatic carriers. In addition to examining the contribution of risk mutations, the existence of protective haplotypes or genes was also investigated. For example, recent work has shown that immune system B cells may contribute to protection from the disease or influence its progression. The above described research has opened new avenues of exploring disease identification, progression and even prediction and could potentially impact treatments in PD.

We are also keenly interested in understanding the relationship between cognitive functions and quality of gait, as well as the risk of falling and the neurophysiological basis of the phenomenon of Freezing of Gait (FOG) in Parkinsonism. Our early work on identifying and quantifying FOG resulted in a standardized validated and widely used questionnaire (FOGQ). In addition, our group makes use of accelerometers and gyroscopes to record gait during usual activities, in both the laboratory setting and in the home environment, to better understand changes in performance during daily activites, medication cycles, habits and behavior. Using specified indices, the importance of the variance between different steps was identified, as a measure of fall risk and as a sensitive measure of sub-clinical changes, susceptibility to cognitive loads and perhaps a marker of disease.

In recent years, we have also been involved in exploring new interventions for the patients with PD. These include exploring the effects of tDCS stimulation and virtual reality to improve motor-cognitive function and functional abilities of patients with PD. This work builds on the study of movement disorders, on the one hand, and on examining ways to ameliorate motor symptoms in patients with PD.

In parallel, our group has been heavily involved in clinical trials phase 1-4 with new technologies treating movement disorders of different kinds, as well as community-based epidemiological studies. Using the database of the second largest HMO in Israel (Macabbi Health Care), we characterized PD in Israel, as well as the risks to develop Parkinson and potential protective factors.

Publications

Bregman N, Kavé G, Mirelman A, Thaler A, Gana Weisz M, Bar-Shira A, Orr-Urtreger A, **Giladi N**, Shiner T. Distinguishing dementia with Lewy bodies from Alzheimer's Disease: What is the influence of the GBA genotype in Ashkenazi Jews? Alzheimer Dis Assoc Disord. 2019

Galperin I, Hillel I, Del Din S, Bekkers EMJ, Nieuwboer A, Abbruzzese G, Avanzino L, Nieuwhof F, Bloem BR, Rochester L, Della Croce U, Cereatti A, **Giladi N**, Mirelman A, Hausdorff JM. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. Parkinsonism Relat Disord. 2019;pii: S1353-8020(19)30022

Maidan I, Fahoum F, Shustak S, Gazit E, Patashov D, Tchertov D, **Giladi N**, Hausdorff JM, Mirelman

A. Changes in event-related potentials during dual task walking in aging and Parkinson's disease. Clin Neurophysiol. 2019;130(2):224-230

Jacob Y, Rosenberg-Katz K, Gurevich T, Helmich RC, Bloem BR, Orr-Urtreger A, **Giladi N**, Mirelman A, Hendler T, Thaler A. Network abnormalities among non-manifesting Parkinson disease related LRRK2 mutation carriers. Hum Brain Mapp. 2019

Maidan I, Jacob Y**, Giladi N**, Hausdorff JM, Mirelman A. Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2019. pii: S1353-8020(19)30082-3

Rozani V, **Giladi N**, Gurevich T, El-Ad B, Tsamir J, Hemo B, Peretz C. Anemia in men and increased Parkinson's disease risk: A population-based large scale cohort study. Parkinsonism Relat Disord. 2019. pii: S1353-8020(19)30103-8

Thaler A, Arad S, Schleider LB, Knaani J, Taichman T, **Giladi N**, Gurevich T. Single center experience with medical cannabis in Gilles de la Tourette syndrome. Parkinsonism Relat Disord. 2019; 61:211-213

Kozlovski T, Mitelpunkt A, Thaler A, Gurevich T, Orr-Urtreger A, Gana-Weisz M, Shachar N, Galili T, Marcus-Kalish M, Bressman S, Marder K**, Giladi N**, Benjamini Y, Mirelman A. Hierarchical data-driven analysis of clinical symptoms among patients with Parkinson's Disease. Front Neurol. 2019; 10:531

LeWitt PA, **Giladi N**, Navon N. Pharmacokinetics and efficacy of a novel formulation of carbidopa-levodopa (Accordion Pill®) in Parkinson's disease. Parkinsonism Relat Disord. 2019. pii: S1353-8020

Galperin I, Hillel I, Del Din S, Bekkers EMJ, Nieuwboer A, Abbruzzese G, Avanzino L, Nieuwhof F, Bloem BR, Rochester L, Della Croce U, Cereatti A**, Giladi N**, Mirelman A, Hausdorff JM. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. Parkinsonism Relat Disord. 2019; 62:85-90.

Peretz C, Rozani V, **Giladi N**, El-Ad B, Tsamir J, Hemo B, Gurevich T. The Modifying Effect of Age on Survival in Parkinson's Disease: A Population-Based Cohort Study. Neuroepidemiology. 2019;14:1-7

Weiss A, Herman T, Mirelman A, Shiratzky SS**, Giladi N**, Barnes LL, Bennett DA, Buchman AS, Hausdorff JM. The transition between turning and sitting in patients with Parkinson's disease: A wearable device detects an unexpected sequence of events. Gait Posture. 2019;67:224-22

Jacob Y, Rosenberg-Katz K, Gurevich T, Helmich RC, Bloem BR, Orr-Urtreger A, **Giladi N**, Mirelman A, Hendler T, Thaler A. Network abnormalities among non-manifesting Parkinson disease related LRRK2 mutation carriers. Hum Brain Mapp. 2019; 40(8):2546-2555.

Teshuva I, Hillel I, Gazit E, **Giladi N**, Mirelman A, Hausdorff JM. Using wearables to assess bradykinesia and rigidity in patients with Parkinson's disease: a focused, narrative review of the literature. J Neural Transm (Vienna). 2019;126(6):699-710

Maidan I, Jacob Y, **Giladi N**, Hausdorff JM, Mirelman A. Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease. Parkinsonism Relat Disord. 2019; 63:77-82

.Mirelman A, Bonato P, Camicioli R, Ellis TD, **Giladi N**, Hamilton JL, Hass CJ, Hausdorff JM, Pelosin E, Almeida QJ. Gait impairments in Parkinson's disease. Lancet Neurol. 2019; 18(7):697-708.

Ortega RA, Groves M, Mirelman A, Alcalay RN, Raymond D, Elango S, Mejia-Santana H, **Giladi N**, Marder K, Bressman SB, Saunders-Pullman R. Evidence for increased completed suicide in first-degree relatives of LRRK2 G2019S mutation Parkinson's disease. J Neurol Neurosurg Psychiatry. 2019;90(7):843-844

Eyal S, Kurz I, Mirelman A, Maidan I, **Giladi N**, Hausdorff JM. Successful negotiation of anticipated and unanticipated obstacles in young and older adults: Not all is as expected. Gerontology. 2019;28:1

LeWitt PA, **Giladi N**, Navon N. Pharmacokinetics and efficacy of a novel formulation of carbidopa-levodopa (Accordion Pill®) in Parkinson's disease. Parkinsonism Relat Disord. 2019; 65:131-138

Agalliu I, Ortega RA, Luciano MS, Mirelman A, Pont-Sunyer C, Brockmann K, Vilas D, Tolosa E, Berg D, Warø B, Glickman A, Raymond D, Inzelberg R, Ruiz-Martinez J, Mondragon E, Friedman E, Hassin-Baer S, Alcalay RN, Mejia-Santana H, Aasly J, Foroud T, Marder K, **Giladi N**, Bressman S, Saunders-Pullman R. Cancer outcomes among Parkinson's disease patients with leucine rich repeat kinase 2 mutations, idiopathic Parkinson's disease patients, and nonaffected controls. Mov Disord. 2019;34(9):1392-1398.

Gazit E, Buchman AS, Dawe R, Curran TA, Mirelman A, **Giladi N**, Hausdorff JM. What happens before the first step? A New Approach to Quantifying Gait Initiation Using a Wearable Senso. Gait Posture. 2019;76:128-135

Goldstein O, Gana-Weisz M, Cohen-Avinoam D, Shiner T, Thaler A, Cedarbaum JM, John S, Lalioti M, Gurevich T, Bar-Shira A, Mirelman A, **Giladi N**, Orr-Urtreger A. Revisiting the non-Gaucher-GBA-E326K carrier state: Is it sufficient to increase Parkinson's disease risk? Mol Genet Metab. 2019;128(4):470-475

Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, **Giladi N**, Mirelman A, Hausdorff JM. Age-associated changes in obstacle negotiation strategies: Does size and timing matter? Gait Posture. 2018; 59:242-247

Saunders-Pullman R, Mirelman A, Alcalay RN, Wang C, Ortega RA, Raymond D, Mejia-Santana H, Orbe-Reilly M, Johannes BA, Thaler A, Ozelius L, Orr-Urtreger A, Marder KS, **Giladi N**, Bressman SB; LRRK2 Ashkenazi Jewish Consortium. Progression in the LRRK2-Asssociated Parkinson Disease Population. JAMA Neurol. 2018

Oren N, Shapira-Lichter I, Lerner Y, Hendler T, **Giladi N**, Ash EL. How attention modulates encoding of dynamic stimuli in older adults. Behav Brain Res. 2018; 25; 347:209-218

Maidan I, Nieuwhof F, Bernad-Elazari H, Bloem BR, **Giladi N**, Hausdorff JM, Claassen JAHR, Mirelman A. Evidence for Differential Effects of 2 Forms of Exercise on Prefrontal Plasticity During Walking in Parkinson's Disease. Neurorehabil Neural Repair. 2018;32(3):200-208.

Mirelman A, Saunders-Pullman R, Alcalay RN, Shustak S, Thaler A, Gurevich T, Raymond D, Mejia-Santana H, Orbe Reilly M, Ozelius L, Clark L, Gana-Weisz M, Bar-Shira A, Orr-Utreger A, Bressman SB, Marder K, **Giladi N**; AJ LRRK2 Consortium. Application of the Movement Disorder Society prodromal criteria in healthy G2019S-LRRK2 carriers. Mov Disord. 2018

Maidan I, Shustak S, Sharon T, Bernad-Elazari H, Geffen N, **Giladi N**, Hausdorff JM, Mirelman A. Prefrontal cortex activation during obstacle negotiation: What's the effect size and timing? Brain Cogn. 2018; 122:45-51

Dagan M, Herman T, Harrison R, Zhou J, **Giladi N**, Ruffini G, Manor B, Hausdorff JM. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord. 2018;33(4):642-646

Ferrazzoli D, Ortelli P, Madeo G, **Giladi N**, Petzinger GM, Frazzitta G. Basal ganglia and beyond: The interplay between motor and cognitive aspects in Parkinson's disease rehabilitation. Neurosci Biobehav Rev. 2018;90:294-308

Thaler A, Bregman N, Gurevich T, Shiner T, Dror Y, Zmira O, Gan-Or Z, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, **Giladi N**, Mirelman A. Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA gene. Parkinsonism Relat Disord. 2018. pii: S1353-8020(18)30239-6

Thaler A, Kliper E, Maidan I, Herman T, Rosenberg-Katz K, Bregman N, Gurevich T, Shiner T, Hausdorff JM, Orr-Urtreger A, **Giladi N**, Mirelman A. cerebral imaging markers of GBA and LRRK2 related Parkinson's disease and their first-degree unaffected relatives. Brain Topogr. 2018. doi: 10.1007

Tankus A, Mirelman A, **Giladi N**, Fried I, Hausdorff JM. Pace of movement: the role of single neurons in the subthalamic nucleus. J Neurosurg. 2018;22:1-6.

Beck Y, Herman T, Brozgol M, **Giladi N**, Mirelman A, Hausdorff JM. SPARC: a new approach to quantifying gait smoothness in patients with Parkinson's disease. J Neuroeng Rehabil. 2018;15(1):49

Parashos SA, Bloem BR, Browner NM, **Giladi N**, Gurevich T, Hausdorff JM, He Y, Lyons KE, Mari Z, Morgan JC, Post B, Schmidt PN, Wielinski CL. What predicts falls in Parkinson disease? Observations from the Parkinson's Foundation registry. Neurol Clin Pract. 2018;8(3):214-222

Thaler A, Gonen T, Mirelman A, Helmich RC, Gurevich T, Orr-Urtreger A, Bloem BR, **Giladi N**, Hendler T; LRRK2 Ashkenazi Jewish consortium. Altered reward-related neural responses in non-manifesting carriers of the Parkinson disease related LRRK2 mutation. Brain Imaging Behav. 2018

Pullman M, Ortega R, Glickman A, Deik A, Raymond D, Marder K, **Giladi N**, Bressman S, Hagenah J, Brüggemann N, Saunders-Pullman R. Increased substantia nigra echogenicity in LRRK2 family members without mutations. Mov Disord. 2018

Rozani V, Gurevich T, **Giladi N**, El-Ad B, Tsamir J, Hemo B, Peretz C. Higher serum cholesterol and decreased Parkinson's disease risk: A statin-free cohort study. Mov Disord. 2018

Matthews DC, Lerman H, Lukic A, Andrews RD, Mirelman A, Wernick MN, **Giladi N**, Strother SC, Evans KC, Cedarbaum JM, Even-Sapir E. FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. Neuroimage Clin. 2018; 20:572-579

Pullman M, Ortega R, Glickman A, Deik A, Raymond D, Marder K, **Giladi N**, Bressman S, Hagenah J, Brüggemann N, Saunders-Pullman R. Increased substantia nigra echogenicity in LRRK2 family members without mutations. Mov Disord. 2018; 33(9):1504-1505

Herman T, Shema-Shiratzky S, Arie L, **Giladi N**, Hausdorff JM. Depressive symptoms may increase the risk of the future development of freezing of gait in patients with Parkinson's disease: Findings from a 5-year prospective study. Parkinsonism Relat Disord. 2018. pii: S1353-8020(18)30398-5

Thaler A, Kozlovski T, Gurevich T, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, **Giladi N**, Mirelman A. Survival rates among Parkinson's disease patients who carry mutations in the LRRK2 and GBA genes. Mov Disord. 2018; 33(10):1656-1660.

Ortega RA, Groves M, Mirelman A, Alcalay RN, Raymond D, Elango S, Mejia-Santana H, **Giladi N**, Marder K, Bressman SB, Saunders-Pullman R. Evidence for increased completed suicide in first-degree relatives of LRRK2 G2019S mutation Parkinson's disease. J Neurol Neurosurg Psychiatry. 2018. pii: jnnp-2018-319364

Nonnekes J, **Giladi N**, Guha A, Fietzek UM, Bloem BR, Růžička E. Gait festination in parkinsonism: introduction of two phenotypes. J Neurol. 2018

Balash Y, Bar-Lev Schleider L, Korczyn AD, Shabtai H, Knaani J, Rosenberg A, Baruch Y, Djaldetti R, **Giladi N**, Gurevich T. Medical Cannabis in Parkinson Disease: Real-Life Patients' Experience. Clinical Neuropharmacology, 40: 268-272, 2017

San Luciano M, Wang C, Ortega RA, **Giladi N**, Marder K, Bressman S, Saunders-Pullman R and the Michael J Fox Foundation LRRK2 Consortium. Sex differences in LRRK2 G2019S and idiopathic Parkinson's Disease. Annals of Clinical and Translational Neurology 4: 801-810, 2017

Maidan I, Rosenberg-Katz K, Jacob Y, **Giladi N**, Hausdorff JM, Mirelman A. Disparate effects of training on brain activation in Parkinson disease. Neurology 89, 1804-1810, 2017

Arie L, Herman T, Shema-Shiratzky S, **Giladi N**, Hausdorff JM. Do cognition and other non-motor symptoms decline similarly among patients with Parkinson's disease motor subtypes? Findings from a 5-year prospective study. Journal of Neurology, 264, 2149-2157, 2017

Lee AJ, Wang Y, Alcalay RN, Mejia-Santana H, Saunders-Pullman R, Bressman S, Corvol JC, Brice A, Lesage S, Mangone G, Tolosa E, Pont-Sunyer C, Vilas D, Schüle B, Kausar F, Foroud T, Berg D, Brockmann K, Goldwurm S, Siri C, Asselta R, Ruiz-Martinez J, Mondragón E, Marras C, Ghate T, **Giladi N**, Mirelman A, Marder K, Michael J. Fox LRRK2 Cohort Consortium. Penetrance Estimate of LRRK2 p.G2019S Mutation in Individuals of Non-Ashkenazi Jewish Ancestry. Movement Disorders, 32, 1432-1438, 2017

Lee AJ, Marder K, Alcalay RN, Mejia-Santana H, Orr-Urtreger A, **Giladi N**, Bressman S, Wang Y. Estimation of genetic risk function with covariates in the presence of missing genotypes. Statistics in Medicine, 36, 3533-3546, 2017

Oren N, Shapira-Lichter I, Lerner Y, Tarrasch R, Hendler T, **Giladi N**, Ash EL. Schema benefit vs. proactive interference: Contradicting behavioral outcomes and coexisting neural patterns. Neuroimage, 158, 271-281, 2017

Dagan M, Herman T, Mirelman A, **Giladi N**, Hausdorff JM.The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. Experimental Brain Research. 235:2463-2472, 2017

Maidan I, Bernad-Elazari H, **Giladi N**, Hausdorff JM, Mirelman A. When is Higher Level Cognitive Control Needed for Locomotor Tasks Among Patients with Parkinson's Disease? Brain Topography, 30, 531-538, 2017

Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, **Giladi N**, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. Brain and Cognition. 115, 41-46, 2017

Oren N, Ash EL, Tarrasch R, Hendler T, **Giladi N**, Shapira-Lichter I. Neural patterns underlying the effect of negative distractors on working memory in older adults Neurobiology of Aging. 53, 93-102, 2017

Artzi M, Even-Sapir E, Lerman Shacham H, Thaler A, Orr Urterger A, Bressman S, Marder K, Hendler T, **Giladi N**, Ben Bashat D, Mirelman A. DaT-SPECT assessment depicts dopamine depletion among asymptomatic G2019S LRRK2 mutation carriers. PLOS ONE. 12, e0175424, 2017

Rozani V, **Giladi N**, El-Ad B, Gurevich T, Tsamir J, Hemo B, Peretz C. Statin adherence and the risk of Parkinson's disease: A population-based cohort study. PLOS ONE. 12: e0175054, 2017

Bregman N, Thaler A, Mirelman A, Helmich RC, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, **Giladi N**, LRRK2 Ashkenazi Jewish consortium. A cognitive fMRI study in non-manifesting LRRK2 and GBA carriers. LRRK2 Ashkenazi Jewish Consortium. Braln Structure & Function. 222, 1207-1218, 2017

Ferrazzoli D, Ortelli P, Maestri R, Bera R, Gargantini R, Palamara G, Zarucchi M, **Giladi N**, Frazzitta G. Focused and Sustained Attention Is Modified by a Goal-Based Rehabilitation in Parkinsonian Patients. Frontiers in Behavioral Neuroscience, 11, 2017

Thaler A, Gurevich T, Bar Shira A, Gana Weisz M, Ash E, Shiner T, Orr-Urtreger A, **Giladi N**, Mirelman A. A "dose" effect of mutations in the GBA gene on Parkinson's disease phenotype. Parkinsonism & Related Disorders. 36, 47-51, 2017

Fiorella Contarino M, Van Den Dool J, Balash Y, Bhatia K, **Giladi N**, Koelman JH, Lokkegaard A, Marti MJ, Postma M, Relja M, Skorvanek M, Speelman JD, Zoons E, Ferreira JJ, Vidailhet M, Albanese A, Tijssen MAJ. Clinical Practice: evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin. Frontiers in Neurology. 8, 2017

Mancini M, Smulders K, Cohen RG, Horak FB, **Giladi N**, Nutt JG. The clinical significance of freezing while turning in Parkinson's disease. Neuroscience, 343, 222-228, 2017

Tankus A, Strauss I, Gurevich T, Mirelman A, **Giladi N**, Fried I, Hausdorff JM. Subthalamic Neurons Encode Both Single- and Multi-Limb Movements in Parkinson's Disease Patients. Scientific Reports, 42467, 2017

Zitser J, Thaler A, Inbar N, Gad A, Faust-Socher A, Paleacu D, Anca-Herschkovitch M, Balash Y, Shabtai H, Ash EL, Merkin L, Manor Y, Kestenbaum M, Bar David A, Peretz C, Naiman T, Bar-Shira A, Orr-Urtreger A, Dangoor N, **Giladi N**, Gurevich T. Two Ethnic Clusters with Huntington Disease in Israel: The Case of Mountain Jews and Karaites. Neurodegenerative Diseases. 17, 281-285, 2017

Thaler A, Gurevich T, Bar Shira A, Gana Weisz M, Ash E, Shiner T, Orr-Urtreger A, **Giladi N**, Mirelman A. A “dose” effect of mutations in the GBA gene on Parkinson’s disease phenotype. Parkinsonism Relat Disord. 2016 pii: S1353-8020(16)30495-3.

Mancini M, Smulders K, Cohen RG, Horak FB, **Giladi N**, Nutt JG. The clinicalsignificance of freezing while turning in Parkinson’s disease. Neuroscience. 2016. pii: S0306-4522(16)30680-7.

Oren N, Shapira-Lichter I, Lerner Y, Tarrasch R, Hendler T, **Giladi N**, Ash EL .How Attention Modulates Encoding of Dynamic Stimuli. Front Hum Neurosci. 2016, 10:50;21

Swan M, Doan N, Ortega RA, Barrett M, Nichols W, Ozelius L, Soto-Valencia J, Boschung S, Deik A, Sarva H, Cabassa J, Johannes B, Raymond D, Marder K, **Giladi N**, Miravite J, Severt W, Sachdev R, Shanker V, Bressman S, Saunders-Pullman R. Neuropsychiatric characteristics of GBA-associated Parkinson disease. J Neurol Sci. 2016;370:63-69.

Giladi N, Nicholas AP, Asgharnejad M, Dohin E, Woltering F, Bauer L, Poewe W. Efficacy of Rotigotine at Different Stages of Parkinson’s Disease Symptom Severity and Disability: A Post Hoc Analysis According to Baseline Hoehn and Yahr Stage. J Parkinsons Dis. 2016;6(4):741-749.

Shiner T, Mirelman A, Gana Weisz M, Bar-Shira A, Ash E, Cialic R, Nevler N, Gurevich T, Bregman N, Orr-Urtreger A, **Giladi N**. High Frequency of GBA Gene Mutations in Dementia With Lewy Bodies Among Ashkenazi Jews. JAMA Neurol. 2016;73(12):1448-1453.

Weiss A, Mirelman A, **Giladi N**, Barnes LL, Bennett DA, Buchman AS, Hausdorff JM. Transition Between the Timed up and Go Turn to Sit Subtasks: Is Timing Everything? J Am Med Dir Assoc. 2016;17(9):864.e9-864.e15.

Ferrazzoli D, Ortelli P, Maestri R, Bera R, **Giladi N**, Ghilardi MF, Pezzoli G Frazzitta G. Does Cognitive Impairment Affect Rehabilitation Outcome in Parkinson’s Disease? Front Aging Neurosci. 2016;8:192.

Weiss A, Brozgol M, **Giladi N**, Hausdorff JM. Can a single lower trunk body-fixed sensor differentiate between level-walking and stair descent and ascent in older adults? Preliminary findings. Med Eng Phys. 2016;38(10):1146-51.

Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, Rikkert MO, Bloem BR, Pelosin E, Avanzino L, Abbruzzese G, Dockx K, Bekkers E, **Giladi N** ,Nieuwboer A, Hausdorff JM. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. Lancet. 2016;388(10050):1170-82.

Rosenberg-Katz K, Herman T, Jacob Y, Kliper E, **Giladi N**, Hausdorff JM. Subcortical Volumes Differ in Parkinson’s Disease Motor Subtypes: New Insights into the Pathophysiology of Disparate Symptoms. Front Hum Neurosci. 2016; .10:35

Rosenberg-Katz K, Maidan I, Jacob Y, **Giladi N**, Mirelman A, Hausdorff JM. Alterations in conflict monitoring are related to functional connectivity in Parkinson’s disease. Cortex. 2016;82:277-86.

Peretz C, Segev H, Rozani V, Gurevich T, El-Ad B, Tsamir J, **Giladi N**. Comparison of Selegiline and

Rasagiline Therapies in Parkinson Disease: A Real-life Study. Clin Neuropharmacol. 2016;39(5):227-31.

Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, Saunders-Pullman R, Raymond D, Doan N, Bressman SB, Marder KS, Alcalay RN, Rao AK, Berg D, Brockmann K, Aasly J, Waro BJ, Tolosa E, Vilas D, Pont-Sunyer C, Orr-Urtreger A, Hausdorff JM, **Giladi N**. Arm swing as a potential new prodromal marker of Parkinson's disease. Mov Disord. 2016;31(10):1527-1534.

Bregman N, Thaler A, Mirelman A, Helmich RC, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, **Giladi N**; LRRK2 Ashkenazi Jewish consortium. A cognitive fMRI study in non-manifesting LRRK2 and GBA carriers. Brain Struct Funct. 2016.

Giladi N, Mirelman A, Thaler A, Orr-Urtreger A. A Personalized Approach to Parkinson's Disease Patients Based on Founder Mutation Analysis. Front Neurol 2016 10;7:71.

Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, **Giladi N**, Deutsch JE, Hausdorff JM, Claassen JA, Mirelman A. The Role of the Frontal Lobe in Complex Walking Among Patients With Parkinson's Disease and Healthy Older Adults: An fNIRS Study. Neurorehabil Neural Repair. 2016 ;30(10):963-971.

Bernad-Elazari H, Herman T, Mirelman A, Gazit E, **Giladi N**, Hausdorff JM. Objective characterization of daily living transitions in patients with Parkinson's disease using a single body-fixed sensor. J Neurol. 2016;263(8):1544-51.

Yogev-Seligmann G, Oren N, Ash EL, Hendler T, **Giladi N**, Lerner Y. Altered Topology in Information Processing of a Narrated Story in Older Adults with Mild Cognitive Impairment. J Alzheimers Dis. 2016 ;53(2):517-33

Peretz C, Gurel R, Rozani V, Gurevich T, El-Ad B, Tsamir J, **Giladi N**. Cancer incidence among Parkinson's disease patients in a 10-yrs time-window around disease onset: A large-scale cohort study. Parkinsonism Relat Disord. 2016 ;28:68-72.

Rozenkrantz L, Gan-Or Z, Gana-Weisz M, Mirelman A, **Giladi N**, Bar-Shira A, Orr-Urtreger A. SEPT14 Is Associated with a Reduced Risk for Parkinson's Disease and Expressed in Human Brain. J Mol Neurosci. 2016 ;59(3):343-50.

Giladi N, Asgharnejad M, Bauer L, Grieger F, Boroojerdi B. Rotigotine in Combination with the MAO-B Inhibitor Selegiline in Early Parkinson's Disease: A Post Hoc Analysis. J Parkinsons Dis. 2016 ;6(2):401-11.

Maidan I, Rosenberg-Katz K, Jacob Y, **Giladi N**, Deutsch JE, Hausdorff JM, Mirelman A. Altered brain activation in complex walking conditions in patients with Parkinson's disease. Parkinsonism Relat Disord. 2016 ;25:91-6.

Valadas A, Contarino MF, Albanese A, Bhatia KP, Falup-Pecurariu C, Forsgren L, Friedman A, **Giladi N**, Hutchinson M, Kostic VS, Krauss JK, Lokkegaard A, Marti MJ, Milanov I, Pirtosek Z, Relja M, Skorvanek M, Stamelou M, Stepens A, Tamás G ,Taravari A, Tzoulis C, Vandenberghe W, Vidailhet M, Ferreira JJ, Tijssen MA. Management of dystonia in Europe: a survey of the European network for the study of the dystonia syndromes. Eur J Neurol. 2016;23(4):772-9.

Frazzitta G, Balbi P, Gotti F, Maestri R, Sabetta A, Caremani L, Gobbi L, Capobianco M, Bera R, **Giladi N**, Ferrazzoli D. Pisa Syndrome in Parkinson's Disease: Electromyographic Aspects and Implications for Rehabilitation. Parkinsons Dis. 2015;2015:437190.

Weiss A, Herman T, **Giladi N**, Hausdorff JM. Association between Community Ambulation Walking Patterns and Cognitive Function in Patients with Parkinson's Disease: Further Insights into Motor-Cognitive Links. Parkinsons Dis 2015:547065.

Thaler A, Helmich RC, Or-Borichev A, van Nuenen BF, Shapira-Lichter I, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, **Giladi N**, Hendler T, Mirelman A; LRRK2 Ashkenazi Jewish consortium. Intact working memory in non-manifesting LRRK2 carriers--an fMRI study. Eur J Neurosci. 2016 ;43(1):106-12.

Elkana O, Eisikovits OR, Oren N, Betzale V, **Giladi N**, Ash EL. Sensitivity of Neuropsychological Tests to Identify Cognitive Decline in Highly Educated Elderly Individuals: 12 Months Follow up. J Alzheimers Dis. 2016;49(3):607-16.

Wang Y, Liang B, Tong X, Marder K, Bressman S, Orr-Urtreger A, **Giladi N**, Zeng D. Efficient Estimation of Nonparametric Genetic Risk Function with Censored Data. Biometrika. 2015 ;102(3):515-532.

Kobo H, Bar-Shira A, Dahary D, Gan-Or Z, Mirelman A, Goldstein O, **Giladi N**, Orr-Urtreger A. Down-regulation of B cell-related genes in peripheral blood leukocytes of Parkinson's disease patients with and without GBA mutations. Mol Genet Metab. 2016;117(2):179-85.

Simon-Tov S, Dinur T, **Giladi N**, Bar-Shira A, Zelis M, Zimran A, Elstein D. Color Discrimination in Patients with Gaucher Disease and Parkinson Disease. J Parkinsons Dis. 2015;5(3):525-31.

Gan-Or Z, Mirelman A, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y, Desautels A, Gagnon JF, Leblond CS, Frauscher B, Alcalay RN, Saunders-Pullman R ,Bressman SB, Marder K, Monaca C, Högl B, Orr-Urtreger A, Dion PA, Montplaisir JY,**Giladi N**, Rouleau GA. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol. 2015 ;2(9):941-5.

Saunders-Pullman R, Alcalay RN, Mirelman A, Wang C, Luciano MS, Ortega RA, Glickman A, Raymond D, Mejia-Santana H, Doan N, Johannes B, Yasinovsky K, Ozelius L, Clark L, Orr-Utreger A, Marder K, **Giladi N**, Bressman SB; AJ LRRK2 Consortium. REM sleep behavior disorder, as assessed by questionnaire, in G2019S LRRK2 mutation PD and carriers. Mov Disord. 2015 ;30(13):1834-9.

Mirelman A, **Giladi N**, Hausdorff JM. Body-Fixed Sensors for Parkinson Disease. JAMA. 2015 ;314(9):873-4.

Gan-Or Z, Orr-Urtreger A, Alcalay RN, Bressman S, **Giladi N**, Rouleau GA. The emerging role of SMPD1 mutations in Parkinson's disease: Implications for future studies. Parkinsonism Relat Disord. 2015 ;21(10):1294-5.

Mirelman A, Bernad-Elazari H, Nobel T, Thaler A, Peruzzi A, Plotnik M, **Giladi N**, Hausdorff JM. Effects of Aging on Arm Swing during Gait: The Role of Gait Speed and Dual Tasking. PLoS One. 2015 ; 10(8):e0136043.

Ziv-Av A, **Giladi N**, Lee HK, Cazacu S, Finniss S, Xiang C, Pauker MH, Barda-Saad M, Poisson L, Brodie C. RTVP-1 regulates glioma cell migration and invasion via interaction with N-WASP and hnRNPK. Oncotarget. 2015 4-19826:(23)6;14

Giladi N, Ziv-Av A, Lee HK, Finniss S, Cazacu S, Xiang C, Waldman Ben-Asher H, deCarvalho A, Mikkelsen T, Poisson L, Brodie C. RTVP-1 promotes mesenchymal transformation of glioma via a STAT-3/IL-6-dependent positive feedback loop. Oncotarget. 2015;6(26):22680-97.

Gan-Or Z, Amshalom I, Bar-Shira A, Gana-Weisz M, Mirelman A, Marder K, Bressman S, **Giladi N**, Orr-Urtreger A. The Alzheimer disease BIN1 locus as a modifier of GBA-associated Parkinson disease. J Neurol. 2015;262(11):2443-7.

Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, **Giladi N**, Hendler T, Hausdorff JM. Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. J Neurol2448-56:(11)262;2015 ..

Hellmann MA, Kakhlon O, Landau EH, Sadeh M, **Giladi N**, Schlesinger I, Kidron D, Abramsky O, Reches A, Argov Z, Rabey JM, Chapman J, Rosenmann H, Gal A, Moshe Gomori J, Meiner V, Lossos A. Frequent misdiagnosis of adult polyglucosan body disease. J Neurol. 2015;262(10):2346-51.

Marder K, Wang Y, Alcalay RN, Mejia-Santana H, Tang MX, Lee A, Raymond D, Mirelman A, Saunders-Pullman R, Clark L, Ozelius L, Orr-Urtreger A, **Giladi N**, Bressman S; LRRK2 Ashkenazi Jewish Consortium. Age-specific penetrance of LRRK2 G2019S in the Michael J. Fox Ashkenazi Jewish LRRK2 Consortium. Neurology. 2015;85(1):89-95.

Nonnekes J, Snijders AH, Nutt JG, Deuschl G, **Giladi N**, Bloem BR. Freezing of gait: a practical approach to management. Lancet Neurol. 2015;14(7):768-78.

Iluz T, Weiss A, Gazit E, Tankus A, Brozgol M, Dorfman M, Mirelman A, **Giladi N**, Hausdorff JM. Can a Body-Fixed Sensor Reduce Heisenberg's Uncertainty When It Comes to the Evaluation of Mobility? Effects of Aging and Fall Risk on Transitions in Daily Living. J Gerontol A Biol Sci Med Sci. 2016;71(11):1459-1465.

Gan-Or Z, Alcalay RN, Bar-Shira A, Leblond CS, Postuma RB, Ben-Shachar S, Waters C, Johnson A, Levy O, Mirelman A, Gana-Weisz M, Dupré N, Montplaisir J, **Giladi N**, Fahn S, Xiong L, Dion PA, Orr-Urtreger A, Rouleau GA. Genetic markers of Restless Legs Syndrome in Parkinson disease. Parkinsonism Relat Disord. 2015;21(6):582-5.

Mirelman A, Alcalay RN, Saunders-Pullman R, Yasinovsky K, Thaler A, Gurevich T, Mejia-Santana H, Raymond D, Gana-Weisz M, Bar-Shira A, Ozelius L, Clark L,Orr-Urtreger A, Bressman S, Marder K, **Giladi N**; LRRK2 AJ consortium . Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene. Mov Disord. 2015;30(7):981-6.

Hassan A, Wu SS, Schmidt P, Simuni T, **Giladi N**, Miyasaki JM, Bloem BR, Malaty IA, Okun MS. The Profile of Long-term Parkinson's Disease Survivors with 20 Years of Disease Duration and Beyond. J Parkinsons Dis. 2015;5(2):313-9.

Bregman N, Regev K, Moore O, **Giladi N**, Ash E. A Simple Tool to Reach Populations at Risk for Developing Dementia and Alzheimer's Disease. J Alzheimers Dis. 2015;46(1):151-5.

Zlotnik Y, Balash Y, Korczyn AD, **Giladi N**, Gurevich T. Disorders of the oral cavity in Parkinson's disease and parkinsonian syndromes. Parkinsons Dis. .2015:379482;2015

Ben Assayag E, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Hallevi H, Shopin L, Auriel E, **Giladi N**, Mike A, Halevy A, Weiss A, Mirelman A, Bornstein NM, Hausdorff JM. Gait measures as predictors of poststroke cognitive function: evidence from the TABASCO study. Stroke. 2015;46(4):1077-83.

Gan-Or Z, Amshalom I, Kilarski LL, Bar-Shira A, Gana-Weisz M, Mirelman A, Marder K, Bressman S, **Giladi N**, Orr-Urtreger A. Differential effects of severe vs mild GBA mutations on Parkinson disease. Neurology. 2015;84(9):880-7.

Maidan I, Bernad-Elazari H, Gazit E, **Giladi N**, Hausdorff JM, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. J Neurol. 2015;262(4):899-908.

Helmich RC, Thaler A, van Nuenen BF, Gurevich T, Mirelman A, Marder KS, Bressman S, Orr-Urtreger A, **Giladi N**, Bloem BR, Toni I; LRRK2 Ashkenazi Jewish Consortium. Reorganization of corticostriatal circuits in healthy G2019S LRRK2 carriers. Neurology. 2015;84(4):399-406.

Poewe W, Seppi K, Fitzer-Attas CJ, Wenning GK, Gilman S, Low PA, **Giladi N**, Barone P, Sampaio C, Eyal E, Rascol O; Rasagiline-for-MSA investigators .Efficacy of rasagiline in patients with the parkinsonian variant of multiple system atrophy: a randomised, placebo-controlled trial. Lancet Neurol. 2015;14(2):145-52.

Herman T, Weiss A, Brozgol M, Wilf-Yarkoni A, **Giladi N**, Hausdorff JM. Cognitive function and other non-motor features in non-demented Parkinson's disease motor subtypes. J Neural Transm (Vienna). 2015;122(8):1115-24.

Alcalay RN, Mejia-Santana H, Mirelman A, Saunders-Pullman R, Raymond D, Palmese C, Caccappolo E, Ozelius L, Orr-Urtreger A, Clark L, **Giladi N**, Bressman S, Marder K; LRRK2 Ashkenazi Jewish Consortium . Neuropsychological performance in LRRK2 G2019S carriers with Parkinson's disease. Parkinsonism Relat Disord 2015 .Feb;21(2):106-10.

Agalliu I, San Luciano M, Mirelman A, **Giladi N**, Waro B, Aasly J, Inzelberg R, Hassin-Baer S, Friedman E, Ruiz-Martinez J, Marti-Masso JF, Orr-Urtreger A, Bressman S, Saunders-Pullman R. Higher frequency of certain cancers in LRRK2 G2019S mutation carriers with Parkinson disease: a pooled analysis. JAMA Neurol 2015 .Jan;72(1):58-65.

Gupte M, Alcalay RN, Mejia-Santana H, Raymond D, Saunders-Pullman R, Roos E ,Orbe-Reily M, Tang MX, Mirelman A, Ozelius L, Orr-Urtreger A, Clark L, **Giladi N**, Bressman S, Marder K. Interest in genetic testing in Ashkenazi Jewish Parkinson's disease patients and their unaffected relatives. J Genet Couns. 2015;24(2):238-46.

Weiss A, Herman T, **Giladi N**, Hausdorff JM. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. J Neural Transm (Vienna). 2015;122(3):403-10.

Oren N, Yogev-Seligmann G, Ash E, Hendler T, **Giladi N**, Lerner Y. The Montreal Cognitive Assessment in cognitively-intact elderly: a case for age-adjusted cutoffs. J Alzheimers Dis. 2015;43(1):19-22.

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Using Functional Imaging to Investigate Affective Neuroscience

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Research

Our group has been applying advanced brain imaging techniques, including functional magnetic resonance imaging (fMRI), Diffusion Tensor imaging (DTI) intracranial and scalp electroencephalography (EEG) and magnetic encephalography (MEG) to study mental processing in the healthy and diseased human brain. Our research theme has focused on portraying the neural underpins of individual emotional experience and expression. The accumulative work in affective neuroscience in the last two decades has paved the way for promising translations of imaging technologies for the cure to mental suffering. For example, the lab has pioneered the development of a new real-time imaging approach for the non-invasive identification of "neural finger-prints" that can reliably depict deep limbic areas through trans-modalities' learning computation (e.g. from fMRI to EEG). This new method enables accessible bed-side Brain Computer Interface procedures aimed to alleviate and/or prevent stress related psychopathologies.

Publications

Rosenberg-Katz, K.., Herman, T., Jacob, Y., Mirelman, A., Giladi, N., **Hendler, T**., & Hausdorff, J.M. (2015). Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. *Journal of Neurology,* 1-9.

Amar, D., Yekutieli, D., Maron-Katz, A., **Hendler, T.,** & Shamir, R. (2015). A hierarchical Bayesian model for flexible module discovery in three-way time-series data. *Bioinformatics, 31(12),* i17-i26.

Ben Simon, E., Oren, N., Sharon, H., Kirschner, A., Goldway, N., Okon-Singer, H., Tauman, R., Deweese, M.M., Keil, A., & **Hendler, T.** (2015). Losing Neutrality: The Neural Basis of Impaired Emotional Control without Sleep. *Journal of Neuroscience, 35(38)*, 13194-13205.

Gilam, G., Lin, T., Raz, G., Azrielant, S., Fruchter, E., Ariely, D., **& Hendler, T.** (2015). Neural substrates underlying the tendency to accept anger-infused ultimatum offers during dynamic social interactions. *NeuroImage, 120*, 400-411.

Okon-Singer, H., **Hendler, T**., Pessoa, L., & Shackman, A.J. (2015). The neurobiology of emotion–cognition interactions: *fundamental questions and strategies for future research. Frontiers in Human Neuroscience, 9(58).*

Thaler, A., Mirelman, A., Helmich, R., van Neunen, B., Gurevich, T., Marder, K., Bressman, S., Orr-Urtreger, A., Bloem, B., **Hendler, T.,** & Giladi, N. (2015). Ventral Striatum Involvement In Non Manifesting Carriers Of The G2019S Mutation In The LRRK2 Gene (P6.077). *Neurology, 84(14).*

Dissanayaka, C., Ben-Simon, E., Gruberger, M., Maron-Katz, A., Sharon, H., **Hendler, T.,** & Cvetkovic, D. (2015). Comparison between human awake, meditation and drowsiness EEG activities based on directed transfer function and MVDR coherence methods. *Medical & Biological Engineering and Computing, 53(7),*599-607.

Glikmann-Johnston, Y., Oren, N**., Hendler, T.,** & Shapira-Lichter, I. (2015). Distinct functional connectivity of the hippocampus during semantic and phonemic fluency. *Neuropsychologia, 69,* 39-49.

Thaler, R. C. Helmich, A. Or-Borichev, B. F.L. van Nuenen, I. Shapira-Lichter, T. Gurevich, A. Orr-Urtreger, K. Marder, S. Bressman, B. R. Bloem, N. Giladi, **T. Hendler**, A. Mirelman[1,2] and the LRRK2 Ashkenazi Jewish consortium(2015). Intact working memory in non-manifesting *LRRK2* carriers – an fMRI study. *European Journal of Neurscience.*

Keynan, J. N., Raz, G., Solnik, S., Gilam, G., Lin, T., Vaisevasser, S., & **Hendler, T**. (2015). Dynamic network analysis uncovers the neural correlates of alexithymia. *Biological Psychiatry*, *77*(9), 46S-46S.

Keynan, J. N., Cohen, A., Raz, G., Jackont, G., Gilam, G., Klovatch, I., ... & **Hendler, T**. (2015). Modulation of deep brain activity and improved emotion regulation via fMRI/EEG neurofeedback. *Biological Psychiatry*, *77*(9), 336S-336S.

Gazit T., Andelman F., Glikmann-Johnston Y., Gonen T., Solski A., Shapira-Lichter I., Ovadia M., Kipervasser S., Neufeld MY., Fried I., **Hendler T**., Perry D. (2015). Probabilistic Machine Learning for the Evaluation of Presurgical Language Dominance. *Journal of Neurosurgery*.

Vaisvaser S., Modai S., Farberov L., Lin T., Sharon H., Gilam A., Volk N., Admon R., Edry L., Fruchter E., Wald I., Bar-Haim Y., Tarrasch R., Chen A., Shomron N., and **Hendler T.** (2015). Neuro-epigenetic indications of acute stress response in humans: the case of microRNA-29c. *Plos One.*

Keynan, J.N, Meir-Hasson, Y., Gilam, G., Cohen, A., Jackont, G., Kinreich, S., Ikar, L., Or-Borichev, A., Etkin, A., Gyurak, A., Klovatch, I., Intrator, N., & **Hendler, T.** (2015). Limbic Activity Modulation Guided by fMRI-Inspired EEG Improves Implicit Emotion Regulation. *Biological Psychiatry.*

Gonen, T., Soreq, E., Eldar, E., Ben-Simon, E., Raz, G., & **Hendler, T.** (2016). Human mesostriatal response tracks motivational tendencies under naturalistic goal conflict. *Social cognitive and affective neuroscience*, *11*(6), 961-972.

Yamin, H., Gazit, T., Tchemodanov, N., Raz, G., Jakont, G., Charles, F., & **Hendler, T.** (2016). Neurofeedback via Intracranial Depth Electrodes.

Shapira-Lichter, I., Klovatch, I., Nathan, D., Oren, N., & **Hendler, T**. (2016). Task-specific Aspects of Goal-directed Word Generation Identified via Simultaneous EEG–fMRI. *Journal of cognitive neuroscience*.

Meir-Hasson, Y., Keynan, J. N., Kinreich, S., Jackont, G., Cohen, A., **Hendler, T.** & Intrator, N. (2016). One-Class FMRI-Inspired EEG Model for Self-Regulation Training. *PloS one*, *11*(5), e0154968.

Yogev-Seligmann, G., Oren, N., Ash, E. L., **Hendler, T.,** Giladi, N., & Lerner, Y. (2016). Altered Topology in Information Processing of a Narrated Story in Older Adults with Mild Cognitive Impairment. *Journal of Alzheimer's Disease*, (Preprint), 1-17.

Bregman, N., Thaler, A., Mirelman, A., Gurevich, T., Gana-Weiss, M., Orr-Urtreger, A., **Hendler, T**., & Giladi, N. (2016). A Cognitive fMRI Study in Non-Manifesting LRRK2 and GBA Carriers (P4. 105). *Neurology*, *86*(16 Supplement), P4-105.

Sharon, H., Maron-Katz, A., Simon, E. B., Flusser, Y., **Hendler, T.,** Tarrasch, R., & Brill, S. (2016). Mindfulness Meditation Modulates Pain Through Endogenous Opioids. *The American Journal of Medicine*.

Shapira-Lichter, I., Weinstein, M., Lustgarten, N., Ash, E., Litinsky, I. **Hendler, T**., & Paran, D. (2016). Impaired diffusion tensor imaging findings in the corpus callosum and cingulum may underlie impaired learning and memory abilities in systemic lupus erythematosus. *Lupus*, 0961203316636471

Gazit, T., Andelman, F., Glikmann-Johnston, Y., Gonen, T., Solski, A., Shapira-Lichter, I., & **Hendler, T.** (2016). Probabilistic machine learning for the evaluation of presurgical language dominance. *Journal of Neurosurgery*, 1-13.

Maron-Katz, A., Vaisvaser, S., Lin, T., **Hendler, T.,** & Shamir, R. (2016). A large-scale perspective on stress-induced alterations in resting-state networks. *Scientific reports*, *6*.

Domani, Y., Bleich-Cohen, M., Stoppelman, N., Tarrasch, R., **Hendler, T**., Meidan, R., ... & Sharon, H. (2016). Oral ketamine for treatment resistant major depression–A double blind randomized controlled trial. *European Psychiatry*, (33), S523.

Lerner, Y., **Hendler, T**., Levit-Binnun, N., & Golland, Y. (2016). Shared feelings: Investigating neural attunement to the emotions of others. *European Psychiatry*, (33), S457-S458.

Lin, T., Simchovitz, A., Shenhar-Tsarfaty, S., Vaisvaser, S., Admon, R., … **Hendler, T**. & Soreq, H. (2016) Intensified vmPFC surveillance over PTSS under perturbed microRNA-608/AChE interaction. *Translational Psychiatry*, (6), 1-8.

Raz, G., Touroutoglou, A., Wilson-Mendenhall, C., Gilam, G., Lin, T., ... **Hendler, T.** & Feldman Barrett, L. (2016). Functional connectivity dynamics during film viewing reveal common networks for different emotional experiences. *Cognitive, Affective, & Behavioral Neuroscience*, 1-15.

N Singer; N Jacobi, T Lin, G Raz, L Shpigelman, G Gilam, R Y Granot, **T Hendler.** Common modulation of limbic network activation underlies musical emotions as they unfold. (2016), NeuroImage, Vol. 141, pp. 517-529.

Oren, N., Ash, E. L., Tarrasch, R., **Hendler, T.,** Giladi, N., & Shapira-Lichter, I. (2017). Neural patterns underlying the effect of negative distractors on working memory in older adults. *Neurobiology of aging*, *53*, 93-102.

Cohen, D., Perry, A., Gilam, G., Mayseless, N., Gonen, T., **Hendler, T.,** & Shamay-Tsoory, S. G. (2017). The role of oxytocin in modulating interpersonal space: A pharmacological fMRI study. *Psychoneuroendocrinology*, *76*, 77-83.

Svanera, M., Benini, S., Raz, G., **Hendler, T.,** Goebel, R., & Valente, G. (2017). Deep driven fMRI decoding of visual categories. *arXiv preprint arXiv:1701.02133*.

Lin, T., Gilam, G., Raz, G., Or-Borichev, A., Bar-Haim, Y., Fruchter, E., & **Hendler, T**. (2017). Accessible Neurobehavioral Anger-Related Markers for Vulnerability to Post-Traumatic Stress Symptoms in a Population of Male Soldiers. *Frontiers in Behavioral Neuroscience*, *11*.

Gilam, G., Lin, T., Fruchter, E., & **Hendler, T.** (2017). Neural indicators of interpersonal anger as cause and consequence of combat training stress symptoms. *Psychological Medicine*, 1-12.

Golland, Y., Levit-Binnun, N., **Hendler, T.,** Lerner, Y. (2017). Neural dynamics underlying emotional transmissions between individuals. Accepted for publication in *Social Cognitive and Affective Neuroscience*.

Grants

2016-2019 US Department of Defense. Emotional Brain Fitness via Limbic Targeted Neurofeedback

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Investigating the Vestibular and Ocular Motor Systems

Positions

Professor, Department of Neurology, Sackler Faculty of Medicine.

Director, Dizziness and Balance Disorders Service, Department of Neurology, Meir Medical Center

Head, Machado-Joseph Disease (MJD) Clinic (recognized by the Israel Ministry of Health)

Research

The vestibular system stabilizes gaze during head movements, ensuring clear vision of the seen world. This is mainly accomplished by the vestibulo-ocular reflex (VOR), which produces compensatory (opposite) eye movements for head rotations. Then, eye position in space is held steady and images do not slip on the retina. During everyday life activities, the vestibular system acts with the optokinetic and visual fixation systems to hold images of the seen world steady on the retina; while saccades, smooth pursuit and vergence eye movements obtain and hold images of objects of interest on the fovea. Moreover, in everyday life activities, the vestibular, visual, ocular motor, propioceptive and motor systems work together to reach exquisite balance, equilibrium and perform accurate motor tasks. Interaction between sensory (vestibular, visual, proprioceptive) and motor (eye movement, locomotion) systems; i.e sensory-motor integration is essential to maintain balance, equilibrium and perform accurate motor tasks including locomotion. Our Vestibular and Eye Movement Laboratory is fully equipped with modern systems for measuring vestibular function, all type of eye movements and balance and gait function.

Our three major ongoing interest and research projects include:

1. Vestibulo-Ocular Reflex (VOR) and eye movement abnormalities as possible biomarkers of Spinocerebellar Ataxia Type 3.

Spinocerebellar Ataxia Type 3 (SCA-3), also known as Machado-Joseph Disease (MJD), is an autosomal dominant neurodegenerative disorder for which genetic testing can reveal those at risk for developing the disease. Quantitative measures that would identify pre-symptomatic gene carriers at the threshold of clinical diagnosis would be extremely valuable in early diagnosis, tracking disease progression, and assessing treatment. This is a crucial subject of investigation not only in SCA-3 but also in other neurodegenerative diseases. Eye movement abnormalities have been reported as reliable neurophysiologic biomarker and even proposed as “a window into disease prevention.” By using bedside vestibular tests and laboratory recording of eye movements, we have described severe VOR deficit and different saccadic abnormalities in patients with SCA-3. Our specific aim is to investigate if VOR and eye movements can be used as biomarkers to quantify the appearance and progress of SCA-3 even pre-symptomatically.

2. Dizziness, vertigo, balance: Clinical and basic research

Dizziness, vertigo and problems with balance are among the most frequent complaints at all ages. Our current research focuses on the following topics:

The contribution of VOR impairment to the perceptual and emotional experience of blurred vision, dizziness and oscillopsia (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).

The relationship between vestibular pathology and the development of anxiety, balance impairment and spatial disorientation (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).

The evaluation of a novel specs device with stabilizing marks on the peripheral visual field to alleviate dizziness.

The search for novel physical and virtual reality strategies to improve balance and alleviate dizziness.

3. Cerebellar Disorders

As our Neurology Department at the Meir Medical Center houses the only Machado-Joseph Clinic in Israel recognized by the Ministry of Health, we therefore have access to most MJD sufferers and many other cerebellar patients in the country and focusing on the following research topics:

Respiratory function in cerebellar degeneration.

Autonomic nervous system function and emotional features in cerebellar diseases.

Cognitive and behavioral changes in cerebellar degeneration.

Physical and pharmacological treatment of cerebellar disorders.

Language and reading difficulties in cerebellar diseases (in collaboration with the School of Education, Tel Aviv University).

The role of the cerebellum in the hedonic experience of music (in collaboration with the Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center).

The mutational origins of Machado-Joseph Disease in the Jew Yemenite subpopulation in Israel (in collaboration with the IBMC - Institute of Molecular and Cell Biology, and IPATIMUP – Institute of Pathology and Molecular Immunology of University of Porto, Portugal).

Publications

Shefer S, **Gordon CR**, Avraham KB, Mintz M. Balance deficit enhance anxiety and balance training decrease anxiety in vestibular mutant mice. Behav Brain Res 2015; 276: 76-83.

Zaltzman R, Sharony R, Klein C, **Gordon CR**. Spinocerebellar ataxia type 3 in Israel: phenotype and genotype of a Jew Yemenite subpopulation. J Neurol 2016; 263:2207-2214.

Carmona S, Martínez C, Zalazar G, Moro M, Batuecas-Caletrio A, Luis L, **Gordon C**. The diagnostic accuracy of truncal ataxia and HINTS as cardinal signs for acute vestibular syndrome. Front Neurol. 2016; 7:125.

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Neurogenetics Syndromes

Positions

Professor, Psychiatry & Sagol School of Neuroscience

President, Israel Society of Biological Psychiatry

Director, The Behavioral Neurogenetics Center

Director, The Child Psychiatry Division, Sheba Medical Center

Research

We have been studying neurogenetics syndromes - 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome for two decades. 22q11.2DS is the most common known microdeletion syndrome. The 22q11.2DS phenotype consists of cleft and cardiovascular anomalies and immunological abnormalities. Additionally, all individuals with 22q11.2DS cope with cognitive deficits and one-third of the patients develop schizophrenia-like psychotic disorders and many manifest with autism spectrum disorder. We study the pathways leading to psychosis, autism and cognitive deficits in 22q11.2DS. Our focus is identifying cognitive, behavioral and psychiatric risk factors associated with the evolution of psychosis in 22q11.2DS. We also study molecular and immunological pathways to psychosis and to the behavioral and cognitive phenotype of the syndrome using blood samples and animal models. We collaborate with many centers from US and Europe under the umbrella of the International Brain and Behavior Consortium funded by the NIMH.

Publications

Dar N, **Gothelf D**, Korn D, Frisch A, Weizman A, Michaelovsky E, Carmel M, Yeshayahu Y, Dubnov-Raz G, Pessach IM, Simon AJ, Lev A, Somech R. Thymic and bone marrow output in individuals with 22q11.2 deletion syndrome. Pediatric Res, 2015;77(4):579-85.

Vorstman J, Breetvelt EJ, Duijff SN, Eliez S, Schneider M, Jalbrzikowski M, Armando M, Vicari S, Shashi V, Hooper SR, Chow EW, Fung WL, Butcher NJ, Young DA, McDonald-McGinn DM, Vogels A, van Amelsvoort T, **Gothelf D**, Weinberger R, Weizman A, Klaassen PW, Koops S,Kates WR, Antshel KM, Simon TJ, Ousley OY, Swillen A, Gur RE, Bearden CE, Kahn RS, Bassett AS; for the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 Deletion Syndrome. JAMA Psychiatry, 2015;72(4):377-85.

Goodwin J, Schoch K, Shashi V, Hooper SR, Morad O, Zalevsky M, **Gothelf D**, Campbell LE. A tale worth telling: the impact of the diagnosis experience on disclosure of genetic disorders. J Intellect Disabil Res. 2015;59(5):474-86.

Mlynarski EE, Sheridan MB, Xie M, Guo T, Racedo SE, McDonald McGinn DM, Gai X, Chow EWC, Vorstman J, Swillen A, Devriendt K, Breckpot J, Digilio MC, Marino B, Dallapiccola B, Philip N, Simon TJ, Roberts AE, Piotrowicz M, Bearden CE, Eliez S, **Gothelf D**, Coleman K, Kates WR, Devoto M, Zackai E, Heine-Suner D, Shaikh TH, Bassett AS, Goldmuntz E, Morrow BE, Emanuel BS, the International Chromosome 22q11.2 Consortium. Copy-Number Variation of the Glucose Transporter Gene SLC2A3 and Congenital Heart Defects in the

22q11.2 Deletion Syndrome. Am J Hum Genet, 2015;96(5):753-64.

Zarchi O, Avni C, Attias J, Frisch A, Carmel M, Michaelovsky E, Green T, Weizman A, **Gothelf D**. Hyperactive auditory processing in Williams syndrome: Evidence from auditory evoked potentials. Psychophysiology. 2015;52(6):782-9.

Weisman O, Feldman R, Burg-Malki M, Keren M, Geva R, Diesendruck G, **Gothelf D**. Mother-Child Interaction as a Window to a Unique Social Phenotype in 22q11.2 Deletion Syndrome and in Williams Syndrome. J Autism Dev Disord, 2015;45(8):2567-77.

Kushnir J, **Gothelf D**, Sadeh A. Assessing fears of preschool children with nighttime fears by a parent version of the fear survey schedule for preschool children. Isr J Psychiatry Relat Sci. 2015;52(1):61-5.

Gazer-Snitovsky M*, Brand-Gothelf A*, Dubnov-Raz G, Weizman A, **Gothelf D**. High Familial Correlation in Methylphenidate Response and Side Effect Profile, J Attention Disord. 2015, 1087054715580844

Dori N, Green T, Weizman A, **Gothelf D**. The effectiveness and safety of antipsychotic and antidepressant medications in individuals with 22q11.2 deletion syndrome, J Child Adolesc Psychopharmacol. 2015;25:1-8.

Spitzer S, Freudenstein O, Peskin M, Tyano S, Shrira A, Pearlson T, Eilam A, Zalsman G, Green T, **Gothelf D**. The Outcome of Severe Internalizing and Disruptive Disorders from Preschool into Adolescence:A Follow-up Study. Isr J Psychiatry Relat Sci. 2015;52(2):100-5.

Mlynarski EE, Xie M, Taylor D, Sheridan MB, Guo T, Racedo SE, McDonald-McGinn DM, Chow EW, Vorstman J, Swillen A, Devriendt K, Breckpot J, Digilio MC, Marino B, Dallapiccola B, Philip N, Simon TJ, Roberts AE, Piotrowicz M, Bearden CE, Eliez S, **Gothelf D**, Coleman K, Kates WR, Devoto M, Zackai E, Heine-Suñer D, Goldmuntz E, Bassett AS, Morrow BE, Emanuel BS; International Chromosome 22q11.2 Consortium. Rare copy number variants and congenital heart defects in the 22q11.2 deletion syndrome. Hum Genet. 2016;135(3):273-85.

Friedman N, Rienstein S, Yeshayahu Y, **Gothelf D**, Somech R. Post-childhood Presentation and Diagnosis of DiGeorge Syndrome. Clin Pediatr (Phila). 2016;55(4):368-73.

Lang C, Nir Z, Brand-Gothelf A, Domachevsky S, Ginton L, Kushnir J, **Gothelf D**. The outcome of children with selective mutism following cognitive behavioral intervention: a follow-up study, European Journal of Pediatrics, 2016;175(4):481-7.

Bar M, Efron M, **Gothelf D**, Kushnir J. The link between parent and child sleep disturbances in children with attention deficit/hyperactivity disorder. Sleep Med. 2016;21:160-4.

Mosheva M, Mekori E, Kantor S, Berg Y, Weizman A, **Gothelf D**. Do Antidepressants Induce Psychosis in Children and Adolescents? A Naturalistic Study in Ambulatory Pediatric Population. J Child Adolesc Psychopharmacol. 2016;26(5):478-84.

Yi JJ, Weinberger R, Moore TM, Calkins ME, Guri Y,. Mcdonald-Mcginn MD, Zackai EH, Emanuel BS, Gur RE, **Gothelf D**, Gur RC. Neurocognitive performance on a Computerized Neurocognitive Battery in 22q11.2 deletion syndrome: A Comparison between US and Israeli cohorts. Brain and Cognition, 2016;106:33-41.

Kufert, Y. M., Nachmani, A., Nativ, E., Weizman, A., & **Gothelf, D**. Association between prematurity and the evolution of psychotic disorders in 22q11. 2 deletion syndrome. Journal of Neural Transmission, 2016, 123(12), 1491-1497.

Segal-Triwitz Y, Kirchen LM, Shani Sherman T, Levav M, Kushnir J, Ariel R, **Gothelf D.** Parents' and Teachers' Perceptions of Abnormal Attention Span of Elementary School-Age Children, Isr J Psychiatry Relat Sci., 2016, in press.

Midbari Kufert Y, Nachmani A, Nativ E, Weizman A, **Gothelf D**. Association between prematurity and the evolution of psychotic disorders in 22q11.2 deletion syndrome. J Neural Transm (Vienna). 2016, 123(12), 1491-1497.

Weinberger R, Yi J, Calkins M, Guri Y, McDonald-McGinn DM, Emanuel BS, Zackai EH, Ruparel K, Carmel M, Michaelovsky E, Weizman A, Gur RC, Gur RE, **Gothelf D**. Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome. Eur Neuropsychopharmacol, 2016, 26(10), 1610-1618.

Grants

2017–2020 National Institute of Psychobiology

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Investigating the Biological Basis of Severe Mental Illness and Drug-Response Mechanisms

Positions

Head, Psychiatry Ward B, Geha Mental Health Center

Senior Lecturer, Sackler Faculty of Medicine

Senior Researcher, Biological Psychiatry Lab, Felsenstein Medical Research Center

Visiting Researcher, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Research

Severe mental illness includes chronic, clinically debilitating disorders such as schizophrenia and mood disorders. Among the most important prognostic factors of people suffering from schizophrenia is the adherence and clinical response to medications, notably antipsychotic compounds. There is a portion of about third of the patients who will not have enough response to medications. The only effective drug for this population is clozapine, yet only half of these patients would response to clozapine. The rest are termed ultra-refractory patients, and currently are devoid of any evidence-based medical therapy.

Our research is focused around deciphering the biological basis of response and refractoriness to antipsychotic compounds, and especially to clozapine. We employ various research methods to study both clinical human samples and animal models of psychotic traits. The main goal of the project is to utilize the information gathered from understanding mechanisms into clinical practice as potential therapeutic targets. Current projects in our lab consist of analysis of biochemical assays of both human and animal tissues, for inflammatory markers, vitamin D, glutamate, neurotrophins, dopamine and other related neurotransmitters.

Another field of psychobiology research in our lab is the relationship between the immune system and the brain in pathological conditions. There is growing evidence that neuroinflammatory factors are involved in the pathophysiologic mechanisms leading to schizophrenia, along with genetic components. We study the 22q11.2 deletion syndrome (22q11.2DS). Individuals with this syndrome have a microdeletion of a section of the long arm of chromosome 22 and have a characteristic phenotype including immunological abnormalities and other pathologies. Individuals with 22q11.2DS have a 30% risk of developing schizophrenia. As a result, this syndrome is an optimal genetic model for studying the interaction between the immune system and schizophrenia.

Depression is another mental disorder that we are investigating in our lab in order to evaluate the relationship between abnormalities in the immune system and this mental condition.

Our lab is located at the heart of the intersection between basic science and clinical practice. It is physically located at the Belinson campus, in close

proximity to the Geha Mental Health Center. The staff is composed of senior clinical researchers, as well as senior neuroscientists, working in collaboration. We aim to bring together clinical information with animal model data to eventually take back as therapeutic interventions for a population with severe illness and urgent unmet needs.

Publications (Krivoy)

Landau Z, Hadi-Cohen R, Boaz M, **Krivoy A**, Amit BH, Zalsman G, Levi M, Shoval G Risk factors for weight gain and metabolic syndrome in adolescents with psychiatric disorders: a historical prospective study. J Child Adolesc Psychopharmacol. 2015;25(2):160-7

Krivoy A, Balicer RD, Feldman B, Hoshen M, Zalsman G, Weizman A, Shoval G. Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study. Br J Psychiatry. 2015;206(4):297-301

Lavon O, Eisenkraft A, Blanca M, Raveh L, Ramaty E, **Krivoy A**, Atsmon J, Grauer E, Brandeis R.Is rivastigmine safe as pretreatment against nerve agents poisoning? A pharmacological, physiological and cognitive assessment in healthy young adult volunteers. Neurotoxicology. 2015;49:36-44

Krivoy A, Balicer RD, Hoshen M, Feldman B, Zalsman G, Weizman A, Shoval G, The impact of age and gender on adherence to antidepressants: a four-year population-based cohort study Psychopharmacology (Berl). 2015;232(18):3385-90

Hochman E, Valevski A, Onn R, Weizman A, **Krivoy A**. Seasonal pattern of manic episode admissions among bipolar I disorder patients is associated with male gender and presence of psychotic features. J Affect Disord. 2015;190:123-127

Barzilay R, Lobel T, **Krivoy A,** Shlosberg D, Weizman A, Katz N. Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behaviour. Eur Psychiatry. 2015;31:8-12.

Hollander S, Hochman E, Shoval G, Taler M, Trommer S, Hermesh H, Weizman A, **Krivoy A**. The association between serum creatine kinase, mood and psychosis in inpatients with schizophrenia, bipolar and schizoaffective disorders. Psychiatry Res. 2016;238:333-7.

Krivoy A, Balicer RD, Hoshen M, Feldman B, Zalsman G, Weizman A, Shoval G, Adherence to antidepressant is associated with lower mortality: a four year population-based cohort study, J Clin Psychiatry. 2016;77(5):e566-72.

Schapir L, Lahav T, Zalsman G, **Krivoy A**, Sever J, Weizman A, Shoval G. Cigarette smoking, alcohol and cannabis use in patients with pervasive developmental disorders. Subst Use Misuse. 2016:1-6

Shalit N, Barzilay R, Shoval G, Shlosberg D, Mor N, Zwigenhaft N, Weizman A, **Krivoy A,** Characteristics of synthetic cannabinoid and natural cannabis users admitted to a psychiatric hospital: a comparative study, J Clin Psychiatry. 2016;77(8):e989-95

Hochman E, **Krivoy A**, Schaffer A, Weizman A, Valevski A, Antipsychotic adjunctive therapy to mood stabilizers and 1-year rehospitalisation rates in bipolar disorder: A cohort study. Bipolar Disord. 2016;18(8):684-691

Krivoy A, Gil-Ad I, Tarasenko I, Weizman A, Taler M, Trans-generation enrichment of clozapine-responsiveness trait in mice using a subchronic hypo-glutamatergic model of schizophrenia: A preliminary study. Behav Brain Res. 2017;323:141-145

Krivoy A, Hochman E, Sendt KV, Hollander S, Vilner Y, Selakovic M, Weizman A, Taler M. Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. Schizophr Res. 2018;192:226-231

Shoval G, Stubbs B, Balicer RD, Feldman B, Hoshen M, Zalsman G, Sagy R, Hochman E, Weizman A, **Krivoy A**. Low adherence to antidepressants is associated with increased mortality in Parkinson disease patients. Parkinsonism Relat Disord. 2017;43:92-96

Krivoy A, Stubbs B, Balicer RD, Weizman S, Feldman B, Hoshen M, Zalsman G, Hochman E, Shoval G. Low adherence to antidepressants is associated with increased mortality following stroke: A large nationally representative cohort study. Eur Neuropsychopharmacol. 2017; 27(10):970-976.

Lowe P*, **Krivoy A***, Eromona W, Porffy L, Henriksdottir E, Shergill SS. When the drugs don't work - treatment resistant schizophrenia, serotonin and serendipity. Ther Adv Psychopharmacol. 2018;8(1):63-70.

Gur S, Weizman S, Stubbs B, Matalon A, Meyerovitch J, Hermesh H, **Krivoy A**. Mortality, morbidity and medical resources utilization of patients with schizophrenia: A case-control community-based study. Psychiatry Res. 2018;260:177-181.

Krivoy A*, Onn R*, Vilner Y, Hochman E, Weizman S, Paz A, Hess S, Sagy R, Kimhi-Nesher S, Kalter E, Friedman T, Friedman Z, Bormunt G, Trommer S, Valevski A, Weizman A. Vitamin D supplementation in chronic schizophrenia patients treated with clozapine:

a randomized, double-blind, placebo-controlled clinical trial. EBioMedicine. 2017;26:138-145.

Shvartzman Y, **Krivoy A,** Valevski A, Gur S, Weizman A, Hochman E, Adjunctive antidepressants in bipolar depression: A cohort study of six- and twelve-months rehospitalization rates. Eur Neuropsychopharmacol. 2018;28(3):353-360.

Zohar N, Hochman E, Katz N, **Krivoy A**, Weizman A, Barzilay R, Association between elevated C-reactive protein and manic polarity in acute psychiatric inpatients with affective symptomatology, Neuropsychobiology. 2017;76(3):166-170.

Grants

National Institute of Psychobiology in Israel

Stanley Medical Research Institute

The Israel National Institute for Health Policy Research

Publications – Taler

Gil-Ad I, Amit BH, Hayardeni L, Tarasenko I, **Taler M**, Gueta RU, Weizman A. Effects of the anti-multiple sclerosis immunomodulator laquinimod on anxiety and depression in rodent behavioral models. *J Mol Neurosci*. 2015, 55:552-60

Bloch K, Gil-Ad I, Tarasenko I, Vanichkin A, **Taler M**, Hornfeld SH, Vardi P, Weizman A. Intracranial pancreatic islet transplantation increases islet hormone expression in the rat brain and attenuates behavioral dysfunctions induced by MK-801 (dizocilpine). *Horm Behav*. 2015, 72:1-11

Taler M, Vered I, Globus R, Shbiro L, Weizman A, Weller A, Gil-Ad I. Attenuated Weight Gain with the Novel Analog of Olanzapine Linked to Sarcosinyl Moiety (PGW5) Compared to Olanzapine. *J Mol Neurosci*. 2016, 58:66-73

Amitai M, **Taler M**, Carmel M, Michaelovsky E, Eilat T, Yablonski M, Orpaz N, Chen A, Apter A, Weizman A, Fennig S. The Relationship Between Plasma Cytokine Levels and Response to Selective Serotonin Reuptake Inhibitor Treatment in Children and Adolescents with Depression and/or Anxiety Disorders. *J Child Adolesc Psychopharmacol*. 2016, 26:727-732.

Hollander S, Hochman E, Shoval G, **Taler M**, Trommer S, Hermesh H, Weizman A, Krivoy A. The association between serum creatine kinase, mood and psychosis in inpatients with schizophrenia, bipolar and schizoaffective disorders. *Psychiatry Res*. 2016, 30;238:333-337

Krivoy A, Gil-Ad I, Tarasenko I, Weizman A, **Taler M**. Trans-generation enrichment of clozapine-responsiveness trait in mice using a subchronic hypo-glutamatergic model of schizophrenia:A preliminary study. *Behav Brain Res*. 2017, 14;323:141-145

Segal-Gavish H, Gazit N, Barhum Y, Ben-Zur T, **Taler M**, Hornfeld SH, Gil-Ad I, Weizman A, Slutsky I, Niwa M, Kamiya A, Sawa A, Offen D, Barzilay R. BDNF overexpression prevents cognitive deficit elicited by adolescent cannabis exposure and host susceptibility interaction. *Hum Mol Genet*. 2017, 26:2462-2471

Bloch K, Gil-Ad I, Vanichkin A, Hornfeld SH, Koroukhov N, **Taler M**, Vardi P, Weizman A. Intracerebroventricular Streptozotocin Induces Obesity and Dementia in Lewis Rats: Rat Model of Dementia Associated with Obesity. *J Alzheimers Dis*. 2017;60 (1):121-136Mekori–Domachevsky E, **Taler M**, Shoenfeld Y, Gurevich M, Sonis P, Weisman O, Weizman A, Gothelf D. Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome Are Associated with Psychosis and Cognitive Deficits. *Journal of Clinical Psychiatry*. 2017, 78(9)

Zohar AH, Eilat T, Amitai M, **Taler M**, Bari R, Chen A, Apter A, Weizman A, Fennig S. An exploratory study of adolescent response to fluoxetine using psychological and biological predictors. PeerJ. 2018, 10;6:e4240.

Krivoy A, Hochman E, Sendt KV, Hollander S, Vilner Y, Selakovic M, Weizman A, **Taler M.** Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. *Schizophr Res*. 2018, 192:226-231.

Grants

National Institute of Psychobiology in Israel

TEL AVIV UNIVERSITY

Dr. Yulia Lerner, Ph.D.

Neurodegeneration Lab: Cognitive Neuroscience Research

Positions

Senior Lecturer, Sackler Faculty of Medicine

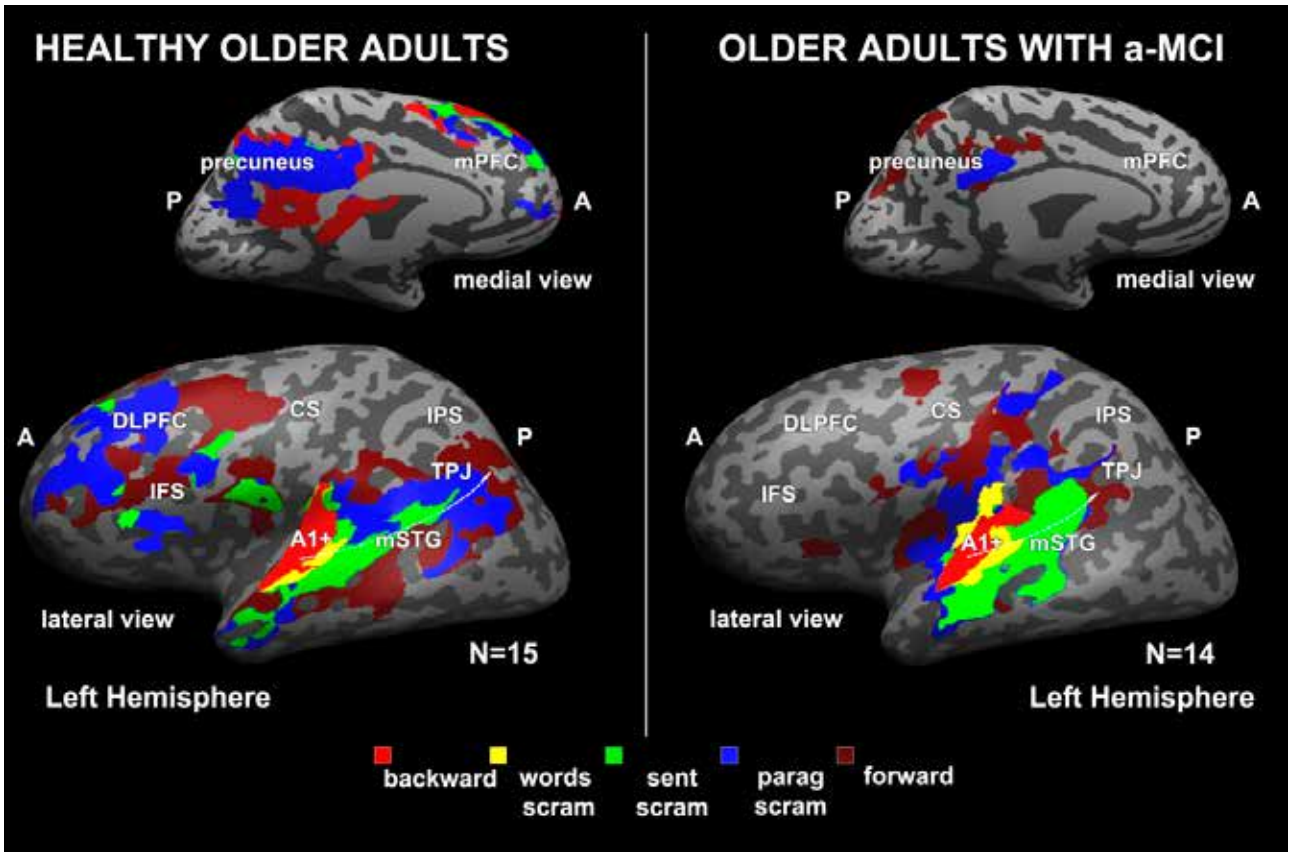
Senior Researcher, Tel Aviv Sourasky Medical Center

Research

Our lab focuses on study neural activity undergoing complex real-life events. The research involves functional and structural brain imaging, neuropsychological assessments and physiological measurements. We apply our paradigms to neuro-psychiatric disorders (e.g. mild cognitive impairment (MCI), schizophrenia, etc.), for the understanding the pathological conditions. To study factors of vulnerability in a causal manner we apply prospective imaging approach or comparing groups of affected to unaffected individuals under similar conditions (e.g. older adults and MCI, patients with schizophrenia and their unaffected siblings). While applying multi-modal paradigms, we are concentrated on developing methods for identification of "functional neuromarkers" for the disease.

Main research topics

- Investigation of human brain responses and behavior under natural conditions
- The architecture of neural circuits involving in processing of non-verbal information
- Developing functional neuromarkers for abnormal cognitive states



Hierarchical organization in healthy older adults and participants with aMCI during story processing

Publications

Golland Y., Levit-Binnun N., Hendler., **Lerner Y**. (2017) Neural dynamics underlying emotional transmissions between individuals. SCAN, May, 01-12. *doi:10.1093/scan/nsx049*

Oren N., Shapira-Lichter, I., **Lerner Y.**, Tarrasch R., Hendler T., Giladi N., Ash E. (2016) How attention modulates encoding of dynamic stimuli. *Front. Hum Neurosci.* doi.org/10.3389/fnhum.2016.00507

Yogev-Seligmann G., Oren N., Ash E., Hendler T., Giladi N., **Lerner Y.** (2016) Altered topology in information processing of a narrated story in older adults with mild cognitive impairment. *J Alzheimers Dis, 53*, 517-533.

Farbood M., Heeger D., Marcus G., Hasson U., **Lerner Y.** (2015) The neural processing of hierarchical structure in music and speech at different timescales. *Front. Neurosci. 9:157. doi: 10.3389/fnins.2015.00157.*

Oren N., Yogev-Seligmann G., Ash E., Hendler T., Giladi N., **Lerner Y.** (2015) The Montreal cognitive assessment in cognitively-intact elderly: A case for age-adjusted cutoffs. *J Alzheimers Dis, 43(1), 19-22*.

Dr. Shaul Lev-Ran, M.D.

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Positions

Sackler Faculty of Medicine

Physician-in-Chief, Lev Hasharon Medical Center

Research

We study the association between drug use and psychiatric disorders. We harness epidemiological and clinical approaches aimed at improving the understanding of mental health related aspects of drug use.

Specifically, much of our current reseach focuses on psychiatric outcomes of cannabis use. In recent decades, there has been a significant increase in the prevalence of cannabis use, as well as in the potency of cannabis consumed. This holds several medical and social implications, some of which are yet unclear. We focus on exploring mental-health related outcomes of cannabis use by conducting epidemiological research using large population-based samples and analysis of "big-data" based on internet-based sources. In addition, we expolore specific neuro-biological and neurocognitive aspects of heavy cannabis use by utilizing advanced functional technologies such as Transcranial Magnetic Stimulation (TMS). Our studies regarding the effects of cannabis on depression and anxiety are commonly cited in World Heatlh Organization publications, and our reports on mental-health related aspects of medical marijuana and prescription opioids have served as a based for national policy papers.

Publications

Feingold D, Nitzan U, Ratzoni G, **Lev-Ran S**. Clinical correlates of alcohol abuse among adolescent psychiatric inpatients in Israel. Isr J Psychiatry Relat Sci. 2015;51(4):258-261.

Lev-Ran S, Feingold D, Rudinski, Katz S, Lerner A. Schizophrenia and Hallucinogen Persisting Perceptual Disorder: a clinical investigation. American Journal on Addictions 2015;24(3):197-9

Feingold D, Fox J, Rehm J, **Lev-Ran S.** Natural Outcome of Cannabis Use Disorder: a Three-Year Longitudinal Follow-Up. Addiction; 2015;110(12):1963-74

Aspis A, Feingold D, Weiser M, Rehm J, Shoval G**, Lev-Ran S.** Cannabis Use and Mental Health-Related Quality of Life among Individuals with Depressive Disorders. Psychiatry Research. 2015;230(2):341-9.

Feingold D, Weiser M, Rehm J, **Lev-Ran S**. The association between cannabis use and anxiety disorders: results from a population-based representative sample. European Neuropsychopharmacology. 2016;26(3):493-505.

Nitzan U, Beckerman T, Beker G, Fennig S, Lichtenberg P**, Lev-Ran S**, Walter G, Bloch Y

Expertise in treating depression: the effect of specialty and seniority on discussing and evaluating SSRI side effects. Annals of General Psychiatry. 2016;15:5.

Lev-Ran S, Shteinmetz Y, Weiser M. Attitudes towards substance use and substance use disorders among medical students in Israel**.** Drugs: Education, Prevention and Policy. 23;484-491.

Shalit N, Shlosberg D, Shoval G, Feingold D, **Lev-Ran S.** Sex differences in the bidirectional longitudinal association between cannabis use and suicidality. Journal of Affective Disorders. 2016;205:216-224.

Feingold, D, Goor-Aryeh, I, Bril, S, Delayahu Y, **Lev-Ran, S**. Addiction to prescription opioids and medicinal cannabis among patients suffering from chronic pain. Pain Medicine. 2016.

Kovatch M, Feingold D, Elkana O, **Lev-Ran S.** Evaluation and comparison of tools for assessing prescription opioid addiction among chronic pain

patients. International Journal of Methods in Psychiatric Research. 2016.

Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, **Lev-Ran S**. Misuse of prescription opioids among chronic pain patients suffering from anxiety: A cross-sectional analysis. Gen Hosp Psychiatry. 2017;47:36-42

Dahan S, Levi G, Behrbalk P, Bronstein I, Hirschmann S, **Lev-Ran S**. The Impact of 'Being There': Psychiatric Staff Attitudes on the Use of Restraint. Psychiatr Q. 2017;doi: 10.1007/s11126-017-9524-9.

Lev-Ran S, Feingold D, Goodman C, Lerner AG. Comparing triggers to visual disturbances among individuals with positive vs negative experiences of hallucinogen-persisting perception disorder (HPPD) following LSD use. Am J Addict. 2017;26(6):568-571

Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, **Lev-Ran S**. Depression and anxiety among chronic pain patients receiving prescription opioids and medical marijuana. J Affect Disord. 2017;218:1-7

Feingold D, Rehm J, **Lev-Ran S**. Cannabis use and the course and outcome of major depressive disorder: A population based longitudinal study. Psychiatry Res. 2017;251:225-234

Feingold D, Goor-Aryeh I, Bril S, Delayahu Y, **Lev-Ran S**. Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain. Pain Med. 2017;18(2):294-306

Taub S, Feingold D, Rehm J, **Lev-Ran S**. Patterns of Cannabis Use and Clinical Correlates among Individuals with Major Depressive Disorder and Bipolar Disorder. Compr Psychiatry. 2018;80:89-96

Yom-Tov E, **Lev-Ran S**. Adverse reactions associated with cannabis consumption as evident from search engine queries. JMIR Public Health Surveill. 2017;3(4)

Feingold D, Goldberger N, Haklai Z, **Lev-Ran S.** Fatal Overdoses of Prescription Opioids in Israel 2005-2014. Eur Addict Res. 2017;23(6):276-283

Feingold D, **Lev-Ran S**. Primary Addictive Substances Used among Patients Treated in a Hospital-Based Addiction Medicine Service. Isr J Psychiatry Relat Sci. 2017;54(2):41-46

Dr. Abigail Livny-Ezer, Ph.D.

Department of Diagnostic Imaging
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Functional Neuroimaging Laboratory

Positions

Head, Functional Neuroimaging Laboratory, Department of Diagnostic Imaging, Sheba Medical Center, affiliated to Sackler Faculty of Medicine

Researcher, Sagol Neuroscience Center, Sheba Medical Center.

Research

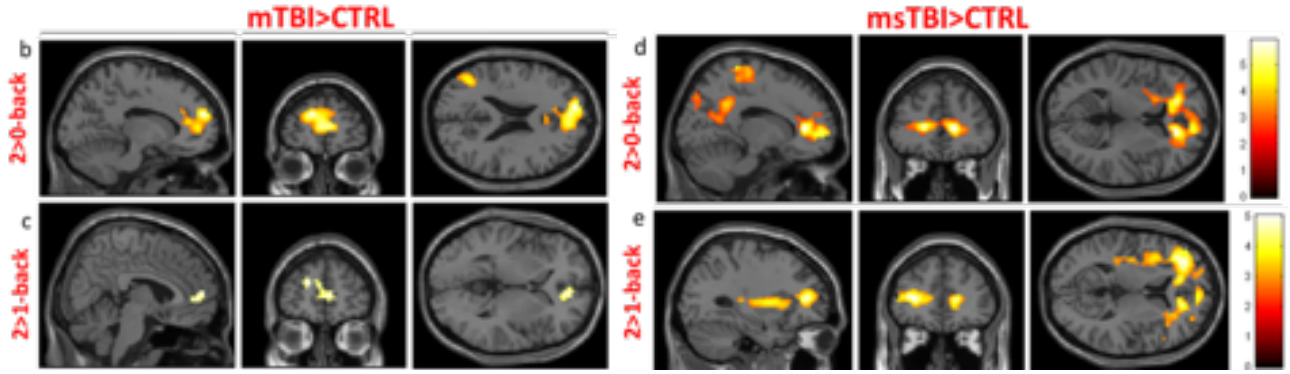
The Functional NeuroImaging Lab Studies brain pathologies, in particular the way the brain reorganizes due to brain injury (TBI). We use various tools including: advanced structural MRI and fMRI protocols using tailor-made fMRI tasks to examine the deficits after TBI. We apply also extensive neuropsychological batteries in order to investigate cognitive impairments. Furthermore, we examine symptoms and emotional status using validated questionnaires and scales. This data is integrated and analyzed to identify networks and patterns which will further our understanding of neuropathology and neuronal reorganization. Our research aims to improve the prediction of brain pathology's progression, to plan medical and rehabilitative interventions for the well-being of patients with brain diseases and head injuries.

Publications

Livny A., Biegon A., Kushnir T., Harnof S., Hoffman C., Fruchter E., Weiser M. Mild Traumatic Brain Injury Linked to Persistent Cognitive Deficits and Smaller Insular Volume. Journal of Neurotrauma. 2017; 34:1466-1472.

Weinstein A., **Livny A.,** Weizman A. Brain imaging studies on the cognitive, pharmacological and neurobiological effects of cannabis in humans: Evidence from studies of adult users. Current Pharmaceutical Design. 2016.

Livny A., Ravona Springer R., Heymann T., Priess R. Kushnir T., Tsarfaty G., Rabinov L., Moran R., Hoffman H., Cooper I., Greenbaum L., Silverman J., Sano M., Johnson S., Bendlin B., Schnaider Beeri M. Long-term variability in glycemic control is associated with white matter hyperintensities



The relation between severity of TBI and working-memory brain activation during an n-back task. Maximum intensity projections in three orthogonal views of the brain (from left to right: sagittal, coronal and axial) depict areas of significant activation ($p<0.005$, $k>100$) in a one-tailed-t statistic contrasting MR signal increases. The color scale shows t-values to the right. a, c: 2->0-back= high WM load; b,d: 2->1-back= WM load increase; CTRL= controls; mTBI= mild TBI; msTBI= moderate-severe TBI. mTBI patients further activated bilateral prefrontal and left parietal regions. msTBI patients revealed greater activation than controls in frontal, parietal and limbic regions.

in APOE4 genotype carriers with type 2 diabetes. Diabetes Care. 2016; 39(6): 1056-9.

Krasovsky, T., Landa, J., Bar, O., Ahonniska-Assa, J., **Livny, A**., Tsarfaty, G., Silberg, T. Functional plasticity in the absence of structural change: Apraxia and body scheme disorder 10 years after childhood brain injury. Journal of Child Neurology. 2017; 32:505-511.

Weinstein A., **Livny A.**, Weizman A. Brain imaging studies on the cognitive, pharmacological and neurobiological effects of cannabis in humans: Evidence from studies of adult users. Current Pharmaceutical Design. 2016; 22:6366-6379.

Greenbaum L., Heymann A., Sharvit-Ginon I., Alkelai A., **Livny A.**, Beeri M., Shelly S., Ganmore I., Ravona-Springer R. The CADM2 gene is associated with processing speed performance –evidence among elderly with Type 2 Diabetes. World Journal of Biological Psychiatry. 2017; 5:1-7.

Livny A., Ravona-Springer R., Heymann A., Priess R., Kushnir T, Tsarfaty G., Rabinov L., Moran R, Tik N., Cooper I., Greenbaum L., Silverman J., Sano M., Bendlin BB, Buchman AS, Schnaider Beeri M. The haptoglobin 1-1 genotype modulates the association of glycemic control with hippocampal volume in elderly with type 2 diabetes. Diabetes. 2017; 66:2927-2932.

Livny A., Reichenberg A, Fruchter E., Yoffe R., Goldberg S., Fenchel D., Burshtein S., Bachar E., Davidson M., Weiser M. A population-based longitudinal study of symptoms and signs before the onset of psychosis. American Journal of Psychiatry 2017 [Epub ahead of print].

Reviews

Weinstein A., **Livny A.**, Weizman A. New developments in brain research of internet gaming disorder. Neuroscience & Biobehavioral Reviews. 2017; 75:314-330.

Dr. Nicola Maggio, M.D., Ph.D.

Department of Neurology and Neurosurgery
Sackler Faculty of Medicine

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The Role of Neuroinflammation and Neurocoagulation in the Pathophysiology of Neurological Disorders

Positions

Senior Lecturer, Sackler Faculty of Medicine

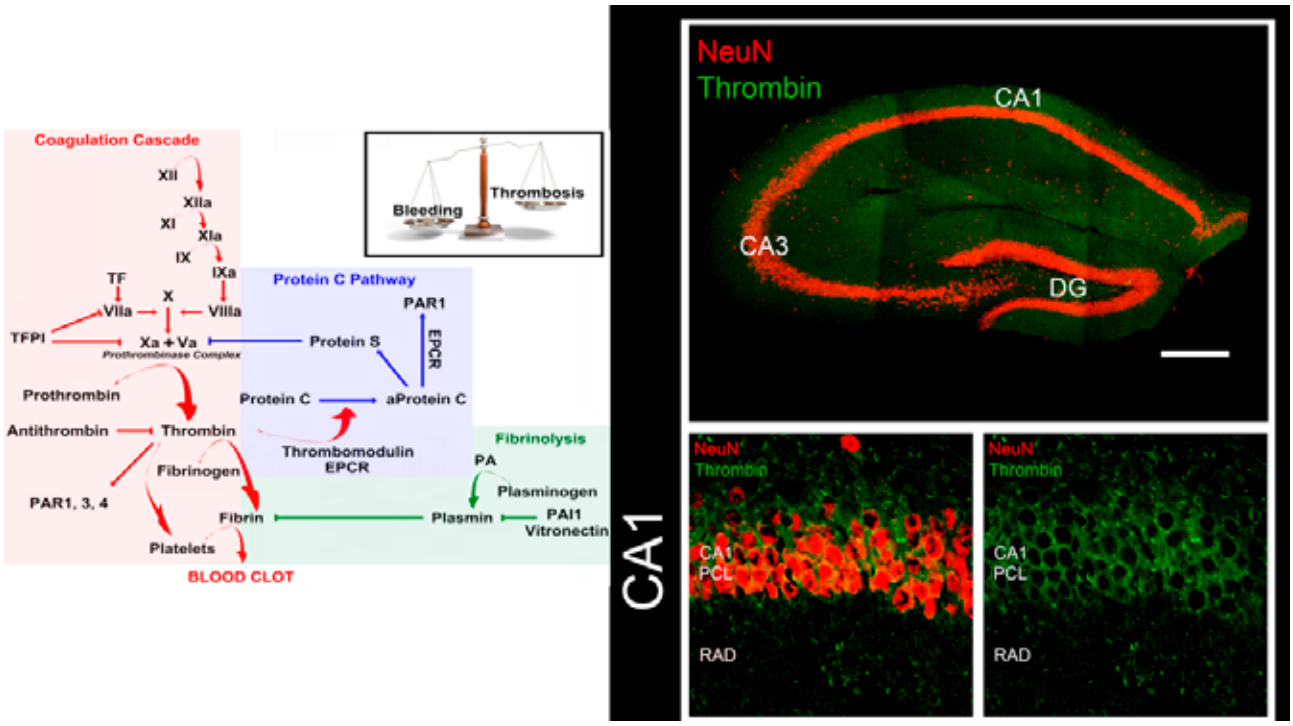
Senior Neurologist and Neurophysiologist, Department of Neurology, Chaim Sheba Medical Center, Tel HaShomer

Research

Our research focuses on the understanding of the role of coagulation factors, as well as their interaction with neuroinflammation in the physiology and pathophysiology of the nervous system. We have recently discovered that thrombin, the factor that ignites the coagulation cascade, is synthesized in the brain and has a fundamental role in regulating synaptic plasticity. However, we have also shown that high concentrations of thrombin (that reach the brain upon haemorrhage) can cause seizures and epilepsy. Our research has contributed in designing novel compouds that are currently being tested in order to counteract the pathogenic actions of thrombin in the brain. We apply cutting-edge technologies including mouse genetic tools, behavioural analysis, electrophysiology and molecular and cellular biology.

Publications

Bushi D., Ben Shimon M., Shavit Stein E., Chapman J., **Maggio N.***, Tanne D.* (2015) Increased thrombin activity following reperfusion after ischemic stroke alters synaptic transmission in the hippocampus. Journal of Neurochemistry, 135(6):1140-8. *equal contributors and last authors.



The coagulation pathways play fundamental roles in the physiology and pathophysiology of the nervous system. Immunofluorescence analysis reveals the expression pattern of thrombin in the hippocampus.

Itzekson-Hayosh Z., Shavit-Stein E., Katzav A, Rubovitch V., **Maggio N**, Harnof S, Chapman J, Pick CG (2015) Minimal traumatic brain injury in mice – PAR-1 and thrombin related changes. Journal of Neurotrauma, 33(20):1848-1854.

Willems L.M., Zahn N., Hick M., Ferreirós N., Scholich K., **Maggio N.**, Deller T., Vlachos A. (2016) Sphingosine-1-phosphate receptor inhibition prevents denervation-induced dendritic atrophy. Acta Neuropathologica Communications. 4:28.

Givaty G, **Maggio N.**, Cohen OS, Blatt I and Chapman J (2016) Early pathology in sleep studies of patients with familial Creutzfeldt-Jakob Disease. The Journal of Sleep Research, (5):571-575.

Schuldt G., Galanis C., Strehl A., Schiener S., Hick M., Lenz M., Deller T., **Maggio N.**, Vlachos (2016) Inhibition of Protease-Activated Receptor 1 (PAR1) does not affect dendritic homeostasis of cultured mouse dentate granule cells. (2016) Frontiers in Neuroanatomy;10:64.

Israel S, **Maggio N.**, Ekstein D, Zaid H., Firer M, Bederovsky Y, Noyman I, Gendelman Marton R, Blatt I, Brautbar H, Marom E, Nahlieli Din D, Berman E, Sabag D, Ingber A, Eyal S. (2016) Genetic risk factors for antiepileptic drug-induced hypersensitivity reactions in Israeli population. Epilepsia, 57(10):e205-e209.

Golderman V., Shavit-Stein E., Tamarin I., Rossman Y., Shrot S., Rosenberg N., **Maggio N.***, Chapman J.*, Eisenkraft A.* (2016) The organophosphate paraoxon and its antidote obidoxime inhibit thrombin activity and affect coagulation *in vitro*.PlosOne, 2016 Sep 30;11(9):e0163787. doi: 10.1371/journal.pone.0163787. *Equal contributors and last authors.

Gera O., Shavit-Stein E., Bushi D., Harnof S., Weiss R., Golderman V., Dori A., **Maggio N.**, Ben Shimon M., Finegold K., Chapman J. (2016) Novel Expression and Localization of Protein C Pathway Components in the Peripheral Nervous System. Neuroscience;339:587-598. d

Lenz M., Ben Shimon M., Vlachos A.* and **Maggio N.*** (2016) Pilocarpine- induced status epilepticus is associated with changes in the actin-modulating protein synaptopodin and alterations in long term potentiation in the mouse hippocampus. Neural Plasticity, accepted, in press. *Equal contributors and last authors.

Maggio N., Firer M., Zaid H., Bederovsky Y., Aboukaoud M., Gandelman-Marton R., Noyman I., Ekstein D., Blatt I., Marom E., Schwartzberg E., Israel S., Brautbar C., Ingber A., Eyal S. (2016) Causative drugs of Stevens Johnson syndrome and toxic epidermal necrolysis in Israel. Journal of Clinical Pharmacology, in press.

Prof. Shimon Rochkind, MD., Ph.D.

Research Center for Nerve Reconstruction (RCNR)
Division of Peripheral Nerve Reconstruction
Department of Neurosurgery
Tel Aviv Sourasky Medical Center

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Investigating Reconstruction of Peripheral and Central Nervous Systems Following Injury

Positions

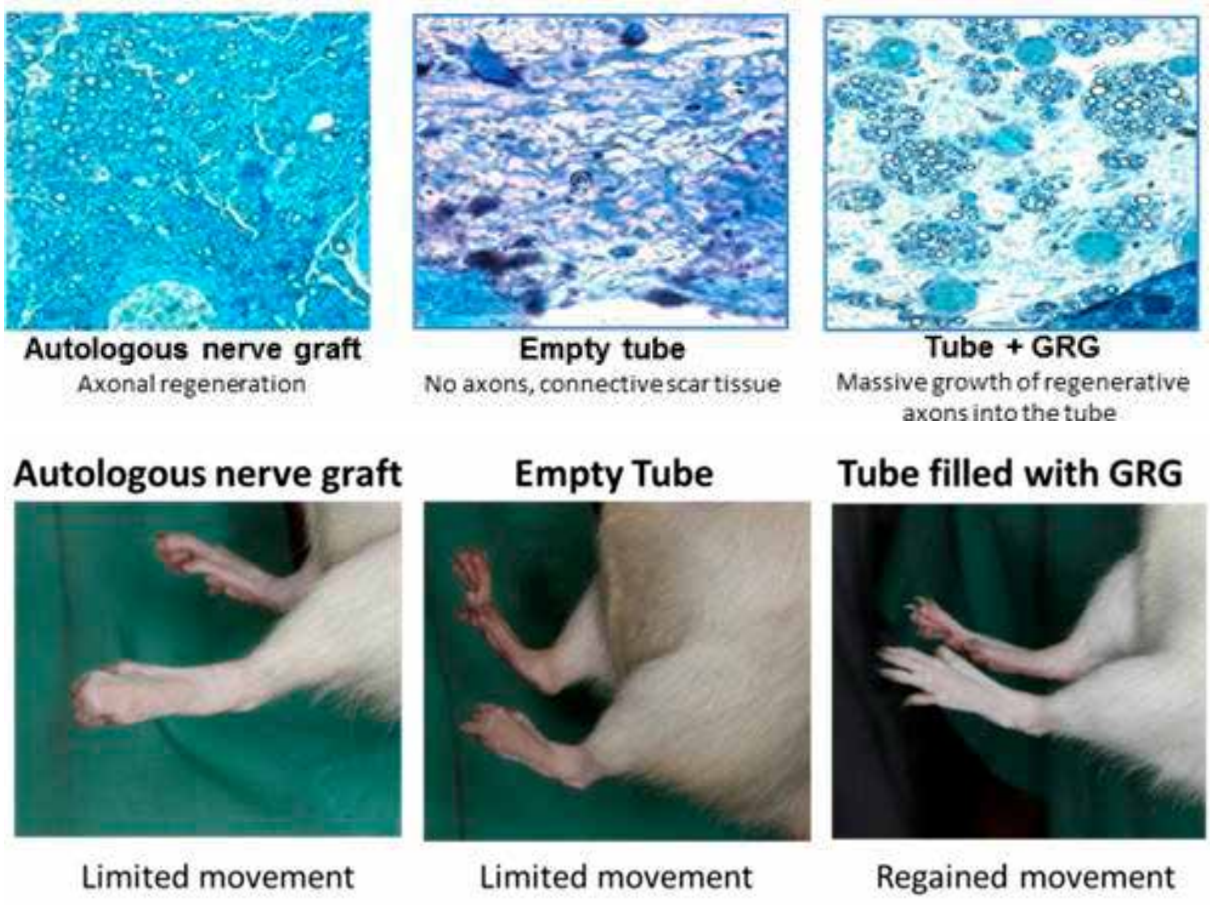
Associate Professor, Sackler Faculty of Medicine

Director, Division of Peripheral Nerve Reconstruction, Tel Aviv Sourasky Medical Center

Research

The research group is involved in projects targeting improvement in nerve reconstruction and rehabilitation from several aspects, aiming at the creation of innovative treatments to both peripheral nerve (PN) and spinal cord (SC) injuries. RCNR major projects include:

Creation of artificial nerve for nerve reconstruction using the innovative Guiding Regenerative Gel (GRG) to improve and accelerate regeneration of peripheral nerve injury (PNI) with massive defect. The GRG is a special milieu that was developed in collaboration with Prof. Zvi Nevo from Tel-Aviv University, Israel. The unique composition of GRG has recently been shown to be as efficient as autologous nerve graft, promoting axonal growth and sprouting without dependence on the addition of any external growth factors. In a short-term *in vivo* study it was shown that GRG loaded into a conduit promoted axonal sprouting of nerve cells and enabled the regeneration of a 15mm long nerve gap in rats,



which is not possible when bridging with an empty conduit (regeneration of up to 7mm). Therefore, the GRG allows a simpler procedure with less side effects, since its implantation does not involve other nerve origin, sensation loss or cosmetic defect as the "gold standard" treatment, therefore, GRG can provide a promising simple of the shelf solution for clinical use for complete PNI.

Based upon our encouraging results with the GRG, which shed light on the utilization of this innovative composite implant to bridge a gap, we postulate to improve this approach and attempt reconstruction of experimental complete SCI. Since astroglial scarring is one of the main obstacles for axonal growth and therefore spinal cord recovery, we have developed an Antigliotic Guiding Regenerative Gel (AGRG) which contains Guiding Regenerative Gel (GRG), and was proven to promote axonal sprouting and survival as well as antigliotic agents, which presented *in vitro* highly significant antigliotic activity, while reducing the amount of GAGs by more than 84%, thus inhibiting scar growth barrier formation in the site of injury.

The effect of laser phototherapy (low power laser irradiation) was explored on neuronal cells and peripheral nerve. In nerve cell cultures, laser irradiation significantly accelerated axonal sprouting (Rochkind et al., Lasers Surg Med, 2009). Animal studies in a model of incomplete peripheral nerve injury showed that laser phototherapy has an immediate protective effect, maintains functional activity of the injured nerve, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord and significantly increases axonal growth and myelinization. In a model of complete peripheral nerve injury with segmental loss, the laser-treated group showed more intensive axonal growth and morphological reconnection compared with the control group (Rochkind. Neurosurgical Focus, 2009). Recently, we found that in early stages of muscle atrophy, laser phototherapy may preserve the denervated muscle by maintaining creatine kinase activity and the amount of acetylcholine receptors. (Rochkind and Shainberg, Photomed Laser Surg, 2013). The current projects are intended to test and validate the beneficial effect of laser phototherapy on severely injured PN with a view to move forward to clinical study.

Publications

Rochkind S, Shainberg A. Muscle Response to Complete Peripheral Nerve Injury: Changes of Acetylcholine Receptor and Creatine Kinase Activity over Time. Journal of Reconstructive Microsurgery; doi: 10.1055/s-0037-1598619; 2017.

Mandelbaum-Livnat M.M, Almog M, Nissan M, Loeb E, **Rochkind S**. Photobiomodulation in Peripheral Nerve Injury with Aspect to Muscle Response. Photomedicine and Laser Surgery; 34(12):638-645; 2016.

Meyer C, Wrobel S, Raimondo S, **Rochkind S**, Heimann C, Shahar A, Ziv-Polat O, Geuna S, Grothe C, Haastert-Talini K. Peripheral Nerve Regeneration Through Hydrogel-Enriched Chitosan Conduits Containing Engineered Schwann Cells for Drug Delivery. Cell Transplantation; 25(1):159-82; 2016.

Regev GJ, Drexler M, Sever R, Dwyer T, Khashan M, Lidar Z, Salame K, **Rochkind S**. Neurolysis for the treatment of sciatic nerve palsy associated with total hip arthroplasty. The Bone & Joint Journal; 97-B(10):1345-9; 2015.

Shapira Y, Tolmasov M, Nissan M, Reider E, Koren A, Biron T, Bitan Y, Livnat M, Ronchi G, Geuna S, **Rochkind S**. Comparison of results between chitosan hollow tube and autologous nerve graft in reconstruction of peripheral nerve defect: An experimental study. Microsurgery; 36(8):664-671; 2015.

Grants

2017-2019 German Israeli Foundation, Development of GRG advanced chitosan nerve guides – NerveMatrix.

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The Neuronal Encoding of Human Speech

Positions

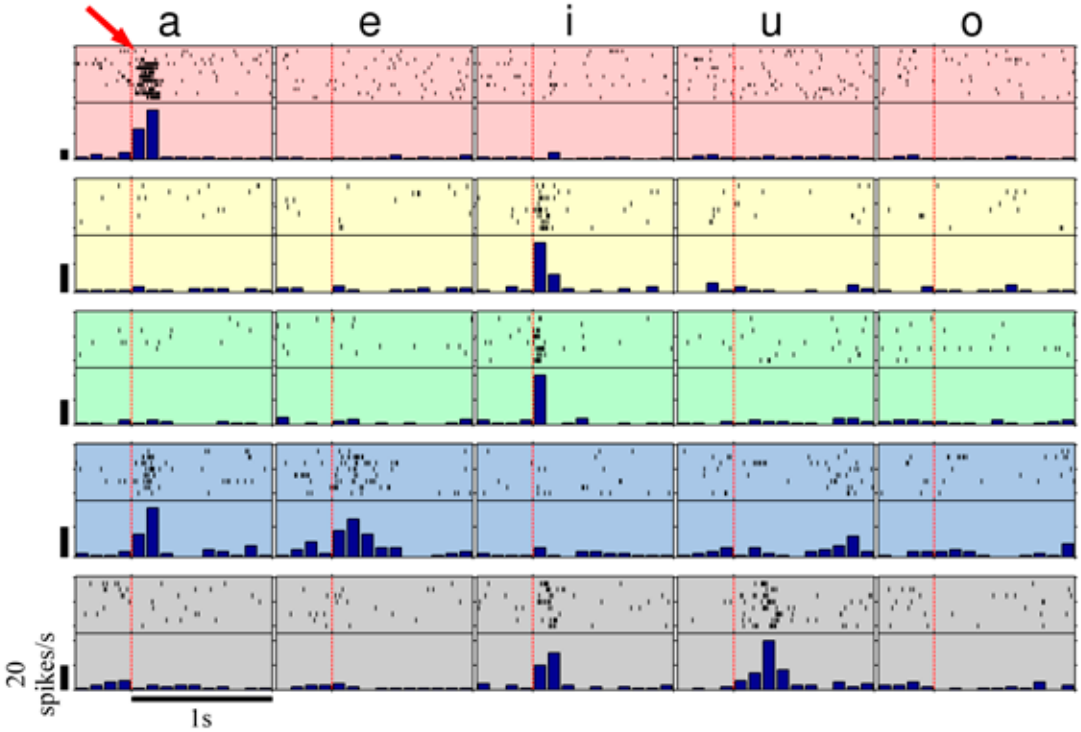
Senior Lecturer, Sackler Faculty of Medicine and Sagol School of Neuroscience

Senior Researcher and Neurophysiologist, Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center ("Ichilov")

Research

We study the neuronal representation of speech production, perception and imagery in the human brain. We explore the acoustic, phonetic and phonological levels, and the deterioration in speech due to neurological disorders, for example in Parkinson's disease. Our main focus is the encoding of speech features by single neurons (for example, see Figure 1). We also aim to develop brain-machine interfaces for restoring speech faculties in completely paralyzed persons by decoding their neuronal activity (i.e., inferring speech contents solely from spiking activity).

We take advantage of a unique clinical "opportunity" to work with neurosurgical patients undergoing implantation of electrodes for clinical reasons. Experiments are conducted intra-operatively with awake patients with movement disorders or in the ward, with epilepsy patients. Understanding the neuronal representation of human speech is essential for understanding the underlying mechanisms of speech disorders, for the development of new



Medial–frontal units that we have discovered, with high specificity to vowels. Raster plots and peri-stimulus time histograms of five units (rows) during the articulation of the five vowels a, e, i, u and o (columns). The response of each unit is specific to one or two vowels only.
Red vertical dashed lines indicate speech onset. All vertical scale bars correspond to firing rates of 20 spikes/s (from: Tankus *et al.*, Nature Communications, 2012).

therapeutic procedures, and for restoration of the ability to speak. The research thus bears enormous potential to greatly improve the quality of life of millions of people around the globe.

Publications

O. Perez, R. Mukamel, **A. Tankus**, Y. Yeshurun and I. Fried: Preconscious prediction of a driver's decision using intracranial recordings. *Journal of Cognitive Neuroscience*, 27(8):1492–1502, 2015.

T. Iluz, A. Weiss, E. Gazit, **A. Tankus**, M. Brozgol, M. Dorfman, A. Mirelman, N. Giladi, J.M. Hausdorff: Can a body-fixed sensor reduce Heisenberg's uncertainty when it comes to the evaluation of mobility? Effects of aging and fall risk on transitions in daily living. *Journals of Gerontology: Medical Sciences*, 1–9, 2015.

A. Tankus, I. Strauss, T. Gurevich, A. Mirelman, N. Giladi, I. Fried, J. M. Hausdorff. Subthalamic neurons encode both single- and multi-limb movements in Parkinson's disease patients. Scientific Reports, 7(42467), 2017.

A. Tankus, I. Fried. Degradation of neuronal encoding of speech in the subthalamic nucleus in Parkinson's disease. Neurosurgery, 2018.

A. Tankus, A. Mirelman, N. Giladi, I. Fried, J. M. Hausdorff. Pace of movement: the role of single neurons in the subthalamic nucleus. Journal of Neurosurgery, 2018.

Chapter

A. Tankus and J.M. Hausdorff. Deep brain stimulation in Parkinson's disease: effects on gait and postural control. In F.A. Barbieri and R. Vitório, editors, Locomotion and Posture in Older Adults – The Role of Aging and Movement Disorders, Springer, Chapter 25, pages 385–396, 2017.

.Prof. Avraham Weizman, M.D
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Investigating the Biological Basis of Psychiatric Disorders

Positions

Full Professor, Sackler Faculty of Medicine

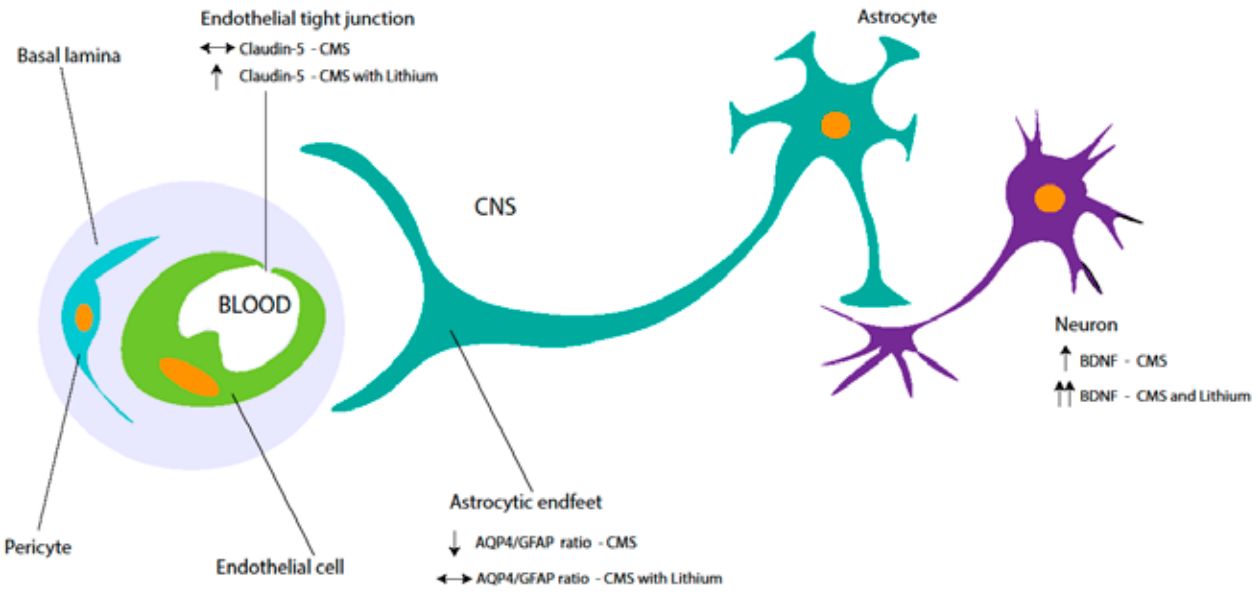
Head of the Laboratory of Biological Psychiatry, FMRC

Head of the Research Unit, GMHC

Research

Our laboratory is driven by the belief that combining pre-clinical and clinical research is the key to modern translational research. We investigate brain mechanisms of mental disorders, currently focusing on neurodevelopmental disorders, development of new strategies for the treatment of psychotic disorders and psychopharmacology of mental disorders.

Our research goals are to identify genetic and environmental factors that contribute to the emergence of psychosis and depression, as well as cognitive decline. To this end we study the role of genetic variants, neuro-anatomical changes, profiles of gene expression and neuro-endocrine and neuro-immune alterations in the pathophysiology of these disorders. We attempt to identify neural, molecular pathways and brain-circuits associated with pathological behaviors. The accumulated results are used to develop new therapeutic strategies based on novel targets. We, together with Dr. Eldar Hochman from GMHC and Dr. Michal Taler and Dr. Shay Henry Hornfeld from FMRC, recently found a novel lithium mechanism of action at the BBB. In another project we developed with Dr. Konstantin Bloch, Prof. Pnina Vardi and others from FMRC, a novel strategy for the treatment of Alzheimer-like metabolic dementia that responded to transplantation of pancreatic islets.



Regulatory effect of lithium on hippocampal blood-brain barrier integrity in a rat model of depressive-like behavior.

On the clinical level, we assess the efficacy and tolerability of psychopharmacological agents in the treatment of pediatric and adult mental disorders, especially psychotic and mood disorders. In a recent collaboration with Prof. Doron Gothelf from Sheba Medical Center and Dr. Elena Michaelovski and Dr. Miri Carmel from FMRC, we identified genetic and epi-genetic pathways that may be involved in the emergence of psychosis in patients with 22q11.2DS. In a series of pivotal studies in the field of drug addiction that was done in collaboration with Prof. Gal Yadid from Bar Ilan University, we demonstrated that the neurosteroid DHEA can attenuate drug use in subjects with addictive behaviors. With Dr. Amir Krivoy from GMHC and Dr. Michal Taler we also found that the cognitive performance of treatment resistant schizophrenia patients maintained on clozapine, may benefit from the addition of vitamin D.

Publications (out of 150)

Poyurovsky M, **Weizman A**. Treatment of Antipsychotic-Induced Akathisia: Role of Serotonin 5-HT_{2a} Receptor Antagonists. Drugs. 2020 May 8.

Gur S, Taler M, Bormant G, Blattberg D, Nitzan U, Vaknin-Dembinsky A, BrillL, Krivoy A, **Weizman A**, Hochman E. Lack of association between unipolar or bipolar depression and serum aquaporin-4 autoantibodies. Brain Behav Immun. 2020May 5:S0889-1591(20)30495-5.

Kahana M, **Weizman A**, Gabay M, Loboda Y, Segal-Gavish H, Gavish A, Barhum Y,Offen D, Finberg J, Allon N, Gavish M. Liposome-based targeting of dopamine to the brain: a novel approach for the treatment of Parkinson's disease. Mol Psychiatry. 2020.

Zeineh N, Denora N, Laquintana V, Franco M, **Weizman A**, Gavish M. Efficaciousness of Low Affinity Compared to High Affinity TSPO Ligands in the Inhibition of Hypoxic Mitochondrial Cellular Damage Induced by Cobalt Chloride in Human Lung H1299 Cells. Biomedicines. 2020;8:E106.

Carmel M, Michaelovsky E, Weinberger R, Frisch A, Mekori-Domachevsky E, Gothelf D, **Weizman A**. Differential methylation of imprinting genes and MHC locusin 22q11.2 deletion syndrome-related schizophrenia spectrum disorders. World J Biol Psychiatry. 2020:1-12.

Bloch K, Hornfeld SH, Dar S, Vanichkin A, Gil-Ad I, Vardi P, **Weizman A**. Long-term effects of intracranial islet grafting on cognitive functioning in a rat metabolic model of sporadic Alzheimer's disease-like dementia. PLoS One.2020;15:e0227879.

Krivoy A, Satz J, Hornfeld SH, Bar L, Gaughran F, Shoval G, Hochman E, **Weizman A**, Taler M. Low levels of serum vitamin D in clozapine-treated schizophrenia patients are associated with high levels of the proinflammatory cytokine IL-6. Int Clin Psychopharmacol. 2020.

Amitai M, Taler M, Ben-Baruch R, Lebow M, Rotkopf R, Apter A, Fennig S, **Weizman A**, Chen A. Increased circulatory IL-6 during 8-week fluoxetine treatment is a risk factor for suicidal behaviors in youth. Brain Behav Immun. 2019 S0889-1591(19)31330-3.

Zeineh N, Nagler R, Gabay M, **Weizman A**, Gavish M. Effects of Cigarette Smokeon TSPO-related Mitochondrial Processes. Cells. 2019;8:694.

Cohen K, **Weizman A**, Weinstein A. Modulatory effects of cannabinoids on brain neurotransmission. Eur J Neurosci. 2019;50:2322-2345.

Monga S, Nagler R, Amara R, **Weizman A**, Gavish M. Inhibitory effects of the two novel TSPO ligands 2-Cl-MGV-1 and MGV-1 on LPS-induced microglial activation. Cells. 2019; 8:486. doi: 10.3390/cells8050486.

Bloch K, Dar S, Vanichkin A, Gil-Ad I, Vardi P, **Weizman A**. Trafficking of grafted pancreatic islets into the brain lateral ventricles: implications for cognition. Transplantation. 2019;103:e137-e138.

Michaelovsky E, Carmel M, Frisch A, Salmon-Divon M, Pasmanik-Chor M, **Weizman A**, Gothelf D. Risk gene-set and pathways in 22q11.2 deletion-related schizophrenia: a genealogical molecular approach. Transl Psychiatry. 2019;9:15. doi: 10.1038/s41398-018-0354-9.

Azrad M, Zeineh N, **Weizman A**, Veenman L, Gavish M. The TSPO Ligands2-Cl-MGV-1, MGV-1, and PK11195 Differentially Suppress the Inflammatory Response of BV-2 Microglial Cell to LPS. Int J Mol Sci. 2019;20:E594.

Poyurovsky M, **Weizman A**. Very Low-Dose Mirtazapine (7.5 mg) in treatment of acute antipsychotic-associated akathisia. J Clin Psychopharmacol. 2018;38:609-611.

Lax E, Warhaftig G, Ohana D, Maayan R, Delayahu Y, Roska P, Ponizovsky AM,**Weizman A**, Yadid G, Szyf M. A DNA methylation signature of addiction in T cells and Its reversal with DHEA intervention. Front Mol Neurosci. 2018;11:322.

Bloch K, Gil-Ad I, Vanichkin A, Hornfeld SH, Taler M, Dar S, Azarov D, Vardi P, **Weizman A**. Intracranial

transplantation of pancreatic islets attenuates cognitive and peripheral metabolic dysfunctions in a rat model of sporadic Alzheimer's Disease. J Alzheimers Dis. 2018;65:1445-1458.

Poleg S, Golubchik P, Offen D, **Weizman A**. Cannabidiol as a suggestedcandidate for treatment of autism spectrum disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019;89:90-96.

Yadid G, Ahdoot-Levi H, Bareli T, Maayan R, **Weizman A**. Dehydroepiandrosterone and addiction. Vitam Horm. 2018;108:385-412.

Golubchik P, Levy T, **Weizman A**. The effect of methylphenidate treatment onpsychopathic behavior of patients having attention-deficit hyperactivity disorderwith and without oppositional defiant disorder. Int Clin Psychopharmacol. 2018;33:330-333.

Mekori-Domachevsky E, Taler M, Shoenfeld Y, Gurevich M, Sonis P, Weisman O, **Weizman A**, Gothelf D. Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome are associated with psychosis and cognitive deficits. J Clin Psychiatry. 2017 Nov/Dec;78(9):e1219-e1225.

Bloch K, Gil-Ad I, Vanichkin A, Hornfeld SH, Koroukhov N, Taler M, Vardi P, **Weizman A**. Intracerebroventricular streptozotocin induces obesity and dementia in Lewis Rats: Rat model of dementia associated with obesity. J Alzheimers Dis. 2017;60:121-136.11:3263-3272.

Krivoy A, Hochman E, Sendt KV, Hollander S, Vilner Y, Selakovic M, **Weizman A**, Taler M. Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. Schizophr Res. 2018;192:226-231.

Yuhas Y, Ashkenazi S, Berent E, **Weizman A**. Ketamine upregulates eNOS expression in human astroglial A172 cells: Possible role in its antidepressive properties. J Neuroimmunol. 2017;305:75-81.

Weinstein A, Livny A, **Weizman A**. New developments in brain research of internet and gaming disorder. Neurosci Biobehav Rev. 2017;75:314-330.

Weinstein A, Livny-Ezer A, **Weizman A**. Brain imaging studies on the cognitive ,pharmacological and neurobiological effects of cannabis in humans: Evidence from studies of adult users. Curr Pharm Des. 2016;22:6366-6379.

Maayan R, Hirsh L, Yadid G, **Weizman A**. Dehydroepiandrosterone attenuates cocaine-seeking behaviour independently of corticosterone fluctuations. J Neuroendocrinol. 2015;27:819-26. doi:10.1016/bs.vh.2018.04.001.

Yuhas Y, Ashkenazi S, Berent E, **Weizman A**. Immunomodulatory activity of ketamine in human astroglial A172 cells: Possible relevance to its rapid antidepressant activity. J Neuroimmunol. 2015;282:33-8.

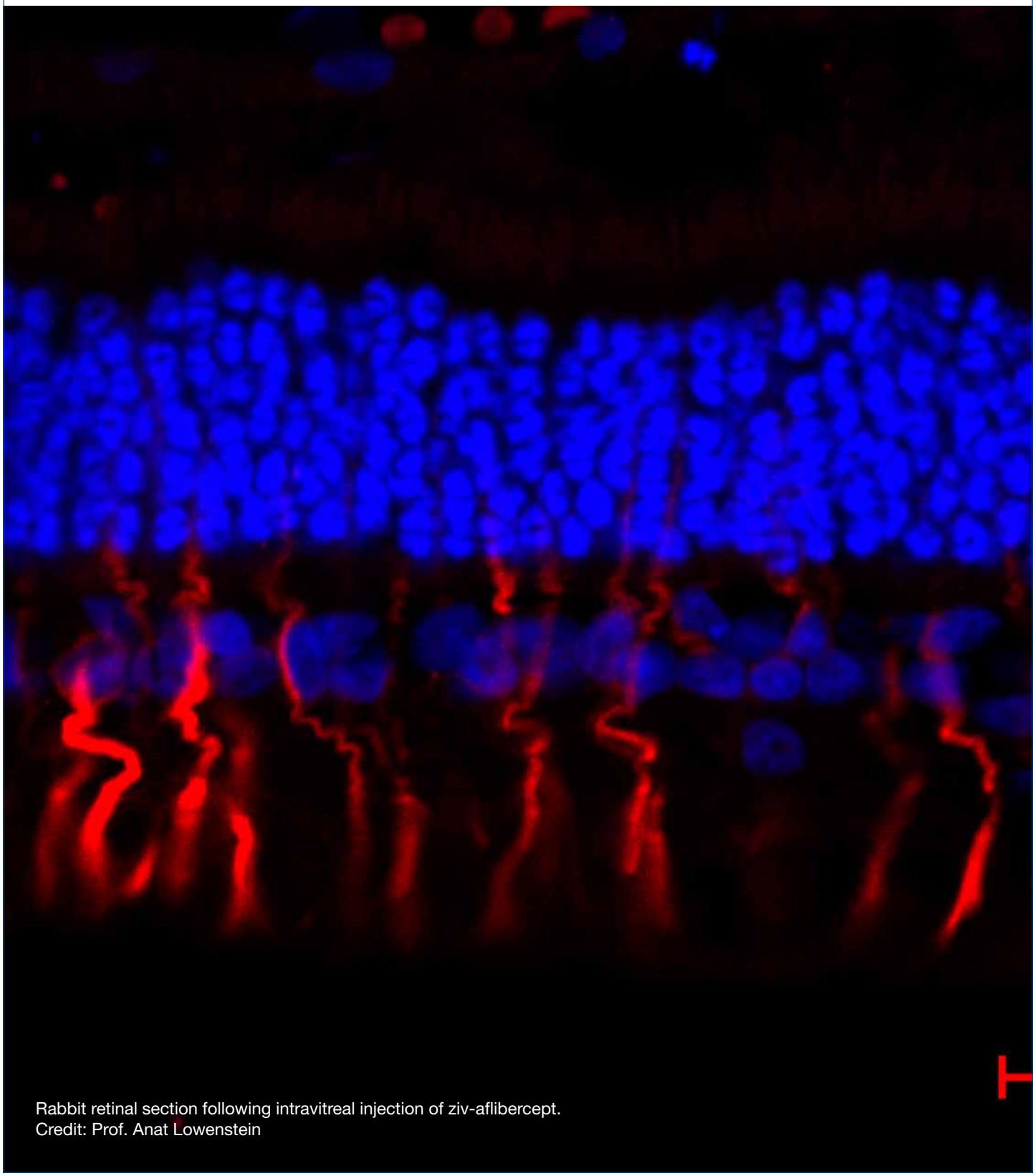
Ohana D, Maayan R, Delayahu Y, Roska P, Ponizovsky AM, **Weizman A**, Yadid G, Yechiam E. Effect of dehydroepiandrosterone add-on therapy on mood, decision making and subsequent relapse of polydrug users. Addict Biol. 2016;21:885-94.

Edelson MG, Shemesh M, **Weizman A**, Yariv S, Sharot T, Dudai Y. Opposing effects of oxytocin on overt compliance and lasting changes to memory. Neuropsychopharmacology. 2015;40:966-73.

Grants

2018 – 2020 Mayer Foundation for Scientific Research

Ophthalmology



Rabbit retinal section following intravitreal injection of ziv-aflibercept.
Credit: Prof. Anat Lowenstein

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Head, Research team

Department of Ophthalmology

Stem Cells Laboratory of Ophthalmology

Positions, Dr. Aya Barzelay, M.D., Ph.D.

Head, Research team

Department of Ophthalmology

Stem Cells Laboratory of Ophthalmology

Research

Development of novel stem cells therapy for retinal degeneration diseases using mesenchymal stem cells that are isolated from subcutanoues fat of patients. Development of minimally invasive methods to isolate stem cells from the patient. Growing stem cells at the laboratory and studying their ability to develop into retinal cells. Developing methods to transplant stem cells into mice retinas in mice models of retinal degeneration.

Main research topics

-To isolate and characterize human adipose tissue derived mesenchymal stem cells from patients.

-developing minimally invasive methods for isolation and transplantation of stem cells to the patient

- Induce differentiation of ASCs into retinal cells. Designated for retinal transplantations of differentiated ASCs.

- Study the paracrine activity of ASCs in the hypoxic environment. Designated for retinal transplantations of activated ASCs.

- Evaluate the therapeutic potential of stem cells transplantations to retina in animal model of Retinal degeneration

Team

Prof. Adiel Barak, M.D.

Dr. Aya Barzelay, M.D., Ph.D.

Publications

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, Entin-Meer M, Gur E, Loewenstein A, **Barak A**. Power-assisted liposuction versus tissue resection for the isolation of adipose tissue-derived mesenchymal stem cells: phenotype, senescence, and multipotency at advanced passages. Aesthet Surg J. 2015;35(7):NP230-40.

Barzelay A, Weisthal Algor S, Katz S, Niztan A, Mezad-Koursh D, Neudorfer M, Goldstein M, Meilik B, Loewenstein A, Barak A. Adipose derived mesenchymal stem cells migrate and rescue RPE in the setting of oxidative stress". Stem Cells Int, 2018.

Antheby R, **Barzelay A**, Barak A. Vitrectomy in patients 85 years of age and older: surgical outcomes and visual prognosis. Clin Interv Aging. 2018;13:243-249.

Leshno A, **Barzelay A**, Barak A, Neudorfer M. Diagnosis of peripheral retinoschisis using ultrasound biomicroscopy, Ophth Surg Lasers Imaging Retina, 2019.

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, Gur E, Loewenstein A, Barak A. Isolation of adipose tissue derived mesenchymal stem cells using power assisted liposuction versus tissue resection: phenotype, senescence and multipotency at early and advanced passages. Aesthet Surg J. 2015;35(7):NP230-40.

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, Gur E, Loewenstein A, Barak A. High glucose in culture media of adipose derived mesenchymal stem cells – gene expression alteration and early senescence. Stem Cell Regen Med. 2020.

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Investigating Age-Related Macular Edema and Diabetic Retinopathy

Positions

Professor of Ophthalmology, Sackler Faculty of Medicine

Assistant Dean, Sackler Faculty of Medicine

Head, Department of Ophthalmology

Incumbent, Sydney A. Fox Chair in Ophthalmology

President, Israeli Ophthalmological Society

Associate editor, *International Journal of Retina and Vitreous*

Editor in Chief, *Case Reports in Ophthalmology*

Chairperson, National Ethics Review Board Committee, State of Israel Ministry of Health

Board member, Israeli Council of Surgery and Anesthesia

Chair, Academia Ophthalmologica Internationalis

General Secretary of the Board, Euretina Society

International Committee Member, Macula Society

Research

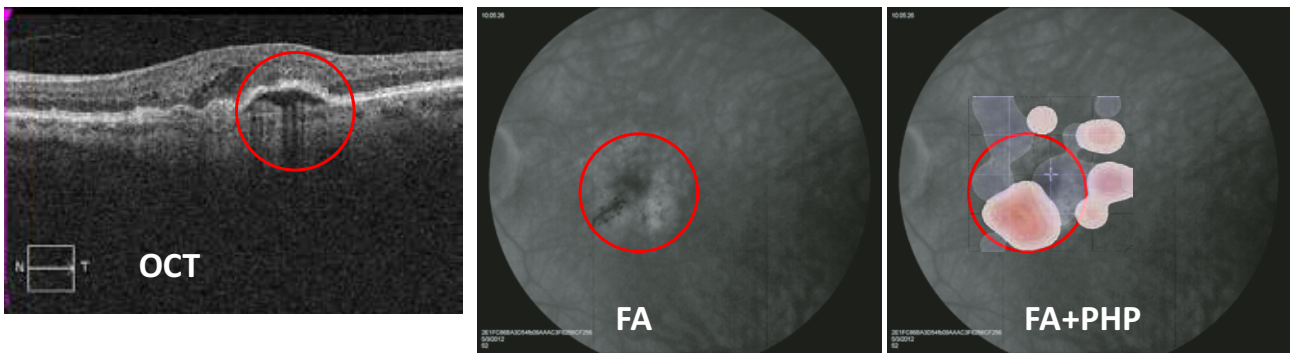
Publications

Veritti D, Sarao V, Francescutti L, Rota N, Loewenstein A, Borrelli E, Sadda S, Lanzetta P. Optical coherence tomography angiography findings in diabetic retinopathy. Expert Rev Ophthalmol. 2017;12:475-484.

Bar-Sela SM, Zayit-Soudry S, Massarweh A, Mane I, Perlman I, Loewenstein A. Retinal toxicity of intravitreal melphalan in albino rabbits. J Clin Exp Ophthalmol. 2018;9(1):707.

Zur D, Iglicki M, Busch C, Inverinizzi A, Mariussi M, Loewenstein A, International Retina Group. OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology. 2018;125:267-275.

Iglicki M, Busch C, Zur D, Okada M, Mariussi M, Chhablani JK, Cebeci Z, Fraser-Bell S, Chaikitmongkol V, Couturier A, Giancipoli E, Lupidi M, Rodriguez-Valdés PJ, Rehak M, Fung AT, Goldstein M,



Retinal imaging (Optical coherence tomography- OCT and Fluorescein angiography- FA) of a very early neovascular macular degeneration lesion detected by the preferential hyperacuity perimetry technology developed for early detection of macular degeneration.

Loewenstein A. Dexamethasone implant for diabetic macular edema in

naïve compared with refractory eyes: The International Retina Group Real-Life 24-month multicenter study. The IRGREL-DEX study. Retina. 2019;39-44-51

Iglicki M, Zur D, Busch C, Okada M, Loewenstein A. Progression of diabetic retinopathy severity after treatment with dexamethasone implant: a 24-month cohort study the "DR-Pro-DEX Study". Acta Diabetologica. 2018;55:541-547.

Iglicki M, Lavaque A, Ozimek M, Negri HP, Okada M, Chhablani J, Busch C, Loewenstein A, Zur D. Biomarkers and predictors for functional and anatomic outcomes for small gauge pars plana vitrectomy and peeling of the internal limiting membrane in naïve diabetic macular edema: The VITAL Study. PLoS One. 13(7).

Sarao V, Veritti D, Maurutto E, Rassu N, Borrelli E, Loewenstein A, Sadda S, Lanzetta P. Pharmacotherapeutic management of macular edema in diabetic subjects undergoing cataract surgery. Expert Opin Pharmacother. 2018;19:1551-1563.

Lisnayansky M, Kapelushnik N, Ben-Bassat A, Marom M, Khananshvili D, Loewenstein A, Giladi M, Haitin Y. Reduced activity of Geranylgeranyl diphodphate synthase mutant is involved in bisphosphonate-induced atypical fractures. Mol Pharmacol. 2018;94:1-10.

Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: “Is there a big change on the horizon?” Clin Ophthalmol. 2018;12:2137-2143.

Barzelay A, Weisthal Algor S, Nitzan A, Katz S, Benhamou M, Nakdimon I, Azmon N, Gozlan S, Mezad-Koursh D, Neudorfer M, Goldstein M, Meilik B, Loewenstein A, Barak A. Adipose-derived mesenchymal stem cells migrate and rescue RPE in the setting of oxidative stress. Stem Cells Int. 2018.

Rabina G, Barequet D, Mimouni M, Rabinovitch Y, Wolf Y, Barak A, Loewenstein A, Schwartz S. Carotid artery endarterectomy effect on choroidal thickness: One-year follow up. J Ophthalmol. 2018.

Moisseiev E, Loewenstein A. novel long-acting pharmacotherapy for exudative age related macular degeneration. Curr Pharm Des. 2018;24(41): 4860-4863

Rabina G, Azem N, Barequet D, Barak A, Loewenstein A, Schwartz S. Silicone oil tamponade effect on macular layer thickness and visual acuity. Retina. 2020; 40(5):998-1004.

Moisseiev E, Loewenstein A. [Intravitreal Injection – A Small Procedure for the Eye, A Giant Leap for Ophthalmology]. Harefuah. 2019;158(2): 121-125.

Cohen E, Rosenblatt A, Bornstein S, Loewenstein A, Barak A, Schwartz S. Wide-angeled endoillumination vs. traditional scleral buckling surgery for retinal detachment – a comparative study. Clin Ophthalmol. 2019;13: 287-293.

Sharma A, Kumar N, Kuppermann B, Bandello F, Loewenstein A. Biologics, biosimilars, and boibetters: Different terms or different drugs? Eye. 2019;33:1032-1034.

Moisseiev E, Loewenstein A, Moshiri A, Yiu G. The management of retinal detachment: Techniques and perspectives 2018. J Ophthalmol. 2019.

Busch C, Iglicki M, Okada M, Gabrielle PH, Cohen S, Mariussi M, Amphornphruet A, Cebeci Z, Chaikitmongkol V, Couturier A, Fraser-Bell S, Fung AT, Iannetta D, Radecka L, Lains I, Rodrigues TM, Lupidi M, Ozimek M, Sala-Puigdollers, Rehak M, Loewenstein A, Zur D. Causative pathogens of endophthalmitis after intravitreal anti-VEGF Injection: An international multicenter trial. Ophthalmologica. 2019;241(4): 211-219.

Busch C, Fraser-Bell S, Zur D, Rodriguez-Valdes PJ, Cebeci Z, Lupidi M, Fung AT, Gabrielle PH, Giancipoli E, Chaikitmongkol V, Okada M, Lains I, Santos AR, Kunavisarut P, Sala-Puigdollers A, Chhablani J, Ozimek M, Hilely A, Unterlauft JD, Loewenstein A, Iglicki M, Rehak M; International Retina Group. Real-world outcomes of observation and treatment in diabetic macular edema with very good visual acuity: the OBTAIN Study. Acta Diabetol. 2019;56(7): 777-784

Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Biotherapeutics and Immunogenicity: Ophthalmic Perspective. Eye (Lond). 2019;33(9): 1359-1361.

Zur D, Iglicki M, Loewenstein A. The role of steroids in the management of diabetic macular edema. Ophthalmic Res. 2019;62(4): 231-236.

Iglicki M, Zur D, Fung A, Gabrielle PH, Lupidi M, Santos R, Busch C, Rehak M, Cebeci Z, Charles M, Masarwa D, Schwartz S, Barak A, Loewenstein A for the International Retina Group. TRActional Diabetic reTInal detachment surgery with co-adjuvant intravitreal dexamethasONe implant: the TRADITION STUDY. Acta Diabetol. 2019;56 (10): 1141-1147.

Sharma A, Kumar N, Bandello F, Loewenstein A, Freund KB. Understanding intravitreal silicone

oil droplets due to intravitreal injections. Retina. 2019;39(7): 1233-1235.

Kodjikian L, Bellocq D, Bandello F, Loewenstein A, Chakravarthy u, Koh A, Augustin A, de Smet MD, Chhablani J, Tufail A, Garcia-Layana A, Sudhalkar A, Mathis T. First-line treatment algorithm and guidelines in center-involving diabetic macular edema. Eur J Ophthlmol. 2019;29(6): 573-584.

Sadda S, Campbell J, Dugel P, Holekamp N, Kiss S, Loewenstein A, Augustin A, Shih V, Xu X, Wykoff C, Whitcup S. Relationship between duration and extent of edema and visual acuity outcome with ranibizumab in diabetic macular edema: a post hoc analysis of protocol I data. Eye (Lond). 2020; 34: 480-490.

Sharma A, Kuppermann B, Bandello F, Loewenstein A. Understanding biosimilars and its regulatory aspects across the globe: An ophthalmology perspective. Br J Ophthalmol. 2020;104(1): 2-7.

Korobelnik JF, Lu C, Katz TA, Dhoot DS, Loewenstein A, Arnold J, Staurenghi G. Effect of baseline subretinal fluid on treatment outcomes in VIVID-DME and VISTA-DME studies. Ophthalmol. Retina. 2019;3:663-669.

Iglicki M, Loewenstein A, Barak A, Schwartz S, Zur D. Outer Retinal Hyperreflective Deposits (ORYD): a new OCT feature in Naive Diabetic Macular Oedema after PPV with ILM Peeling. Br J Ophthalmol. 2019-314523.

Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, Midena E, Sivaprasad S, Tadayoni R, Wolf S, Loewenstein A. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). Ophahtlmologica. 2019;242(3): 123-162.

Lisnyansky M, Yariv E, Segal O, Marom M, Loewenstein A, Ben-Tal N, Giladi M, Haitin Y. Metal coordination is crucial for geranylgeranyl diphosphate synthase-bisphosphonate interactions: a crystallographic and computational analysis. Mol Pharmacol. 2019;96(5): 580-588.

Lisnyansky Bar-El M, Lee SY, Ki AY, Kapelushnik N, Loewenstein A, Chung KY, Schneidman-Duhovny D, Giladi M, Newman H, Haitin Y. Structural characterization of full-length human dehydrodolichyl diphosphate using an integrative computational and experimental approach. Biomolecules. 2019;9(11):E660.

Trivizki O, Zur D, Goldenberg D, Rabina G, Fleissig E, Barak A, Shulman S, Loewenstein A, Schwartz S. A Novel finding of hyperreflective material in the silicone-retina interface: An optical coherence tomography and histopathological study. Retina 2019.

Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Faricimab: Expanding horizon beyond VEGF. Eye (Lond). 2019.

Sharma A, Parachuri N, Kumar N, Kuppermann BD, Bandello F, Loewenstein A, Regillo CD.

Diabetic macular edema management: A potential cost-effective treatment strategy to be explored. Ophthalmol Retina. 2019;3(11): 1009-1011

Moisseiev E, Loewenstein A. How to manage patients with center-involving diabetic macular edema and good visual acuity? An answer to a common clinical question. Eye (Lond). 2019;33(11): 1677-1678.

Busch C, Fraser-Bell S, Iglicki M, Lupidi M, Couturier A, Chaikitmongkol V, Giancipoli E, Rodrigues-Valdes PJ, Gabrielle PH, Lains I, Santos AR, Cebeci Z, Amphornphruet A, Degenhardt V, Untrlauft JD, Cagini C, Mane-Tauty V, D'Amico Ricci G, Hindi I, Agrawal KK, Chhablani J, Loewenstein A, Zur D, Rehak M; International Retina Group. Real-world otcomes of non-reponding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results. Acta Diabetol. 2019;56(12):1341-1350.

Sharma A, Kuppermann BD, Bandello F, Lanzetta P, Zur D, Park SW, Yu HG, Saravanan VR, Zacharias AK, Barreira AK, Iglicki M, Miassi F, Veritti D, Tsao S, Makam D, Jain N, Loewenstein A. Intraocular Pressure (IOP) after Intravitreal Dexamethasone Implant (Ozurdex) amongst different geographic populations-GEODEX-IOP study. Eye (Lond). 2019.

Sharma A, Kumar N, Bandello F, Loewenstein A, Kuppermann BD. Need of education on biosimilars amongst ophthalmologists: combating the nocebo effect. Eye (Lond). 2019.

Weinberg T, Loewenstein A. The role of steroids in treating diabetic macular oedema in the era of anti-VEGF. Eye (Lond). 2019.

Sharma A, Hafeez Faridi M, Kumar N, Parachuri N, Sharma R, Kuppermann BD, Bandello F, Loewenstein A, Regillo CD. immunogenicity and efficacy after switching from original ranibizumab to a ranibizumab biosimilar: Real-world data. Eye (Lond). 2020;34(6):1008-1009.

Wong DT, Lambrou GN, Loewenstein A, Pearce I, Okada AA. Suspending treatment of neovascular age-related macular degeneration in cases of futility. Retina. 2019.

Moisseiev E, Loewenstein A. Initial treatment of macular oedema due to central vein occlusion- which anti-VEGF agent to choose? Eye (Lond). 2020;34(2): 219-220.

Sharma A, Kumar N, Kuppermann BD, Loewenstein A, Bandello F. Brolucizumab: is extended VEGF suppression on the horizon? Eye (Lond). 2020;34(3): 424-426.

Moisseiev E, Loewenstein A. Abicipar Pegol- a novel anti-VEGF therapy with a long duration of action. Eye (Lond). 2020; 34(4): 605-606.

Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Ophthalmic biosimilars and biologics-role of endotoxins. Eye (Lond). 2020; 34(4): 614-615.

Zur D, Iglicki M, Sala-Puigdollers A, Chhablani J, Lupidi M, Fraser-Bell S, Mendes TS, Chaikitmongkol V, Cebeci Z, Dollberg D, Busch C, Invernizzi A, Habot-Wilner Z, Loewenstein A for the International Retina Group. Disorganization of retinal inner layers as a biomarker in patients with diabetc macular oedema treated with dexamethasone implant. Acta Ophthalmol. 2020;98(2): e217-e223.

Rosenblatt A, Udaondo P, Cunha-Vaz J, Sivaprasad S, Bandello F, Lanzetta P, Kodjikian L, Goldstein M, Habot-Wilner Z, Loewenstein A; ARTES Study Group. A collaborative retrospective study on the efficacy and safety on intravitreal dexamethasone impant (ozurdex) in patients with diabetic macular edema: The European DME registry study. Ophthalmology. 2020;127(3): 377-393.

Wong TY, Lanzetta P, Bandello F, Eldem B, Navarro R, Lovestam-Adrian M, Loewenstein A. Current concepts and modalities for monitoring the fellow eye in neovascular age-related macular degeneration: An expert panel consensus. Retina. 2020;40(4): 599-611.

Leshno A, Stolovitch C, Barak A, Loewenstein A, Mezad-Koursh D. Pediatric Publication Trends in Leading GENERAL Ophthalmology Journals for 20 Years. J Pediatr Ophthalmol Stabismus. 2020;57(2): 78-84.

Kaur R, Singh H, Samira S, Kumar N, Parachuri N, Sharma R, Francesco B [sic], Loewenstein A, Bilongy Y, Hafees Faridi M, Sharma A. MII RetCam assisted smartphone-based fundus imaging (MSFI)-A boon for paediatric retinal imaging. Eye (Lond). 2020.

Busch C, Okada M, Zur D, Fraser-Bell S, Rodriguez-Valdes PJ, Cebeci Z, Lupidi M, Fung AT, Gabrielle PH, Giancipoli E, Chaikitmongkol V, Lains I, Santos AR, Kunavisarut P, Sala-Puigdollers A, Chhablani J, Ozimek M, Hilely A, Degenhardt V, Loewenstein A, Iglicki M, Rehak M; International Retinsa Group. Baseline predictors for visual acuity loss during observation in diabetic macular oedema with good baseline visual acuity. Acta Ophthalmol. 2020.

Sharma A, Parachuri N, Kumar N, Sharma R, Bandello F, Kuppermann BD, Loewenstein A. Brolucizumab-key learnings from HAWK and HARRIER. Eye (Lond). 2020.

Lankry P, Loewenstein A, Moisseiev E. Outcomes following laser retinopexy for retinal tears: a comparative study between trainees and specialists. Ophthalmologica. 2020.

Lanzetta P, Sarao V, Scanlon PH, Barratt J, Porta M, Bandello F, Loewenstein A, on behalf of the Vision Acdemy. Fundamental principles of an effective diabetic retinopathy screening program. Acta Diabetol. 2020.

Zur D, Frenkel S, Leshno A, Iglicki M, Ben-Artzi Cohen N, Khoury A, Martínez Cartier M, Barak A, Moroz I, Loewenstein A, Neudorfer M, Vishnevskia-Dai V. Subretinal fluid optical density and spectral-domain optical coherence tomography characteristics for the diagnosis of circumscribed choroidal hemangioma. Ophthalmologica. 2019;241(4):195-201.

Dugel PU, Campbell JH, Kiss S, Loewenstein A, Shih V, Xu X, Holekamp NM, Augustin AJ, Ho AC, Gonzalez VH, Whitcup SM. Association between early anatomic response to anti-vascular endothelial growth factor therapy and long-term outcome in diabetic macular edema: An independent analysis of Protocol I study data. Retina. 2019;39(1):88-97.

Benyamini S, Loewenstein A, Moisseiev E. Evaluation of accuracy and uniformity of the nomenclature of vitreoretinal interface disorders. Retina. 2019.

Sharma A, Parachuri N, Kumar N, Kuppermann BD, Bandello F, Loewenstein A, Regillo CD. Subfoveal neurosensory detachment flattening and observe (SNF-Ob): A novel approach in diabetic macular edema management: A Potential cost-effective treatment strategy to be explored. Ophthalmol Retina. 2019;3(11):1009-1011.

Iglicki M, Busch C, Loewenstein A, Fung AT, Invernizzi A, Mariussi M, Arias R, Gabrielle PH, Cebeci Z, Okada M, Nawrocki J, Michalewska Z, Goldstein M, Barak A, Zur D. Underdiagnosed optic disk pit maculopathy: Spectral domain optical coherence tomography features for accurate diagnosis. Retina. 2019;39(11):2161-2166.

Sharma A, Kumar N, Parachuri N, Sharma R, Bandello F, Kuppermann BD, Loewenstein A. Brolucizumab and immunogenicity. Eye (Lond). 2020.

Iglicki M, Zur D, Negri HP, Esteves J, Arias R, Holsman E, Loewenstein A, Busch C. Results in comparison between 30 gauge ultrathin wall and 27 gauge needle in sutureless intraocular lens flanged technique in diabetic patients: 24-month follow-up study. Acta Diabetol. 2020.

Sharma A, Parachuri N, Kumar N, Sharma R, Bandello F, Kuppermann BD, Loewenstein A. Brolucizumab-another anti-VEGF or beyond. Eye (Lond). 2020.

Korobelnik JF, Loewenstein A. Vision Academy. Communicating with patients with nAMD and their families during the COVID-19 pandemic. Version 2. Graefes Arch Clin Exp Ophthalmol. 2020; 258(6):1335-1337.

Sheth J, Anantharaman G, Kumar N, Parachuri N, Bandello F, Kuppermann BD, Loewenstein A, Sharma A. Pachydrusen: the epidemiology of pachydrusen and its relevance to progression of pachychoroid disease spectrum. Eye (Lond). 2020.

Korobelnik JF, Loewenstein A, Eldem B, Joussen AM, Koh A, Lambrou GN, Lanzetta P, Li X, Lövestam-Adrian M, Navarro R, Okada AA, Pearce I, Rodríguez FJ, Wong DT, Wu L. Guidance for anti-VEGF intravitreal injections during the COVID-19 pandemic. Version 2. Graefes Arch Clin Exp Ophthalmol. 2020 Jun;258(6):1149-1156.

Patil J, Patil L, Parachuri N, Kumar N, Bandello F, Kuppermann BD, Loewenstein A, Sharma A. Smartphone based ROP (S-ROP) screening-opportunities and challenges. Eye (Lond). 2020.

Iovino C, Au A, Chhablani J, Parameswarappa DC, Rasheed MA, Cennamo G, Cennamo G, Montorio D, Ho AC, Xu D, Querques G, Borrelli E, Sacconi R, Pichi F, Woodstock E, Sadda SR, Corradetti G, Boon CJF, van Dijk EHC, Loewenstein A, Zur D, Yoshimi S, Bailey Freund K, Peiretti E, Sarraf D. Choroidal anatomical alterations following photodynamic therapy for chronic central serous chorioretinopathy: a multicenter study. Am J Ophthalmol. 2020:S0002-9394(20)30190-2.

Au A, Hilely A, Scharf J, Gunnemann F, Wang D, Chehaibou I, Iovino C, Grondin C, Farecki ML, Falavarjani KG, Phasukkijwatana N, Battista M, Borrelli E, Sacconi R, Powell B, Hom G, Greenlee TE, Conti TF, Ledesma-Gil G, Teke MY, Choudhry N, Fung AT, Krivosic V, Baek J, Lee MY, Sugiura Y, Querques G, Peiretti E, Rosen R, Lee WK, Yannuzzi LA, Zur D, Loewenstein A, Pauleikhoff D, Singh R, Modi Y, Hubschman JP, Ip M, Sadda S, Freund KB, Sarraf D. Relationship between nerve fiber layer hemorrhages and outcomes in central retinal vein occlusion. Invest Ophthalmol Vis Sci. 2020;61(5):54.

Moisseiev E, **Loewenstein A**, Moshiri A, Yiu G. The management of retinal detachment: Techniques and perspectives. J Ophthalmol. 2017;2017:5807653.

Al-Khersan H, Hariprasad SM, Chhablani J; Dex Implant Study Group. Early response to intravitreal dexamethasone implant therapy in diabetic macular edema may predict visual outcome. Am J Ophthalmol. 2017;184:121-128.

Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, **Loewenstein A**; International Retina Group. Optical coherence tomography biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. Ophthalmology. 2017 Sep 19. pii: S0161-6420(17)32014-6.

Schwartz R, Rozenberg A, **Loewenstein A**, Goldstein M. The relation of somatotypes and stress response to central serous chorioretinopathy. Graefes Arch Clin Exp Ophthalmol. 2017255(12):2307-2315.

Zayit-Soudry S, Vainer I, Zemel E, Mimouni M, Rabena M, Pieramici DJ, Perlman I, **Loewenstein A**. Infliximab exerts a dose-dependent effect on retinal safety in the albino rabbit. Doc Ophthalmol. 2017;135(3):175-185.

Edri I, Goldenberg M, Lisnyansky M, Strulovich R, Newman H, **Loewenstein A**, Khananshvili D, Giladi M, Haitin Y. Overexpression and purification of human cis-prenyltransferase in Escherichia coli. J Vis Exp. 2017;(126).

Habot-Wilner Z, Mazza O, Shahar J, Massarweh A, Mann I, **Loewenstein A**, Perlman I. Safety of intravitreal clindamycin in albino rabbit eyes. Doc Ophthalmol. 2017;135(2):133-146.

Schwartz R, Habot-Wilner Z, Martinez MR, Nutman A, Goldenberg D, Cohen S, Shulman S, Guzner-Gur H, **Loewenstein A**, Goldstein M. Eplerenone for chronic central serous chorioretinopathy-a randomized controlled prospective study. Acta Ophthalmol. 2017;95(7):e610-e618.

Schwartz R, Goldstein M, **Loewenstein A**, Barak A. [Presentation of Ocular Problems Among Displaced Persons from Sudan and Eritrea at the Tel Aviv Medical Center]. Harefuah. 2017;156(1):19-21. Hebrew.

Lanzetta P, **Loewenstein A**; Vision Academy Steering Committee. Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases. Graefes Arch Clin Exp Ophthalmol. 2017;255(7):1259-1273.

Moisseiev E, **Loewenstein A**. Diabetic macular edema: Emerging strategies and treatment algorithms. Dev Ophthalmol. 2017;60:165-174.

Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, Jonas J, Larsen M, Tadayoni R, **Loewenstein A**. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237(4):185-222.

Fleissig E, Barak A, Goldstein M, **Loewenstein A**, Schwartz S. Massive subretinal and subretinal pigment epithelial hemorrhage displacement with perfluorocarbon liquid using a two-step vitrectomy technique. Graefes Arch Clin Exp Ophthalmol. 2017l;255(7):1341-1347.

Giladi M, Edri I, Goldenberg M, Newman H, Strulovich R, Khananshvili D, Haitin Y, **Loewenstein A**. Purification and characterization of human dehydrodolychil diphosphate synthase (DHDDS) overexpressed in E. coli. Protein Expr Purif. 2017;132:138-142.

Wolf S, Bandello F, **Loewenstein A**, Slakter J, Katz T, Sowade O, Korobelnik. Baseline Characteristics of the Fellow Eye in Patients with Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the VIEW Studies. Ophthalmologica. 2016; Jul 23. [Epub ahead of print

Chakravarthy U, Goldenberg D, Young G, Havilio M, Rafaeli O, Benyamini G, **Loewenstein A**. Automated Identification of Lesion Activity in Neovascular Age-Related Macular Degeneration. Ophthalmology. 2016;S0161-6420(16)30098-7.

de Carlo TE, Rosenblatt A, Goldestein M, Baumal CR, **Loewenstein A**, Duker JS. Vascularization of Irregular Retinal Pigment Epithelial Detachments in Chronic Serous Chorioretinopathy Evaluated with OCT Angiography. Ophthalmic Surg Laser Imaging Retina. 2016;47(2):128-33.

Moisseiev E, **Loewenstein A**, Yiu G. The suprachoroidal space: from potential space to a space with potential. Clin Ophthalol.2016;10:173-8.

Augustin AJ, Kupperman BD, Lanzetta P, **Loewenstein A**, Li X-Y, Cui H. Dexamethasone intravitreal implant in previously treated patients with diabetic macular edema: subgroup analysis of the MEAD study. BMC Ophthalmol.2015;15(1):150.

Moisseiev E, Katz G, Moisseiev J, **Loewenstein A**, Goldstein M, Lomnicky Y, Abend Y, Treister G, Goldenberg D, Levkovitch-Verbin H. Switching treatment for neovascular age-related macular degeneration from bevacizumab to ranibizumab: who is likely to benefit from the switch? Retina. 2015;35(7):1323-30.

Dugel PU, Bandellow F, **Loewenstein A**. Dexamethasone intravitreal implant in the treatment of diabetic macular. Clin Ophthalmol. 2015;9:1321-35

Adler G, Shahar J, Kesner R, Rosenfeld E, Fischer N, **Loewenstein A**, Kurtz S. Effect of Pupil Size on Biometry Measurements Using the IOLMaster. Am J Ophthalmol. 2015;159(5):940-4.

Moisseiev E, **Loewenstein A**. Simulation of Laser Retinopexy around Retinal Breaks for Ophthalmologists in Training. Ophthalmologica. 2015;233(1):51-5.

Frenkel T, Moisseiev E, Neudorfer M, **Loewenstein A**, Barak A. Comparison of retinal detachment surgery outcome among patients undergoing pars plana vitrectomy with and without relaxing retinotomy. Graefes Arch Clin Exp Ophthalmol. 2015;253(6)855-64.

Reviews

Nemet A, Moshiri A, Yiu G, **Loewenstein A**, Moisseiev E. A review of innovations in rhegmatogenous retinal detachment surgical techniques. J Ophthalmol. 2017;2017:4310643.

Moisseiev E, **Loewenstein A**. Drug delivery to the posterior segment of the eye. Dev Ophthalmol. 2017;58:87-101.

Bandello F, Battaglia Parodi M, Lanzetta P, **Loewenstein A**, Massin P, Menchini F, Veritti D. Diabetic macular edema. Dev Ophthalmol. 2017;58:102-138.

Zur D, **Loewenstein A**. Postsurgical cystoid macular edema. Dev Ophthalmol. 2017;58:178-190. 2017;58(1):15-17.

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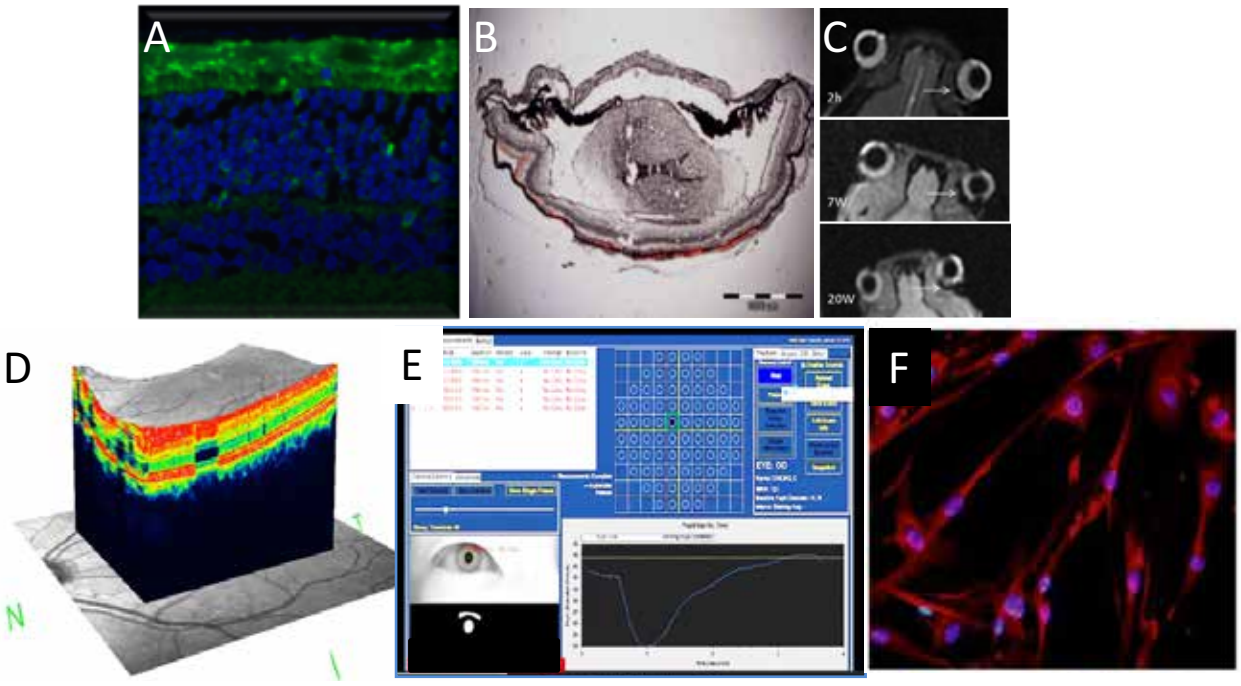

Immunofluorescence analysis (A), histopathology analysis (B) and MRI (C) for monitoring stem cell therapeutic effects in animal models. Multicolor OCT imaging (D) and chromatic multifocal pupilloperimetry (E) for objective structure & function clinical assessment. Nanotherapy for stem cell modulation (F).

Research

We lead basic science, translational medicine and clinical studies in an attempt to solve the unmet needs in neurodegenerative diseases in the eye and brain. The research focuses on clinical trials, basic science and translational medicine aimed at development of novel treatments and diagnostic tools for retinal degeneration and brain pathologies (such as Alzheimer disease and increased intracranial pressure) using a multidisciplinary approach in an attempt to discover treatments and develop drug delivery and diagnostic platforms for studying these leading incurable diseases.

Current research projects include:

- The eye as a window to the brain – using retinal structure and function measurements as novel early and objective biomarkers for brain neurodegeneration diseases (e.g. Alzheimer's disease and multiple sclerosis), brain injuries and brain tumors.

Publications

Meshi A, Belkin A, Koval T, Kornhouser T, Assia EI, **Rotenstreich Y**. An Experimental Treatment of Ocular Quinine Toxicity with High-Dose 9-cis Beta-Carotene. Retin Cases Brief Rep. 2015;9(2):157-61.

van Huet R.A.C, Siemiatkowska A.M, Özgul RK, Hoyng C.B, Banin E, Sharon D, **Rotenstreich Y**, Theelen T, Collin R.W.J. van den Born , Klevering B.J. Retinitis pigmentosa associated with the ciliary MAK gene is relatively mild and includes no syndromic features. Acta Ophthalmologica 2015;93(1):83-94.

Rotenstreich Y, Tzameret A, Kalish SE, Belkin M, Meir A, Treves AJ, Nagler A, Sher I. A novel system for minimally invasive transplantation of bone marrow derived stem cells as a thin layer in the subretina and extravascular spaces of the choroid for treatment of retinal degeneration. Harefua. 154(2):84-88.

Beiderman Y, Belkin M, **Rotenstreich Y**, Zalevsky Z. Experimental Quantification of the Tactile Spatial Responsivity of Human Cornea. J Med Imag. 2(1):016002.

Levy I, Sher I, Corem-Salkmon E, Ziv O, Meir A, Treves AJ, Nagler A, Kalter-Leibovici O, Margel S, **Rotenstreich Y**. Bioactive magnetic near Infra-Red fluorescent core-shell iron oxide/human serum albumin nanoparticles for controlled release of growth factors for augmentation of human mesenchymal stem cell growth and differentiation. J Nanobiotech. 13:34.

Tzameret A, Sher I, Belkin M, Treves AJ, Meir A, Nagler A, Levkovitch-Verbin H, **Rotenstreich Y***, Solomon AS*. (* Equal contribution, corresponding authors) Epiretinal transplantation of human bone marrow mesenchymal stem cells rescues retinal and vision function in a rat model of retinal degeneration. Stem Cell Res. 2015;15(2):387-94.

Chibel R, Sher I, BenNer D, Mahajna M, Achiron A, Haj-Yahia S, Skaat A, Berchenko Y, Oberman B, Kalter-Leibovici O, Freedman L, **Rotenstreich Y**. Chromatic multifocal pupillometer for objective perimetry and diagnosis of patients with Retinitis Pigmentosa. Ophthalmology. 2016 (123):1898-1911.

Rotenstreich Y, Tzameret A, Kalish SA, Bubis Ettel, Belkin M, Moroz I, Rosner M, Levy I, Margel S, Sher I. A minimally invasive adjustable-depth blunt injector for delivery of pharmaceuticals into the posterior pole. Acta Ophthalmologica. 2017;95(3):e197-e205.

Tzameret A, Kalish SA, Sher I, Meir A, Levy I, Margel S, Moroz I, Rosner M, Treves AJ, Nagler A, Belkin M, **Rotenstreich Y**. Long term-safety of transplantation of human bone-marrow mesenchymal stem cells in the extravascular spaces of the choroid of rabbits. Stem Cells International 2017:4061975.

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Research

Our primary research interests focuses on the use of Maccabi's large database to examine multiple dimensions of health care quality, including safety (e.g. adverse effects of IVF, renal effects of chronic medications), efficacy and effectiveness of healthcare technologies (e.g. glycemic control and outcomes in patients treated with new generation therapies for diabetes), medical and economic burden of chronic diseases and health events (e.g. congestive heart failure, hepatitis C infections) as well as pharmacoepidemiology studies such as medication adherence studies (e.g. tamoxifen in breasr cancer patients) and pleiotropic effects (e.g. statins). Our other interests include health effects of low dose ionizing radiation and specifically cancer and cataract.

Publications

Rabinowich L, Steinvil A, Leshem-Rubino E, Berliner S, Zeltser D, Rogowski O, Shalev V, Raz R, Chodick G. Adherence to Statins is associated with reduced incidence of idiopathic venous thromboembolism: real-life data from a large healthcare maintenance organization 8:1817-1821

Makov M, **Chodick G**, Mohnike K, Otonkoski T, Huopio H, Banerjee I, Cave H, Polak M, Christesen HT, Hussain K, Deleon D, Stanley C, Cappa M, Ramos O,Zangen D, Laron Z. Congenital hyperinsulinism, neonatal diabetes and the risk of malignancies: an international collaborative study. Preliminary communication. Diabetic Medicine 2015;32:701-3.

Sella T, Goren I, Shalev V, Shapira H, Zandbank J, Rosenblum J, Kimlin MG, **Chodick G** Incidence Trends of Keratinocytic Skin Cancers and Melanoma in Israel 2006-2011. British Journal of Dermatology 2015;172:202-7.

Peleg N, Zevit N, Shamir R, **Chodick G**, Levy I. Seasonal Influenza Vaccination Rates and Reasons for Non-vaccination in Children with Gastrointestinal Disorders. Vaccine 2015;33:182-6.

Moshe S, Izhaki R, **Chodick G**, Segal N, Yagev Y, Finestone AS, Juven Y. Predictors of return to work with upper limb disorders. Occupational Medicine (Lond). 2015;65:564-9.

Yu J, Goldshtein I, Shalev V, **Chodick G**, Ish-Shalom S, Sharon O, Modi A. Association of gastrointestinal events and osteoporosis treatment initiation in newly diagnosed osteoporotic Israeli women. International Journal of Clinical Practice 2015;69:1007-14.

Diamond G, Senecky Y, Reichman H, Inbar D, **Chodick G**. Parental perception of developmental vulnerability after inter-country adoption: a 10-year follow-up study: longitudinal study after inter-country adoption. International Journal Disability Human Development 2015; 14: 75–80.

Livni G, **Chodik G**, Yaari A, Tirosh N, Ashkenazi S. Attitudes, knowledge and factors related to acceptance of influenza vaccine by pediatric healthcare workers. Journal of Pediatric Infectious Diseases 2015;3:111–117.

Muhsen K, **Chodick G**, Goren S , Anis E , Ziv-Baran T , Shalev V, Cohen D. Change in incidence of clinic visits for all-cause and rotavirus gastroenteritis in

young children following the introduction of universal rotavirus vaccination in Israel. Eurosurveillance 2015;20.

Chodick G, Levin M, Kleinerman RA, Shwarz M, Shalev V, Ashkenazi S, Horev G. Differences in characteristics of pediatric patients undergoing computed tomography between hospitals and primary care settings: implications for assessing cancer follow-up studies. Israel Journal of Health Policy Research 2015;4:33.

Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schöttker B, Shankar A, Shlipak M, Tonelli M, Townend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Ärnlöv J; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514-525.

James MT, Grams ME, Woodward M, Elley CR, Green JA, Wheeler DC, de Jong P, Gansevoort RT, Levey AS, Warnock DG, Sarnak MJ; CKD Prognosis Consortium. A Meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney Injury. American Journal Kidney Diseases 2015;66:602-612.

Tunceli K, Goldshtein I , Yu S, Sharon O, Brodovicz K, Gadir N, Katzeff H, Voss B, Radican L, **Chodick G**, Shalev V, Maor Y, Karasik A. Adherence to treatment guidelines in Type 2 diabetes patients failing metformin monotherapy in a real-world setting. Diabetes Management 2015;5:17-2.

Goldshtein I, Chandler J, Shalev, V, Ish–Shalom, S, Nguyen, AM, Rouach V, **Chodick, G**. Osteoporosis in the community: findings from a novel computerized registry in a large health organization in Israel. Journal of Aging Research & Clinical Practice 2015;4:59-65.

Chodick G, Weitzman D, Shalev V, Weil C, Amital H. Adherence with statins and the risk of psoriasis: A population-based cohort study. British Journal of Dermatology 2015;173:480-7.

Zelber-Sagi S, Ben-Assuli O, Rabinowich L, Green M, Goldstein A, Magid A, Shalev V, Shibolet O, Chodick G. The association between serum levels of uric-acid and Alanine aminotransferase in a population-based cohort. Liver Internaional 2015;35:2408-15.

Nutman A, **Chodick G**, Shalev V. The potential effects of implementing the 2013 ACC/AHA cholesterol guidelines on the use of statins in a large health maintenance organization in Israel. Value in Health Regional Issues 2015;7:22-26.

Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, Chow EK, Kasiske BL, Kovesdy CP, Nadkarni GN, Shalev V, Segev DL, Coresh J, Lentine KL, Garg AX; Chronic Kidney Disease Prognosis Consortium. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. New England Journal of Medicine 2016;374:411-421.

Weil C, Nwankwo C, Friedman M, Kenet G, **Chodick G**, Shalev V. Epidemiology of hepatitis C virus infection in a large Israeli health maintenance organization. Journal of Medical Virology 2016;88:1044-50.

Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, Chodick G, Collins AJ, Djurdjev O, Elley CR, Evans M, Garg AX, Hallan SI, Inker LA, Ito S, Jee SH, Kovesdy CP, Kronenberg F, Heerspink HJ, Marks A, Nadkarni GN, Navaneethan SD, Nelson RG, Titze S, Sarnak MJ, Stengel B, Woodward M, Iseki K; CKD Prognosis Consortium. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. JAMA 2016; 315:164-74.

Sharman Moser S, Yu J, Goldshtein I, Ish-Shalom S, Rouach V, Shalev V, Modi A, **Chodick G**. Cost and Consequences of Nonadherence With Oral Bisphosphonate Therapy: Findings From a Real-World Data Analysis. Annals of Pharmacotherapy 2016;50:262-269.

Goldshtein I, Shalev V, Zigman N, **Chodick G**, Levkovitch-Verbin H. The Maccabi Glaucoma Study: Treatment Patterns and Persistence With Glaucoma Therapy in a Large Israeli Health Maintenance Organization. Journal of Glaucoma 2016;25:e386-91.

Chodick G, Sigurdson AJ, Kleinerman RA, Sklar CA, Leisenring W, Mertens AC, Stovall M, Smith SA, Weathers RE, Veiga LH, Robison LL, Inskip PD. The Risk of Cataract among Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study. Radiation Research 2016;185:366-374.

Kinar Y, Kalkstein N, Akiva P, Levin B, Half EE, Goldshtein I, **Chodick G**, Shalev V. Development and validation of a predictive model for detection of colorectal cancer in primary care by analysis of complete blood counts: a binational retrospective study. JAMIA 2016;0:1–12.

Goldstein D, **Chodick G**, Shalev V, Thorsted BL, Elliott L, Karasik A. Use of Healthcare Services Following Severe Hypoglycemia in Patients with

Diabetes: Analysis of Real-World Data. Diabetes Therapy 2016; 7:295–308.

Simon-Tuval T, Triki N, **Chodick G**, Greenberg D. The association between adherence to cardiovascular medications and healthcare utilization. European Journal of Health Economics 2016;17:603-10.

Ribitzky-Eisner H, Minuhin Y, Greenberg D, Greenberg N, **Chodick G**, Craiu M, Leibovitz E. Epidemiologic and microbiologic characteristics of occult Bacteremia among febrile children in Southern Israel, before and after initiation of the routine antipneumococcal immunization (2005-2012). Pediatric Neonatology 2015; S1875-9572:181-3.

Grams ME, Sang Y, Ballew SH, Gansevoort RT, Kimm H, Kovesdy CP, Naimark D, Oien C, Smith DH, Coresh J, Sarnak MJ, Stengel B, Tonelli M; CKD Prognosis Consortium. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury. Am J Kidney Dis. 2015;66(4):591-601.

Yu J, Goldshtein I, Shalev V, **Chodick G**, Ish-Shalom S, Sharon O, Modi A. Renal Impairment Among Postmenopausal Women With Osteoporosis From a Large Health Plan in Israel. Archives of Osteoporosis.

Goldshtein I, Karasik A, Melzer-Cohen C, Engel SS, Yu S, Sharon O, Brodovicz K, Gadir N , Katzeff HL, Radican L, **Chodick G**, Shalev V, Tunceli K. Urinary albumin excretion with sitagliptin compared to sulfonylurea as add on to metformin in type 2 diabetes patients with albuminuria: a real-world evidence study. Journal of Diabetes and Its Complications.

Goldshtein I, Rouach V, Yu J, **Chodick G**. Role of side effects, physician involvement and patient perception in non-adherence with oral Bisphosphonates. Advances in Therapy.

TavorM., Neufeld MY, **Chodick G**, Zack O, SlodownikD, Moshe S. Vocational factors which predict seizure prognosis in young adults during military service. Epilepsy & Behaviour.

Leibovitz E, David N, Ribitzky-Eisner H, Abo Madegam M, Abuabed S, **Chodick G**, Maimon M, Fruchtman Y. The Epidemiologic, Microbiologic and Clinical Picture of Bacteremia among Febrile Infants and Young Children Managed as Outpatients at the Emergency Room, before and after Initiation of the Routine Anti-Pneumococcal Immunization. International Journal of Environmental Research and Public Health.

Dankner R, Bachner YG, Ginsberg G, Ziv A, Ben David H, Litmanovitch-Goldstein D, **Chodick G**, Balicer RD, Tanne D, Greenberg D. Correlates of well-being among caregivers of long-term community-dwelling stroke Survivors. International Journal of Rehabilitation Research.

Scheuerman O, Barkai G, Mandelboim M, Mishali H, **Chodick G**, Levy I. Human metapneumovirus (hMPV) Infection in immunocompromised children. Journal of Clinical Virology.

Livni, G, Wainstein A, Birk E, **Chodick G**, Levy I. Influenza vaccine, cardiac disease, attitude, vaccination rate. The Pediatric Infectious Disease Journal.

Ben Ami N, Mirovsky Y, **Chodick G**, Shapiro Y. Improving Self-Reported Function and Pain in Chronic Low Back Pain patients: A “Real Life” randomized Control trial. Journal of Orthopaedic & Sports Physical Therapy.

Moshe S, Cinamon T, Zack O, Segal N**, Chodick G**, Krakov A, Tal M.The need for social work services in occupational medicine.Occupational Medicine.

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Biological Monitoring Using Micro and Nano-Sized Particles Distribution Measurement in Biological Samples to Early Detect Health Impairment in Environmental and Occupational Lung Settings

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Research

The "ultrafine hypothesis" suggests that smaller particles are more potent than larger particles at driving inflammation; leading to the initial proposal that respiratory ill health was associated with the number of ambient ultrafine particles. When first introduced in 1994, the "ultrafine hypothesis" met friendly skepticism, with opponents arguing that NSP (nano-sized particles) are very short-lived and disappear through heterogeneous and homogeneous aggregation within seconds or minutes and therefore are toxicologically irrelevant. This skeptical attitude has changed considerably. Research teams across the world are now working now on NSP, and there are multidisciplinary alliances among atmospheric scientists, epidemiologists, clinicians, and toxicologists, among others. Nonetheless, substantial research gaps continue to prevail. Most of the initial assessments of particulate burden and involvement

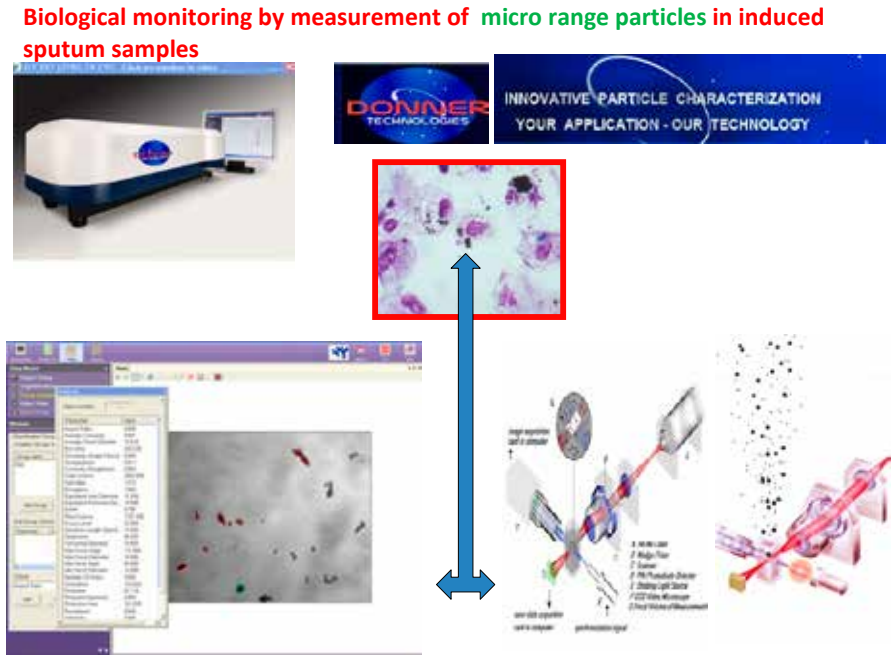

Figure 1

C: Biological monitoring by measuring ultrafine/nano ranged particles in induced sputum samples (MsC thesis of Iris Szwarcfiter)

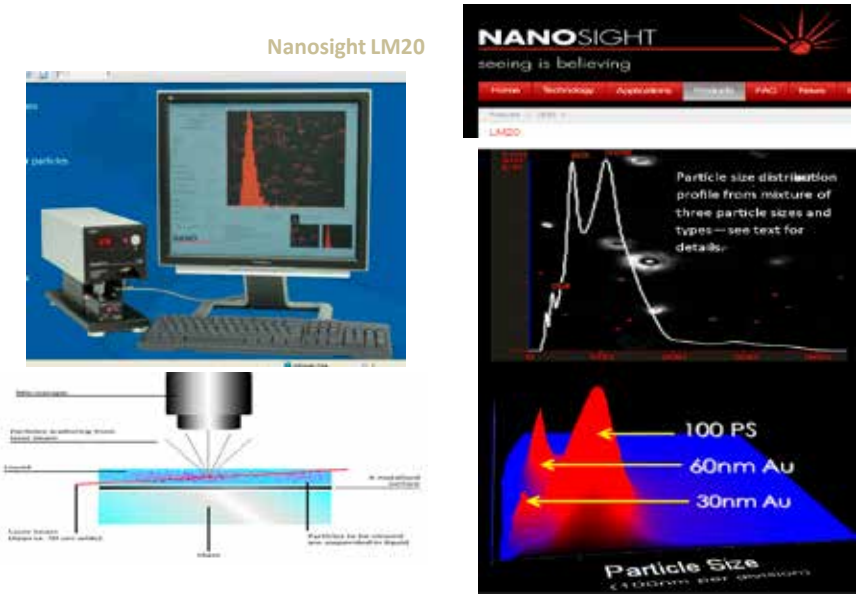

Figure 2

of inflammatory and structural cells in occupational lung diseases were made in studies using fibreoptic bronchoscopy in conjunction with bronchoalveolar lavage (BAL). The relative invasiveness of this technique, however, has restricted the use of bronchoscopy to a limited number of specialised centres, and hampered its development into a practical and suitable tool for screening programmes, exposure evaluation or repeated follow-up of workers exposed to hazardous dust in large populations.

The ongoing search for non-invasive techniques has led to a number of development approaches, such as the examination of cells, quantification of biochemical mediators, and characterization of particulate matter in samples of induced sputum (IS) as well as the quantification of biochemical mediators and characterization of particulate matter in the condensation of exhaled breath exhaled breath condensate (EBC). In the last years, we have concentrated our research on the application of these techniques in occupational and environmental exposures:

- *Particle size distribution (PSD) and dynamic shape characterization (DSC):* The size and shape of the particles will be assessed from the rich cell fraction of the processed plugs with the Eyetech Analyzer and the analyzer's video channel (Donner Technologies, Israel) using a PSD method in the range of 0.5-3,600 based on the time of transition theory where the duration of interaction between beam and particle provides a direct measurement of each particle's size (Fig 1).
- *NSP measurement.* The size and shape of the ultrafine particles ($PM_{0.1}$) are assessed from the rich cell fraction of the processed plugs in the IS sample and the EBC sample, with the NanoSight LM20 using the Nanoparticle Tracking Analysis (NTA) method of visualizing and analyzing particles in liquids that relates the rate of Brownian motion to particle size. The rate of movement is related only to the viscosity of the liquid, the temperature and the size of the particle and is not influenced by particle density or refractive index (Fig 2).

We studied several populations: Workers exposed to hazardous dust at the Israel World Trade Center (WTC), dust-exposed firefighters in the USA ten months after the WTC disaster, dental technicians exposed to beryllium (funded by the Binational Science Foundation BSF 2007-2011), workers exposed to artificial stone dust and asthmatic children in the Tel Aviv area. Our ongoing research is on the field that characterize the mineral compositions of these particles and their biological effect.

Publications

Elalouf O, **Fireman E**, Levartovsky D, Kaufman I, Ori Rogovski O, Ori Elkayam E, Caspi D, Paran D. Decreased diffusion capacity on lung function testing in asymptomatic patients with Systemic Lupus Erythematosus does not predict future lung disease. Lupus 2015.

Benor S, Alcalay Y, Armoni Domany K, Gut G, Soferman S, Kivity S, **E. Fireman** · Ultrafine particle content in exhaled breath condensate in airways of asthmatic children. Submitted to Journal of Breath Research 2015;9(2).

Nirel R, Maimon N, **Fireman E**, Agami S, Eyal A, Peretz A. Respiratory hospitalizations of children living near a hazardous industrial site adjusted for prevalent dust: a case-control study. Int J Hyg Environ Health. 2015;218(2):273-9.

Shtraichman Osnat; Blanc Paul; Ollech Jacob; Fridel Lodmila; Fuks, Leonardo; **E. Fireman,** Kramer Mordechai. Outbreak of autoimmune disease in a silicosis cluster linked to high-silica content artificial stone. Occupational Medicine 2015.

Bar-Shai A, Alcalay Y, Adi Sagiv, A Rotem M, Alon R, and **Fireman E**. Fingerprint of endogenous lung fluid ultra-fine-particles, a novel marker of acute lung inflammation. Respirology 2015.

Fireman-Klein E, Man A, Schwartz Y, **Fireman E.** IGRA guided regulation of prophylactic treatment for latent tuberculosis in Israel. IMAJ. 2015;17(7):405-9.

Lavi A, Potchter O, Omer I, **Fireman E**. Mapping air pollution by biological monitoring in the Tel-Aviv metropolitan area. Int J Environ Health Res 2015:1-15.

Ophir N., Bar Shai A, Alkalay Y, Israeli S, Korenstein R, Krermer M, **Fireman E.** Artificial stone dust-induced functional and inflammatory abnormalities in exposed workers monitored quantitatively by biometrics. ERJ Research. 2016 2:86.

Fireman E, Alcalay Y, Ophir N, Kivity S, Stejskal V Identification of metal sensitization in sarcoid-like metal-exposed patients by the MELISA® lymphocyte proliferation test — a pilot study. Journal of Occupational Medicine and Toxicology. 2016 2: 00086

Litinsky I, **Fireman E**, Paran D, Polachek A, Broide A, Sharabi A, Anouk M, Elkayam O. Induced sputum analysis in subjects with systemic sclerosis. Respir Care. 2016;61(10):1369-73.

Grubstein A, Shtraichman O, **Fireman E**, Bachar GN, Noach-Ophir N, Kramer MR. Radiological evaluation of artificial stone silicosis outbreak: emphasizing findings in lung transplant recipients. J Comput Assist Tomogr. 2016;40(6):923-927

Ophir N, Shai AB, Alkalay Y, Israeli S, Korenstein R, Kramer MR, **Fireman E.** Artificial stone dust-induced functional and inflammatory abnormalities in exposed workers monitored quantitatively by biometrics. ERJ Open Res. 2016.

Survival following lung transplantation for artificial stone silicosis relative to idiopathic pulmonary fibrosis. Rosengarten D, Fox BD, **Fireman E**, Blanc PD, Rusanov V, Fruchter O, Raviv Y, Shtraichman O, Saute M, Kramer MR. Am J Ind Med. 2017;60(3):248-254

Differential pattern of deposition of nanoparticles in the airways of exposed workers. **Fireman E**, Edelheit R, Stark M, Shai AB**.** J Nanopart Res. 2017;19(2):30.

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Using Medical Databases for Personalized Medicine

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Research

The emergence of precision medicine technologies has allowed medical scientists to address complex questions which necessitate very large datasets and patients' numbers. Unlike traditional methods such as randomized trials, the richness of very large sets of data enables more rapid advance toward personalized medicine. At the Maccabi Institute for Research & Innovation, we utilize large real-world databases to investigate clinical issues for better provision of care and improved outcomes. In addition to traditional and pragmatical clinical trials, we condocut multiple observational analysis using advanced data platform to enable data science studies based on Maccabi's database of 2.5M members' medical files. One example for personalized medicine is our newly developed method for identifying individuals at increased risk of harboring colorectal cancer by analyzing their complete blood counts records. We have developed a computational model using a large derivation dataset of over 450 000 Israeli individuals and validated it on 2 separate and independent datasets of primary care patients, consisting of over 139 000 Israeli and over 25 500 UK individuals. Our approach applies novel methods both in feature generation (where we use a set of linear models to handle sparse and irregular measurements along time) and in model construction (where we combined 2 tree-based models – RF and Gradient Boosting). We showed that our approach can detect 50% of CRC cases 3–6 months before diagnosis at 88% specificity in the Israeli dataset and 94% specificity in the UK dataset. The system is already successfully implemented in routine practice at Maccabi.

Publications

Sella T, Goren I, **Shalev V**, Shapira H, Zandbank J, Rosenblum J, Kimlin MG, Chodick G. Incidence Trends of Keratinocytic Skin Cancers and Melanoma in Israel 2006-2011. British Journal of Dermatology 2015;172:202-7.

Endevelt R, Goren I, Sela T, **Shalev V**.Family history intake: a challenge to personalized approaches in health promotion and disease prevention.Isr J Health Policy Res. 2015;4:60.

Yu J, Goldshtein I, **Shalev V**, Chodick G, Ish-Shalom S, Sharon O, Modi A. Association of gastrointestinal events and osteoporosis treatment initiation in newly diagnosed osteoporotic Israeli women. Int J Clin Pract. 2015;69:1007-14.

Muhsen K, Chodick G, Goren S , Anis E , Ziv-Baran T , **Shalev V**, Cohen D. Change in incidence of clinic visits for all-cause and rotavirus gastroenteritis in young children following the introduction of universal rotavirus vaccination in Israel. Eurosurveillance 2015;20

Giladi O, Steinberg DM, Peleg K, Tanne D, Givon A, Grossman E, Klein Y, Avigdori S, Greenberg G, Katz R, **Shalev V**, Salomon O.Head trauma is the major risk factor for cerebral sinus-vein thrombosis. Thromb Res. 2016;137:26-9.

Chodick G, Levin M, Kleinerman RA, Shwarz M, **Shalev V**, Ashkenazi S, Horev G. Differences in characteristics of pediatric patients undergoing computed tomography between hospitals and primary care settings: implications for assessing cancer follow-up studies. Isr J Health Policy Res. 2015;4:33.

Tunceli K, Goldshtein I , Yu S, Sharon O, Brodovicz K, Gadir N, Katzeff H, Voss B, Radican L, Chodick G, **Shalev V**, Maor Y, Karasik A. Adherence to treatment guidelines in Type 2 diabetes patients failing metformin monotherapy in a real-world setting. Diabetes Management 2015;5:17-24.

Goldshtein I, Chandler J, **Shalev V**, Ish–Shalom, S, Nguyen, AM, Rouach V, Chodick, G. Osteoporosis in the community: findings from a novel computerized registry in a large health organization in Israel. J Aging Res Clin Practice 2015;4:59-65.

Chodick G, Weitzman D, **Shalev V**, Weil C, Amital H. Adherence with statins and the risk of psoriasis: A population-based cohort study. British Journal of Dermatology 2015;173:480-7.

Zelber-Sagi S, Ben-Assuli O, Rabinowich L, Green M, Goldstein A, Magid A, **Shalev V**, Shibolet O, Chodick G. The association between serum levels of uric-acid and Alanine aminotransferase in a population-based cohort. Liver Int. 2015;35:2408-15.

Nutman A, Chodick G, **Shalev V**. The potential effects of implementing the 2013 ACC/AHA cholesterol guidelines on the use of statins in a large health maintenance organization in Israel. Value in Health Regional Issues 2015;7:22-26.

Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, Chow EK, Kasiske BL, Kovesdy CP, Nadkarni GN, **Shalev V**, Segev DL, Coresh J, Lentine KL, Garg AX; Chronic Kidney Disease Prognosis Consortium. Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med. 2016;374:411-421.

Weil C, Nwankwo C, Friedman M, Kenet G, Chodick G, **Shalev V**. Epidemiology of hepatitis C virus infection in a large Israeli health maintenance organization. J Med Virol. 2016;88:1044-50.

Sharman Moser S, Yu J, Goldshtein I, Ish-Shalom S, Rouach V, **Shalev V**, Modi A, Chodick G. Cost and Consequences of Nonadherence With Oral Bisphosphonate Therapy: Findings From a Real-World Data Analysis. Ann Pharmacother. 2016;50:262-269

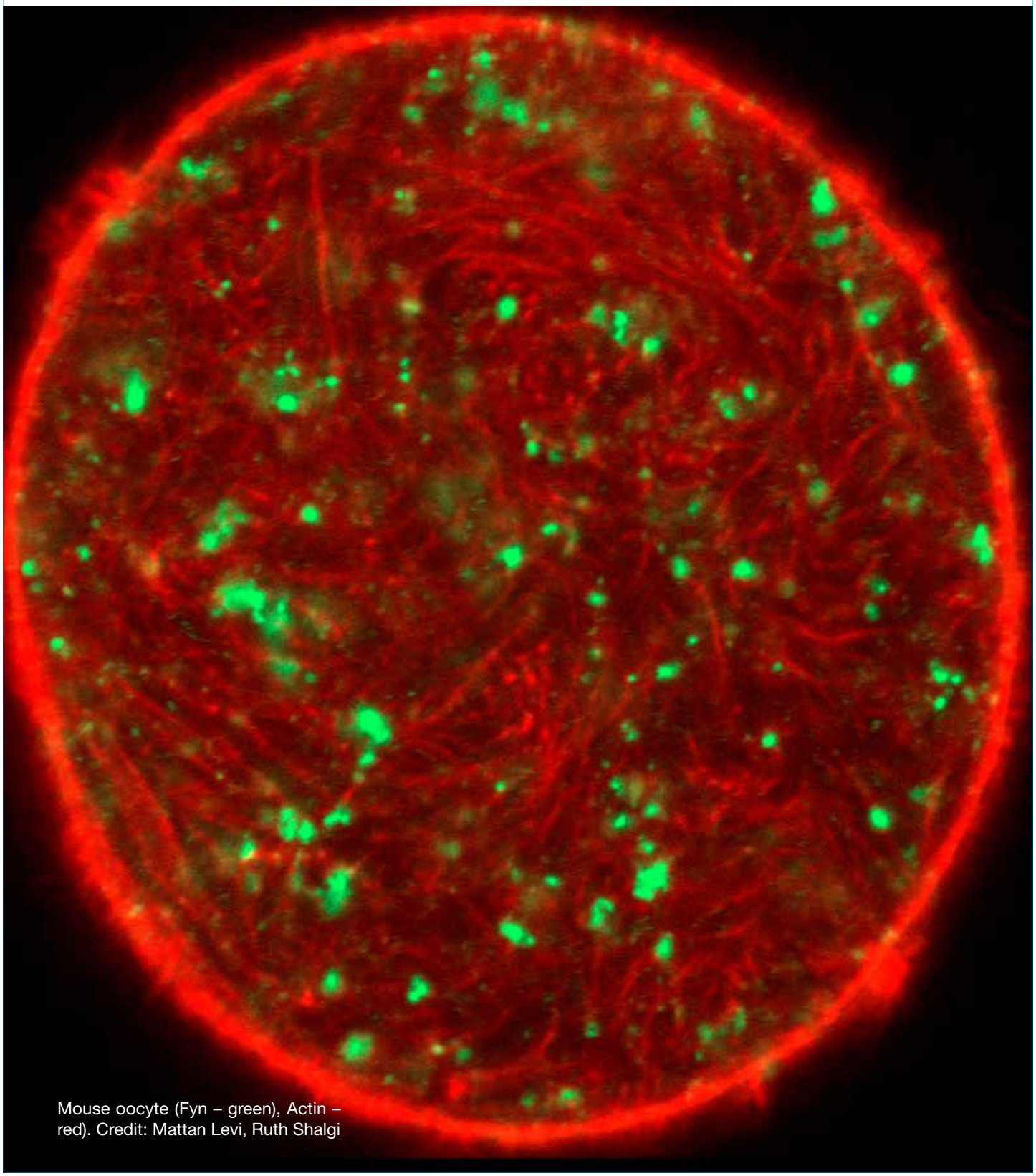
Goldshtein I, **Shalev V**, Zigman N, Chodick G, Levkovitch-Verbin H. The Maccabi Glaucoma Study: Treatment Patterns and Persistence With Glaucoma Therapy in a Large Israeli Health Maintenance Organization. J Glaucoma. 2016;25:e386-91.

Kinar Y, Kalkstein N, Akiva P, Levin B, Half EE, Goldshtein I, Chodick G, **Shalev V**. Development and validation of a predictive model for detection of colorectal cancer in primary care by analysis of complete blood counts: a binational retrospective study. J Am Med Inform Assoc. 2016;0:1–12

Goldstein D, Chodick G, **Shalev V**, Thorsted BL, Elliott L, Karasik A. Use of Healthcare Services Following Severe Hypoglycemia in Patients with Diabetes: Analysis of Real-World Data. Diabetes Therapy

Yu J, Goldshtein I, **Shalev V**, Chodick G, Ish-Shalom S, Sharon O, Modi A. Renal Impairment Among Postmenopausal Women With Osteoporosis From a Large Health Plan in Israel. Archives of Osteoporosis Archives of Osteoporosis 2015;10:

Reproduction



Mouse oocyte (Fyn – green), Actin – red). Credit: Mattan Levi, Ruth Shalgi

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Folliculogenesis and Ovulation in the Human Ovary – Fertility Treatments and Control

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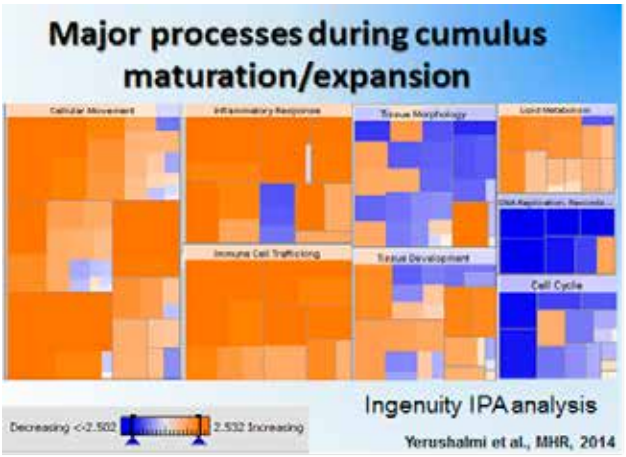
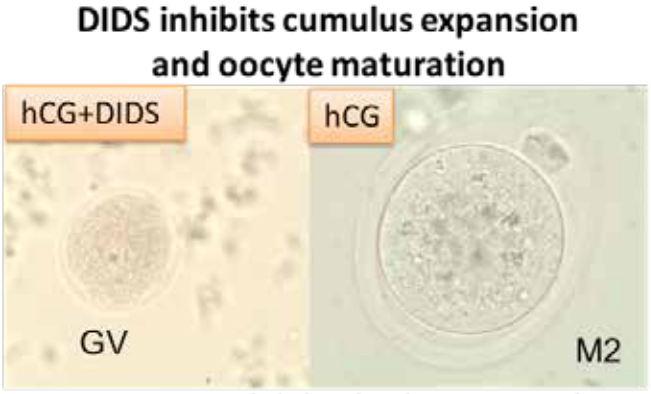
Research

Our laboratory's aim is the molecular characterization of the ovulatory cascade in the human ovary. We undertook to systematically identify novel ovulation-associated genes. Differentially expressed candidate genes (n = 1746) were identified by comparing the transcriptome of cumulus granulosa cells from compact pre-ovulatory germinal vesicle (GV) cumulus oocyte complexes with those of expanded post-ovulatory Metaphase II COCs. We assumed that differentially expressed genes likely serve as regulators of ovulation, cumulus expansion, and/or oocyte maturation. To complete the identification of factors involved in the ovulatory process, we generated a library of global miRNAs involved in this process, and by bioinformatics tools link the ovulatory miRNA library with the mRNA library. The bioinformatics analysis enables us to identify new regulatory mechanisms responsible for the oocyte maturation process and ovulation.

The resulting database provides unprecedented insight into the processes and pathways involved in follicular maturation and ovulation. This effort led us to identify and characterize several new genes involved in the human ovulatory process such as sFRP4, ADAMTS-1, Decorin and Lumican. Recently, prompted by the observation that prostaglandin transporter (PGT) constitutes a highly expressed peri-ovulatory transcript, we set out to investigate the physiological role of this key transporter protein in the ovulatory process. We were able to show that PGT is an indispensable mediator of ovulation, the inhibitors of which may constitute potential novel candidates for non-hormonal contraception (Science Translational Medicine, 2016).

These studies will contribute significantly to the understanding of the complex process of ovulation in





Yerushalmi et al., Science Trans Med, 2016

human which is central to the reproductive processes. The implications of improved understanding of this process may contribute to further development of strategies for in vitro maturation of oocytes and follicles, improve IVF success rates especially in difficult clinical conditions. Genes that their expression levels correlate with oocytes clinical outcome can be future markers for oocyte quality and selection. Elucidating new human ovulatory genes may contribute to our understanding of infertility conditions such as anovulation, and development of novel strategies for fertility control.

Publications

Haas J, Zilberberg E, Machtinger R, Kedem A, **Hourvitz A**, Orvieto R. Do poor-responder patients benefit from increasing the daily gonadotropin dose during controlled ovarian hyperstimulation for IVF? Gynecol Endocrinol. 2015;31(1):79-82.

Lande Y, Seidman DS, Maman E, Baum M, **Hourvitz A.** Why do couples discontinue unlimited free IVF treatments? Gynecol Endocrinol. 2015;31(3):233-6.

Hourvitz A, Yerushalmi GM, Maman E, Raanani H, Elizur S, Brengauz M, Orvieto R, Dor J, Meirow D. Combination of ovarian tissue harvesting and immature oocyte collection for fertility preservation increases preservation yield. Reprod Biomed Online. 2015;31(4):497-505.

Sapoznik S, Bahar-Shany K, Brand H, Pinto Y, Gabay O, Glick-Saar E, Dor C, Zadok O, Barshack I, Zundelevich A, Gal-Yam EN, Yung Y, **Hourvitz A,** Korach J, Beiner M, Jacob J, Levanon EY, Barak M, Aviel-Ronen S, Levanon K. Activation-Induced Cytidine Deaminase Links Ovulation-Induced Inflammation and Serous Carcinogenesis. Neoplasia. 2016;18(2):90-9.

Gil M. Yerushalmi*, Svetlana Markman*, Yuval Yung, Ettie Maman, Sarit Aviel-Ronen, Raoul Orvieto, Eli Y. Adashi, and **Hourvitz A.** The prostaglandin transporter (PGT) as a potential mediator of ovulation. Science Translational Medicine. 2016;8(338):338ra68.

Abdallah Mansur, Michal Adir, Gil Yerushalmi, **Hourvitz A,** Hila Gitterman, Yuval Yung, Raoul Orvieto, Ronit Machtinger. Does BPA Alter Steroid Hormone Synthesis in Human Granulosa Cells In Vitro? Human Reproduction. 2016;31(7):1562-9.

Jigal Haas, Libby Ophir, Eran Barzilay, Ronit Machtinger, Yuval Yung, Raoul Orvieto*, **Hourvitz A*.** Standard hCG vs. double trigger for final oocyte maturation results in different granulosa cells gene expressions. Fertil Steril. 2016;106(3):653-659.

Haas J, Barzilay E, **Hourvitz A,** Dor J, Lipitz S, Yinon Y, Shlomi M, Shulman A. Outcome of early versus late multifetal pregnancy reduction. Reprod Biomed Online. 2016. pii: S1472-6483(16)30463-1.

Lerner-Geva L, Boyko V, Ehrlich S, Mashiach S, **Hourvitz A,** Haas J, Margalioth E, Levran D, Calderon I, Orvieto R, Ellenbogen A, Meyerovitch J, Ron-El R, Farhi A. Possible risk for cancer among children born following assisted reproductive technology in Israel. Pediatr Blood Cancer. 2016.

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Research

Our research center is specialized in fertility preservation. We have a fully equipped basic research laboratory, together with a large clinical database with a significant number of incoming patients. This makes our research center unique for high quality basic research with clinical relevancy. Our research focuses on:

- Ovarian follicle research and the biological clock.
- Cryopreservation / transplantation of ovarian tissue and IVF.
- The effects of toxic agents and chemotherapy on reproduction and gametes.
- Modalities and agents that protect the gametes and prevent toxic damage.
- Genetic injury to the gametes.
- Methods 6to detect cancer cells in tissue.
- Endometrial receptivity.
- Interpreting cancer patients' information regarding endocrine, reproductive and psychological effects.

Publications

Meirow D, Ra'anani H, Shapira M, et al (2016). Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril. 106(2):467-74.

Roness H, Kashi O, **Meirow D** (2016). Prevention of chemotherapy-induced ovarian damage. Fertil Steril. 105(1):20-9.

Carrillo L, Seidman DS, Cittadini E, **Meirow D** (2016). The role of fertility preservation in patients with endometriosis. J Assist Reprod Genet;33(3):317-23.

Meirow D, Roness H, Kristensen SG, Andersen CY (2015). Optimizing outcomes from ovarian tissue cryopreservation and transplantation; activation versus preservation. Hum Reprod. 30(11):2453-6

Shapira M, Raanani H, **Meirow D** et al (2015). BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 104(5):1162-7.

Perri T, **Meirow D**, Ben-Baruch G, Korach J et al (2015). Fertility treatments and invasive epithelial ovarian cancer risk in Jewish Israeli BRCA1 or BRCA2 mutation carriers. Fertil Steril. 103(5):1305-12.

Gavish Z, Roness H, **Meirow D** et al (2015). Follicle activation and 'burn-out' contribute to post-transplantation follicle loss in ovarian tissue grafts: the effect of graft thickness. Hum Reprod. 30(4):1003.

Stem Cells & Regenerative Medicine

An artist's view of how single-cell clones represented by a specific color emerge during kidney development, maintenance, and regeneration. Credit: Dekel Lab, Pediatric Stem Cell Research Institute, Sheba Medical Center.

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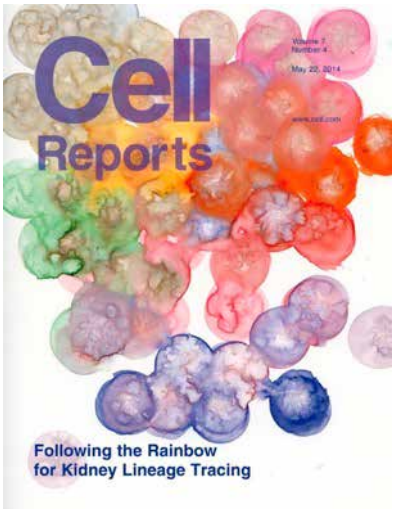
Member, American Society of Clinical Investigation

President, Israel Stem Cell Society



The cover illustration shows how single-cell clones emerge during development, maintenance, and repair to generate a multicolored kidney. *Dekel and colleagues* report that continued growth of the mammalian kidney in adulthood is performed by lineage-restricted clonal progeny that continuously add new epithelial cells to each segment of the kidney and are responsive to Wnt signaling. Lineage-restricted progenitors are also observed in development after renal epithelial induction and during acute renal injury. Rainbow mice, which express one of four alternative fluorescent reporters in each cell, allow genetic lineage tracing of individual clones.

Research

Our laboratory takes a multi-disciplinary approach including genetics, genomics, molecular biology, biochemistry, and the development of preclinical human-mouse models to cast light on fundamental problems of kidney developmental biology, tissue regeneration, and cancer; while, at the same time, holding promise for novel disease therapies. Our central hypothesis is that *normal and transformed tissue stem cells* drive these processes and therefore we aim to discover such cells and study their molecular mechanisms. In the field of human kidney development and pediatric renal cancer (Wilms tumor), we have pioneered the identification and isolation of normal and malignant renal stem/progenitor cells and have shown how these novel cell types are of relevance to human disease; on one hand utilization of the normal stem cells in tissue repair and regeneration and on the other hand development of targeted therapy against cancer stem cells and tumor eradication. These bench discoveries have been fundamental to translation to bedside; our approach for tumor stem cell eradication has already sparked a multicenter clinical trial for the treatment of patients with relapsing Wilms' tumors.

Publications

Accompanying Focus Article: The Stem and Roots of Wilms Tumor, http://dx.doi.org/10.1002/emmm.201202173.

Schlingmann KP, Ruminska J, Kaufmann M, Dursun I, Patti M, Kranz B, Pronicka E, Ciara E, Akcay T, Bulus D, Cornelissen EA, Gawlik A, Sikora P, Patzer L, Galiano M, Boyadzhiev V, Dumic M, Vivante A, Kleta R, **Dekel B**, Levtchenko E, Bindels RJ, Rust S, Forster IC, Hernando N, Jones G, Wagner CA, Konrad M. Autosomal-Recessive Mutations in SLC34A1 Encoding Sodium-Phosphate Cotransporter 2A

Cause Idiopathic Infantile Hypercalcemia. J Am Soc Nephrol. 2016 Feb;27(2):604-14.89.

Romagnani P, Rinkevich Y, **Dekel B**. Current lineage tracing methods to study kidney regeneration, their limitations and advantages. Nat Rev Nephrol. 2015;11(7):420-31

Sanyal M, Morimoto M, Baradaran-Heravi A, Choi K, Kambham N, Jensen K, Dutt S, Dionis-Petersen KY, Liu LX, Felix K, Mayfield C, **Dekel B**, Bokenkamp A, Fryssira H, Guillen-Navarro E, Lama G, Brugnara M, Lücke T, Olney AH, Hunley TE, Polat AI, Yis U, Bogdanovic R, Mitrovic K, Berry S, Najera L, Najafian B, Gentile M, Nur Semerci C, Tsimaratos M, Lewis DB, Boerkoel CF. Lack of IL7Rα expression in T cells is a hallmark of T-cell immunodeficiency in Schimke immuno-osseous dysplasia (SIOD). Clin Immunol. 2015 Oct 21;161(2):355-365.

Pode-Shakked N, Pleniceanu O, Gershon R, Shukrun R, Kanter I, Bucris E, Pode-Shakked B, Tam G, Tam H, Caspi R, Pri-Chen S, Vax E, Katz G, Omer D, Harari-Steinberg O, Kalisky T, **Dekel B**. Dissecting Stages of Human Kidney Development and Tumorigenesis with Surface Markers Affords Simple Prospective Purification of Nephron Stem Cells. Sci Rep. 2016;6:23562.

Gilboa Y, Perlman S, Pode-Shakked N, Pode-Shakked B, Shrim A, Azaria-Lahav E, **Dekel B**, Yonath H, Berkenstadt M, Achiron R. Prenatal diagnosis of 17q12 deletion syndrome: from fetal hyperechogenic kidneys to high risk for autism. Prenat Diagn. 2016 36(11):1027-1032.

Perlman S, Lotan D, **Dekel B**, Kivilevitch Z, Hazan Y, Achiron R, Gilboa Y. Prenatal compensatory renal growth in unilateral renal agenesis. Prenat Diagn. 2016;36(11):1075-1080.

Pleniceanu O, Shukrun R, Omer D, Vax E, Pode-Shakked N, Alfandari H, Kanter I, Kalisky T, Vard-Bloom N, Nagler A, Harari-Steinberg O, Arbiser J, **Dekel B**. PPARκ is central to initiation and propagation of human angiomyolipoma suggesting its potential as a therapeutic target. EMBO Mol Med 2017, In Press.

Reviews and chapters

Pleancianu O, **Dekel B**. Book chapter: Renal Stem Cells in Oxford Textbook of Clinical Nephrology (4th edition, Chief Ed. Neil Turner). Oxford University Press 2015.

Pleancianu O, Dziedzic K, **Dekel B**. From embryonic rudiments to renal stem/progenitor cells in Kidney Development, Disease, Repair and Regeneration, 1st Edition (Ed. Little MH). Elsevier 2015.

Dekel B. The ever expanding kidney repair shop (Invited Editorial). J Am Soc Nephrol. J Am Soc Nephrol. 2016;27(6):1579-8

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Laboratory for the Research of Skin Disease

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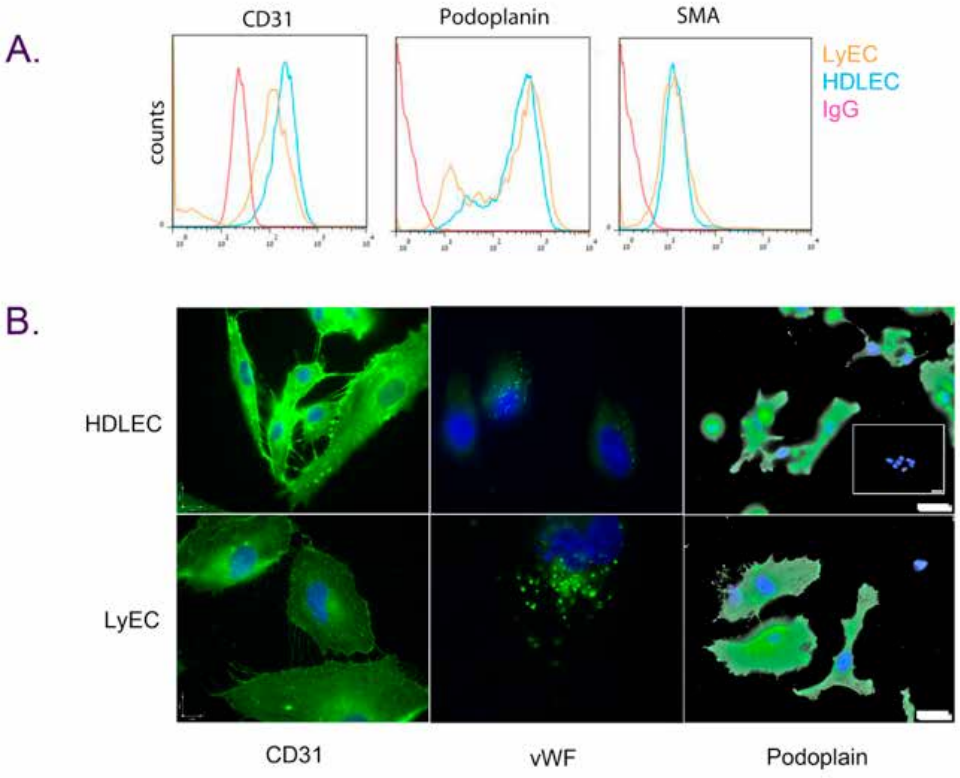
Lab aMnager

Dr. Gil Leichner Ph.D.

Research

We study skin diseases with a focus on angiogenesis and lymphangiogenesis. Deficiency in development or function of the vascular or lymphatic vasculature causes various anomalies in humans, and active angiogenesis and lymphangiogenesis play a significant role in tumor metastasis. The presence of vascular anomalies can cause emotional and social problems. Moreover, some malformations are painful or even life-endangering. Current treatments for these diseases do not achieve optimal results. The goal of my research is to isolate and characterize the endothelial cells, the major cellular component of the vascular malformations in order to develop targeted therapy for these lesions. We apply cutting-edge technologies including molecular biology, and microarray analysis to characterize the molecular paths that regulate the endothelium development. Other areas studied in the lab are editing in psoriasis and Cutaneous graft versus host disease



Isolation and characterization of endothelial cells from lymphatic malformations. FACS (A) and immunofluorescence analyses shows pure lymphatic endothelium phenotype with reduced expression of the differentiation marker CD31.

Publications

Jacoby E, Barzilai A, Laufer J, Pade S, Anikster Y, Pinhas-Hamiel O, **Greenberger S**. Neonatal Hyperpigmentation – Diagnosis of Familial Glucocorticoid Deficiency with a Novel Mutation in MC2R. Pediatr Dermatol**.** Accepted for publication

Vodo D, Sarig O, Peled A, Frydman M, **Greenberger S**, Sprecher E. Autosomal dominant cutis laxa resulting from an intronic mutation in ELN. Exp Dermatol. 2015.

Keidan I, Ben-Menachem E, **Greenberger S**. Safety of extravasated sodium bicarbonate. Resuscitation. 2015.

Helfand AM, Nouriel A, Zisquit J, Barzilai A, **Greenberger S**. Segmental neurofibromatosis presenting with congenital excessive skin folds. Dermatol Pract Concept. 2015;5(2):105-7

Oz-Levi D, Weiss B, Lahad A, **Greenberger S**, Pode-Shakked B, Somech R, Olender T, Tatarsky P, Marek-Yagel D, Pras E, Anikster Y, Lancet D. . Exome sequencing as a differential diagnosis tool: resolving mild trichohepatoenteric syndrome. Clin Genet. 2015;87(6):602-3.

Golan T, Messer AR, Amitai-Lange A, Melamed Z, Ohana R, Bell RE, Kapitansky O, Lerman G, **Greenberger S**, Khaled M, Amar N, Albrengues J, Gaggioli C, Gonen P, Tabach Y, Sprinzak D, Shalom-Feuerstein R, Levy C. Interactions of Melanoma Cells with Distal Keratinocytes Trigger Metastasis via Notch Signaling Inhibition of MITF. Mol Cell. 2015;59(4):664-76.

Unusual forms of cutaneous leishmaniasis due to Leishmania major. Solomon M, **Greenberger S**, Baum S, Pavlotsky F, Barzilai A, Schwartz E. J Eur Acad Dermatol Venereol. 2016;30(7):1171-5.

Dror S, Sander L, Schwartz H, Sheinboim D, Barzilai A, Dishon Y, Apcher S, Golan T, **Greenberger S**, Barshack I, Malcov H, Zilberberg A, Levin L, Nessling M, Friedmann Y, Igras V, Barzilay O, Vaknine H, Brenner R, Zinger A, Schroeder A, Gonen P, Khaled M, Erez N, Hoheisel JD, Levy C. Melanoma miRNA trafficking controls tumour primary niche formation. Nat Cell Biol. 2016;18(9):1006-17.

Zafrir Y, Baum S, **Greenberger S**, Lyakhovitsky A, Barzilai A. Alopecia Areata. Harefuah. 2016;155(10):622-625.

Schachter O, Perla D, **Greenberger S,** Barzilai A, Baum S. Traditional Chinese medicine in treatment of atopic dermatitis. Harefuah. 2016;155(10):596-599.

Shreberk-Hassidim R, Neumark M, **Greenberger S,** Goldstein G, Hassidim A, Dukler Y, Maly A, Stepensky P, Molho-Pessach V. Cutaneous chronic graft versus host disease following allogeneic haematopoietic stem cell transplantation in children: A retrospective study. Acta Derm Venereol. 2017; 98(2):206-211.

Cohen H, Barash H, Meivar-Levy I, Molakandov K, Ben-Shimon M, Gurevich M, Zoabi F, Har-Zahav A, Gebhardt R, Gaunitz F, Gurevich M, Mor E, Ravassard P, **Greenberger S**, Ferber S. The Wnt/B-catenin pathway determines the predisposition- and the efficiency of liver to pancreas reprogramming. Hepatology 2018; 68(4):1589-1603.

Manevitz-Mendelson E, Leichner GS, Barel O, Davidi-Avrahami I, Strasser Ziv L, Eyal E, Pessach I, Rimon U, Barzilai A, Hirshberg A, Chechekes K, Amariglio N, Rechavi G, Yaniv K, **Greenberger S**. Somatic NRAS mutation in patient with Generalized Lymphatic Anomaly. Angiogenesis 2018; 21(2):287-298.

Shallev L, Kopel E, Feiglin A, Leichner GS, Avni D, Sidi Y, Eisenberg E, Barzilai A, Levanon EY, **Greenberger S**. Decreased A-to-I RNA editing as a source of keratinocytes' dsRNA in psoriasis. RNA. 2018; 24(6): 828–840.

Taieb Y, Baum S, Ben Amitai D, Barzilai A, **Greenberger S**. The use of methotrexate for treating childhood atopic dermatitis: A multicenter retrospective study. J Dermatolog Treat. 2018; 30(3):240-244.

Meivar-Levy I, Zoabi F, Nardini G, Manevitz-Mendelson E, Leichner GS, Zadok O, Gurevich M, Mor E, Dima S, Popescu I, Barzilai A, Ferber S, **Greenberger S.** The role of the vasculature niche on insulin-producing cells generated by transdifferentiation of adult human liver cells. Stem Cell Res Ther. 2019; 10(1):53.

Greenberger S, Landov H, Confino Y, Vaknine H, Avivi C, Baum S, Barzilai A. Immunophenotype of pediatric-onset mastocytosis does not correlate with clinical course. Pediatr Dermatol. 2019; 36(4):477-481.

Frizinsky S, Rechavi E, Barel O, Najeeb RH, **Greenberger S**, Lee YN, Simon AJ, Lev A, Ma CA, Sun G, Blackstone SA, Milner JD, Somech R, Stauber T. Novel MALT1 mutation linked to immunodeficiency, immune dysregulation, and an abnormal T cell receptor repertoire. J Clin Immunol. 2019; 39(4):401-413.

Barkai G, Stauber T, Somech R, **Greenberger S.** Bacille Calmette-Guerin (BCG) complication in severe combined immunodeficiency deficiency

(SCID) children – a case series. Infect Dis (Lond). 2019;51(8):585-592.

Levy-Shraga Y, Barel O, Javasky E, Barzilai A, **Greenberger S**. Neonatal osteoma cutis due to a mutation in GNAS. Pediatr Dermatol. 2019; 36(5):732-734.

Sandbank S, Molho-Pessach V, Farkas A, Barzilai A, **Greenberger S**. Oral and topical sirolimus for vascular anomalies: a multicentre study and review. Acta Derm Venereol. 2019; 99(11):990-996.

Tirosh I, Spielman S, Barel O, Ram R, Stauber T, Paret G, Rubinsthein M, Pessach I, Gerstein M, Anikster Y, Shukrun R, Dagan A, Adler K, Pode-Shakked B, Volkov A, Perelman M, Greenberger S, Somech R, Lahav E Majmundar A, Padeh S, Hildebrandt F, Vivante A. Whole

exome sequencing in childhood onset lupus frequently detects single gene etiologies. Pediatr Rheumatol Online J. 2019;17(1):52.

Maoz K, **Greenberger S**, Maly A, Merims S, Tirosh I, Barzilai A, Molho-Pessach V. Subcutaneous granuloma annulare mimicking dermatomyositis. Pediatr Dermatol. 2020. 82(6):1535-1537.

Gabrielli S, Le M, Netchiporouk E, Miedzybrodzki B, Baum S, **Greenberger S**, Staubach-Renz P, Ben-Shoshan M. Chronic urticaria in children can be controlled effectively with updosing second-generation antihistamines. J Am Acad Dermatol. 2020; 82(6):1535-1537.

Ben Mordehai Y, Faibish H, Astman N, **Greenberger S**, Barzilai A, Baum S. Characteristics of patients with bullous pemphigoid: comparison of classic bullous pemphigoid to non-bullous pemphigoid. J Eur Acad Dermatol Venereol. 2020;34(1):161-165.

Maoz K, **Greenberger S***, Maly A, Merims S, Tirosh I, Barzilai A, Molho-Pessach V. *equal contribution. Subcutaneous granuloma annulare mimicking dermatomyositis. Pediatr Dermatol. 2020. *equal contribution

Gabrielli S, Le M, Netchiporouk E, Miedzybrodzki B, Baum S, **Greenberger S**, Staubach-Renz P, Ben-Shoshan M. Chronic urticaria in children can be controlled effectively with updosing second-generation antihistamines. J Am Acad Dermatol. 2020.

Atias Z, Pederson JM, Mishra HK, **Greenberger S**. The effect of natural matrix biopolymer membrane on hard-to-heal venous leg ulcers: a pilot randomized clinical trial. J Wound Care. 2020;29(5):295-302.

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Positions

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Research

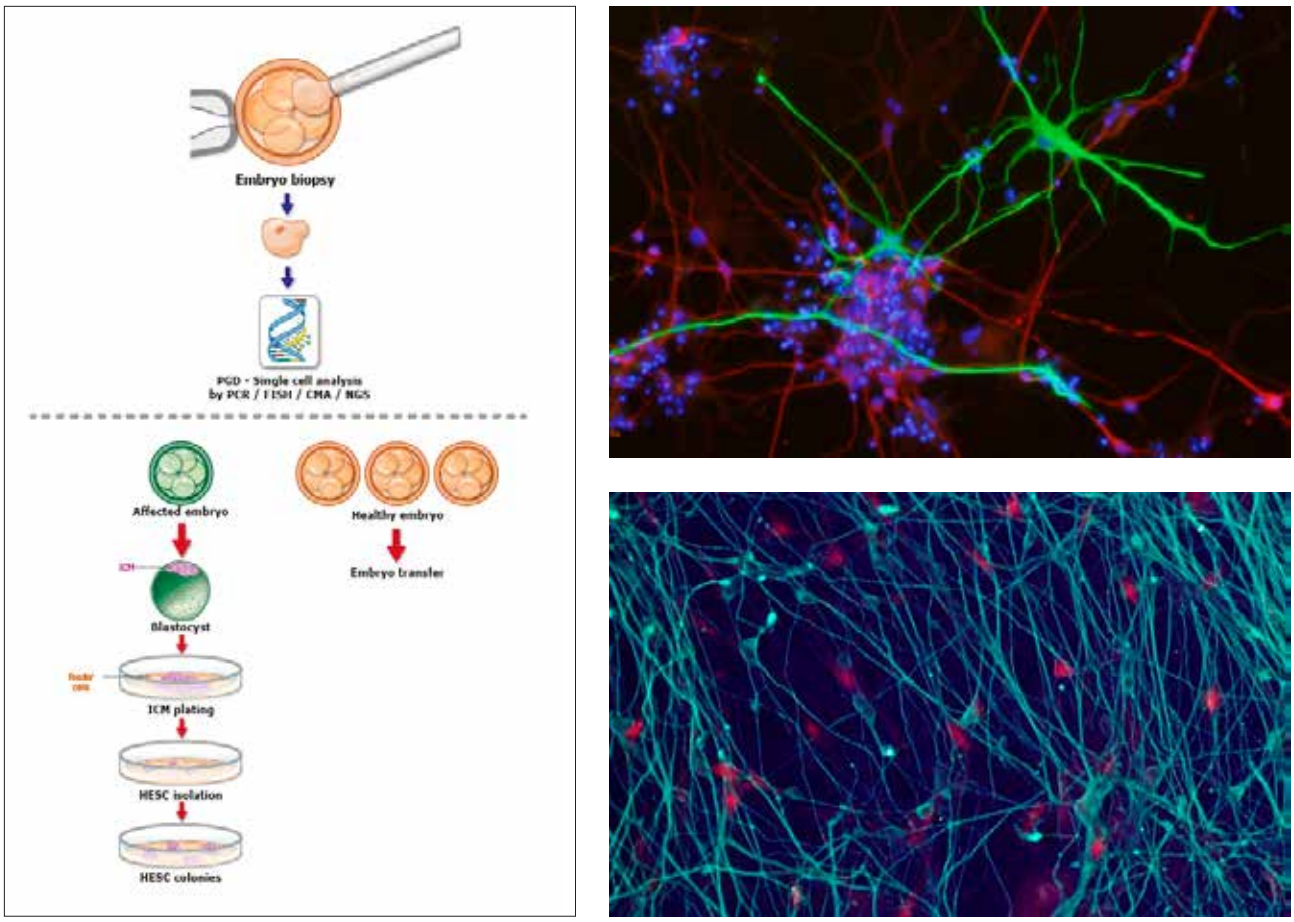
The Wolfe PGD-Stem Cell Lab focuses on studying issues related to early embryonic and developmental processes, genetic disorders and different aspects of cell therapy using our unique collection of PGD-derived human embryonic stem cells (hESCs).

We derive hESCs directly from affected embryos, which are obtained as a by-product of the preimplantation genetic diagnosis (PGD) procedure. PGD is performed for couples at high risk of transmitting a genetic defect and who wish to ensure the birth of a healthy child. It requires in vitro fertilization (IVF), which makes the pre-implantation embryos available for biopsy and single-cell molecular analysis. Following IVF-PGD, embryos diagnosed as being disease-free are transferred into the uterus for implantation, whereas the affected embryos that would be otherwise discarded are used to establish hESC lines that carry the naturally inherited mutations. This setup provides the benefit of efficient coordination between the generously donated affected embryos and the stem cell lab that focuses on researching these very unique samples. By means of these capabilities, we have already established >50 mutant hESC lines associated with 18 different inherited disorders.

These lines make it possible for us to study the molecular and pathophysiological mechanisms underlying the genetic disease of which they were diagnosed. In addition, since we have a large collection of hESC lines derived under the same conditions, we are able to perform different studies on the pluripotent, genetic and epigenetic properties of these cells.

Publications

Telias, M., and **Ben-Yosef, D**. (2015). Neural stem cell replacement: a possible therapy for



Left: HESCs are derived from PGD embryos affected by genetic disorders. Right: Neurons derived from HESCs: A. Neurons (MAP2, red) and glia (GFAP, green) from fragile X HESCs at day 128 of differentiation. B, C Neurons (Tuj1, green) from normal HESCs express FMRP (red) throughout differentiation (B, C: early and late differentiation, respectively). D. Neurons (Tuj1, green) created by transcription factor induced directed differentiation silence FMRP (red) by day 14 (Tuj1neg rat astrocyte feeder cells are labeled; whereas Tuj1pos HESC derived neurons are not).

neurodevelopmental disorders? Neural Regen Res *10*, 180-182.

Telias, M., Kuznitsov-Yanovsky, L., Segal, M., and **Ben-Yosef, D**. (2015). Functional Deficiencies in Fragile X Neurons Derived from Human Embryonic Stem Cells. J Neurosci *35*, 15295-15306.

Telias, M., Mayshar, Y., Amit, A., and **Ben-Yosef, D**. (2015). Molecular mechanisms regulating impaired neurogenesis of fragile X syndrome human embryonic stem cells. Stem Cells Dev *24*, 2353-2365.

Shpiz, A., Kalma, Y., Frumkin, T., Telias, M., Carmon, A., Amit, A., and **Ben-Yosef**, **D**. (2015). Human embryonic stem cells carrying an unbalanced translocation demonstrate impaired differentiation into trophoblasts: an in vitro model of human implantation failure. Mol Hum Reprod *21*, 271-280.

Shpiz, A., **Ben-Yosef, D**., and Kalma, Y. (2016). Impaired function of trophoblast cells derived from translocated hESCs may explain pregnancy loss in women with balanced translocation (11;22). J Assist Reprod Genet *33*, 1493-1499.

Bar-El, L., Kalma, Y., Malcov, M., Schwartz, T., Raviv, S., Cohen, T., Amir, H., Cohen, Y., Reches, A., Amit, A., and **Ben-Yosef, D**. (2016). Blastomere biopsy for PGD delays embryo compaction and blastulation: a time-lapse microscopic analysis. J Assist Reprod Genet *33*, 1449-1457.

Telias, M., Segal, M., and **Ben-Yosef, D**. (2016). Immature Responses to GABA in Fragile X Neurons Derived from Human Embryonic Stem Cells. Front Cell Neurosci *10*, 121.

Yedid, N., Kalma, Y., Malcov, M., Amit, A., Kariv, R., Caspi, M., Rosin-Arbesfeld, R., and **Ben-Yosef, D**. (2016). The effect of a germline mutation in the APC gene on beta-catenin in human embryonic stem cells. BMC Cancer *16*, 952.

Malcov M, Gold V, Peleg S, Frumkin T, Azem F, Amit A, **Ben-Yosef D**, Yaron Y, Reches A, Barda S, Kleiman SE, Yogev L, Hauser R. Improving preimplantation

genetic diagnosis (PGD) reliability by selection of sperm donor with the most informative haplotype. Reproductive Biology and Endocrinology; 15(1):31 2017.

Frumkin T, Peleg S, Gold V, Reches A, Asaf S, Azem F, **Ben-Yosef D**, Malcov M. Complex chromosomal rearrangement-a lesson learned from PGS. J. Assisted Reproduction and Genetics, 2017

Kalma Y, Bar-El L, Asaf-Tisser S, Malcov M, Reches A, Hasson J, Amir Azem F, **Ben-Yosef D**. Optimal timing for blastomere biopsy of 8-cell embryos for preimplantation genetic diagnosis. Hum. Reprod. 2017

Frumkin T, Peleg S, Gold V, Reches A, Asaf S, Azem F, **Ben-Yosef D**, Malcov M. Complex chromosomal rearrangement-a lesson learned from PGS. J Assist Reprod Genet. 2017

Renal System

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Optimazing Graft Survival in Patients after Kidney Transplantation

Positions

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Research

Kidney transplantation is the treatment of choice for patients with end stage kidney disease (ESKD). However long-term survival of kidney allograf is suboptimal with only minimal improvement during the last years. In our research we try to find the optimal immunosuppression that will minimize immunological insult to the kidney allograft as well as the risk of infection malignancy and cardiovascular disease. We focus on the blood level of tacrolimus, the potent component of the immunosuppressant regimen. We use statistical and mathematical tools to optimize the treatment for each patient in order to get maximal graft survival with minimal complications. We also try to evaluate the risk factors for post-transplant complication in order to impliments appropriate preventive measures to minimize the risk. Our study aims are to find clinical and molecular characteristics the will able us to implement personalized Madison for each patient with maximal graft survival and minimal complications rate.

Publications

Boas H, Mor E, Michowitz R, **Rozen-Zvi B**, Rahamimov R. The impact of the israeli transplantation law on the socio-demographic profile of living kidney donors. Am J Transplant. 2015 Apr;15(4):1076-80.

Lichtenberg S, Korzets A, Zingerman B, GreenH, Erman A, Gafter U, **Rozen- Zvi B**. An intradialytic increase in serum interleukin-6 levels is associated with an increased mortality in hemodialysis patients. Int J Artif Organs. 2015;38(5):237-43.

Zingerman B, Herman-Edelstein M, Erman A, Bar Sheshet Itach S, Ori Y, **Rozen-Zvi B**, Gafter U, Chagnac A. Effect of acetazolamide on obesity-induced glomerular hyperfiltration: A randomized controlled trial. PLoS One, 2015;10(9):e0137163.

Shepshelovich D, Leibovitch C, Klein A, Zoldan S, Milo G, Shochat T, **Rozen-Avi B**, Gafter-Gvili A, Lahav M. The syndrome of inappropriate antidiuretic hormone secretion: Distribution and characterization according to etiologies. Eur J Intern Med. 2015;26(10):819-24.

Shepshelovich D, Leibovitch C, Klein A, Zoldan S, Shochat T, Green H, **Rozen-Zvi B**, Lahav M, Gafter-Gvili A. Yield of workup for patients with idiopathic presentation of the syndrome of inappropriate antidiuretic hormone secretion. Eur J Intern Med. 2016;32:60-4.

Goldvaser H, **Rozen-Zvi B**, Yerushalmi R, Gafter-Gvili A, Lahav M, Shepshelovich D. Malignancy Associated SIADH: Characterization and Clinical Implications. Acta Oncol. 2016;55(9-10):1190-1195.

Shepshelovich D, **Rozen-Zvi B**, Avni T, Gafter U, Gafter-Gvili, A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. Am J Kidney Dis. 2016.

Rozen-Zvi B, Lichtenberg S, Green H, Cohen O, Chagnac A, Mor E, Rahamimov R. Cytomegalovirus-negative kidney transplant recipients are at an increased risk for malignancy after kidney transplantation. Clin Transplant. 2016;30(9):980-5.

Shepshelovich D, Yelin D, Bach LO, Halevy N, Ziv Y, Green H, **Rozen-Zvi B**, Ben-Zvi H, Bishara J, Gafter-Gvili A, Yahav D. Chills during hemodialysis: Prediction and prevalence of bacterial infections - A retrospective cohort study. Am J Med. 2017;130(4):477-481

Rozen-Zvi B, Schneider S, Lichtenberg S, Green H, Cohen O, Gafter U, Chagnac A, Mor E,

Rahamimov R. Association of the combination of time-weighted variability of tacrolimus blood level and exposure to low drug levels with graft survival after kidney transplantation. Nephrol Dial Transplant. 2017;32(2):393-399.

Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, **Rozen-Zvi B**, Gafter-Gvili A. Medication-induced SIADH: distribution and characterization according to medication class. Br J Clin Pharmacol. 2017;83(8):1801-1807.

Lichtenberg S, Rahamimov R, Green H, Fox BD, Mor E, Gafter U, Chagnac A, **Rozen-Zvi B**. The incidence of post-transplant cancer among kidney transplant recipients is associated with the level of tacrolimus exposure during the first year after transplantation. Eur J Clin Pharmacol. 2017;73(7):819-826.

Green H, Lichtenberg S, Rahamimov R, Livneh A, Chagnac A, Mor E, **Rozen-Zvi B**. Familial Mediterranean fever is associated with increased mortality after kidney transplantation - A 19 years' single center experience. Transplantation 2017;101(10):2621-2626.

Shimon O, Green H, Eliakim-Raz N, **Rozen-Zvi B**, Ben-Zvi H, Zohar I, Bishara J, Yahav D. Gram-negative bloodstream infections in hemodialysis patients: A retrospective study. Clin Nephrol. 2018;90(2):117-124.

Steinmetz T, Witberg G, Chagnac A, Green H, Sagie A, **Rozen-Zvi B**, Kornowski R. Transcatheter aortic valve implantation versus conservative treatment in chronic kidney disease patients. EuroIntervention. 2018;14(5):e503-e510.

Diker-Cohen T, **Rozen-Zvi B**, Yelin D, Akirov A, Robenshtok E, Gafter-Gvili A, Shepshelovich D. Endocrinopathy-induced euvolemic hyponatremia. Intern Emerg Med. 2018;13(5):679-688.

van Dijk TY, Rahamimov R, Chagnac A, van Dijk DJ, Mor E, Shlomai A, **Rozen-Zvi B**. The effect of cause, timing, kidney function recovery, and recurrent events on the prognosis of acute kidney injury in kidney transplant recipients. Clin Transplant. 2018;32(10):e13398.

Rahamimov R, Tifti-Orbach H, Zingerman B, Green H, Schneider S, Chagnac A, Mor E, Fox BD, **Rozen-Zvi B**. Reduction of exposure to tacrolimus trough levels variability is associated with better graft survival after kidney transplantation, Eur J Clin Pharmacol. 2019;75(7):951-958.

Schechter A, Gafter-Gvili A, Shepshelovich D, Rahamimov R, Gafter U, Mor E, Chagnac A, **Rozen-Zvi B**. Post Renal Transplant Anemia: Severity, Causes and their association with graft and patient survival. BMC Nephrol. 2019;20(1):51

Green H, Nesher E, Aizner S, Israeli M, Klein T, Zakai H, Rahamimov R, **Rozen-Zvi B**, Mor E. Long-term results of desensitization protocol with and without rituximab in sensitized kidney transplant recipients. Clin Transplant. 2019;33(6):e13562.

39. Frenkel Rutenberg T, Bdeir A, **Rozen-Zvi B**, Rosenthal Y, Velkes S, Weiss A, Beloosesky Y. Rate and outcome of acute kidney injury following hip fracture surgery in diabetic older patients treated with renin-angiotensin-aldosterone antagonists. Drugs Aging. 2019;36(7):667-674.

Shepshelovich D, Tau N, Green H, **Rozen-Zvi B**, Issaschar A, Falcone M, Coussement J, Zusman O, Manuel O, Mor E, Torre-Cisneros J, Yahav D. Immunosuppression reduction in liver and kidney transplant recipients with suspected bacterial infection: A multinational survey. Transpl Infect Dis. 2019:e13134.

Yahav D, Sulimani O, Green H, Margalit I, Ben-Zvi H, Mor E, **Rozen-Zvi B**. Immunosuppression reduction in kidney transplant recipients during bacterial infection-A retrospective study. Clin Transplant. 2019:e13707.

Rahamimov R, van Dijk TY, Molcho M, Vahav I, Mor E, Ben Dor N, Goldman S, **Rozen-Zvi B**. Acute Kidney Injury and Long-Term Risk for Cardiovascular Events in Patients after Kidney Transplantation. Kidney Blood Press Res. 2019;19:1-9.

Edel Y, Avni T, Shepshelovich D, Reich S, **Rozen-Zvi B**, Elbaz M, Leibovici L, Molad Y, Gafter-Gvili A. The safety of pulse corticosteroid therapy-Systematic review and meta-analysis. Semin Arthritis Rheum. 2020;50(3):534-545.

Molcho M, **Rozen-Zvi B**, Shteinmats T, Ben Dor N, Vahav I, Nesher E, Rahamimov R. Temporal changes of proteinuria after kidney transplantation: association with cardiovascular morbidity and mortality. J Nephrol. 2020.

Amitai I, Rozovski U, El-Saleh R, Shimony S, Shepshelovich D, **Rozen-Zvi B**, Raanani P, Gafter-Gvili A, Gurion R. Risk factors for high-dose methotrexate associated acute kidney injury in patients with hematological malignancies. Hematol Oncol. 2020.

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