

Sackler Faculty of Medicine Preclinical Research 2018

Sections

Cancer and Molecular Therapies	7
Cardiovascular Research and Diseases	35
Dental Health and Medicine	48
Diabetes, Metabolic and Endocrine Diseases	57
Genomics & Personalized Medicine	73
Hearing, Language & Speech Sciences and Disorders	93
Infectious Diseases	113
Inflammatory and Autoimmune Diseases	129
Medical Education and Ethics	137
Nervous System and Brain Disorders	142
Nursing, Occupational and Physical Therapy	185
Public Health	220
Reproduction, Development and Evolution	239
Stem Cells and Regenerative Medicine	255

Cover images (from bottom left, clockwise):

Image 1: Human embryonic stem cell derived cardiomyocytes stained with fluorescent antibodies. The cardiac marker alpha-actinin (green), calcium channel modulator, Ahnak1 (red) – Shimrit Oz, Nathan Dascal.

Image 2: Islet of Langerhans containing insulin-producing beta-cells (green) and glucagon-producing alpha-cells (red) – Daria Baer, Limor Landsman.

Image 3: β -catenin in *C. elegans* vulva – Michal Caspi, Limor Broday, Rina Rosin-Arbesfeld.

Image 4: Stereocilia of a sensory outer hair cell from a mouse inner ear – Shaked Shivatzki, Karen Avraham.

Image 5: Electron scanning micrograph of middle ear ossicles from a mouse ear stained with pseudo colors – Shaked Shivatzki, Karen Avraham.

Image 6: Resistin-like molecule alpha (red), eosinophil major basic protein (green) and DAPI (blue) staining of asthmatic mice – Danielle Karo-Atar, Ariel Munitz.

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 Preclinical 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 limited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians in 181 Sackler 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, Professor Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Meir Lahav, Prof. Ami Fishman, and Assistant to the Dean, Ms. Michal Gilboa.

Table of Contents

Cancer and Molecular Therapies	7
Dr. Yaron Carmi, Ph.D.	8
Prof. Neta Erez, Ph.D.	10
Prof. Zvi Fishelson, Ph.D.	12
Prof. Tamar Geiger, Ph.D.	14
Prof. Shai Israeli, M.D.	17
Prof. Yona Keisari, Ph.D.	21
Prof. Rafi Korenstein, Ph.D.	23
Prof. Rina Rosin-Arbesfeld, Ph.D.	25
Prof. Ronit Satchi-Fainaro, Ph.D.	27
Prof. Yosef Shiloh, Ph.D.	31
Prof. Ilan Tsarfaty, Ph.D.	33
Cardiovascular Research and Diseases	35
Prof. Bernard Attali, Ph.D.	36
Prof. Nathan Dascal, Ph.D.	38
Dr. Michal Katz-Leurer, Ph.D.	40
Prof. Daniel Khananshvili, Ph.D.	42
Prof. Jonathan Leor, M.D.	45
Dental Health and Medicine	48
Dr. Lihi Adler-Abramovich, Ph.D.	49
Prof. Tamar Brosh, Ph.D.	52
Prof. Ilana Eli, D.M.D.	54
Dr. Rachel Sarig, Ph.D., D.M.D.	55
Diabetes, Metabolic and Endocrine Diseases	57
Prof. Shimon Efrat, Ph.D.	58
Prof. Koret Hirschberg, Ph.D.	60
Dr. Limor Landsman, Ph.D.	62
Prof. Drorit Neumann, Ph.D.	64
Prof. Edgar Pick, M.D., Ph.D.	66
Prof. Haim Werner, Ph.D.	68
Prof. Efrat Wertheimer, MD., PhD.	71
Genomics & Personalized Medicine	73
Prof. Gil Ast, Ph.D.	74
Prof. Karen B. Avraham, Ph.D.	76
Dr. Ran Elkon, Ph.D.	79
Prof. David Gurwitz, Ph.D.	80
Prof. Carmit Levy, Ph.D.	83
Prof. Zvi (Gregory) Livshits, Ph.D.	85
Dr. Noam Shomron, Ph.D.	88
Hearing, Language & Speech Sciences and Disorders	93
Dr. Noam Amir, D.Sc.	94
Prof. Ofer Amir, Ph.D.	96

Dr. Daphne Ari-Even Roth, Ph.D.	98
Dr. Katy Borodkin, Ph.D.	100
Dr. Yael Henkin, Ph.D.	102
Prof. Minka Hildesheimer, Ph.D.	104
Prof. Liat Kishon-Rabin, Ph.D.	106
Prof. Tova Most, Ph.D.	108
Prof. Chava Muchnik, Ph.D.	110
Prof. Dorit Ravid, Ph.D.	111

Infectious Diseases

113

Dr. Natalia T. Freund, Ph.D.	114
Prof. Fuad Iraqi, Ph.D.	116
Dr. Oren Kobiler, M.D., Ph.D.	118
Prof. Nir Osherov, Ph.D.	119
Prof. Udi Qimron, Ph.D.	121
Dr. Dor Salomon, Ph.D.	123
Prof. Esther Segal, Ph.D.	125
Dr. Ella Sklan, Ph.D.	127

Inflammatory and Autoimmune Diseases

129

Prof. Ariel Munitz, Ph.D.	130
Dr. Mordechay (Motti) Gerlic, Ph.D.	132
Prof. Ronit Sagi-Eisenberg, Ph.D.	135

Medical Education and Ethics

137

Prof. Yechiel Michael Barilan, M.D., M.A.	138
Dr. Orit Karnieli-Miller, Ph.D.	140

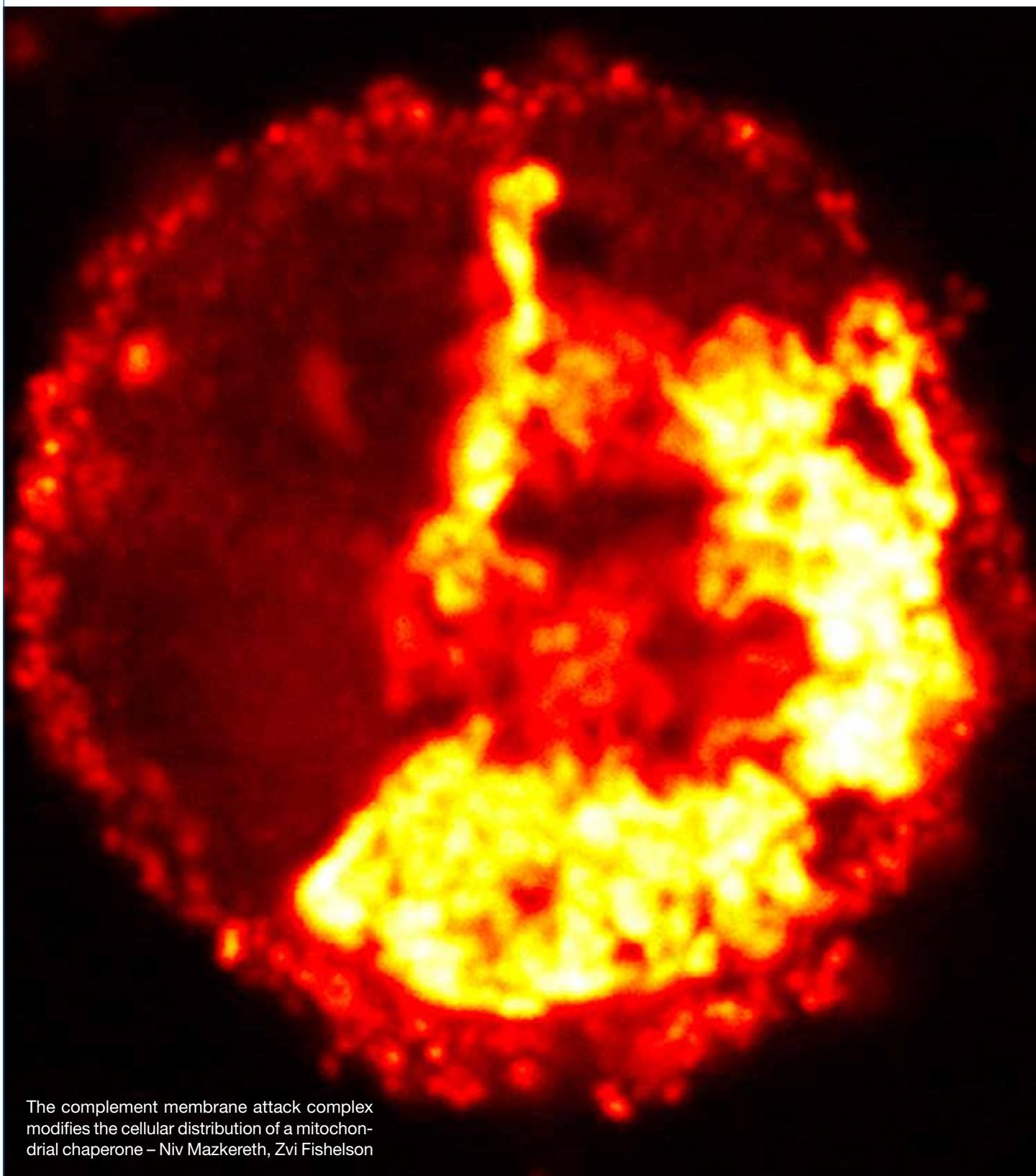
Nervous System and Brain Disorders

142

Prof. Ruth Ashery-Padan, Ph.D.	143
Prof. Hagit Eldar-Finkelman, Ph.D.	145
Dr. Jason Friedman, Ph.D.	147
Prof. Illana Gozes, Ph.D.	149
Dr. Yoni Haitin, Ph.D.	153
Prof. Talma Hendler, M.D., Ph.D.	155
Prof. Dario G. Liebermann, Ph.D.	159
Prof. Ilana Lotan, Ph.D.	161
Dr. Yuval Nir, Ph.D.	163
Dr. Moshe Parnas, Ph.D.	165
Dr. Eran Perlson, Ph.D.	166
Prof. Chaim G. (Chagi) Pick, Ph.D.	168
Prof. Moshe Rehavi, Ph.D.	172
Dr. Moran Rubinstein, Ph.D.	174
Prof. Naphtali Savion, Ph.D.	176
Prof. Inna Slutsky, Ph.D.	178
Prof. Arieh S. Solomon, M.D., Ph.D.	180

Dr. Eran Stark, M.D., Ph.D.	181
Dr. Ido Tavor, Ph.D.	183
Nursing, Occupational and Physical Therapy	185
Dr. Michal Avrech Bar, Ph.D., O.T.	186
Dr. Tami Bar-Shalita, Ph.D., O.T.	188
Prof. Sivia Barnoy, R.N., Ph.D.	190
Dr. Orit Bart, Ph.D., OTR	192
Prof. Ruth Defrin, Ph.D.	194
Dr. Michal Itzhaki, R.N., Ph.D.	197
Dr. Ilya Kagan, R.N., Ph.D.	199
Prof. Silvia Koton, Ph.D., M.Occ.H., R.N.	201
Dr. Lena Lipskaya-Velikovsky, Ph.D., O.T.	203
Dr. Alon Kalron, Ph.D., P.T.	204
Dr. Youssef Masharawi, Ph.D., B.P.T.	207
Dr. Semyon Melnikov, R.N. Ph.D.	209
Dr. Sigal Portnoy, Ph.D.	211
Dr. Debbie Rand, Ph.D., O.T.	213
Prof. Navah Z. Ratzon, Ph.D., O.T.	215
Dr. Angela Ruban, Ph.D.	217
Dr. Miriam Theilla, Ph.D.	218
Public Health	220
Prof. Daniel I. Cohen, Ph.D.	221
Prof. Jiska Cohen-Mansfield, Ph.D.	224
Prof. Yariv Gerber, Ph.D.	227
Prof. Uri Goldbourt, Ph.D.	229
Dr. Khitam Muhsen, Ph.D.	232
Dr. Chava Peretz, Ph.D.	235
Dr. Laura (Leah) J. Rosen, Ph.D.	237
Reproduction, Development and Evolution	239
Dr. Limor Broday, Ph.D.	240
Dr. Yankel Gabet, D.M.D., Ph.D.	241
Prof. Israel Hershkovitz, Ph.D.	244
Prof. Michael M. Kozlov, Ph.D.	246
Dr. Hila May, Ph.D.	248
Prof. Ruth Shalgi, Ph.D.	250
Prof. Ronen Zaidel Bar, Ph.D.	253
Stem Cells and Regenerative Medicine	255
Prof. Dafna Benayahu, Ph.D.	256
Dr. Chen Luxenburg, Ph.D.	258
Dr. Michael Milyavsky, Ph.D.	260

Cancer and Molecular Therapies



The complement membrane attack complex
modifies the cellular distribution of a mitochondrial chaperone – Niv Mazkereth, Zvi Fishelson



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Cellular and Molecular Mechanisms of Antigen-Restricted Tumor Immunity

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

The goal of our work is to provide a detailed understanding of the mechanisms, signals and molecular pathways that regulate discriminating self from non-self and give rise to tumor-specific cytotoxic T cell immunity. Our specific aims are to address the following: 1) What are the cellular and molecular elements that enable the immune system to recognize subtle antigenic variations from self to initiate a cytotoxic immune response? 2) How is the specificity of the induced immune response

determined? In other words, what is the process by which the presentation of diverse antigens by DC is reduced to activation of specific effector T cells? Understanding the means by which DC and T cells communicate to initiate antigen-restricted tumor immunity and how these processes are regulated will provide a roadmap for designing novel, more potent cancer immunotherapies.

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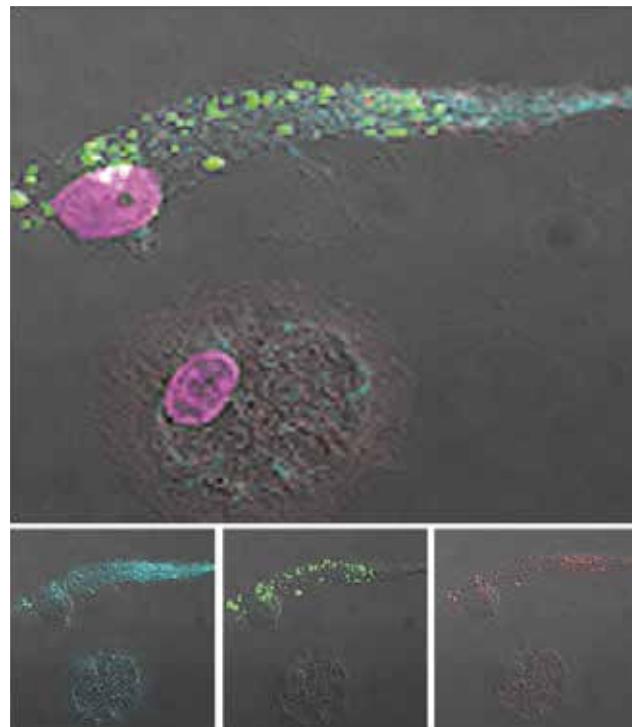
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Grants

2017	Alon Award for Outstanding Young Scientists
2017	Swiss Bridge Award: <i>Elucidating the Mechanisms by Which Tumor-Binding Antibodies Enable T Cells Infiltration into the Tumor Microenvironment</i>



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Cancer Related Inflammation in Tumor Progression and Metastasis

Position

Associate Professor, Sackler Faculty of Medicine
Chair, Department of Pathology

Research

The main goal of our laboratory is to uncover stromal pathways that contribute to tumorigenesis and metastasis. In particular, we combine transgenic mouse models of cancer as well as clinical data to study the role of inflammation and cancer-associated fibroblasts in facilitating lung metastasis of breast cancer, and to uncover the role of neuroinflammation mediated by astrocytes in melanoma brain metastasis.

Extensive research has led to the understanding that **tumors are more than just cancer cells**: stromal cells in the tumor microenvironment play a crucial role in all stages of tumor initiation and progression, and cancer research is no longer focused only on the pathways inside tumor cells, but rather on tumors as multi-cellular organs.

The major cause of cancer mortality is metastasis to distant organs. Currently, metastatic cancers are incurable and available therapies can only prolong life to a limited extent. Therefore, uncovering the mechanisms that facilitate metastasis is an urgent

and unmet clinical need. Nevertheless, changes in the metastatic microenvironment that enable the growth of disseminated tumor cells are poorly characterized, and are the major focus of our research.

Expanding our understanding of the early stages of metastatic growth is an essential prerequisite for the discovery of novel target molecules for the development of targeted therapeutics that may prevent, rather than try to cure, metastatic disease

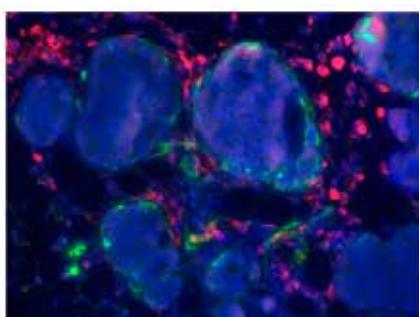
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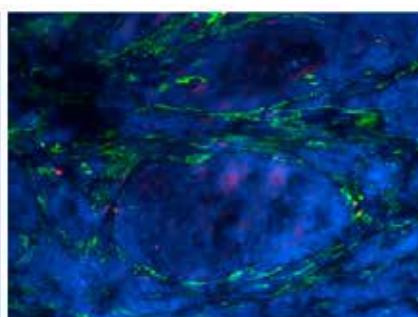
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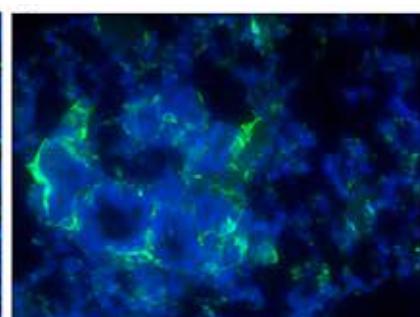
A



B



C



A, B: Cancer Associated Fibroblast (CAF) accumulate around mammary tumors in tissue Sections from the MMTV-PyMT transgenic mouse model. Green-aSMA, Blue-DAPI, Red-FSP-1. **C:** Immunofluorescent staining showing activated fibroblasts in lung metastases in MMTV-PyMT mice. Blue- DAPI. Green –aSMA.

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Grants

2014–2017	Association for International Cancer Research (AICR)
2014 – 2017	Melanoma Research Alliance SABAN FAMILY FOUNDATION-TEAM SCIENCE AWARD
2014 – 2017	Israel Cancer Research Foundation (ICRF). Research Career Development Award
2015–2019	European Research Council (ERC) Starting Grant



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Molecular Analysis of Cancer Immunoresistance

Positions

Professor, Sackler Faculty of Medicine
President, International Complement Society
President, European Complement Network
Advisory Editor, *Molecular Immunology*
Associate Editor, *Frontiers in Molecular Innate Immunity*

Research

The long-term goal of our research is to develop a novel treatment for immune resistant cancers. Our research includes characterization of the mechanism of complement-dependent cytotoxicity and of the basis for elevated resistance of cancer cells to cell death, and design of novel reagents that sensitize cancer cells to cell death. Research methods used include analyses of cell growth and death and mitochondrial activity, western blotting, enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, confocal fluorescence microscopy, Fluorescence-activated Cell Sorting (FACS), peptide analysis by mass spectrometry, electron microscopy, and analysis of cancer growth in animal models.

Publications

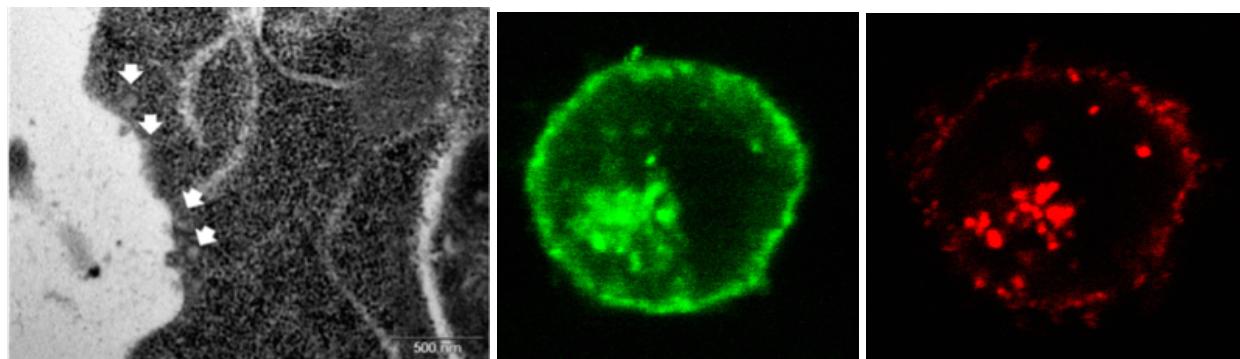
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EM analysis demonstrates elevated formation of endosomes in K562 cells responding to an ongoing immune attack (left). Caveolin-1 (green) and complement C9 (red) co-localize in early and late endocytic vesicles of K562 cancer cells following complement attack on the cells (right 2 panels).

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Kemper C., Pangburn M. K. and **Fishelson Z.** Complement Nomenclature 2014. *Molec. Immunol.* 61: 56-58, 2014.

Grants

2015-2020	Complement-dependent cytotoxicity of cancer cells: toxic and evasion mechanisms (ISF)
2016-2018	The mitochondrion-plasma membrane interaction at super-resolution microscopy (VW Lower Saxony grant, binational with Germany (Dr. Alex Egner, Goettingen))



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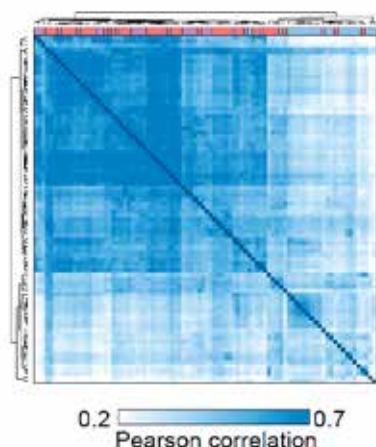
Cancer Proteomics

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our main interest is to understand the mechanisms of cancer progression and drug resistance. We use state-of-the-art **mass spectrometry-based proteomics** to obtain a system-wide view of the proteomes of cancer clinical samples of tumors and body fluids. Analysis of the changes in protein levels and the modifications that occur during tumor development is aimed to discover novel regulators of transformation. Identification of cancer biomarkers in body fluids such as serum and plasma, opens new possibilities to translate these results to diagnostic tests in clinical use. Among the many identified regulators, we focus on **metabolic remodeling in cancer**. Combining proteomic and metabolomic techniques, we investigate the involvement of metabolism in cancer transformation, regulation of cell proliferation and invasion. Combination of these technologies with biochemical and genetic methods shows the significance of these candidates to cancer development and may suggest novel markers and drug targets.



Correlation matrix of proteomes of breast cancer and healthy tissue

Publications

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Grants

2012-2017 Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease

2012-2017 Israel Science Foundation (ISF) Grant: The role of metabolic pathways in the regulation of breast cancer progression.

2015-2020 European Research Council- ERC starting grant: Topoproteomic profiling of breast cancer heterogeneity

2014-2017 Israel Ministry of Science and Technology: Proteogenomic analysis of breast cancer

Reviews

Shenoy, A. & **Geiger, T.***. Super-SILAC: Current trends and future perspectives. *Expert Reviews of Proteomics* 12, 13-19 (2015). *Corresponding author.



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Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions

Professor, Sackler Faculty of Medicine

Chair, MD-PhD program

Dora and Gregorio Shapiro Chair of Hematological Malignancies

Research

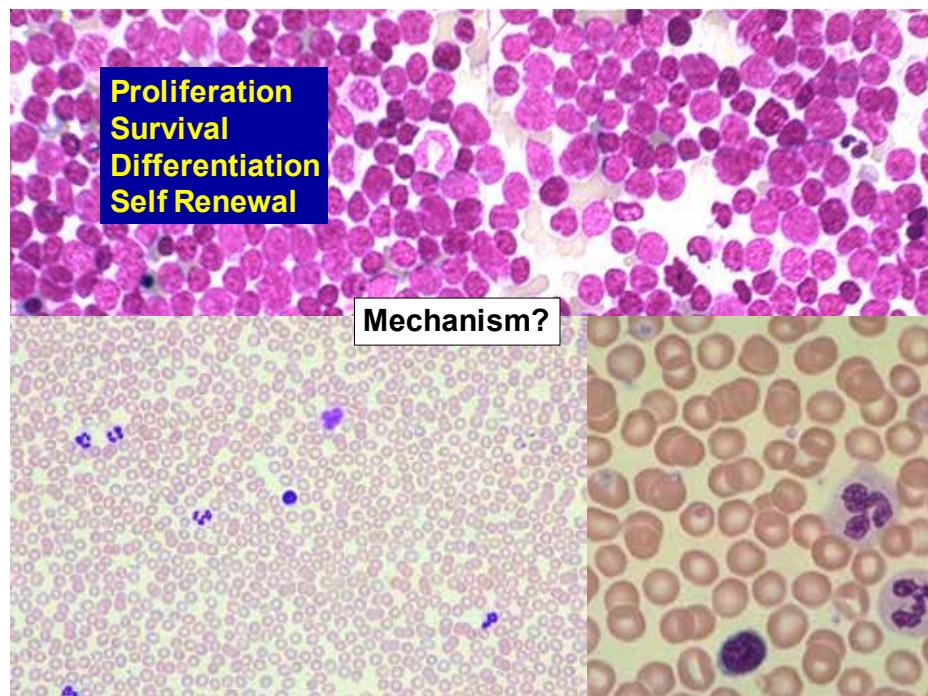
We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

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. 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



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

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 causes 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.

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Reviews

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Grants

2014-2017	EU ERA-NET TRANSCANCER "TRANSALL" Validation of biomarkers for the diagnosis and risk stratification of childhood ALL
2014-2018	BSF Functional analysis of ERG GATA1
2014-2018	ISF Modelling T-lympho-myeloid leukemia
2014-2017	ISF-NSFC Hematopoietic transcription factors in leukemia – mouse models and human leukemias
2014-2017	The Israel Science Foundation (ISF) and the National Natural Science Foundation of China (NSFC), PIs Izraeli, Shai (Israel) Chen, Sai-Juan (China)
2014-2017	Israel Ministry of Health ERA-NET EU programs, PIs Izraeli, Shai (Israel), multiple Europeans PIs
2014-2018	Israel Science Foundation
2014-2018	USA-Israel Bi-National Scientific Foundation, PIs Izraeli, Shai (Israel); Crispino, John (USA)
2015-2018	DOD USAMRMC
2016-2018	Children With Cancer UK, PI Enver, Tariq (UCL), co-PI Izraeli, Shai
2016-2019	German Israel Foundation



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Development of Cancer Treatments Integrating Radiotherapy or Electrochemical Ablation and Immunotherapy

Positions

Professor Emeritus, Sackler Faculty of Medicine

Roberts-Guthman Chair in Immunopharmacology

President, Israeli Society for Cancer Research

Associate Editor, *Mediators of Inflammation*

Research

Cancer is currently the most devastating chronic disease affecting humankind. Today solid malignant tumors are mainly treated by surgery and/or radiotherapy to eradicate the local primary lesion, and chemotherapy, that is administered mainly to destroy remaining local or distant malignant cells. In spite of the advancement in preventing and treating cancer, morbidity and mortality remain high, especially in cases when tumors are highly metastatic, or cannot be completely removed. The main goal of our research projects is to develop *in situ* tumor ablation treatments of primary tumors and incorporate them with systemic chemotherapy and immuno-stimulatory agents, into combined treatment protocols.

In order to achieve efficient primary tumor ablation we developed two novel and powerful treatment modalities for solid cancer, which can be used instead or in combination with surgery. The first treatment, developed with Prof. Rafi Korenstein (Dept. Physiology & Pharmacology), is base on the use of intratumoral unipolar pulsed electric currents for the ablation (ECTA) of solid primary tumors. ECTA can be enforced by the concomitant use of chemotherapeutic agents in the treatment of tumors. The second cancer treatment, developed with Prof. Itzhak Kelson (School of Physics & Astronomy), is based on insertion into the tumor of radioactive wires that spread in the tumor alpha emitting atoms and can also be augmented by chemotherapy.

Our teams proved that these treatment modalities effectively destroy primary tumors, and reduce the metastatic load in experimental animal and human cancer models of melanoma, breast, colon, prostate, pancreas, lung, and squamous cell carcinomas. We found that *in situ* ablation of primary antigenic tumors led to the activation of immunological reactions, destroying remaining malignant cells in the primary tumor as well as in distant metastases.

Immunopharmacological methods aimed to stimulate the patient's immune response against the cancer after local tumor ablation can make use of several approaches and we currently study the following: (1) Immunostimulation by adjuvants such as the oligonucleotides, CpG, which enforce weak immune reactions. (2) Inhibition of immunosuppressive mechanisms such as T-regulatory and Myeloid Derived Suppressor cells (MDSC). (3) Combination with inhibitors of immunological checkpoints such as anti CTLA-4 or anti PDL1/PD1.

Publications

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Books

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Grants

2016-2018 Ramot- Alpha Tau Medical Research Contract



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Interaction of Nanomaterials and Electromagnetic Fields with Cells

Positions

Professor Emeritus, Sackler Faculty of Medicine

Chair, Commission K of the Israel National Committee for Radio Science of Israel Academy of Sciences and Humanities on Electromagnetics in Biology and Medicine

Editorial Board, *Bioelectromagnetics*

Research

The research activity addresses the following lines of research:

Adsorption and uptake of nanoparticles by cells in relation to drug delivery and toxicity; Enhancement of uptake by electrical and chemical means. Treatment of cancer by electrochemical based approach; assessment of genetic and epigenetic risks following in-vitro exposure to electromagnetic fields associated with cell phone communication. Physiological regulation and underlying mechanism of cell membrane-cortical skeleton nanoscale mechanical fluctuations. Research methods used include routine cell biology and biochemical methodologies with emphasis on special cutting edge light microscopies

possessing nanometric resolution such as Digital Holographic Microscopy (see below).

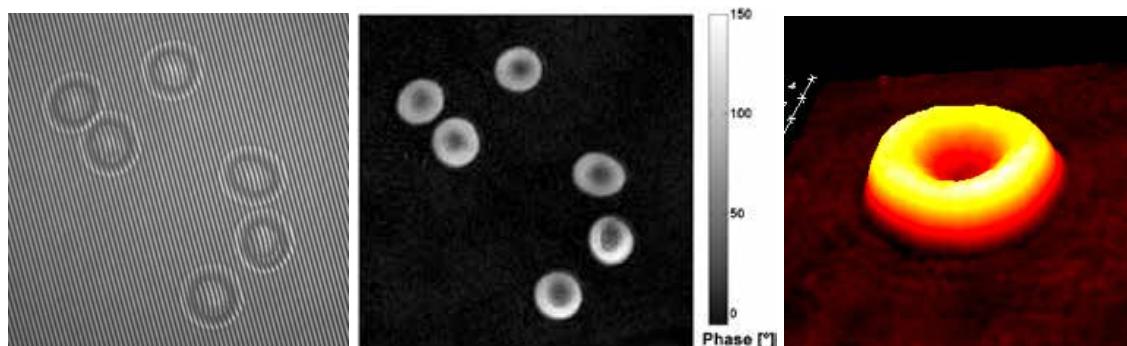
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Hologram image of red blood cells (left), reconstructed phase image (middle) and 3D reconstruction of a single red blood cell (right)

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Chapter

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Grants

2015-2018 European Commission – Horizon 2020 ERA-NET funded consortium on “Establishing nanomaterial grouping/classification strategies according to toxicity and biological effects for supporting risk assessment” (achronym “NanoToxClass”).

2016-2019 European Commission – Horizon 2020 EC funded consortium on “High level Integrated Sensor for Nanotoxicity Screening (achronym “HISENTS”).



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The Wnt Signaling Pathway and Colorectal Cancer

Position

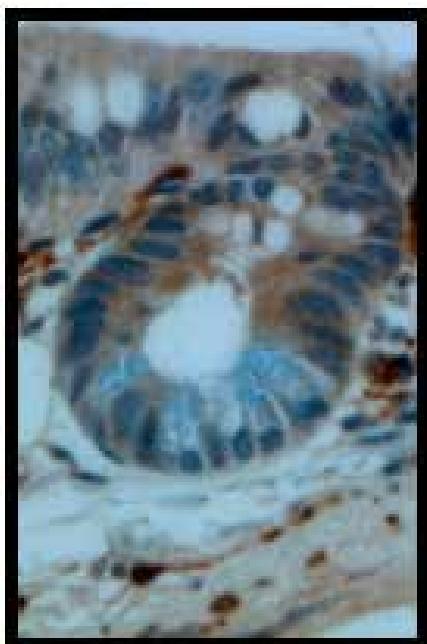
Associate Professor, Sackler Faculty of Medicine
Chair, Search Committee

Research

The Wnt signaling pathway is involved in virtually every aspect of human development, as well as in adult homeostasis. Hyperactivation of this pathway has been linked to a wide range of cancers and especially colorectal cancer. Our aim is to understand the molecular events underlying Wnt signal transduction, as well as develop novel therapeutic strategies to fight colorectal cancer.

Current projects in the lab include:

1. Identifying and characterizing new Wnt signaling components.
2. Developing new anti-colorectal cancer treatment strategies.



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

Publications

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Grants

2014-2017	ISF
2015-2017	Rising Tide Foundation
2015-2018	Gateway for Cancer Research
2016-2018	Kamin
2016-2018	Sponsored research – Cempra



Prof. Ronit Satchi-Fainaro, Ph.D.

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Angiogenic Switch Using Rationally-Designed Theranostic Nanomedicines

Positions

Chair, Department of Physiology and Pharmacology

Professor, Sackler Faculty of Medicine

President, Israeli Chapter of the Controlled Release Society (ICRS)

Chair, Tel Aviv University Institutional Animal Care and Use Committee (IAUCUC)

Faculty Coordinator, Postgraduate Program in Nanotechnology

Associate Editor, *Advanced Drug Delivery Reviews*

Associate Editor, *Nanomedicine: Nanotechnology, Biology and Medicine*

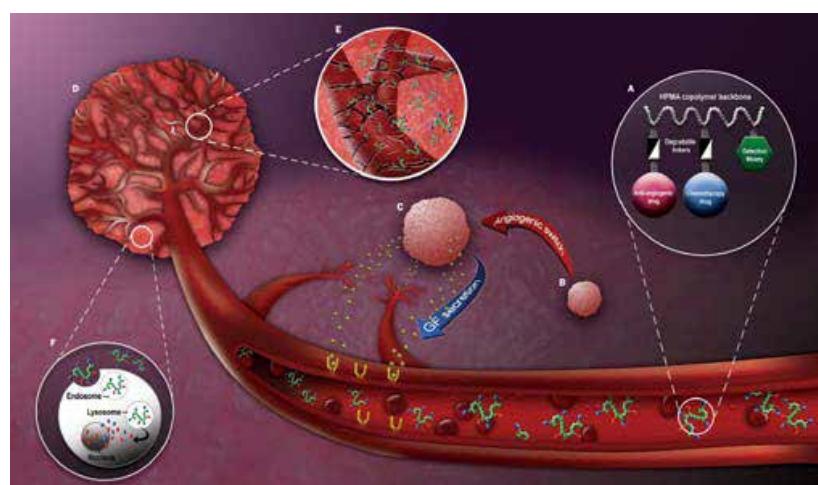
Co-Editor-in-Chief, *Clinical Cancer Drugs*

Research

Our research interests include investigations relating to tumor biology, tumor dormancy, mechanism of action of angiogenesis inhibitors, self-assembly of polymeric architectures and novel approaches to target cancer. Throughout, we have maintained an interest in understanding the biological rationale for the design of polymer therapeutics suitable for

transfer into clinical testing. Our primary interests are the molecular basis of tumor angiogenesis and the rational design of polymer therapeutics. Our research includes identification and characterization of genes and microRNAs associated with the switch from a dormant avascular tumor phenotype to a fast-growing angiogenic tumor in human cancers and their corresponding mouse models.

We focus on the design and characterization of novel drug delivery platforms, including dendrimers and hyperbranched polymer-based nanoparticles, and the design of highly-selective targeting molecules integrating biology, chemistry, protein engineering, computational approaches, material sciences and nanotechnology to selectively guide drugs into pathological sites. Our vision is that novel approaches to target anticancer, anti-angiogenic drugs, miRNA and siRNAs to endothelial and tumor cells to potentially treat angiogenesis-dependent diseases could transform cancer into a chronically-manageable disease. Research methods used include sequencing, gene cloning, quantitative RT-PCR, immunofluorescence, cell culture, scanning electron microscopy, mass spectrometry, MALS, AFM, NMR, HPLC, *in situ* hybridization, bioinformatics, polymer chemistry, molecular imaging, angiogenesis



The angiogenic switch and the use of nanomedicines such as Polymer Therapeutics to treat angiogenic tumors. The enhanced permeability and retention (EPR) effect allows nanoconjugates to extravasate through the tumor leaky vessels, accumulate in the tumor bed selectively and internalize into the tumor epithelial and tumor endothelial cells via endocytosis.

assays, animal models of cancer (human xenografts in mice, syngeneic and transgenic mice models), pharmacokinetics and pharmacodynamics and 3D printing.

Publications

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Grants

2012-2017	Israel National Nanotechnology Initiative (INNI), Focal Technology Area in nanotechnology, "Theranostic Nanomedicines for Personalized Medicine"
2014-2019	European Research Council (ERC) Consolidator Award. PolyDorm: "Uncovering the molecular and cellular mechanism of tumor dormancy for the rational design of theranostic nanomedicines"
2014-2018	Israel Science Foundation (ISF) Grant
2014 – 2017	Melanoma Research Alliance SABAN Family Foundation-Team Science Award



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The ATM-Mediated DNA Damage Response

Positions

Professor Emeritus, Sackler Faculty of Medicine
David and Inez Myers Chair in Cancer Genetics
ICRF Research Professorship

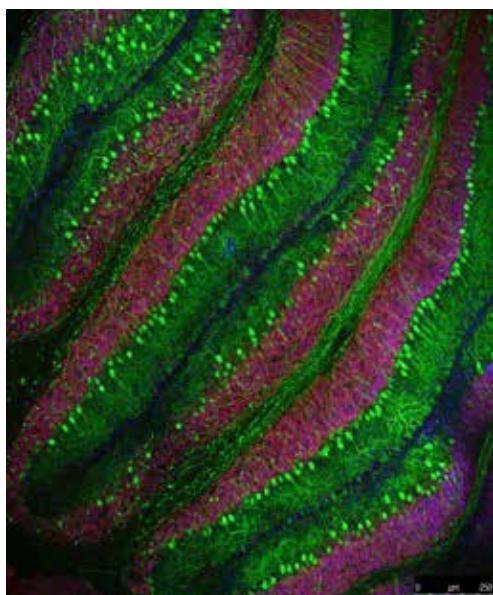
Research

Our laboratory investigates the cellular DNA damage response. This research stems from our interest in the human genetic disorder ataxia-telangiectasia (A-T), in which a central axis of the DNA damage response is missing.

Genetic defects in the DNA damage response lead to genomic instability syndromes, which usually include tissue degeneration, cancer predisposition, and sensitivity to specific DNA damaging agents. A prototype genomic instability syndrome is A-T. The disease is characterized by neuronal degeneration,

immunodeficiency, chromosomal instability, sensitivity to ionizing radiation, and cancer predisposition. Our lab has been investigating A-T since its establishment in 1985. In 1995, after 8 years of intensive work, we identified the gene that is defective (mutated) in A-T patients and called it *ATM* (A-T, Mutated). We went on to study the activity of its product, the ATM protein, which turned out to be an enzyme with an activity called “protein kinase”.

Our current research is aimed at a broader understanding of the ATM-mediated DNA damage response. Particular attention is paid to the molecular and physiological basis of A-T, which may eventually lead to new treatment modalities for the disease. We investigate this system with cell biology methods, gene targeting in mice, and systems biology strategies including high-throughput screens, advanced proteomics and bioinformatics. A study is underway aimed at understanding the DNA damage response in the part of the brain called the cerebellum, which is badly damaged in A-T patients. Another project is searching for a drug treatment for A-T patients based on our recent understanding of the disease.



Microscopic image of a slice of mouse cerebellum in culture. The cells stained green are called Purkinje cells. These cells are the first to be damaged and lost in A-T patients. Such cultures are used to study the DNA damage response in this complex organ.

Publications

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Rasmussen LJ, **Shiloh Y**, Bergersen LH, Sander M, Bohr VA, Tønjum T. (2013) DNA damage response, bioenergetics, and neurological disease: the challenge of maintaining brain health in an aging human population. *Mech Ageing Dev.* 134:427-33

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using organotypic cultures. *Methods in Molecular Biology* 1599:419-430.

Barzilai, A., Schumacher, B., and **Shiloh, Y.** (2017) Genome instability: linking ageing and brain degeneration. *Mechanisms of Ageing and Development* 161 (PtA):4-18.

Shiloh, Y., and Lederman, H. (2017) Ataxiatelangiectasia (A-T): an emerging dimension of premature ageing. *Ageing Research Reviews* 33:76-88.

Grants

2014 – 2021	Israel Cancer Research Fund (ICRF Professorship)
2014 – 2017	Israel Science Foundation (Joint ISF-NSFC Program with the National Natural Science Foundation of China)
2015 – 2020	The A-T Children's Project
2016 – 2017	The A-T Ease Foundation
2016- 2020	US-Israel Binational Science Foundation
2015 – 2017	Dr. Miriam and Sheldon G. Adelson Medical Research Foundation



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Met Proto-Oncogene and its Ligand, HGF/SF and Breast Cancer

Position

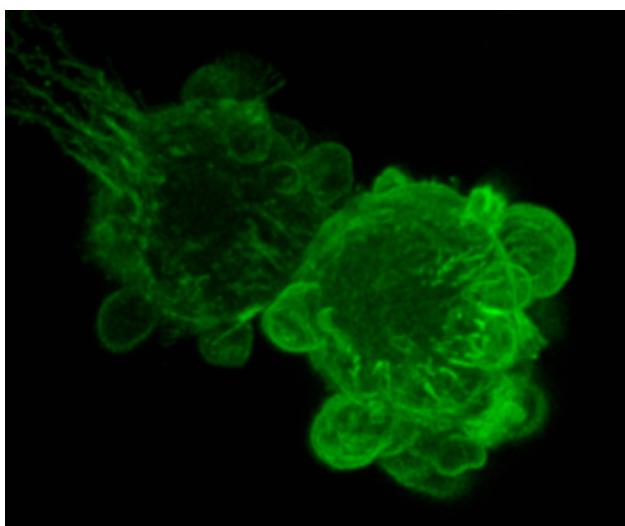
Associate Professor, Sackler Faculty of Medicine
Director, Sackler Cellular and Molecular Imaging Center (SCMIC)

Research

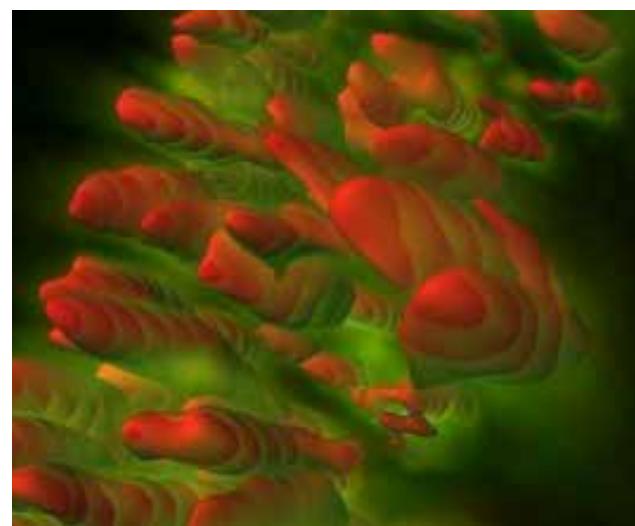
Breast cancer is the most common malignant disease in western women. In the majority of cases the cause of death in cancer patients is not the primary tumors, but complications derived from metastases at distant sites. The *met* proto-oncogene product (Met – a receptor tyrosine kinase) and its ligand, hepatocyte growth factor/scatter factor (HGF/SF), mediate cell motility and proliferation *in vitro* and tumorigenicity, angiogenesis and metastasis *in vivo*. Mimp/Mtch2, a mitochondrial carrier homologue cloned in our lab, is induced by Met-HGF/SF signaling and is involved in metabolic and bioenergetic processes. We have previously shown that activation of Met by HGF/SF induces an increase in tumor blood volume in a dose-dependent manner. Mimp/Mtch2 reduces cells

proliferation *in vitro* and tumor growth *in vivo*. Several anti-Met targeted therapies are in development and some have entered phase III clinical trials.

The goal of our studies is to further understand the role of Met-Mimp/Mtch2 in cancer progression and metastasis, and to develop modalities for personalizing targeted Met therapy. Fluorescent tagged-Met proteins were used to study Met mitogenic effect on cells. Met induced cell motility is mediated by the formation of membrane structures such as ruffles, pseudopodia and blebs. Over expression of GFP-Met WT results in its constitutive activation, cell rounding and detachment, and dynamic non-apoptotic membrane blebbing. Bleb retraction results in numerous membrane microspikes where CFP-Met WT, YFP-actin and membrane markers accumulate. Expression of Dominant-Negative (DN) YFP-Met alone did not induce any membrane blebbing, and co-expression of CFP-Met WT and YFP-Met DN significantly reduces membrane blebbing. Using confocal based molecular imaging we also show that Mimp/Mtch2 reduces the levels of reactive oxygen



Met localization in blebbing cells



Mimp localization in mitochondrial cells (Red inner mitochondria marker, Green Mimp-GFP)

species ROS and prevents the HGF/SF induced increase in ROS. Mimp/Mtch2 also reduces the polarization of the mitochondrial membrane potential.

To study Met activation by HGF/SF *in vivo*, we used a xenograft mouse model in which DA3 cells expressing the fluorescent protein mCherry (DA3-mCherry) are injected orthotropically into mice mammary glands. Contrast media ultrasound-based Met functional molecular imaging (FMI) demonstrated that HGF/SF-induced increased hemodynamics is dependent on Met concentration and can be dramatically reduced upon inhibition of the receptor and its signaling pathway; Whole animal spectral imaging enabled detection of sub-millimeter metastases demonstrating fast developing micrometastatic spread of the tumor; Macro to Micro and two photon confocal imaging demonstrated HGF/SF-induced changes in blood flow at single vessel resolution, localization of metalloprotease and catapsine activity at the tumor edge and increase in single cell motility.

Met molecular imaging demonstrated that Met signaling modulation plays a major role in breast cancer tumor growth and development. These emerging MI modalities may help tailor Met-targeted therapy.

Publications

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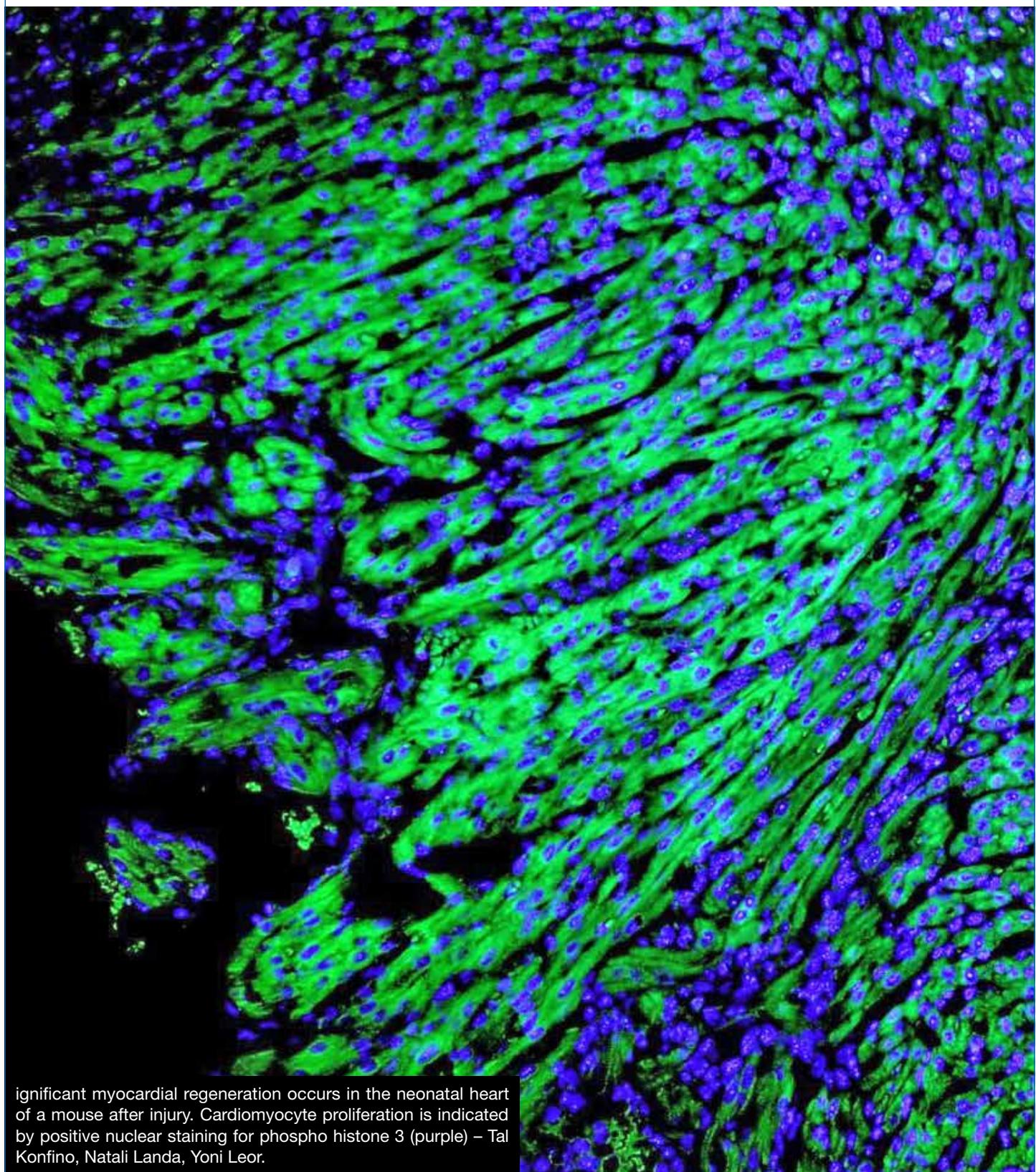
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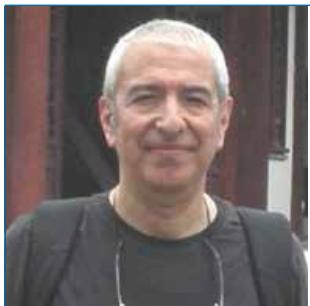
Grants

2017-2019 Israel Science Foundation

Cardiovascular Research and Diseases



Significant myocardial regeneration occurs in the neonatal heart of a mouse after injury. Cardiomyocyte proliferation is indicated by positive nuclear staining for phospho histone 3 (purple) – Tal Konfino, Natali Landa, Yoni Leor.



Normal and Diseased Potassium Channels in Human Brain and Heart

Position

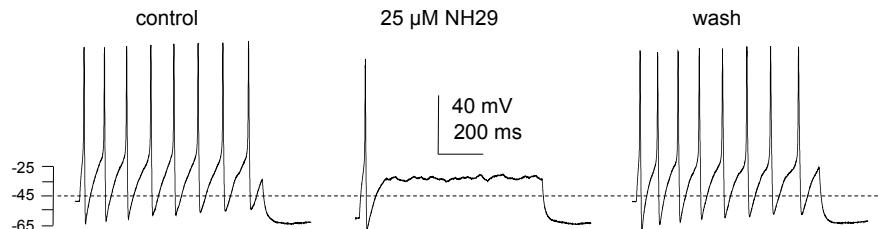
Professor, Sackler Faculty of Medicine

Andy Libach Professorial Chair in Clinical Pharmacology and Toxicology

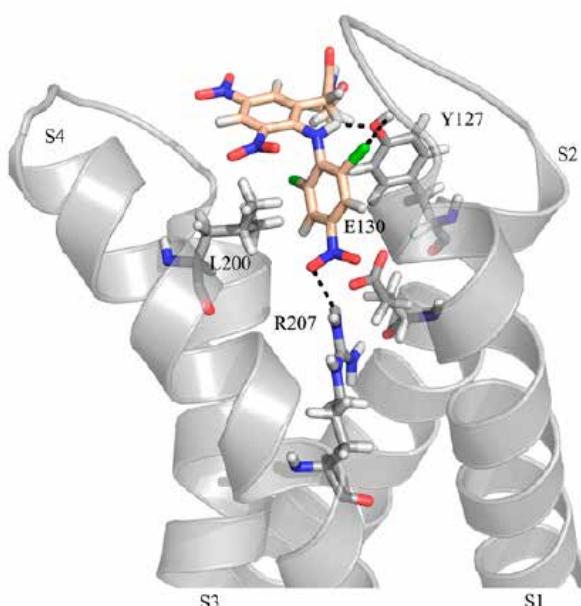
Research

Reaching an understanding in molecular terms of the mechanisms by which changes in membrane potential regulate cellular events is the main

concern of our research. We focus our interest on potassium channels because they play crucial roles in many cellular functions such as shaping cardiac and neuronal action potentials, tuning neuronal firing patterns, synaptic integration or modulating neurotransmitter release. Using the powerful combination of molecular biology, biophysics, biochemistry and electrophysiology, our research aims at elucidating the structural, biophysical and physiological attributes of potassium channels in human brain and heart and whose mutations lead to



Activation of M-type potassium channels by our homemade NH29 opener inhibits evoked spike discharge in dorsal root ganglion sensory neurons.



Docking of the NH29 gating-modifier molecule onto the voltage sensor domain of the Kv7.2 potassium channel.

major neurological and cardiovascular disorders like epilepsy, myokymia, atrial or ventricular fibrillation.

Publications

Manuscripts

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Grants

2013-2017	Israel Academy of Science, (ISF:1215/13). Role of SK4 Ca ²⁺ -activated K ⁺ channels in the developing human cardiac pacemaker using embryonic stem cell-derived cardiomyocytes as a model. (PI).
2013-2017	Fields Fund for Cardiovascular Research (Co-PI).
2014-2017	Israel Science Foundation-China (The ISF-NSFC joint program, 2092/14)



Prof. Nathan Dascal, Ph.D.

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Signal Transduction by Neurotransmitters in Brain and Heart in Health and Disease

Position

Professor of Physiology, Sackler Faculty of Medicine
Morris and Helen Mauerberger Chair for
Neuropharmacology

Research

Electrical activity of excitable cells is their most important feature, which allows the performance of fundamental functions of brain, heart and muscle. We are addressing a key issue in modern cardiology and neurobiology: how neurotransmitters regulate cardiac cells and neurons by acting on ion channels – proteins that underlie the electrical activity in these cells; and how errors in these processes cause disease. Main projects in the lab:

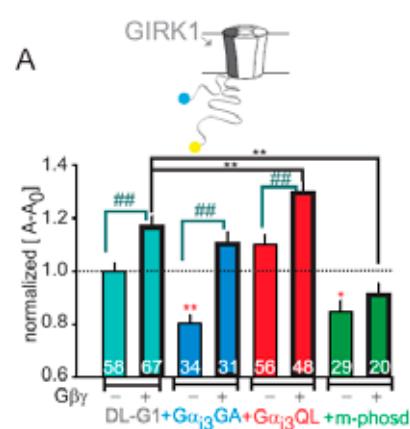
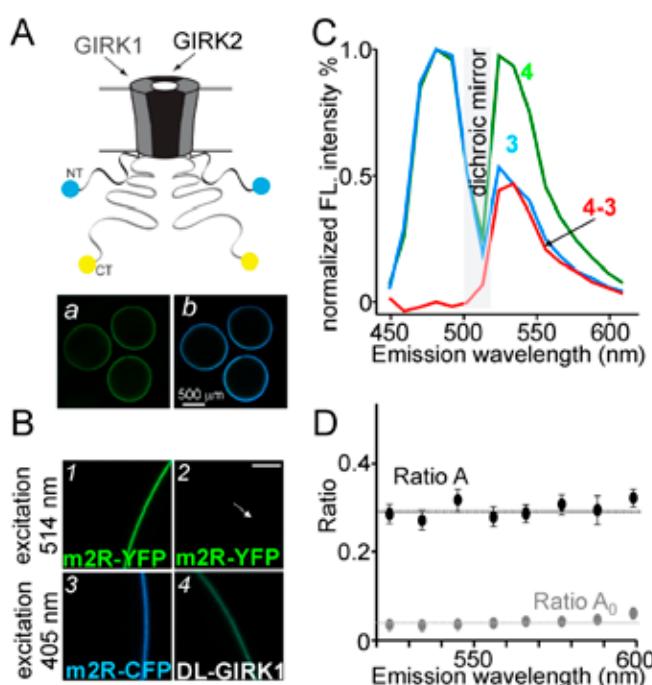
Function and regulation of receptors, G proteins, Ca^{2+} and K^+ channels in health and disease; Ion channel-

related hereditary cardiac and neurological disorders (channelopathies); Mechanisms of coupling of G protein-coupled receptors with effectors; Molecular mechanisms of bipolar disorder.

Research methods: Electrophysiology, Neurophysiology, Heterologous Expression, Protein Biochemistry, Fluorescence Resonance Energy Transfer (FRET), Molecular biology, Mathematical and Kinetic Modeling and Simulation, Immunocytochemistry

Publications

Edvardson S, Oz S, Abulhijaa FA, Taher FB, Shaag A, Zenvirt S, **Dascal N** & Elpeleg O. (2013). Early infantile epileptic encephalopathy associated with a high voltage-gated calcium channelopathy. *J Med Genet* **50**, 118-123



Studying Girk channels expressed in a heterologous system (*Xenopus* oocytes). Intramolecular fluorescence resonance energy transfer (i-FRET) shows interactions of cytosolic N- and C-termini of the channel. **A**, Girk channel labeled with two fluorescent proteins. **B**, Imaging the expressed fluorescent proteins with a confocal microscope. **C, D**, Example of use of FRET analysis to study conformational changes in the channel caused by neurotransmitter, G proteins or drugs. **E**, $\text{G}\alpha$ and $\text{G}\beta\gamma$ synergistically alter the conformation of Girk1 subunit.

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Weisbrod, D., Peretz, A., Ziskind, A., Menaker, N., Oz, S., Barad, L., Eliyahu, S., Itskovitz-Eldor, J., **Dascal, N.**, Khananshvili, D., Binah, O., and Attali, B. (2013) SK4 Ca^{2+} activated K^+ channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA* 110, E1685-1694.

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2014-2018 Li⁺ regulates neuronal ion channels: molecular mechanisms and relation to bipolar disorder. Israel Science Foundation (ISF)

2015-2018 Molecular mechanisms of disease caused by dysfunction of cardiovascular GIRK channels. Joint Israel-India grant managed by ISF (with Prof. A.K. Bera, IIT)



Dr. Michal Katz-Leurer, Ph.D.

Department of Physical Therapy
Steyer School of Health Professions
Sackler Faculty of Medicine



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Investigating the Cardiac Autonomic System Among Brain Damaged Patients

Position

Senior Lecturer

Chair, Department of Physical Therapy

Research

Stroke, traumatic brain injury and cerebral palsy are the most common causes of physical disability. Autonomic instability is common phenomenon post brain damage, with signs and symptoms of hyper-stimulation of the sympathetic nervous system. We study the connections between physical disability and the cardiac autonomic regulation system. We assess the cardiac autonomic response to different stimulus and its immediate and long-lasting adaptation to different physical training protocols.

Publications

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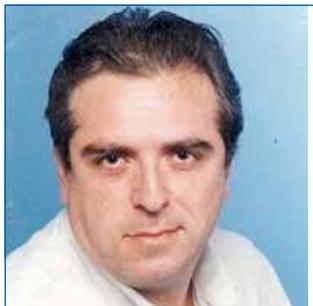
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Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

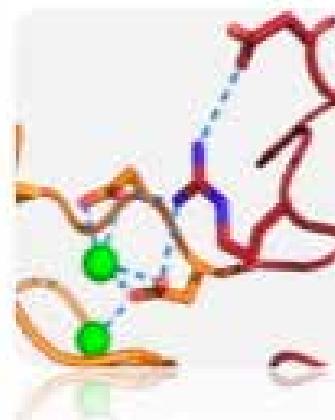
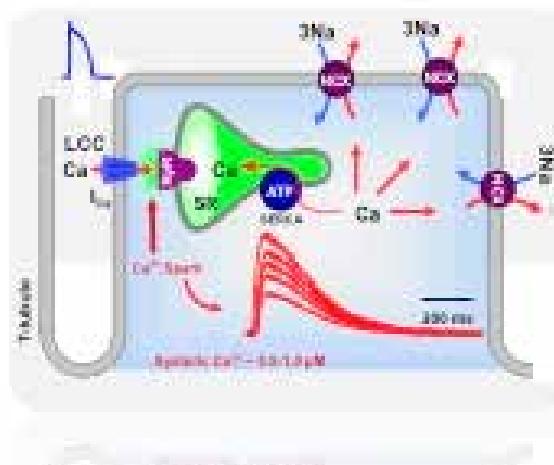
Positions

Professor, Sackler Faculty of Medicine

Research

Calcium (Ca^{2+}) is a major regulator in the living cell. In many cell-types the $\text{Na}^{+}/\text{Ca}^{2+}$ exchanger proteins (NCX) represent a major Ca^{2+} extruding system and thus, play a key role in regulating the Ca^{2+} -dependent events in the cell. Three NCX genes form numerous splice variants, which are expressed in a tissue-specific manner to regulate excitation-contraction coupling in heart, long-term potentiation and learning in brain, blood pressure, immune responses, neurotransmitter and hormone secretion, kidney Ca^{2+} reabsorption, mitochondrial bioenergetics, etc. Altered expression and regulation of NCX proteins is a chief contributor to Ca^{2+} -driven tissue-remodeling in heart failure, cerebral ischemia, hypertension, diabetes, renal malfunction, muscle dystrophy, etc. For example, in cardiac disease a single isoform/splice variant (NCX1.1) is overexpressed, thereby representing a primary concern for life-threatening arrhythmias and contractile malfunction. Selective

pharmacological targeting of NCX variants is expected to recover Ca^{2+} homeostasis in predefined cell types and thus, may improve desired activity of altered tissues/organs. Since this breakthrough remains challenging our research efforts are focused on two principle issues: a) To resolve structure-activity relationships underlying the function and regulation of diverse NCX variants; b) To develop new experimental approaches for selective pharmacological targeting of tissue-specific NCX variants with a goal of providing new opportunities for preventing and effective treatment of harmful diseases. In this respect we investigate structure-activity relationships in the wild-type and mutated proteins by exploring a wide spectrum of techniques (stopped-flow and ion-flux assays, FRET, SAXS, ITC, X-ray crystallography, confocal microscopy, patch-clamp, etc). In searching the regulatory mechanisms of CBD1 and CBD2 domains we found that the tissue-specific splice segment, located on CBD2, shapes the regulatory specificity of the primary Ca^{2+} sensor located on CBD1. These findings may allow the identification of drug candidates targeting the disease-related NCX variants.



Publications

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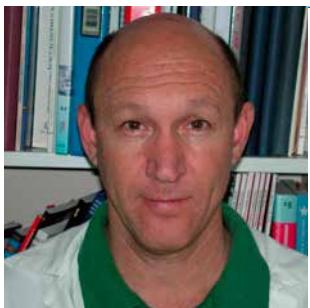
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Grants

2013-2017 Fields Center of Molecular Cardiology

2014-2018 Israeli Science Foundation



Prof. Jonathan Leor, M.D.

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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

David Halpern Professor of Cellular and Molecular Cardiology

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

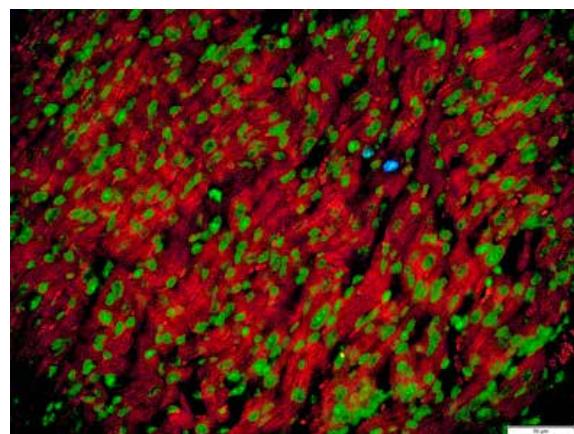
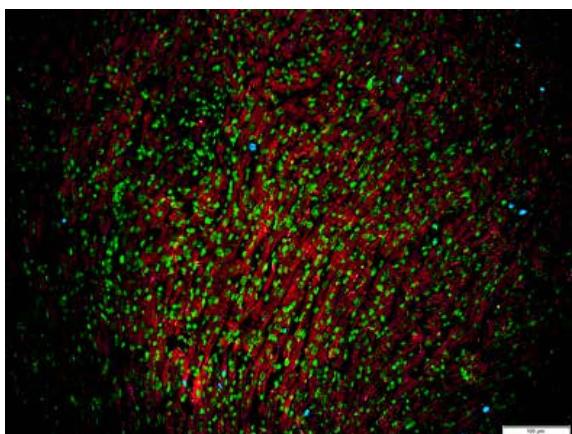
work on the development of novel nano-therapies for cardiovascular disease.

Publications

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.

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Grants

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

Dental Health and Medicine





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Bioinspired Materials for Nanotechnological Application

Positions

Senior Lecturer, Sackler Faculty of Medicine

Affiliated, TAU Center for Nanoscience and Nanotechnology

Research

Work in our Laboratory of Bioinspired Materials is focused on mimicking self-assembly processes that occur in nature, including biomineralization and the organization of short peptides and amino acids into ordered nanostructures. We are a material science laboratory with an emphasis on organic chemistry and medical-biological applications. The group is developing new organic materials that are used for various applications, such as 3D hydrogels for bone tissue regeneration, which exhibit extraordinary mechanical properties and durability, along with biocompatibility and controlled drugs release. A central technique is the formation of hybrid hydrogels, using two or more different building blocks, resulting in a 3D hydrogel with novel and diverse properties that can be easily fine-tuned. In addition, the laboratory is interested in antimicrobial activity of nanostructures for coatings and incorporation into composite materials for dental medicine application.

Publications

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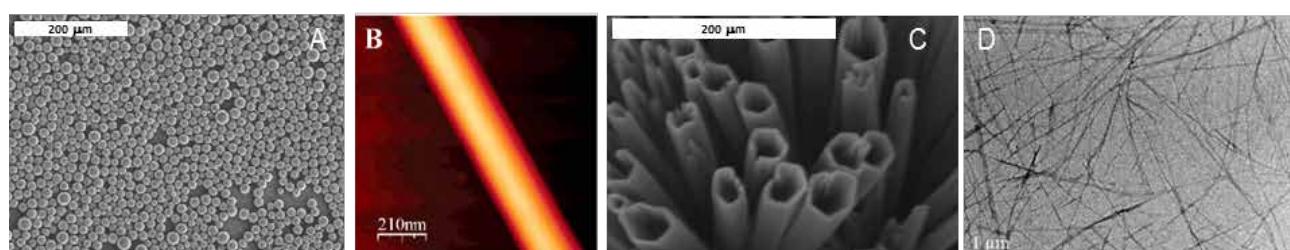
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Self-Assembled Nano-Structures: **(A)** Scanning electron microscopy micrograph of peptide nanospheres. **(B)** Atomic force microscopy image of a peptide nanotube. **(C)** Array of ordered vertically aligned peptide nanotubes. **(D)** Transmittance electron microscopy micrograph of 3D hydrogel demonstrating the presence of elongated fibrils.

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Ben-Nun Y, Fichman G, **Adler-Abramovich L**, Turk B, Gazit E, Blum G. Cathepsin nanofiber substrates as potential agents for targeted drug delivery. *J Control Release*. 2017;257:60-67.

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Arginine-presenting peptide hydrogels decorated with hydroxyapatite as biomimetic scaffolds for bone regeneration. *Biomacromolecules*; 2017, 18, 3541-3550.

Reviews

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Grants

2016 – 2019	Model system for biominerization and bone formation in microgravity, Space Program, Ministry of Science, Technology and Space.
2017-2020	Synthesis and characterization of 3D nanostructure for bone tissue regeneration, Israel Science Foundation (ISF) - New-Faculty Equipment Grants.
2017-2021	Biomineralized self-assembled peptide hydrogel scaffolds for bone tissue regeneration, Israel science foundation (ISF) - Individual Research Grants.
2017-2021	Smart bionanomaterials for solar-driven hydrogen production, Israel Science Foundation (ISF) - Research Centers
2017-2022	SNOW-Non woven smart materials, Maagad-Israeli Innovation Authority
2018-2020	Development of dental materials with anti-biofilm properties, Kamin-Israeli Innovation Authority
2018-2021	Developing a platform of peptides nano-structures containing enzymes capable of degrading signal molecules involved in cell to cell communication, Ministry of Agriculture



Prof. Tamar Brosh, Ph.D.

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Biochemical Aspects of Dental Restorations and Orthodontic Tooth Movement

Positions

Professor, Sackler Faculty of Medicine

Head, Department of Oral Biology

Research

Biomechanical behavior and response to dental treatments are studied in our laboratory and our *in vivo* studies.

Restorative materials, including bonding materials, are tested for performance (e.g., durability and strength). We work on improving their properties by combining nano-tubes with the materials (in cooperation with the Molecular Microbiology and Biotechnology Department). For this, we study their shear strength (Fig. a), diametral-tensile strength and shear bond strength.

Aiming to understand the phenomenon of vertical root fractures, we work on evaluating the influence of various posts materials (used in endodontic treatment) on root-surface strain development by measuring the surface strains with strain gauges.

Regarding orthodontics, we try to understand the behavior and influence of transparent aligners on the movement of teeth *in vivo* (Fig. b).

Publications

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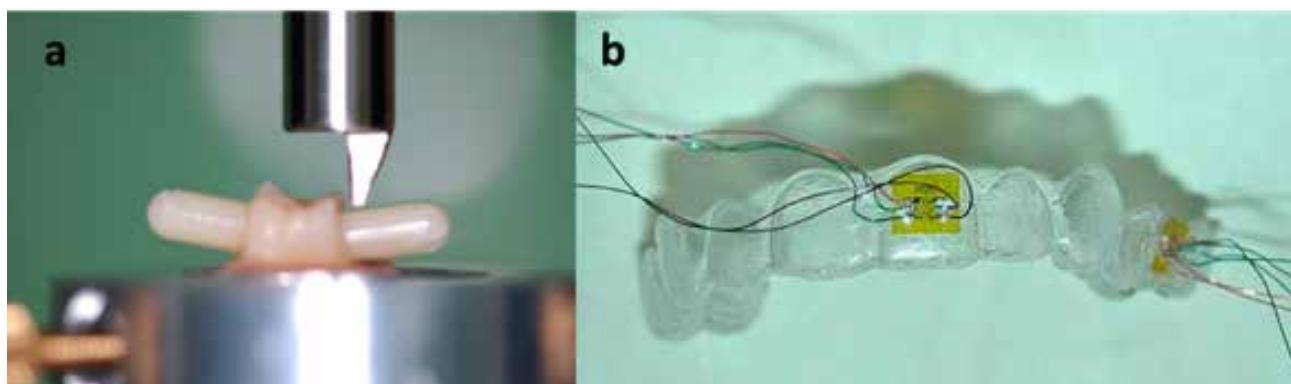
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a. Shear bond test experiment. b. Transparent aligner equipped with strain gauges

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Prof. Ilana Eli, D.M.D.

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Behavioral Sciences in Dentistry

Positions

Professor, Sackler Faculty of Medicine

Research

Our group specializes particularly in the field of behavioral sciences in dentistry including clinical hypnosis, oro-related behavioral dysfunctions, psycho physiological aspects of acute and chronic pain, and stress in clinical and other settings.

Research topics:

1. Stress, pain and behavior in dental care
2. Oro-related behavioral dysfunctions (dental fear, anxiety and phobia, excessive gagging reflex)
3. Chronic orofacial pain and TMD
4. Psychosocial factors in pain
5. Sexual and oral functioning

Publications

E. Elran, G. Bronner , N. Uziel, **I. Eli**, ND Kitrey, G. Raviv. Impact of vaginal penetration difficulties on sexual function of women and their male partners. *The European Journal of Contraception and Reproductive Health Care*, 19:352-358, 2014

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Chapters

I. Eli and R. Gatchel. Psychosocial and Behavioral Modes of Orofacial Pain. In: *Orofacial Pain*, B. Sessle (Ed.), IASP Press, Seattle, USA 251-268



Dr. Rachel Sarig, Ph.D., D.M.D.

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Facial and Dental Anthropology: Evolutionary Aspects in Physiological and Pathological Processes in Human Dentition

Position

Lecturer, Maurice and Gabriela Goldschleger School of Dental Medicine, Sackler Faculty of Medicine

Research

Many of the current oral diseases and malformations have their roots in our evolutionary history. Knowing the evolutionary processes that led to the current shape and size of our skull and mandible may greatly bear on our understanding of phenomena such as malocclusions (i.e., crowding, rotation, overbite), dental malformations (i.e. impaction, missing and supernumerary teeth) and oral diseases (caries, attrition, periodontal diseases). Treatment strategy should take into consideration evolutionary reasoning involved in shaping our face and jaws, ignoring them may end, in the long run, in treatments' failure.

Understanding the evolutionary constraints that have acted through time on our masticatory system may

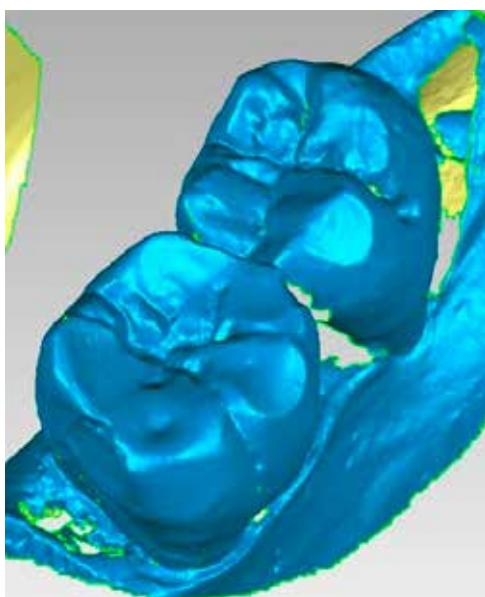
help us planning and establishing better treatment strategies. Long-term evolutionary processes such as decrease in jaws and teeth size, higher prevalence of impacted teeth and the loss of teeth in the arch, are all important factors that should be considered.

Publications

R. Sarig, N. Lianopoulos, I. Hershkovitz, AD. Vardimon. The arrangement of the interproximal interface in the human permanent dentition. *Clinical Oral Investigation*, 17, 731–738, 2013.

J. Abbas, K. Hamoud, H. May, N. Peled, **R. Sarig**, D. Stein, D. Alperovitch-Najenson, I. Hershkovitz. Socioeconomic and physical characteristics of degenerative lumbar spinal stenosis individuals. *Spine*, 38, 554–556, 2013.

N. Shpack, RG. Bar-Ness, D. Gazit, **R. Sarig**, AD. Vardimon. Efficacy of three hygienic protocols in reducing biofilm adherence to removable



Malocclusion of developmental origin already present in early anatomically modern humans (AMH) (the present case being the oldest known case, dated to ca. 100,000 years) (A). Morphological evaluation of molar teeth using 3D scanning and geometric morphometric analysis (B).

thermoplastic appliance. *Angle Orthodontics*, 84, 161-170, 2013.

R. Sarig, V. Slon, J. Abbas, H. May, N. Shpack, A.D. Vardimon, I. Hershkovitz. Malocclusion in early anatomically modern human: a reflection on the etiology of modern dental misalignment. *PLoS One*, 8, e80771, 2013.

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Sarig, R., Gopher, A., Barkai, R., Rosell, J., Blasco, R., Weber, G.W., Fornai, C., Sella-Tunis, T., Hershkovitz, I. How did the qesem cave people use their teeth? Analysis of dental wear patterns. *Quaternary International*, 398, 136-14. 2016.

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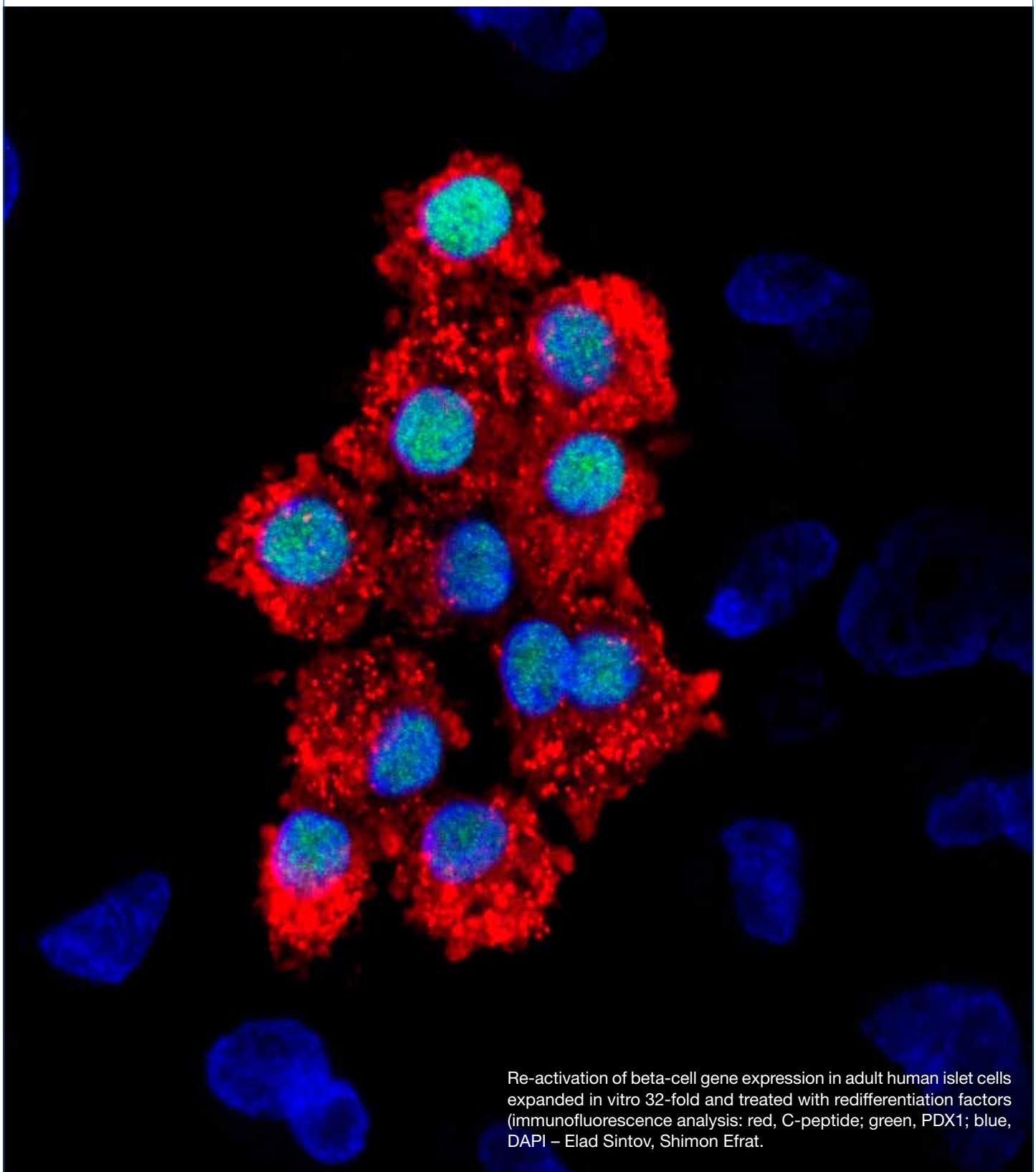
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Grants

2016-2019 Israel Science Foundation

Diabetes, Metabolic and Endocrine Diseases



Re-activation of beta-cell gene expression in adult human islet cells expanded in vitro 32-fold and treated with redifferentiation factors (immunofluorescence analysis: red, C-peptide; green, PDX1; blue, DAPI – Elad Sintov, Shimon Efrat).



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Cell Replacement Therapy for Diabetes

Position

Professor, Sackler Faculty of Medicine
Chair, Department of Human Molecular Genetics and Biochemistry
Nancy Gluck Regan Chair in Juvenile Diabetes

Research

Our research focuses on the development of a cell replacement therapy for diabetes, in which the insulin-producing pancreatic beta cells are destroyed or malfunction.

Our approaches for generation of an abundant source of cells for transplantation include expansion and differentiation in tissue culture of beta cells from human organ donors, as well as differentiation of human stem cells into insulin-producing cells.

Publications

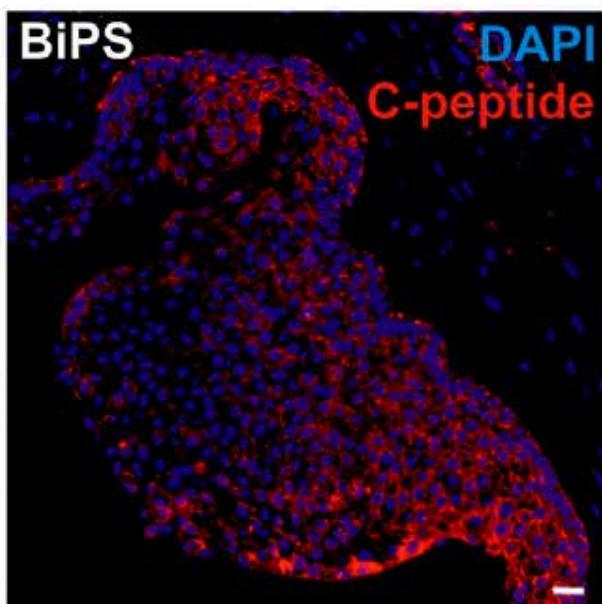
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Sintov E, Nathan G, Knoller S, Pasmanik-Chor M, Russ HA, **Efrat S** (2015) Inhibition of ZEB1 expression induces redifferentiation of adult human β cells expanded in vitro. *Sci Rep* 5:13024.

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Friedman-Mazursky O, Elkon R, Efrat S (2016) Redifferentiation of human islet β cells expanded in vitro by inhibition of ARX. *Sci Rep* 6:20698.



Pluripotent stem cells derived from human beta cells can be greatly multiplied in tissue culture and then induced to redifferentiate into insulin-producing cells. Red, staining for insulin; blue, cell nuclei.

Turner M, Shenhav L, Wesolowska-Andersen A, Bennett AJ, Barrett A, Gloyn AL, McCarthy MI, Beer NL, **Efrat S.** (2017) Genes associated with pancreas development and function maintain open chromatin in iPSCs generated from human pancreatic beta cells. *Stem Cell Reports.* pii: S2213-6711(17)30427-7.

Reviews

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Bar Y, Efrat S (2014) The Notch pathway in beta-cell growth and differentiation. In The Pancreatic Beta

Cell, Litwack G (ed.), Vitamins and Hormones vol. 95, Academic Press/Elsevier, pp. 391-405.

Efrat S (2016) Mechanisms of adult human β -cell in-vitro dedifferentiation and redifferentiation. *Diabetes Obes Metab* (in press).

Grants

2012-2017 Innovative Medicines Initiative (IMI)

2013-2017 Israel Science Foundation (ISF)

2015-2017 Kadimastem Ltd.

2015-2018 Rosetrees Trust



Prof. Koret Hirschberg, Ph.D.

Department of Pathology
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Intracellular Membrane Trafficking

Position

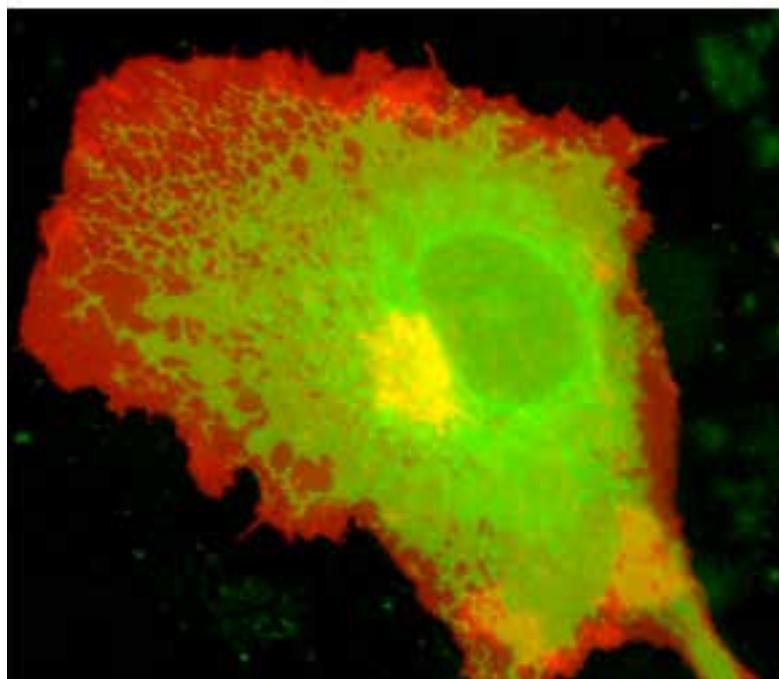
Professor, Sackler Faculty of Medicine

Research

Our laboratory focuses on investigating the protein and membrane interactions that delineate membrane transport processes. We are especially interested in the functions of cargo recognition, concentration and targeted delivery to distinct cellular membranes. All transport processes use the membrane as their final substrate for example: fusion, budding, generation of distinct domains and the establishment of curvature. Combined, these functions shape the cellular transport machinery, one of the major systems that maintain homeostasis communication and response to the external environment in health and disease.

To understand these processes in detail, one must recognize that protein–protein as well as protein–lipid interactions are involved. Studying the latter, namely protein–lipid interaction is challenging since these interactions are less specific and complex experimental systems are to be used. In other words, to study the association between a protein to its proximal native lipid environment, membranes cannot be disrupted or solubilized.

In our laboratory, we combine traditional biochemical analysis with live cell imaging and quantitative kinetic modeling to gather information on the dynamic features of the cellular secretory transport machinery. Experiments are carried out using expression of fluorescent protein tagged proteins in living intact cells using laser scanning confocal microscopes. We use a range of state-of-the-art experimental setups



The secretory membrane system: PM (red), Golgi apparatus (yellow) and ER (green).

such as: Time-lapse imaging, three-dimensional reconstruction, multicolor imaging, photobleaching/photoactivation-based manipulations and Bi-Molecular fluorescent complementation (BiFC). Kinetic modeling and simulation software is often used to extract values of kinetic coefficients or to perform model testing from the wealth of information hidden in the images sequences.

Publications

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Skalka N., Caspi M., Lahav-Ariel L., Loh Y.P., **Hirschberg K**., Rosin-Arbesfeld R. Carboxypeptidase E (CPE) inhibits the secretion and activity of Wnt3a. *Oncogene* 35, 6416-28. 2016.

Yonemura Y., Li X., Muller K., Kramer A., Atigbire P., Mentrup T., Feuerhake T., Kroll T., Shomron O., Nohl R., Arndt H.D., Hoischen C., Hemmerich P., **Hirschberg K**., Kaether C., Inhibition of cargo export at ER exit sites and the trans-Golgi network by the secretion inhibitor FLI-06, *J Cell Sci.* 129, 3868-77. 2016. *- co-corresponding author

Nevo-Yassaf I, Lovelle M., Nahmias Y., **Hirschberg K** *, Sklan E. H.*. Live cell Imaging and analysis of lipid droplets biogenesis in HCV infected cells. *Methods*. S1046-2023,16, 30491-1. 2017. *- co-corresponding author

Grants

2016-2018 Jerom Lejune Foundation

2016-2019 Israel Science Foundation (ISF)



Dr. Limor Landsman, Ph.D.

Department of Cell and
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Beta-Cell Function and Dysfunction: the Role of Microenvironmental Cues

Position

Senior Lecturer, Sackler Faculty of Medicine

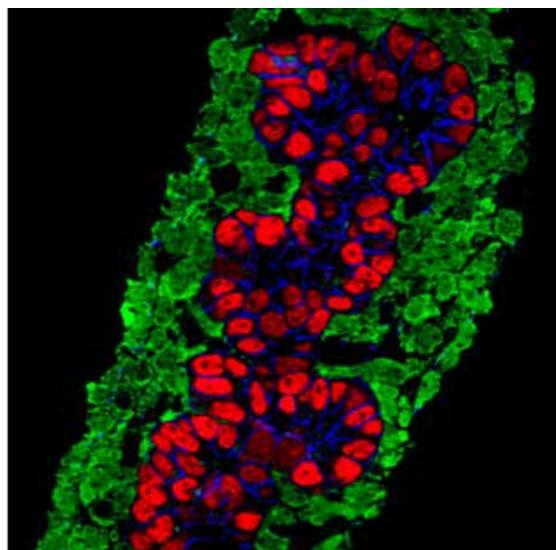
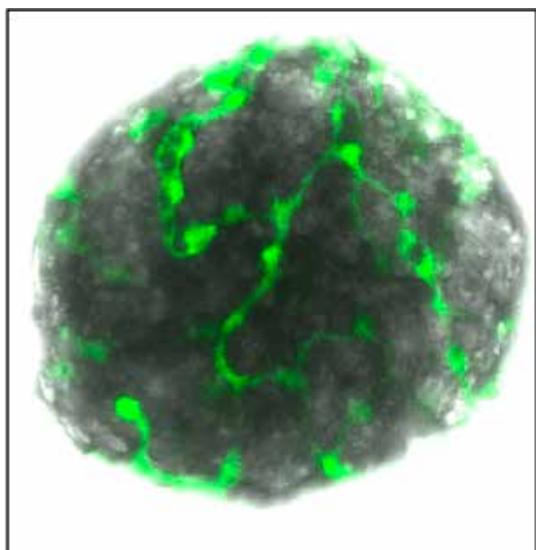
Research

Maintenance of blood glucose levels is dependent upon the tight regulation of insulin secretion from pancreatic beta-cells. Insufficient insulin secretion, whether due to reduced beta-cell numbers, or impaired beta-cell function, leads to diabetes. Our group studies how insulin-producing beta-cells maintain their functionality in health, and how it is lost in diabetes. To this end, we research the cross talk between insulin-producing cells and cells in their microenvironment. Our results indicate the pivotal role of pericytes in the regulation of insulin secretion, and blood glucose levels. Using transgenic mouse models, we study how insulin-producing cells

communicate with their microenvironment, and how this communication is affected during diabetes.

In addition, we study how the pancreas develops during embryogenesis. Our findings, along with previous findings, help to consolidate that pancreas mesenchymal cells are crucial for proper pancreas and beta-cell embryonic development. Using transgenic mouse models, we investigate what signals are produced by mesenchymal cells, and how these signals may guide beta-cell development.

In summary, our goals are to uncover the different aspects of pancreas biology, namely its development in the embryo, and its function in the adult. We aim to answer these scientific questions by focusing on the interplay between beta-cells and other pancreatic cell types in both healthy and diseased mouse models.



Beta-cell microenvironment in the embryonic and adult pancreas. Left, Mesenchymal cells (green) surround the developing pancreatic bud (red and blue) and support normal organogenesis. Right, Pericytes (green) form a network around the Islet of Langerhans (gray) in the adult pancreas and support insulin secretion from beta-cells.

Publications

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Guo T., **Landsman L.**, Li N., Hebrok M. (2013) Factors expressed by murine embryonic pancreatic mesenchyme enhance generation of insulin-producing cells from hESCs. *Diabetes* 62:1581-92.

Sasson A., Rachi E., Sakhneny L, Baer D., Lisnyansky M., Epshtain A. and **Landsman L.** (2016) Islet pericytes are required for beta-cell maturity. *Diabetes*, 65:3008-3014.

Russ HA, **Landsman L**, Moss CL, Higdon R, Greer RL, Kaihara K, Salomon R, Kolker E, and Hebrok M. (2016) Dynamic proteomic analysis of pancreatic mesenchyme reveals novel factors that enhance human embryonic stem (hESC) to pancreatic cell differentiation. *Stem Cells International*. 6183562

Epshtain A, Sakhneny L and **Landsman L.** (2017) Isolating and analyzing cells of the pancreas mesenchyme by flow-cytometry. *JoVE* 119, e55344

Hibsher D, Epshtain A, Oren N and **Landsman L.** (2016) Pancreatic mesenchyme regulates islet cellular

composition in a patched/hedgehog-dependent manner. *Sci Rep* 6, 38008.

Epshtain A, Rachi E, Sakhneny L, Mizrahi S, Baer D and **Landsman L.** (2017) Neonatal pancreatic pericytes support beta-cell proliferation. *Mol Metab*, 6, 1330-1338.

Grants

2013-2018	European Research Council (ERC) Starter Grant β-cell dysfunction in diabetes: elucidating the role of islet-associated mesenchymal cells
2014-2017	Israel Ministry of Health Elucidating the role of pancreatic mesenchyme secreted factors in beta-cell function and diabetes progression
2016 – 2018	German-Israeli Foundation (GIF), with Dr. Francesca Spagnoli
2017 - 2019	European Foundation for the Study of Diabetes (EFSD) / Novo Nordisk Programme for Diabetes Research in Europe



Prof. Drorit Neumann, Ph.D.

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Erythropoietin and Its Receptor in Health and Disease – Basic and Clinical Aspects

Positions

Professor, Sackler Faculty of Medicine

Head, Dr. Miriam and Sheldon Adelson Graduate School of Medicine, Sackler Faculty of Medicine

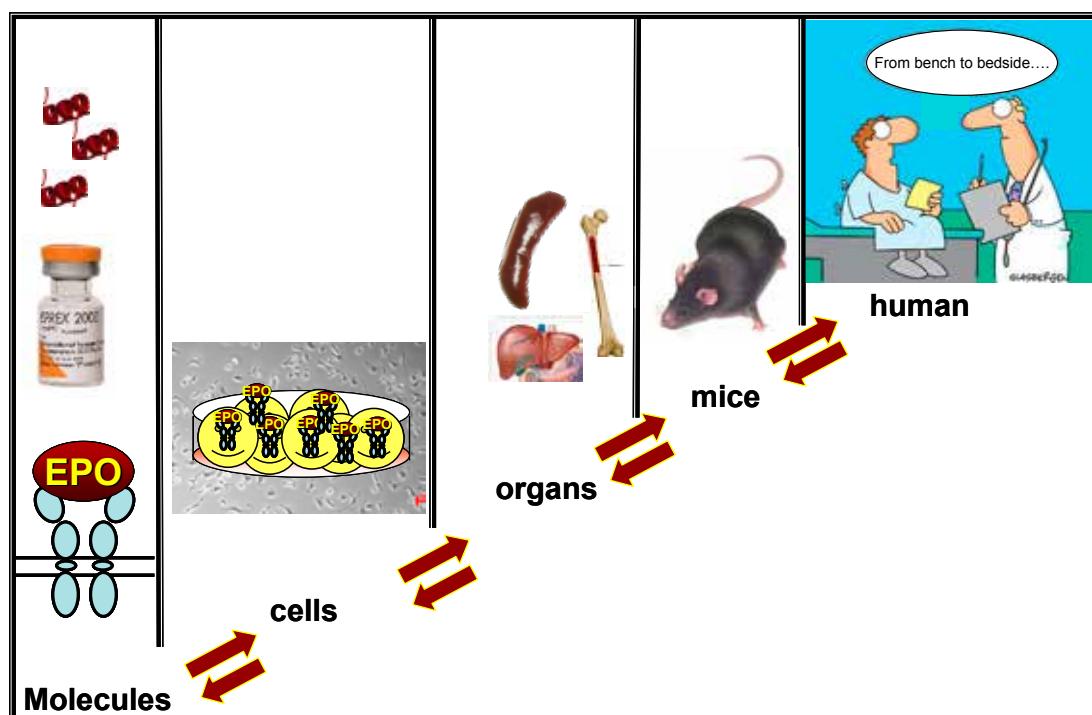
Research

Our research is focused on erythropoietin (EPO), the major hormone that regulates erythropoiesis, operating via activation of its cell surface receptor (EPO-R) on erythroid progenitor cells. Our choice to work on this EPO/EPO-R system was initiated to employ it as a model for understanding basic mechanisms of hormone/receptor function and regulation. Through this research, in a longstanding collaboration with Prof. Mittelman from the Sourasky Medical Center, we made a novel, original discovery, suggesting that EPO may actually act as a pleiotropic hormone with anti-neoplastic, immunomodulatory activities. Our research is thus focused on both

the basic mechanisms of hormone/receptor interaction, as well as the function of this hormone as an immunomodulator, and as we have most recently shown, a regulator of bone metabolism (in collaboration with Dr. Yankel Gabet from the Department of Anatomy and Anthropology, Sackler Faculty of Medicine). The studies are based on a variety of in-vitro and murine experimental models, and also include an avenue of elucidating the relevance and possible clinical application of the results.

Publications

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Bento C., M Percy, H. Cario*, B. Gardie, T. M. Magalhães, R. van Wijk, S. Perrotta, D. R. Fulvi, H. Almeida, C. Rossi, F. Girodon, M. Åström, **D. Neumann**, S. Schnittger, B. Landin, M. Minkov, M. L. Randi, S. Rives, L. Ribeiro, S. Hermouet, M. F. McMullin*, on behalf of ECE-Consortium§ Genetic basis of Congenital Erythrocytosis: mutation update and online databases. *Hum Mut*, 35:15–26 (2014).

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Ohana Haim Y., N. Deshet Unger, M. C. Souroujon, M. Mittelman and **D. Neumann** Resistance of LPS-activated bone marrow derived macrophages to apoptosis mediated by dexamethasone *Sci. Rep.* 4: 4323 (2014).

Gross M., N. Ben-Califa, M. F. McMullin, M. J. Percy, C. Bento, H. Cario, M. Minkov and **D. Neumann**. Polycythemia-inducing mutations in the erythropoietin receptor (EPOR): Mechanism and function as elucidated by epidermal growth factor receptor (EGFR) – EPOR chimeras. *Br. J. Haematol.* 165:519-28 (2014).

Maxwell P., F. Melendez-Rodríguez, K. B Matchet, J. Aragones, N. Ben-Califa, H. Jaekel, L. Hengst, H. Lindner, A. Bernardini, U. Brockmeier, J. Fandrey, F. Grunert, H. Oster, M. Mittelman, M. El-Tanani, M. Thiersch, E. M. Schneider Gasser, M. Gassmann, D. Dangoor, R. J. Cuthbert, A. Irvine, A. Jordan, T. Lappin, J. Thompson and **D. Neumann**. Novel antibodies directed against the human erythropoietin receptor: creating a basis for clinical implementation. *Br. J. Haematology* 168:429-42 (2015). *The work represents efforts of European consortium EpoCan, FP7 call, coordinated by Prof D. Neumann.

Hiram-Bab S., T. Liron, N. Deshet-Unger, M. Mittelman, M. Gassmann, M. Rauner, K. Franke, B. Wielockx, **D. Neumann** and Y.I Gabet. Erythropoietin directly stimulates osteoclast precursors and induces bone loss. *FASEB J.* 29(5):1890-900, (2015) Commentary on manuscript: *Nat Rev Endocrinol.* 11:2643-2644. 2015

Rauner M, K. Franke, M. Murray RP Singh, S. Hiram-Bab, U. Platzbecker, M. Gassmann, M. Socolovsky, **D. Neumann**, Y. Gabet, T. Chavakis, LC Hofbauer, B. Wielockx. Increased EPO levels are associated with bone loss in mice lacking phd2 in epo-producing cells. *J Bone Miner Res.* 31:1877-1887 (2016).

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Chapters and Reviews

Ohana Y., Liron T., Prutchi-Sagiv, S., Mittelman M. Souroujon M.C. and **D. Neumann** Erythropoietin second edition Handbook of Biologically Active Peptides (Abba J. Kastin, ed.), Elsevier, San Diego, pp 1619-1626 (2013).

Hiram-Bab S, **Neumann D**, Gabet Y. Erythropoietin in bone - Controversies and consensus. *Cytokine*. 89:155-159 (2017).

Hiram-Bab S., **Neumann D**. and Gabet Y. Context-Dependent Skeletal Effects of Erythropoietin. *Vitam Horm.* 105:161-179 (2017).

Grants

2015-2017	Israel Cancer Association – Erythropoietin in multiple myeloma – improving outcome without compromising bone
2017-2021	Israel Science Foundation - A Role for Erythropoietin in Regulation of Bone Metabolism by Monocytes and B cells
2018-2020	German Israeli Foundation (Together with Y. Gabet, TAU and B. Wielockx and M. Rauner, Dresden) – Pathophysiological impact of erythropoietin on bone density and strength



Prof. Edgar Pick, M.D., Ph.D.

Department of Clinical Microbiology and
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Assembly of the Superoxide-Generating NADPH Oxidase Complex in Health and Disease

Position

Professor Emeritus, Sackler Faculty of Medicine

Julius Friedrich Cohnheim Laboratory of Phagocyte Research

Member, Editorial Board, *The FASEB Journal*

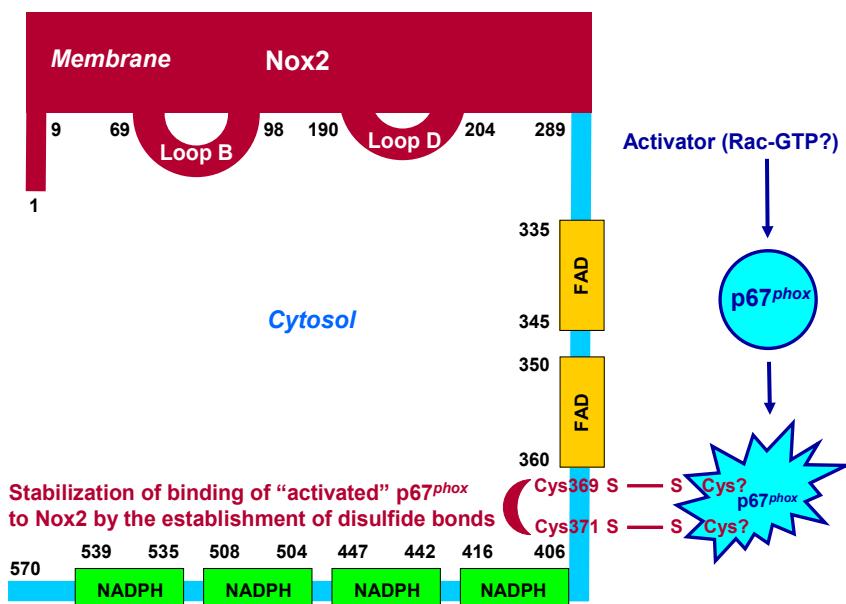
Member, Editorial Board, *International Journal of Hematology Research*

Research

We are studying the production of reactive oxygen species (ROS) by phagocytes. ROS are generated by an enzyme complex, known as the NADPH oxidase. Our group is responsible for many of the seminal advances in the biochemistry and molecular biology of the NADPH oxidase complex, including: the standard micro-assay for the measurement of ROS (1130 citations); the design of a universally used

method for measuring H₂O₂ production by cells in culture (1084 citations); the development of the first cell-free system of ROS production leading to the discovery of the cytosolic oxidase components (377 + 366 = 743 citations); the discovery of the role of the small GTPase Rac in oxidase activation (951 citations); the introduction of “peptide walking” to identify sites of protein-protein interaction, and the construction of chimeric cytosolic oxidase activators. The laboratory is equipped for the performance of advanced biochemical and molecular biology techniques.

The most recent interest of our group is focused on the mapping of the hotspots of interaction between the catalytic oxidase component Nox2 and the cytosolic activator p67^{phox}. We found that the dehydrogenase region of Nox2 (residues 288-570) contains a Cys-Gly-Cys (CGC) triad (residues 369-371), which serves as a binding site for p67^{phox}. This finding is based



Schematic representation of the stabilization of binding of “activated” p67^{phox} to the dehydrogenase region of Nox2, involving the establishment of disulfide bonds between cysteines 369 and 371 in Nox2 and yet unidentified cysteines in p67^{phox}

on a novel methodology, designed by us, in which we measure the binding of recombinant p67^{phox} to an array of synthetic overlapping peptides covering the sequence of the dehydrogenase region of Nox2. Two Nox2 peptides that share the CGC triad, at their C- and N-termini, respectively, were found to bind p67^{phox}. “Mutating” either C369 or C371 to R resulted in loss of p67^{phox} binding. Chemical reduction of CGC-containing peptides also led to loss of binding. Linking the two cysteines by a disulfide bond resulted in a marked increase in binding. We concluded that binding of p67^{phox} to the catalytic component of the NADPH oxidase complex is redox regulated and involves the establishment of disulfide bonds between p67^{phox} and Nox2. The CGC triad might have a dual role by acting both as a protein disulfide isomerase (PDI) and by providing the cysteines for the establishment of disulfide bonds with p67^{phox}. This novel hypothesis rests on the evidence that the CGC motif mimics functionally and structurally the CGHC catalytic site of members of the PDI family. Recently, we showed that a recombinant Nox2 construct possesses

PDI activity, exhibits limited sequence similarity with PDIA3, and reacts with an anti-PDIA3 antibody. These findings have a key *in vivo* equivalent because a C369R mutation in human Nox2 causes Chronic Granulomatous Disease (CGD), an inborn defect resulting in the inability of phagocytes to produce ROS, leading to the failure to resist infections by bacteria and fungi.

Publications

Roos, D., van Buul, J. D., Tool, A. T. J., Matute, J. D., Marchal, C. M., Hayee, B., Köker, M. Y., de Boer, M., van Leeuwen, K., Segal, A. W., **Pick, E.**, and Dinauer M. C. Two CGD families with a hypomorphic mutation in the activation domain of p67-phox. *J. Clin. and Cell. Immunol.* 5:3, 2014

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role in the interaction with p67phox. *J Leukoc Biol.* 98:859-74, 2015

Bechor, E., Dahan, I., Fradin, T., Berdichevsky, Y., Zahavi, A., Federman Gross, A., Rafalowski, M., and **Pick, E.** The dehydrogenase region of the NADPH oxidase component Nox2 acts as a protein disulfide isomerase (PDI) resembling PDIA3 with a role in the binding of the activator protein p67phox. *Front. Chem.* 3:3, 2015

Dahan, I., Smith S. M. E., and **Pick, E.** A Cys-Gly-Cys triad in the dehydrogenase region of Nox2 plays a key role in the interaction with p67phox. *J. Leukoc. Biol.* 98: 859-874, 2015

Pick, E. Absolute and relative activity values in assessing the effect of NADPH oxidase inhibitors. *Antiox. Redox Signal.* 23: 1250-1251, 2015

Chapters/Reviews

Pick, E., Cell-Free NADPH Oxidase Activation Assays – “*In Vitro Veritas*”, In *Neutrophil Methods and Protocols*, 2nd Edition (Quinn, M. T., and DeLeo, F. R., eds), 339-403. Humana Press, 2014.

Pick, E., Role of the Rho GTPase Rac in the activation of the phagocyte NADPH oxidase: Outsourcing a key task. *Small GTPases*, 5(1), 2014.

Grants

2017-2018 Blavatnik Center for Drug Research, Synthetic peptides preventing the uncoupling of an autoinhibitory loop in the cytosolic component p67phox as models for the design of small molecular weight NADPH oxidase inhibitors

2017-2020 Israel Science Foundation (ISF), Uncoupling of an intramolecular bond in the cytosolic component p67-phox is the crucial event in the activation of the NADPH oxidase in phagocytes



Prof. Haim Werner, Ph.D.

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Molecular Biology of the Insulin-Like Growth Factor System

Positions

Professor, Sackler Faculty of Medicine

Head, Yoran Institute for Human Genome Research

Lady Davis Chair in Biochemistry

Research

The insulin-like growth factors (IGF1, IGF2) are a family of hormones with important roles in growth and development. The biological actions of the IGFs are mediated by the IGF1 receptor (IGF1R), a cell-surface receptor related to the insulin receptor. The IGF1R signaling pathway has an important role in the biochemical chain of events linking obesity, diabetes, and cancer. Our work is aimed at understanding the molecular and cellular events responsible for IGF1R expression in cancer. These studies are expected to generate information that might translate into more efficient IGF1R targeting approaches. Furthermore, a better understanding of the molecular biology of the IGF system will have important ramifications in areas such as obesity, metabolic syndrome, diabetes, and cancer research. Specific topics include:

- Interplay between the IGF signaling pathways and cancer genes (p53, BRCA).
- IGF1R targeting as a therapeutic approach in cancer.
- Epigenetic mechanisms in cancer development.
- Biological activities of insulin analogues.
- Metabolism and cancer.

Publications

Sarfstein, R., Friedman, Y., Attias-Geva, Z., Fishman, A., Bruchim, I. and **Werner, H.** (2013) Metformin down-regulates the insulin/IGF-I signaling pathway and inhibits different uterine serous carcinoma cells

proliferation and migration in p53-dependent or -independent manners. *PLoS One* 8:e61537.

Bitelman, C., Sarfstein, R., Sarig, M., Attias-Geva, Z., Fishman, A., **Werner, H.** and Bruchim, I. (2013) IGF1R-directed targeted therapy enhances the cytotoxic effect of chemotherapy in endometrial cancer. *Cancer Lett.* 335:153-159.

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Rubinfeld, H., Kammer, A., Cohen, O., Gorshtain, A., Cohen, Z.R., Hadani, M., **Werner, H.** and Shimon, I. (2014) IGF1 induces cell proliferation in human pituitary tumors – Functional blockade of IGF1 receptor as a novel therapeutic approach in non-functioning tumors. *Mol Cell Endocrinol.* 390:93-101.

Bruchim, I., Sarfstein, R., Reiss, A., Flescher, E. and **Werner, H.** (2014) IGF1R tyrosine kinase inhibitor enhances the cytotoxic effect of methyl jasmonate in endometrial cancer. *Cancer Lett.* 352:214-219.

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activities in skin keratinocytes. *Arch. Physiol. Biochem.*, 121:32-39.

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Shinderman Maman, E., Cohen, K., Weingarten, C., Nabriski, D., Twito, O., Baraf, L., Hercbergs, A., Davis, P.J., **Werner, H.**, Ellis, M. and Ashur-Fabian, O. (2016) The thyroid hormone-avb3 integrin axis in ovarian cancer: regulation of gene transcription and MAPK-dependent proliferation. *Oncogene* 35:1977-1987.

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Grants

2014-2018	“Mechanistic insights into IGF1-dependent longevity genes”. U.S.-Israel Binational Science Foundation.	2017-2018	Sackler School of Medicine, Tel Aviv University,
2014-2019	“Investigation of metabolic genes associated with cancer protection pathways in a rare congenital IGF1 deficiency”. Israel Science Foundation.		“Identification of thioredoxin-interacting protein (TXNIP) as a novel metabolic tumor suppressor gene”. Israel Cancer Association.
2016-2017	“Nuclear IGF1R translocation adds a new layer of signaling control”. Hendrik and Irene Gutwirth Fund for Diabetes Mellitus Research,		



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Role of the Insulin Receptor in Skin and Implications to Diabetes

Position

Senior Lecturer, Sackler Faculty of Medicine

Co-editor Diabetes/Metabolism Research and Reviews

D-Cure scientific committee

Research

The insulin receptor (IR) is one of the best-studied tyrosine kinase receptors. The receptor transmits insulin actions, and functions in the metabolic regulation of glucose in insulin sensitive tissues – muscle, liver and adipose tissue. In recent years, however, additional roles have emerged for the IR in various tissues including the regulation of transcription and translation, cell proliferation, differentiation and more.

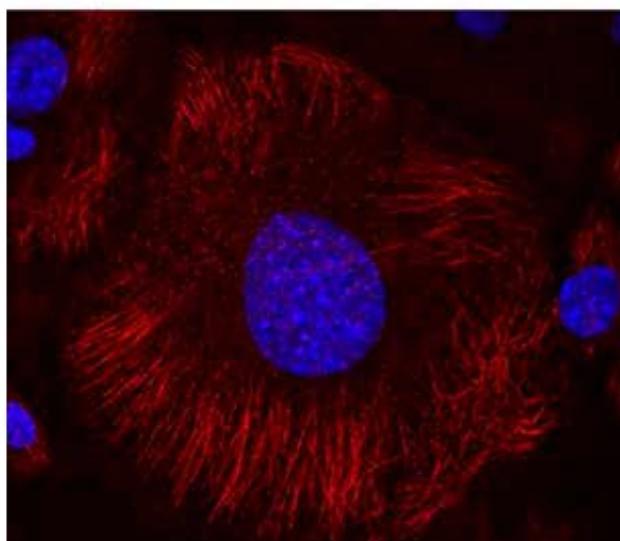
Our research interests center on the role of insulin and the IR in skin. The importance of insulin and the IR in skin is evident when insulin action is impaired in insulin resistance and diabetes: One of the major

known insulin resistance- and diabetes-associated skin complications is the impaired wound healing leading to amputations, increased illness and high mortality rates. Another skin complication associated with insulin resistance and diabetes is the marked increase in the risk, aggression, and recurrence of non-melanoma skin cancer.

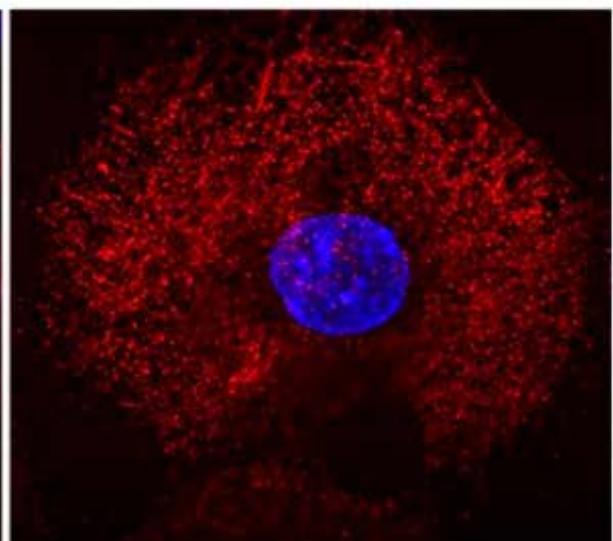
We have identified a previously unknown unique signaling pathway in which insulin via the IR regulates the assembly of the cellular cytoskeleton in skin cells. As can be seen in the figure attached below, IR inactivation, mimicking insulin resistance, led to a striking abnormality in the structure and assembly of cytoskeleton filaments in the skin epithelial cells.

Such an abnormality in cytoskeleton assembly can explain the observed changes in cellular division, proliferation and migration of IR null skin cells. Furthermore, since these processes are involved in wound healing from one hand as well as in tumorigenesis on the other hand, the disassembled cytoskeleton could be part of the pathogenesis

Control



IR null



leading to the development of the diabetes-associated skin pathologies.

In order to prove the importance of insulin and the IR in skin, and more specifically to wound healing and to skin tumorigenesis, we generated a skin-specific IR null mouse. In this mouse, the IR is inactivated only in the skin epidermis, without the development of hyperglycemia or other biochemical changes. By studying this mouse, we demonstrated that lack of epidermal IR by itself led to severely impaired wound healing. Furthermore, in another set of studies we demonstrated that IR inactivation in skin led to a marked decrease in transformation of skin cells *in vitro* as well as in skin tumorigenesis *in vivo*. Moreover, IR inhibition led to the reversal of transformation of transformed skin cells.

Our results indicate that the skin itself is abnormal in diabetes as a result of impaired insulin signaling, and that it should become an independent target for treatment and prevention of diabetes-associated skin pathologies. This research will lead to new means to reverse and prevent diabetes-associated skin complications from developing, effectively treat them, and halt their progression.

Publications

Solomon Zemler R, Weingarten G, Sarfstein R, Laron Z, Werner H, **Wertheimer E**. Insulin analogues display atypical differentiative activities in skin keratinocytes. *Arch Physiol Biochem*. 2015; 121:32-9.

Falik Zaccai TC, Kalfon L, Klar A, Elisha MB, Hurvitz H, Weingarten G, Chechik E, Fleisher Sheffer V, Haj Yahya R, Meidan G, Gross-Kieselstein E, Bauman D, Hershkovitz S, Yaron Y, Orr-Urtreger A, **Wertheimer E**. Two novel mutations identified in familial cases with Donohue syndrome. *Mol Genet Genomic Med*. 2014; 2:64-72.

Grants

2016-2017 Industry – Ramot TAU Technology Transfer Company

Patent

US 14/521,494 Methods and Compositions for Treating Cancer

Genomics & Personalized Medicine



Modified from Rukov JL, Shomron N. MicroRNA pharmacogenomics: Post-transcriptional regulation of drug response. *Trends Mol Med*. 2011



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Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders & Cancer

Positions

Professor, Sackler Faculty of Medicine

Boris Quentin Chair in Pathological Chemistry

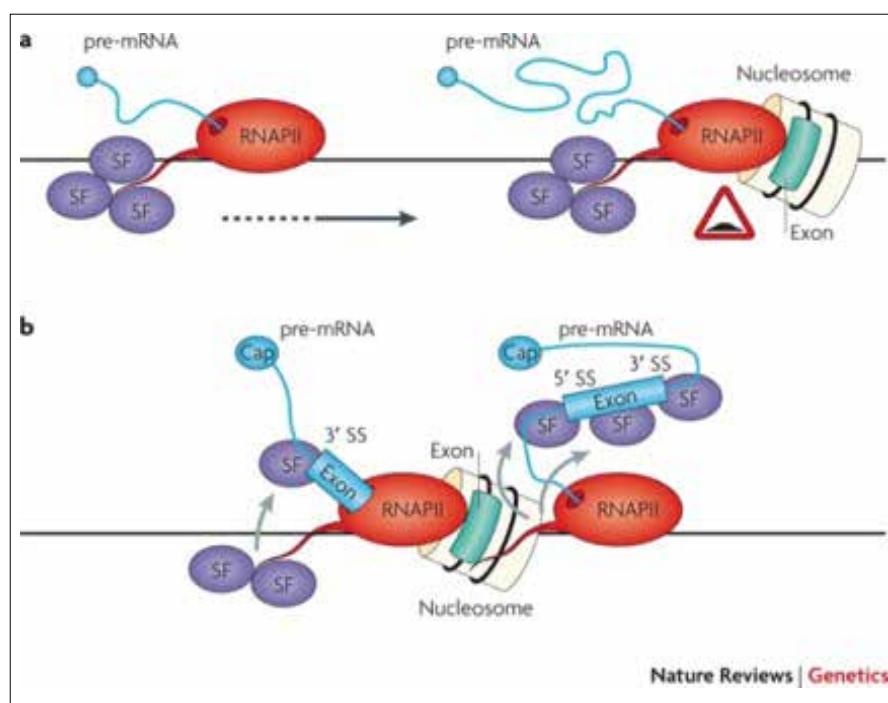
Research

By utilizing the unique strengths of our research group in bioinformatic analyses as well as in genomic and advanced molecular biology methodologies, we are able to make groundbreaking discoveries in the field of alternative splicing. We study how alternative splicing generates higher level of organism complexity, especially in human. However, this comes with a price, and alternative splicing also inflicts many genetic disorders and cancer. Our research involves these two facets of alternative splicing. On one hand, we found how new functions evolved via the generation of new exons (mostly in human). We have also showed how different layers

of gene expression affect each other, and found that chromatin organization and epigenetic markers (DNA methylation) mark the exon-intron structure. We also found that during the evolution of warm-blooded organisms two exon-intron gene architectures developed, and these also reflect the different effects of mutations on splicing in cancer and other genetic disorders. On the other hand, we study the impact of splicing abnormalities on colon and lung cancer, and we have recently discovered a new therapy for Familial Dysautonomia, a neurodegenerative disease caused by a splicing defect in the nervous system.

Publications

Naftelberg S, **Ast G***, Perlson E* (2017). Phosphatidylserine improves axonal transport by inhibition of HDAC and has potential in treatment of neurodegenerative diseases. *Neural Regen Res.* 12:534-537 *Co-corresponding author.



Nucleosome occupancy marks exons and is coupled to transcription. **a.** RNA polymerase II (RNAPII), associated with different splicing factors (SFs), travels along the gene and transcribes it. When RNAPII reaches an area with high nucleosome occupancy and encounters specific histone modifications that mark an exon, it is slowed down. **b.** This panel shows RNAPII and the nucleosome at the point at which their coupling marks the exon boundaries for the splicing machinery. RNAPII transcribes the exon and SFs detach from the carboxy-terminal domain of RNAPII and bind to the 3' splice site (3' SS) region of the precursor mRNA (pre-mRNA). During transcription elongation, additional SFs bind intronic and exonic splicing regulatory elements and the 5' SS.

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Reviews

Gelfman S, Ast G. (2013) When epigenetics meets alternative splicing: the roles of DNA methylation and GC architecture. *Epigenomics*. 5:351-3

Hollander D, Naftelberg S, Lev-Maor G, Kornblith AR, **Ast G**. How are short exons flanked by long introns defined and committed to splicing? *Trends Genet*. 2016.

Naftelberg S, **Ast G**, Perlson E. Phosphatidylserine improves axonal transport by inhibition of HDAC and has potential in treatment of neurodegenerative diseases. *Neural Regen Res*. 2017;12:534-537.

Grants

2013-2018	Israel Science Foundation, Identification of novel determinants of splicing regulation 2014-
2017	ISF-UGC (India) Binational Grant, Transcriptomic and proteomic analyses of colon cancer alternative splicing
2016-2017	ISF – Broad Institute, Site-specific DNA methylation
2016-2019	DKFZ-MOST, Network-based analysis of alternative splicing regulation
2017-2018	Israel Cancer Association (ICA), Analyses of alternative splicing aberrations in ovary cancer



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Genomic Analysis of Hereditary Hearing Loss

Positions

Professor, Sackler Faculty of Medicine

Vice Dean for Preclinical Affairs, Sackler Faculty of Medicine

Drs. Sarah and Felix Dumont Chair for Research of Hearing Disorders

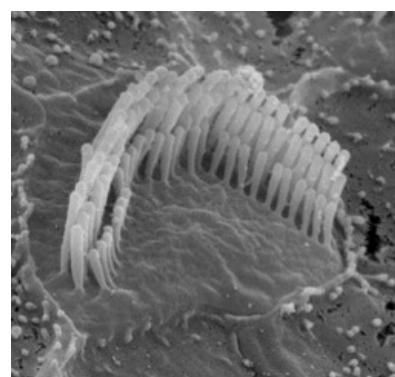
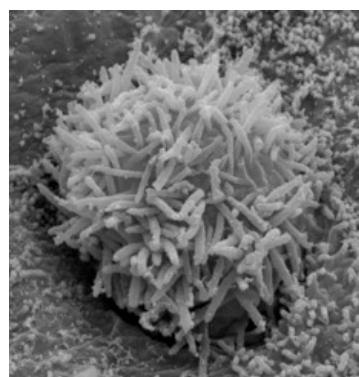
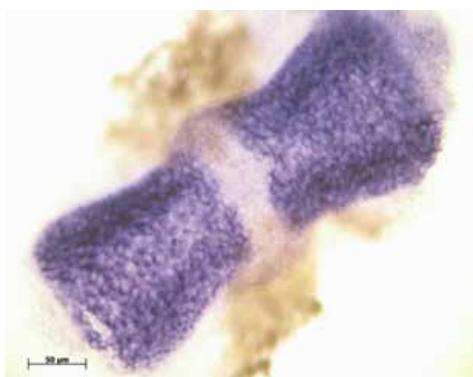
President, Israel Society of Auditory Research

Associate Editor, *European Journal of Human Genetics*

Research

Our primary interest is the genetic basis of hereditary hearing loss or deafness. Our group is working towards the identification, characterization and regulation of genes associated with hereditary hearing loss. For gene discovery, we focus on the Israeli Jewish and Palestinian Arab populations in the Middle East. Our studies have led to the identification of mutations in over 30 genes, since this is a genetically heterogeneous disease. We are employing deep sequencing, also known as massively parallel sequencing, to identify mutations using the latest genomic technology. Our work has provided the

link between gene discovery and clinical diagnosis in genetic clinics in medical centers throughout Israel. In addition, we have studied the auditory and vestibular systems of a dozen mouse mutants, focusing on mutation identification, morphological and functional analysis of the organ of Corti and its cells, and behavioral analysis of hearing and balance disorders. This has allowed us to define the pathways leading to deafness in mouse models for human deafness. We have demonstrated that microRNAs are essential for development and function of inner ear hair cells in vertebrates through microRNA expression, mouse mutants and target identification. We have recently isolated long non-coding RNAs (lncRNAs) by RNA-seq from the cochlear and vestibular sensory epithelium. Reconstruction and filtering of the transcriptome of the inner ear led to 3,239 lncRNA genes, yielding 721 novel lncRNAs. We are now working on understanding their mechanisms in the auditory and vestibular systems. Finally, we are building epigenomic maps of DNA methylation, chromatin structure, and histone modifications of the auditory system and integrating them with transcriptomics to establish pathway-specific transcriptional regulatory networks (TRNs).



Wild type and mutant hair cell bundles in the PCKO mouse, lacking microRNAs in the inner ear, demonstrated by scanning electron microscopy (2 left panels). *In situ* hybridization reveals expression of the microRNA-182 in the inner ear crista (right).

Publications

Manuscripts

Horn, H.F.* , Brownstein, Z.* , Lenz, D.R., Shrivatzki, S., Dror, A.A., Dagan-Rosenfeld, O., Friedman, L.M., Roux, K.J., Kozlov, S., Jeang, K.-T., Frydman, M., Burke, B., Stewart, C.L., and **Avraham, K.B.** (2013) The LINC complex is essential for hearing. *J. Clin. Invest.* 123:740-750

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Brownstein, Z.* , Abu-Rayyan, A.* , Karfunkel-Doron, D., Sirigu, S., Davidov, B., Shohat, M., Frydman, M., Houdusse, A., Kanaan, M., **Avraham, K.B.** (2013) Novel myosin mutations for hereditary hearing loss revealed by targeted genomic capture and massively parallel sequencing. *Eur J Hum Genet.* 22:768-75.

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Dror A.A., Lenz, D.R., Shrivatzki, S., Cohen, K., Ashur-Fabian, O. and **Avraham, K.B.** (2014) Atrophic thyroid follicles and inner ear defects reminiscent of cochlear hypothyroidism in *Slc26a4*-related deafness. *Mamm. Genome.* 25:304-316.

Rudnicki, A., Isakov, O., Ushakov, K., Shrivatzki, S., Weiss, I., Friedman, L.M., Shomron, N. and **Avraham**,

K.B. (2014) Next-generation sequencing of small RNAs from inner ear sensory epithelium identifies microRNAs and defines regulatory pathways. *BMC Genomics.* 15:484.

Sokolov, M., Brownstein, Z., Frydman, M. and **Avraham, K.B.** (2014) Apparent phenotypic anticipation in autosomal dominant connexin 26 deafness. *J. Basic Clin. Physiol. Pharmacol.* 25:289-292.

Jones, C., Qian, D., Kim, S.M., Li, S., Ren, D., Knapp, L., Sprinzak, D., **Avraham, K.B.**, Matsuzaki, F., Chi, F. and Chen, P. (2014) Ankrd6 is a mammalian functional homolog of *Drosophila* planar cell polarity gene diego and regulates coordinated cellular orientation in the mouse inner ear. *Dev. Biol.* 395:62-72.

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Bhonker, Y., Abu-Rayyan, A., Ushakov, K., Amir-Zilberstein, A., Shrivatzki, S., Yizhar-Barnea, O., Elkan-Miller, T., Tayeb-Fligelman, E., Kim, S.M., Landau, M., Kanaan, K., Chen, P., Matsuzaki, F., Sprinzak, D., **Avraham, K.B.** (2015) The GPSM2/LGN GoLoco motifs are essential for hearing. *Mamm. Genome.* 27:29-46.

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Perl, K., Ushakov, K., Pozniak, Y., Yizhar-Barnea, O., Bhonker, Y., Shrivatzki, S., Geiger, T., **Avraham, K.B.***, Shamir, R. (2016)* Reduced changes in protein compared to mRNA levels across non-proliferating tissues. *BMC Genomics.* 18:305. *Shared authorship.

Ushakov, K., Koffler-Brill, T., Rom, A., Perl, K., Ulitsky, I., **Avraham, K.B.** (2017) Genome-wide identification and expression profiling of long non-coding RNAs in auditory and vestibular systems. *Sci. Rep.*, 7:8637.

Reviews and Chapters

Brownstein, Z., Shrivatzki, S. and **Avraham, K.B.** (2013) Molecular Etiology of Deafness and Cochlear Consequences. In: Deafness. (A. Kral, A.N. Popper, R.R. Fay, eds). Springer-Verlag, NY. 47:17-39.

Higashi, T., Lenz, D.R., Furuse, M. and **Avraham, K.B.** (2013) A "Tric" to tighten cell-cell junctions in the cochlea for hearing. *J. Clin. Invest.* 123:3712-3715.

Idan, N., Brownstein, Z., Shavitzi, S., and **Avraham, K.B.** (2013) Advances in genetic diagnosis for hereditary hearing loss. *J Basic Clin Physiol Pharmacol.* 24:165-170.

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Ushakov, K., Rudnicki, A., **Avraham, K.B.** (2013) MicroRNAs in sensorineural diseases of the ear. *Front Molec Neurosci.* 6:52.

Bhonker, Y., Ushakov, K., **Avraham, K.B.** (2014) Human Gene Discovery for Understanding Development of the Inner Ear and Hearing Loss. In: Development of Auditory and Vestibular Systems. Fourth Edition. (R. Romand, I. Varela, eds). Elsevier.

Karfunkel-Doron, D., Brownstein, Z. and **Avraham, K.B.** (2014) Genomic Applications in Audiological Medicine. In: Genomic Medicine Principles and Practice. Second Edition. (D. Kumar, C. Eng, eds). Oxford University Press. 663-682.

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Avraham, K.B. What's hot about otoferlin. (2016) *EMBO J.* 35:2502-2504.

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Doetzlhofer, A. and **Avraham, K.B.** (2016) Insights into inner ear-specific gene regulation: epigenetics and non-coding RNAs in inner ear development and regeneration. *Semin. Cell Dev. Biol.* 65:69-79.

Yizhar-Barnea, O. and **Avraham, K. B.** (2017) Single cell analysis of the inner ear sensory organs. *Int J Dev Biol.* 61:205-213.

Grants

2011 – 2017 Gene Discovery for Hearing Loss in Middle East by Massively Parallel Sequencing, National Institutes of Health, Co-PI: Moien Kanaan

2014 – 2017 Epigenetic Regulation in the Mammalian Inner Ear. Binational Science Foundation. Co-PI: R. David Hawkins.

2016 – 2019 Identification of a Network of Short and Long Noncoding RNAs Controlling Mammalian Inner Ear Development. Israel Science Foundation. Foundation.

2018-2020 Function of microRNAs in the peripheral and central auditory system. German-Israeli Foundation for Scientific Research and Development (GIF). Co-PI: Hans Gerd Nothwang



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Genomic-scale Bioinformatics Exploration of Gene Regulation

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our research focuses on understanding mechanisms of gene regulation, which is an intricate multi-layer process. We apply bioinformatics methods to elucidate, on a genomic scale, how gene expression is regulated at the layers of gene transcription, transcript stability and protein translation. We aim at discovering how interruptions in these regulatory mechanisms contribute to the development of human pathological conditions, and how natural genomic variation affects our predisposition to common human diseases. Our analyses are based on novel deep-sequencing techniques that greatly boost our ability to systematically study gene regulation and decipher regulatory layers that were until recently largely unexplored.

Publications

Korkmaz G, Lopes R, Ugalde AP, Nevedomskaya E, Han R, Myacheva K, Zwart W, **Elkon R***, Agami R*. Functional genetic screens for enhancer elements in the human genome using CRISPR-Cas9. *Nat Biotechnol.* 2016, 34:192-8. (* Co-corresponding author)

Friedman-Mazursky O, **Elkon R**, Efrat S. Redifferentiation of expanded human islet β cells by inhibition of ARX. *Sci Rep.* 2016; 6:20698.

Creemers EE, Bawazeer A, Ugalde AP, van Deutekom HW, van der Made I, de Groot NE, Adriaens ME, Cook SA, Bezzina CR, Hubner N, van der Velden J, **Elkon R**, Agami R, Pinto YM. Genome-wide polyadenylation maps reveal dynamic mRNA 3'-end formation in the failing human heart. *Circ Res.* 2016, 118:433-8.

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Genomic Biomarkers for CNS Drug Response

Positions

Associate Professor, Sackler Faculty of Medicine
Director, National Laboratory for the Genetics of Israeli Populations

Senior Editor, *Pharmacogenomics*

Editorial Board: *Trends in Molecular Medicine*, *Genome Medicine*, *CNS Drugs*, *Drug Development Research*, *Pharmaceutical Biology* *Genomic Medicine*

Member of the NIH Pharmacogenomics Research Network (PGRN)

in clinical cohorts of major depression patients, lending support for our novel research approach.

A recent publication from our lab has been cited in a report by Scientific American: Unraveling the Mystery of How Antidepressant Drugs Work:

<http://www.scientificamerican.com/article/unraveling-the-mystery-of-ssris-depression/>

In addition to the research on genomic biomarkers, we are involved in research on bioethics and societal aspects of human genomics research.

Research

Our lab, serving as the National Laboratory for the Genetics of Israeli Populations (<http://nlgip.tau.ac.il>), was established in 1995 by the Israeli Academy for Sciences and Humanities as the National Biobank of Israel. The biobank includes DNA samples and immortalized lymphoblastoid cell lines from over 2000 unrelated healthy donors representing the large genetic diversity of Jewish, Arab and Druze communities of Israel. This novel resource has been applied by hundreds of research groups in Israel and abroad.

Our primary interest is in finding genomic biomarkers for the response to CNS drugs – , for improving personalized medicine with respect to both treatment efficacy and safety. Our research is currently focused on drugs for treating major depression, bipolar disorder, and Alzheimer's disease. These CNS diseases inflict huge societal costs, and biomarkers are needed for better treatment. We use human immortalized lymphoblastoid cell lines from unrelated healthy donors for comparing drug response and searching for genomic biomarkers, including mRNA for genes, and non-coding RNAs such as microRNAs (miRNAs) and small nucleolar RNAs (snoRNAs).

Among genes that we identified as tentative genomic biomarkers for the response to anti-depressant drugs, two genes, CHL1 and ITGB3, have been replicated

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biomarkers, Israel Science Foundation. Jointly with Illana Gozes

2014 – 2018 LITHOMICS: Lithium response biomarkers: comparative RNA sequencing of patients` lymphocytes and immortalized lymphoblastoid cell lines for personalized treatment of bipolar disorder, US – Israel Binational Science Foundation (BSF). Jointly with Peter Zandi, Thomas Schulze, Fernando Goes, James Potash, John Kelsoe



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microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position

Associate Professor, Sackler Faculty of Medicine

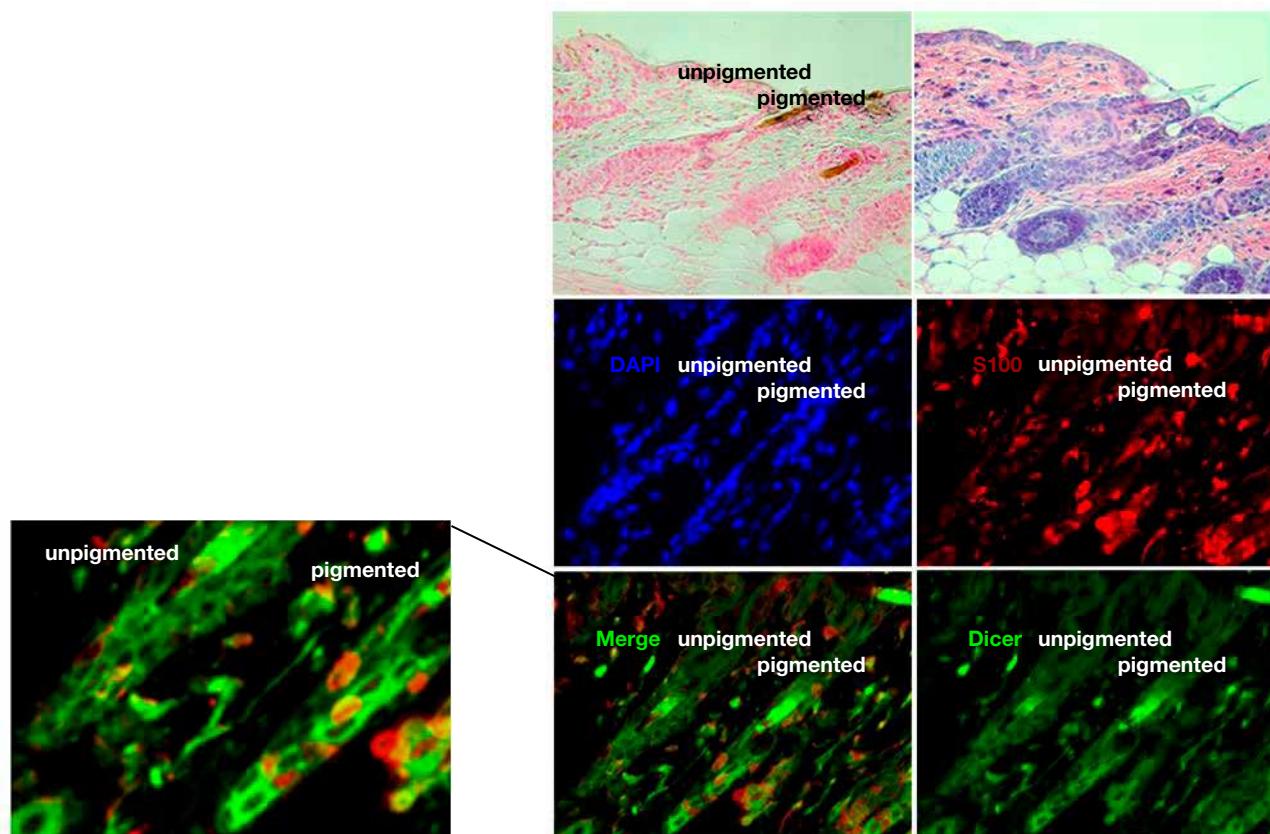
Research

Our scientific interests involve the role of microRNAs in development, differentiation and malignant transformation. Focusing our studies on melanocytes will provide the foundation for developing novel approaches in the prevention, diagnosis, and

treatment of skin cancer in general and melanoma in particular. In addition, we are intrigued by the possibility of using these systems as a model for exploring basic microRNA biogenesis beyond the cell specific context.

Publications

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Skin section, subject to H&E (left) and Fontana-Masson staining of melanin (right), shows pigmented and unpigmented regions of (floxed/floxed); Dct(Cre/Cre); Dct-lacZ; K14-scf mouse skin. Immunofluorescent staining of the skin section indicates expression of DICER (green) and S100 (red) (400x magnification). S100-stained epidermal and hair follicle melanocytes appear red; DAPI-stained nuclei appear blue. Merged image shows co-localization of DICER and S100 in the pigmented area of the skin (merge) compared to unpigmented region. Arrows in enlarged merge picture indicate the S100 and DICER co-localization.

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Grants

2016-2019 Melanoma Research Alliance (MRA)

2016-2021 European Research Council (ERC)



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Genetic and Metabolic Research of Age-Dependent Chronic Degenerative Disease

Positions

Professor Emeritus, Sackler Faculty of Medicine

Pollak Chair of Biological Anthropology

Honorary Research Fellow, King's College Medical School, London, UK

Research

Our research is focused on age-related chronic degenerative disease, such as osteoporosis, osteoarthritis, including disc degeneration disease and muscle mass loss – sarcopenia. The prevalence of sarcopenia is as high as 30% for those above 60 years old. In the elderly, the loss of muscle mass is correlated with profound physical impairment and disability with severe clinical consequences, including mobility loss, osteoporosis, osteoarthritis, increased fracture risk, dyslipidemia, insulin resistance, and increased mortality. However, it is also often developed at a much younger age. Despite the above clinical significance and despite the fact that a strong familial component in muscular mass variation is well established, there is almost a total lack of

molecular genetic studies of this trait. This is in a great contradiction to studies concerning the other two body composition components: bone and fat mass, for each of which many dozens of studies have been published during the past two decades. It is therefore timely and imperative to invest extensive scientific research in the genetic and metabolic mechanisms of early and rapid muscle mass loss. The other important subject of our current research is low back pain, representing most common musculoskeletal disorder in general human population. However, it is still unclear which individuals develop it. We examine the contribution of genetic factors, lumbar disc degeneration and other potential risk factors in a general human population.

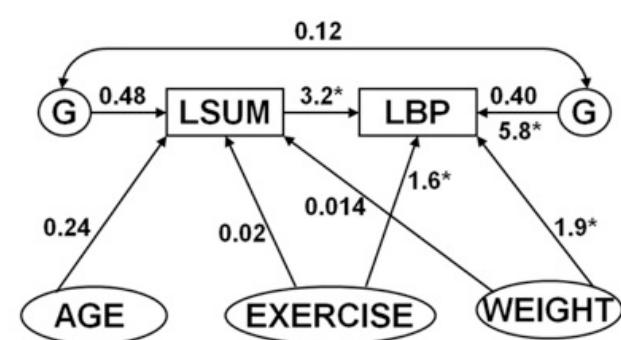
Publications

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Path diagram of the main risk factors for low back pain (LBP) in middle-age women. The figure shows contribution of various factors to LBP, including genetic effects (G) and lumbar disc degeneration (LSUM). The results presented as variance components (portions) and odds ratios (marked by *). According to Livshits et al 2011, Ann Rheumat Dis.

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Grants

2013-2017 **Genetics, Genomics and Metabolomics of the Low Back Pain and Spinal Disc Degeneration in Complex Arab Pedigrees in Israel**. Israel Science Foundation (ISF).



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Genomics and Gene Regulation by Small RNAs

Positions

Senior Lecturer, Sackler Faculty of Medicine

Academic Director, ScienceAbroad

Editor-in-Chief, *Genetics Research*

Research

Our laboratory focuses on the analysis of regulation of gene expression aimed at understanding human disease. Combining high-throughput methods and bioinformatics, one aspect of our team's research explores microRNA regulation in order to reach a global, systems perspective of the mechanistic roles microRNAs play during disease development. Among our projects:

- Identification of a microRNA molecule that controls several oncogenes. Their discovery is paving the way for a potentially revolutionary drug for cancer treatment.
- Revealing the influence of microRNAs on pharmacogenomics and personalized medicine, thus leading to tailored drugs for cancer treatment.
- Exposing pathogens in human tissues based on deep sequencing of small RNA molecules followed by subtraction and assembly of the various genomes.

Publications

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Epidermolysis. *Am J Dermatopathol*. 2017;39(6):440-444.

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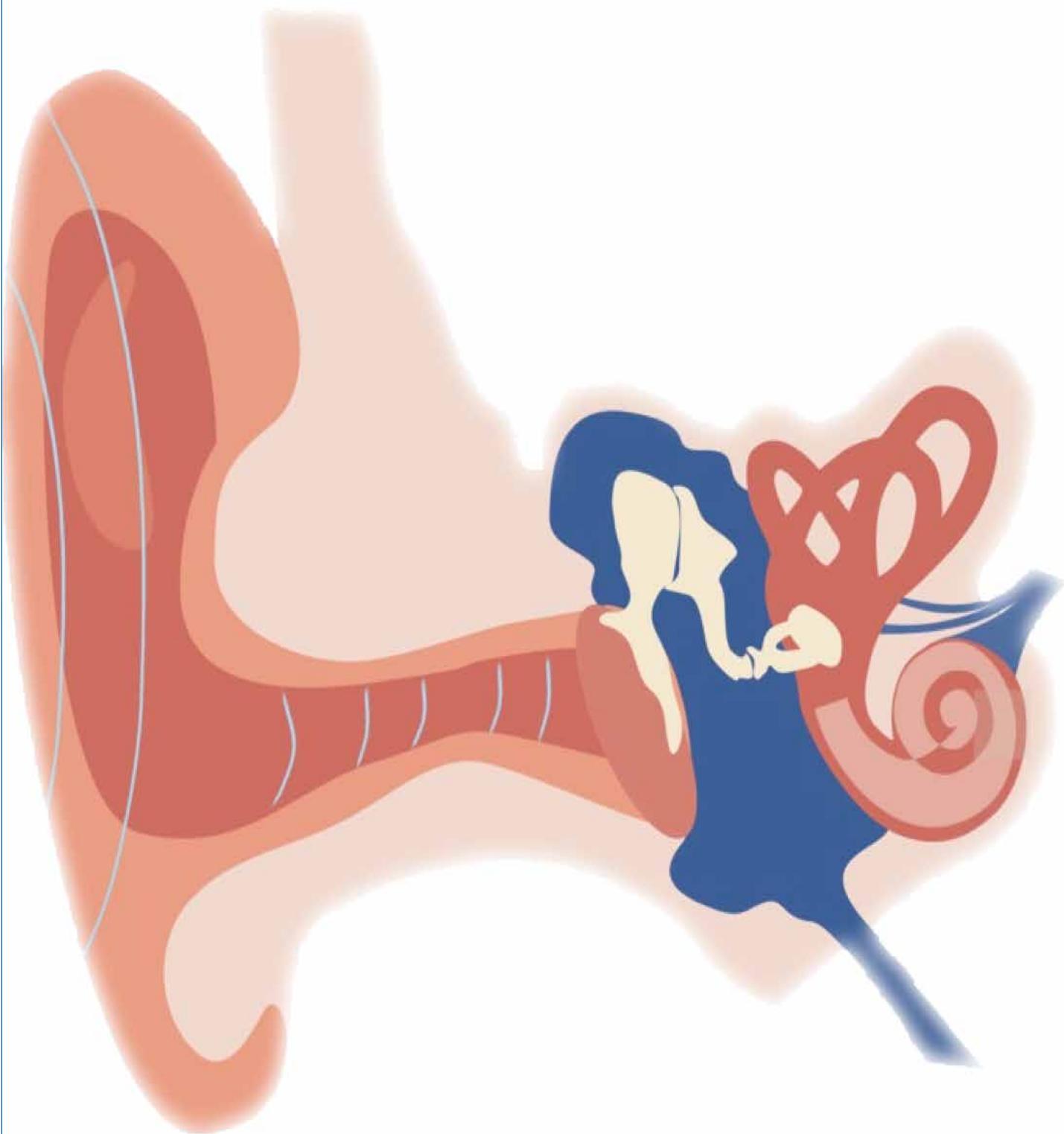
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Grants

2015-2018	Interdisciplinary grant of the Israeli Ministry of Science, Technology and Space on the Science, Technology and Innovation for the Third Age
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Hearing, Language & Speech Sciences and Disorders





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Paralinguistic Communication, Phonetics and Psychoacoustics

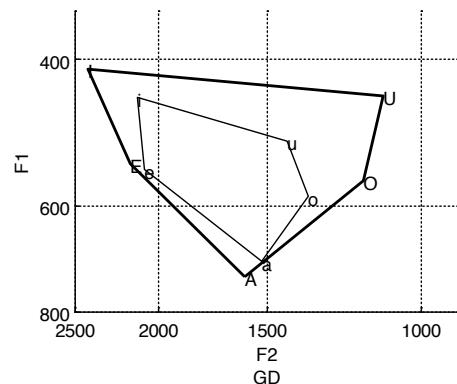
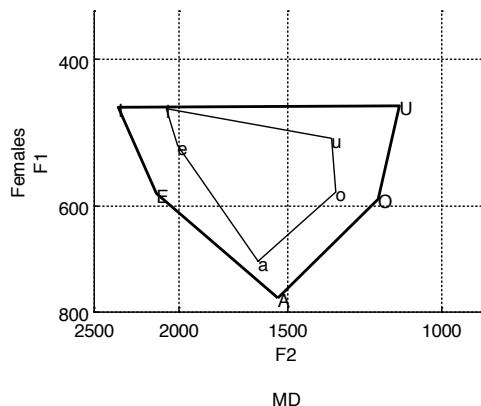
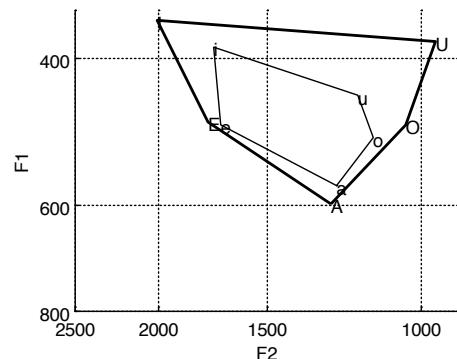
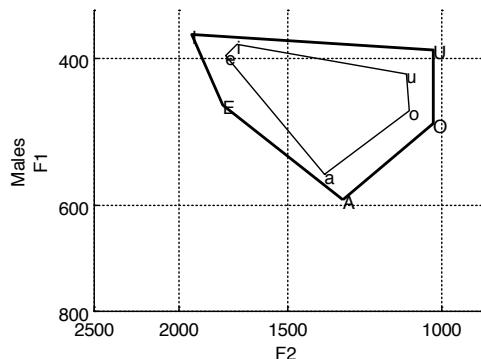
Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our interests lie on the frontier between signal processing and human communication in both speech and music. One general field we have been involved in in recent years is the paralinguistic aspect of verbal communication. In this research my colleagues and we have been exploring two main directions:

1. Emotion: Production and perception of emotions in speech, mostly in Hebrew, along with several excursions into cross lingual studies – Hebrew/German and Hebrew/Arabic. I've been looking at emotions as expressed in many different settings: films, event recollection, interviews, psychotherapy, and acted with conflicting textual and prosodic content.
2. Pragmatics: Production and perception of word stress (i.e. "I love my cat" vs. "I love my cat"), in Hebrew and Arabic, and lately also the manifestations of lexical stress in Hebrew.



Vowel spaces of Spoken Arabic in a Galilean Dialect (GD) and a "Muthallath Dialect" (MD) for men and women. External polygons are long vowels, internal polygons are short vowels. Note that short vowels are more centralized, and exhibit larger differences between dialects.

We have also been interested in signal processing aspects of music and musical acoustics for a very long time. Recent works we have participated in have been related to vibrato in the singing voice: quantifying it and relating it to factors such as singer proficiency, vocal warmup and singing style. Situated in the heart of the Middle East, we have become interested in acoustic phonetics of Hebrew and Spoken Arabic. Along with our colleagues, we have studied Hebrew vowels in everyday, connected speech, and in several dialects of Spoken Arabic, which have been studied very little. For example, vowel spaces of a Galilean dialect and the Kfar Kassem dialect are presented in the figure below.

Finally, the perceptual aspects of the subjects above have led us to examine their interaction with psychoacoustic thresholds. Starting with frequency perception thresholds, and now branching into intensity and spectral thresholds, our collaborators and we have been looking at their correlation to perception of emotion and music.

Publications

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Voice, Speaking Rate, Stuttering and Fluency Disorders

Positions

Associate Professor, Sackler Faculty of Medicine

Research

Our research, as well as our clinical interest, focuses on two major fields: *Stuttering* and *Voice*. In the area of stuttering and other fluency disorders, we are interested in identifying and measuring various fluency characteristics, providing normative data on speaking rate in Hebrew and exploring therapeutic approaches for stuttering, cluttering and other related fluency disorders. To this end, we are conducting studies on the perception of stuttering, and on the acoustic properties of speaking rate, normal disfluency and stuttering. In addition, we are currently collaborating with researchers in other research centers in a study that utilizes advanced methods for brain imaging related to stuttering and language.

In the area of voice, we are highly interested in characterizing vocal properties related to different physical, physiological and emotional conditions, and on the professional voice. This line of research involves exploring and identifying acoustic, aerodynamic, perceptual and acoustic measures that differentiate, for example, between people with and without laryngeal pathologies, people who

experience various emotional or social conditions, and women at different hormonal conditions and phases (e.g., using birth-control pills, pregnancy, menstrual cycle, etc.).

Publications

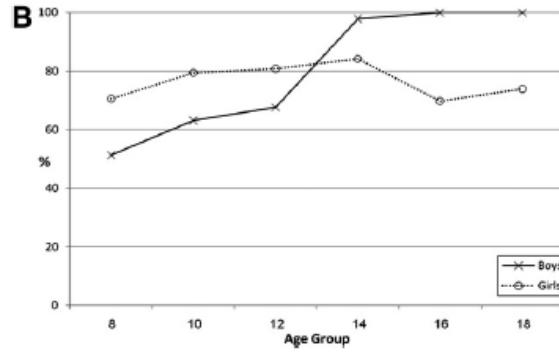
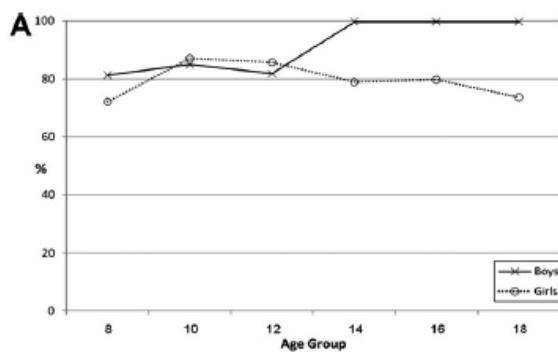
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Correct gender identification rates for boys and girls in the six age groups for (A) sentences and (B) vowels.

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Grants

2017-2012 Israel Science Foundation, Cerebral and cerebellar white matter pathways controlling Speech Rate



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Learning and Plasticity and Early Detection of Hearing Loss – Clinical Implications

Positions

Lecturer, Sackler Faculty of Medicine

Research

Our research focuses on two main fields:

(a) Learning and plasticity in the auditory system:

Our research goal focuses on investigating perceptual learning and plasticity in the auditory system throughout the life span. Our interest in this area is motivated by the constant need in clinical practice to seek for better understanding of the learning characteristics and limitations of brain plasticity in the auditory modality which will in turn contribute to the better development of habilitation strategies in a variety of populations with hearing difficulties. We conduct behavioral studies in adults and children (i.e. single and multi-session training) using both non-verbal and verbal stimuli in order to explore the different characteristics of skill learning in the auditory system such as the time course of learning, the role of sleep for the establishment of delayed gains in performance, the generalization of the learning gains to untrained conditions etc. In order to provide evidence for functional plasticity in the neural encoding of sounds in the auditory system following training, we are currently also utilizing electrophysiological measures. Specifically, we record auditory brainstem responses to speech stimuli which provide us with a unique opportunity to follow changes in the neural signatures of the acoustic properties of the input signal (e.g., pitch tracking, harmonics, onset timing etc) that occur before and following training. We plan to explore the learning characteristics and limitations of brain plasticity in the auditory modality in different populations (e.g. middle-aged, elderly adults, hearing impaired, auditory processing disorders etc.) using both behavioral and electrophysiological measures.

(b) Early detection of hearing loss in neonates and its clinical implications:

Our interest in this field is motivated by the growing evidence that early identification of hearing loss and intervention prior to six months of age can diminish the negative impact of hearing loss on speech and language acquisition. One line of research we conduct focuses on the prevalence and characteristics of hearing loss among different populations of infants such as infants with very low birth weight infants and congenital cytomegalovirus infection. Universal newborn hearing screening allows us not only identify special populations at risk for hearing loss but also, for the first time, to follow the developmental milestones of these children at a very young age and assess the communicative skills of infants with different types of hearing loss (e.g., unilateral hearing loss, mild hearing loss). These early communicative skills are known to be necessary to language and speech development. Thus, another line of research focuses on the effects of different degrees of hearing loss (e.g., unilateral hearing loss) on early auditory and pre-lexical productions. Learning the consequences of early detection and as a result early intervention provides insights to the ability to reverse the negative influence of auditory deprivation due to brain plasticity in young children.

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Language Processing in Healthy and Brain Damaged Bilingual Speakers

Position

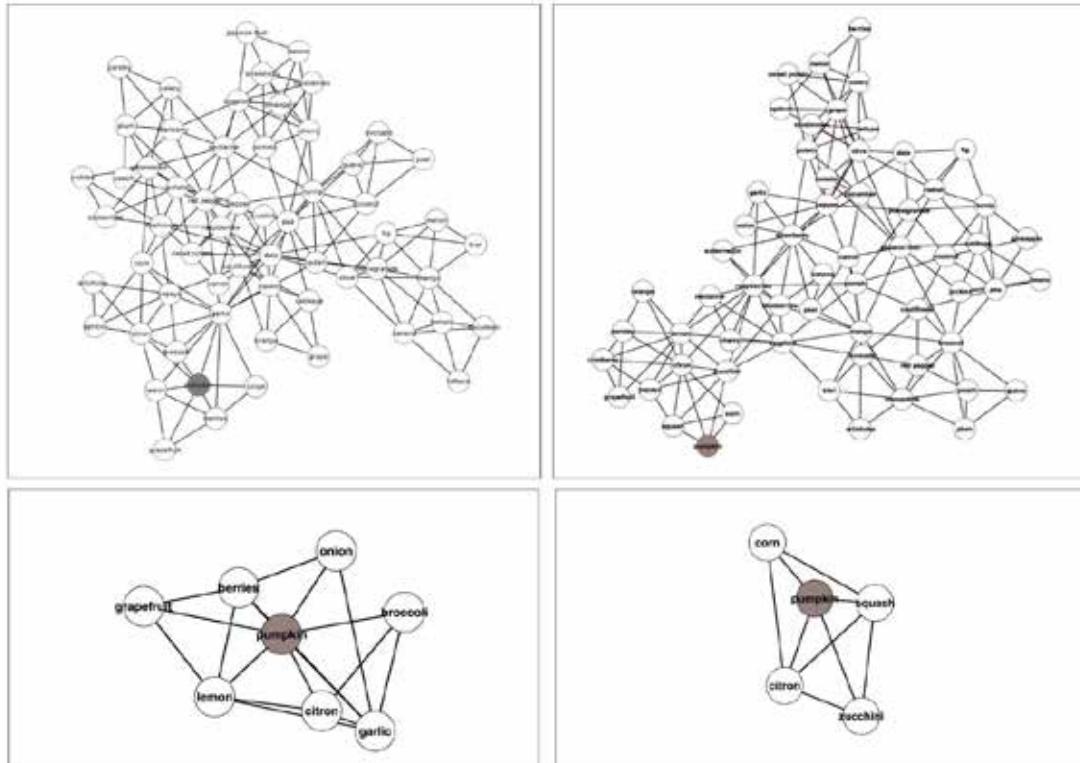
Lecturer, Sackler Faculty of Medicine

Research

Many individuals in the contemporary society are required to use more than one language in everyday life. Research in our laboratory focuses on these speakers and explores how they process their languages. We apply behavioral and neuroimaging methods (fMRI and tDCS), both in healthy adults and in individuals with a language disorder following

brain damage, such as aphasia. Current projects in the lab address the following questions:

1. What determines the differences among individuals in how successful they are in learning a second language? In one project, we look at the role of semantic processing and cognitive flexibility in vocabulary learning. In another, we study the interplay between auditory and motor systems in predicting the ability to acquire a foreign language pronunciation.
2. How using a language (to speak, listen, write or read) is different in native vs non-native language?



Organization of lexical networks in non-native language (Hebrew, left panels) and native language (English, right panels). Upper panels show the full network and the lower panels – the node *pumpkin* and its direct neighbors. The figures and the accompanying analyses suggest that non-native words are more densely connected to their neighbors and tend less to group into communities compared to native language words.

The conditions under which second language acquisition occurs are often less than ideal; for instance, second language is often acquired at an older age and used less frequently than the native language. In our lab, we have been investigating how these acquisition circumstances may affect the organization of lexical-semantic knowledge and the processing of words by the left and the right cerebral hemispheres.

3. What are the patterns and the mechanisms of language impairment and language recovery in bilingual and multilingual speakers? Some bilinguals with aphasia regain control of both languages in parallel, while in others language recovery is non-parallel (e.g., one language may be more impaired than the other, despite comparable premorbid proficiency). Our research aims at elucidating the factors predicting recovery patterns in these speakers and examines the cross-language effects of treatment on communicative abilities. We also study the interplay between neurobiological factors (such as the specific localization of the brain insult) and environmental factors (such as language proficiency) in determining spontaneous and treatment-induced neuroplasticity and its relevance to communicative abilities.

The research conducted in our laboratory can advance the current understanding of processes related to adult language learning, representation, processing, and breakdown.

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Auditory Processing in the Normal and Impaired Auditory System

Positions

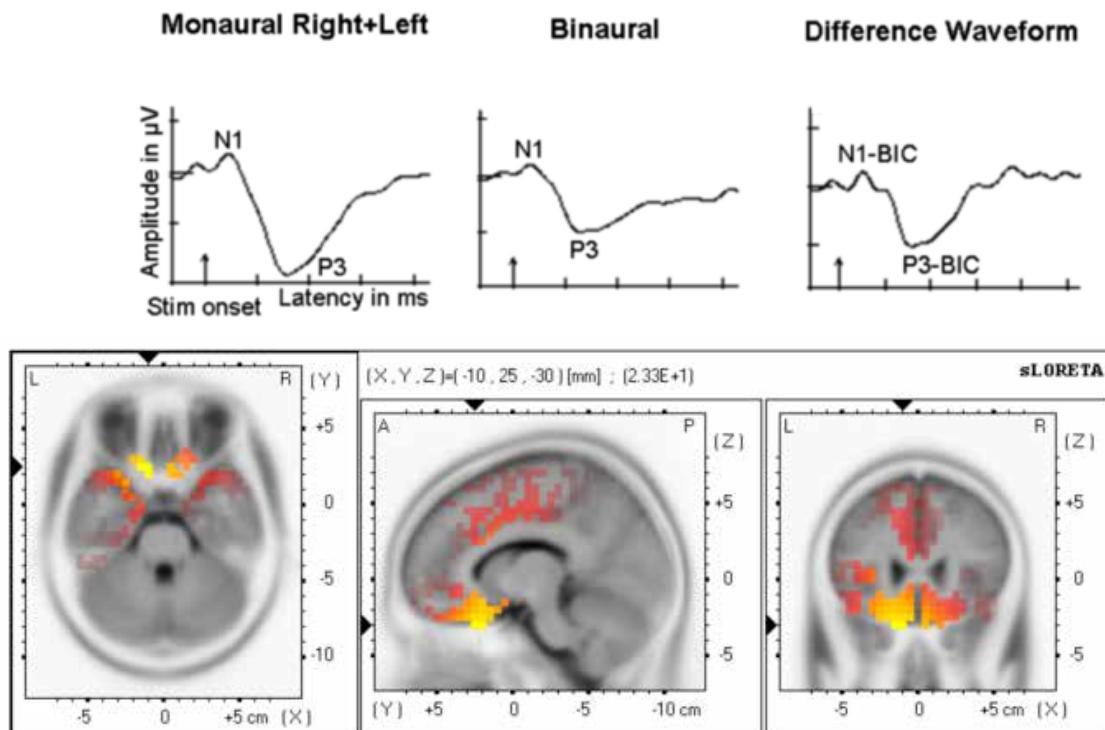
Senior Lecturer, Department of Communication Disorders, Sackler Faculty of Medicine

Head, Hearing, Speech, and Language Center, Sheba Medical Center, Tel Hashomer

Research

Research focuses on neurophysiologic and behavioral manifestations of auditory processing, as well as the relation between the two, in the normal and impaired auditory system. By means of event-related potentials (ERPs), voltage changes recorded from the scalp

that trace events in time known to reflect discrete stages of neural processing, and a functional imaging technique (sLORETA), we study the time-course and cortical activation patterns during auditory (speech) processing. Of special interest are patients that have experienced bilateral and/or unilateral auditory deprivation and are habilitated by cochlear implants (CI) and/or hearing aids (HA). Currently under study are neurophysiologic processes that underlie: (1) Binaural processing in children that were sequentially or simultaneously implanted, in those using CI and HAs (bimodal hearing), and in those with HAs; and (2) Auditory-cognitive processing in elderly patients with CI.



Grand average waveforms of normal hearing children elicited during a speech discrimination task presented monaurally and binaurally. Shown are the sum of monaural right and left waveforms, the binaural response, and the difference waveform (Binaural interaction component=Sum of right+left -binaural response). Also shown are sLORETA images indicating the major site of activation during P3-BIC in the inferior and medial frontal gyri, (BA 11, 25) and orbital gyrus (BA 47) bilaterally.

Additional lines of research incorporate neurophysiologic and behavioral measures for studying: (1) The effect of auditory processing disorders (APD) on perceptual and post-perceptual stages of linguistic processing; and (2) The involvement of the peripheral and central auditory system in selective mutism and autism.

Understanding normal and impaired auditory processing contributes to the formation of rehabilitative technologies and approaches for auditory disorders.

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Hearing Science and Clinical Audiology

Position

Professor Emeritus, Sackler Faculty of Medicine

Research

- Normal and abnormal auditory function
- Brain plasticity in cochlear Implants, Auditory Processing Disorders (APD)
- Clinical Audiology

Our research has been conducted in two areas:

A. Study of inner ear function in guinea pigs under three conditions: hypoxia, acoustic over-stimulation and differentiation. The study of these subjects has required the development of three special experimental techniques:

- A method of chronic implantation of an electrode into the facial nerve canal to enable longitudinal follow-up of hearing function in the awake state.
- A rheological model, which was developed for research on cochlear hypoxia in guinea pigs.
- A surgical method to completely eliminate the auditory efferent innervation to the cochlea while ensuring the animal's full recovery from this procedure. Thus it is possible to study the hearing function over time without the influence of the efferent system with the guinea pigs in an awake state.

B. Research on auditory plasticity in human subjects

The cochlear implant is a rehabilitative alternative in which an electrode inserted into the inner ear, directly stimulates the auditory nerve. Research is conducted in the area of programming the implant and speech perception using the implant. The research deals with the plasticity of the auditory system in acquisition of hearing and language skills and contributes basic theoretical and clinical knowledge about the importance of the auditory feedback to normal speech and hearing development and function.

Hearing in neonates and Auditory Processing Disorders: The Transient Evoked Oto-Acoustic Emission (TEOAE) is applied in hearing screening in neonates. Research was conducted to examine the reliability and validity of the test. We also investigated the development and activity of the efferent inhibitory system in newborns and premature babies using the suppression of the TEOAE test. We suggested the use of the test as a clinical tool for evaluation of auditory brain-stem function in neonates. We postulate that central auditory processing disorders (CAPD) manifested later in life can already be detected at this early stage of life using this method. We plan to continue to investigate the development of the efferent system and its importance for hearing throughout the life span, from childhood to old age, under difficult listening conditions and in subjects with communication disorders.

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‘Bottom-Up’ and ‘Top-Down’ Processes in Human Auditory Perception and Recognition

Position

Professor, Sackler Faculty of Medicine
Head, Steyer School of Health Professions
Committee Member, Israel Auditory Society of Research

Research

Our research focuses on understanding the influence and relative contribution of sensory information (“bottom-up” processes) compared to cognitive capabilities and listening experience (“top-down” processes) on the perception of speech and language development. We test our hypotheses in a range of special populations including hearing-impaired infants, children and adults with cochlear implants and/or hearing aids, children on the autistic spectrum, bilingual and trilingual children and adults and middle-aged and elderly adults. We always compare performance with the typically developing population. We develop tests that are aimed to assess different levels of sensory, linguistic and cognitive processing. These include psychoacoustic tests of frequency, temporal and intensity resolution that involve non-speech auditory stimuli, linguistic tests that involve phonetic, word, and sentence material in optimal and degraded or difficult listening conditions (e.g. background noise, time-compressed speech, multi-talker, multi-accented) and cognitive tasks, such as, selective auditory attention using auditory adaptation of the ‘stroop’ task for attending relevant and irrelevant information (e.g. lexical-emotional stroop). In order to understand the influence of repeated exposure to auditory stimuli on performance, we train our subjects in single- or in multiple sessions thus providing us with insights to the auditory memory systems. We use different training tasks that involve the implicit and explicit memory systems that are assumed to be analogues to language learning in infants and in older children. We utilize

primarily behavioral measures that are occasionally supplemented with electrophysiological measures. Our studies are conducted in an infant speech perception/language lab which is unique of its kind in the country and is equipped to test different infant populations with behavioral techniques, and in an acoustically treated state-of-the art psychoacoustic lab. Understanding the factors that influence speech perception throughout the life span have important implications in the design of aural rehabilitation for the hearing impaired and intervention protocols in populations with developmental delays.

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Kishon-Rabin L. & Boothroyd A. The Role of Hearing for Speech and Language Acquisition and Processing. In D. Ravid and A. Baron, (eds): *Handbook of Communication Disorders: Theoretical, Empirical, and Applied Linguistic Perspectives*. Mouton de Gruyter, Inc. In Press.

Kishon-Rabin L, Segal O. Beyond Hearing: Use of Parent Questionnaires for Assessing Auditory Functioning in Hearing-Impaired Infants. In L. Eisenberg (ed): *Clinical Management of Children with Cochlear Implants (2nd edition)*. San Diego, Plural Publishing, Inc. In press.



Prof. Tova Most, Ph.D.

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Speech and Hearing Sciences and Rehabilitative Audiology

Position

Professor, Sackler Faculty of Medicine and School of Education

Dean of Students, Tel Aviv University

Research

- Speech perception and production by the hearing impaired
- The implications of hearing loss on communication, cognitive and socio-emotional functioning in school, in the family and in general
- Educational Audiology
- Auditory rehabilitation of people with hearing loss

Our research focus is on evaluating the hearing and communication profile of individuals with a hearing loss and understanding the relationship between these functions and their functional management in various life environments. This research analysis expands the knowledge and understanding of theoretical models that examine the functioning of the individual with a hearing loss and constitutes a scientific basis for the development of intervention programs suited to the hearing and communication profile.

Our research activities focus on two main areas:

1. Research in the field of speech perception and communication through spoken language of individuals with a hearing loss.

We focus on the perception of suprasegmental and paralinguistic features of the spoken message. These provide information on the communication intentions of the speaker (e.g. asking a question in comparison to stating a fact) as well as the speaker's emotional state.

2. Research of the ramifications of a hearing loss and communication difficulties on the individual's ability to function in various life environments:

educational system, home and work environment, as well as the ramifications of the hearing loss and the communication difficulties on the people in the individual's environment.

Our research focuses on the relationship between hearing loss and communication function through the use of spoken language in general and the speech intelligibility in particular.

With the current trend to integrate children with a hearing loss into regular educational frameworks either individually or in a group, we also investigate the effect of hearing loss on the pupil's ability to function within these frameworks. This research is carried out in different sectors of the population (Jewish (secular & orthodox) and Arab), and on a range of age groups.

Within the framework of the research examining the implications of hearing loss on the different aspects of a child's life, we investigate not only the individual's functioning but also those aspects that relate to the people in their environment such as their parents, siblings and teachers.

Publications

Michael, R. Cinamon R.G. & **Most, T.** (2013) The contribution of perceived parental support to the career self-efficacy of deaf, hard of hearing, and hearing adolescents. *JDSDE*, 18, 329-343.

Ziv, M., **Most, T.** & Cohen, S. (2013) Understanding of emotions and false beliefs among children with normal hearing versus children with hearing loss. *JDSDE* 18, 161-174.

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Luntz, M., Egra-Dagan, D., Attias, J., Yehudai, N., **Most, T.**, & Shpak, T. (2014). From hearing with a cochlear implant and a contralateral hearing aid (ci/ha) to hearing with two cochlear implants (ci/ci): a within-subject design comparison. *Otology & Neurotology*, 35, 1682-1690.

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Zaidman-Zait, A., **Most, T.**, Tarash, R., & Haddad, E. (2017). Mothers' and fathers' involvement in intervention programs for deaf and hard of hearing children. *Disability and Rehabilitation*, 1-9.

Books

Most, T. & Ringvald, D. (Eds.) (2014). Theoretical and applied aspects in rehabilitation and education of deaf and hard of hearing individuals. MOFET Publishing House. Tel Aviv (In Hebrew).

Chapters

Levie, R., Ravid, R., Freud, T., and Most, T. (2014). Spelling Abilities in Hebrew-Speaking Children with Hearing Loss. In Barbara Arfe, Julie Dockrell and Virginia Berninger (Eds.): Writing Development in Children with Hearing Loss, Dyslexia or Oral Language Problems: Implications for Assessment and Instruction. Oxford University Press. New-York New-York. Chapter 6, pp. 70-84.

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Tzach, N. & **Most, T.** (2016). The Inclusion of Deaf and Hard of Hearing Students in Mainstream Classrooms: Classroom Participation and its Relationship to Communication, Academic and Social Performance. In Marc Marschark, Venetta Lampropoulou, and Emmanouil Skordilis (Eds.): Diversity in Deaf Education, Oxford University Press. Chapter 13, pp 355-380.

Zaidman -Zait, A., & **Most, T.** Assessment of Pragmatic Abilities among Deaf and Hard of Hearing Learners in Relation to Social Skills. In Marc Marschark & Harry Knoors (eds.): Evidence-Based Practice in Deaf Education. Oxford University Press. Accepted for publication 20.6.17



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Hearing Science and Clinical Audiology

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Communication Disorders,
Tel Aviv University

Senior Audiologist, Speech and Hearing Center,
Sheba Medical Center

Research

One of our main research areas is related to the effect of noise on speech perception, in young, middle aged and elderly populations. A major complaint of hearing impaired and normal hearing adults is the difficulty to understand speech in the presence of noise. Our attempt to address this challenging problem encompasses several aspects:

- a. Improving the signal to noise ratio in sensory aids (hearing aids and cochlear implants). Recently we demonstrated a significant beneficial effect of a single channel Cochlear-based Noise Reduction Algorithm (CNRA) in hearing aids users and cochlear implants recipients. Further investigation is required for improving CNRA performance at lower SNRs and in different noise spectra.
- b. Investigating the influence of aging on the recognition of speech in background noise: Aging is known to induce physio-pathological changes in the entire auditory pathways. While there is a comprehensive documentation of this difficulty amongst elderly people aged 65 years and above, limited information is available on middle-aged listeners.

Another topic in our research is the estimation of the potential risk for hearing loss as a result of listening to music with Personal Listening Devices (PLDs). We are studying the function of the efferent auditory system in normal and pathological populations such as children and adults with Auditory Processing Disorders and Childhood Selective Mutism.

Cochlear Implants are another area of research interest. In particular we are studying the characteristic features of the electrical nerve response in cochlear implant recipients.

Publications

C. Muchnik, D. Ari-Even Roth, M. Hildesheimer, M. Arie, Y. Bar-Haim, Y. Henkin (2013) Abnormalities in auditory efferent activities in children with selective mutism. *Audiology & Neurotology*, 18:353-61, 2013.

Y. Shapira, L. Migirov, Y. Yaar-Soffer, **C. Muchnik**, M. Hildesheimer, Y. Henkin. Pain in cochlear implant recipients – An uncommon, yet serious consequence of cochlear implantation. *The Laryngoscope* 125:1946-1951, 2015.

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R. Kaplan-Neeman, **C. Muchnik**, N. Amir. Listening to music with personal listening devices: monitoring the noise dose using a smartphone application. *International Journal of Audiology*, 56:400-407, 2017.



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Language Acquisition and Development of Linguistic Literacy

Position

Professor, School of Education and Sackler Faculty of Medicine

Vice-President, International Association for the Study of Child Language

Member, Academie Europea

Research

We study the ways Israeli infants, toddlers, children and adolescents acquire the structures, meanings and functions of spoken and written Hebrew (and Arabic). Empirical and theoretical exploration of linguistic phenomena are conducted against general models of language and cognitive acquisition, on the one hand, and the typological properties and constraints of Hebrew (and Semitic) verbal expression, on the other. Human development is taken as the critical context within which native language learning can take place in children. Specific areas of current investigation are (*inter alia*) acquisition of Hebrew verb structure (root and *binyan*) and semantics in mother-child dyads, children's peer talk and children's storybooks; linguistic input (maternal talk) to children and the relationship to their development in different socio-economic contexts; the emergence of syntactic constructions in children's development language; prepositions and prepositional phrases in spoken and written Hebrew development; the development of written text production abilities across the school years; narrative acquisition and narrative theory; morpho-syntactic constructions in learning to spell Hebrew.

Publications

Schiff, D. & **D. Ravid**. 2013. Morphological processing in Hebrew-speaking reading-disabled students. *Journal of Learning Disabilities*, 46, 220-229.

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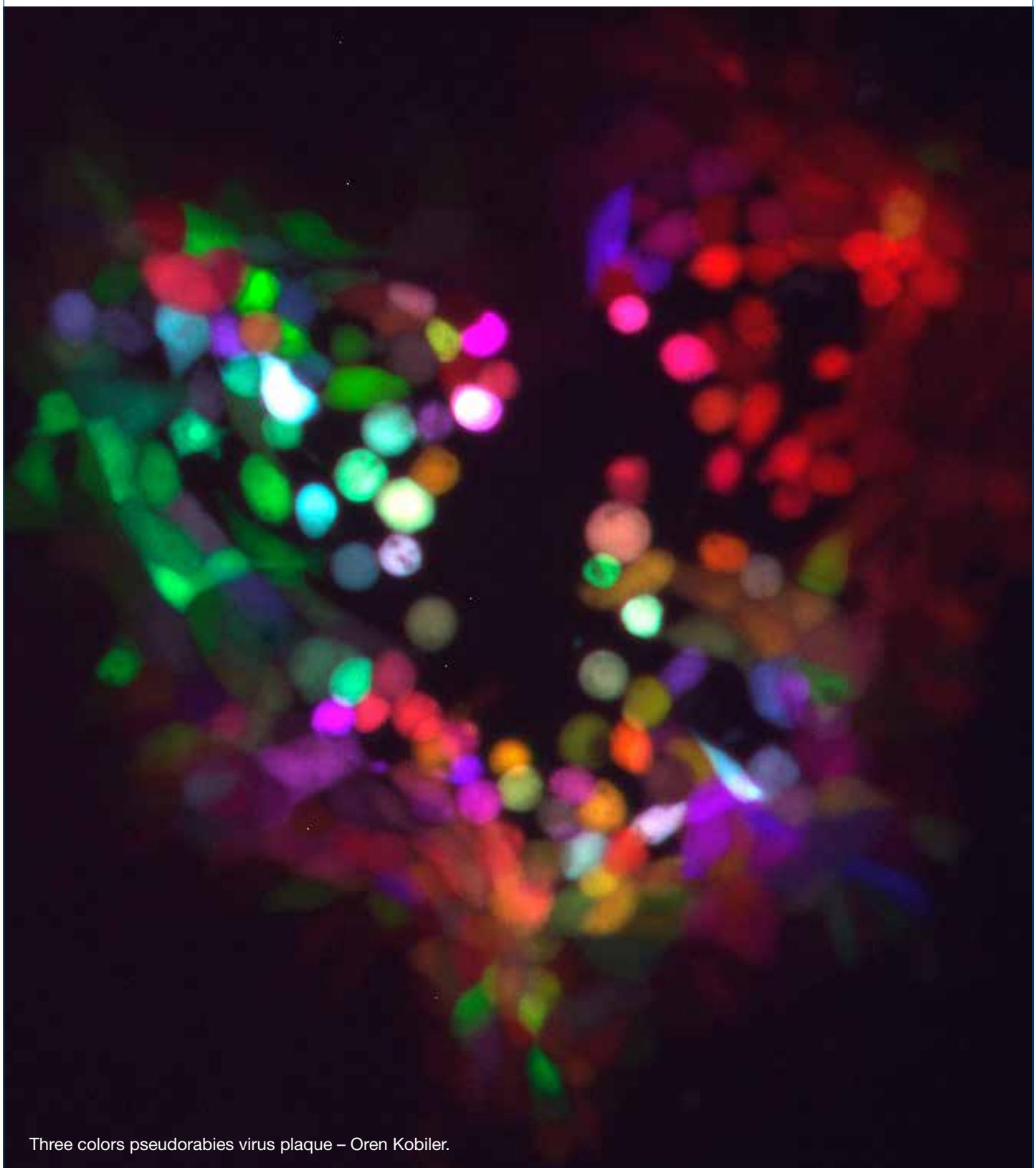
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Grants

2013-2017	Verb structure and Semantics in Development. Israel Science Foundation.
2017-2021	Research grant, Israel Science Foundation

Infectious Diseases



Three colors pseudorabies virus plaque – Oren Kobiler.



Dr. Natalia T. Freund, Ph.D.

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Human Antibody Responses in Health and Disease

Position

Senior Lecturer, Sackler Faculty of Medicine

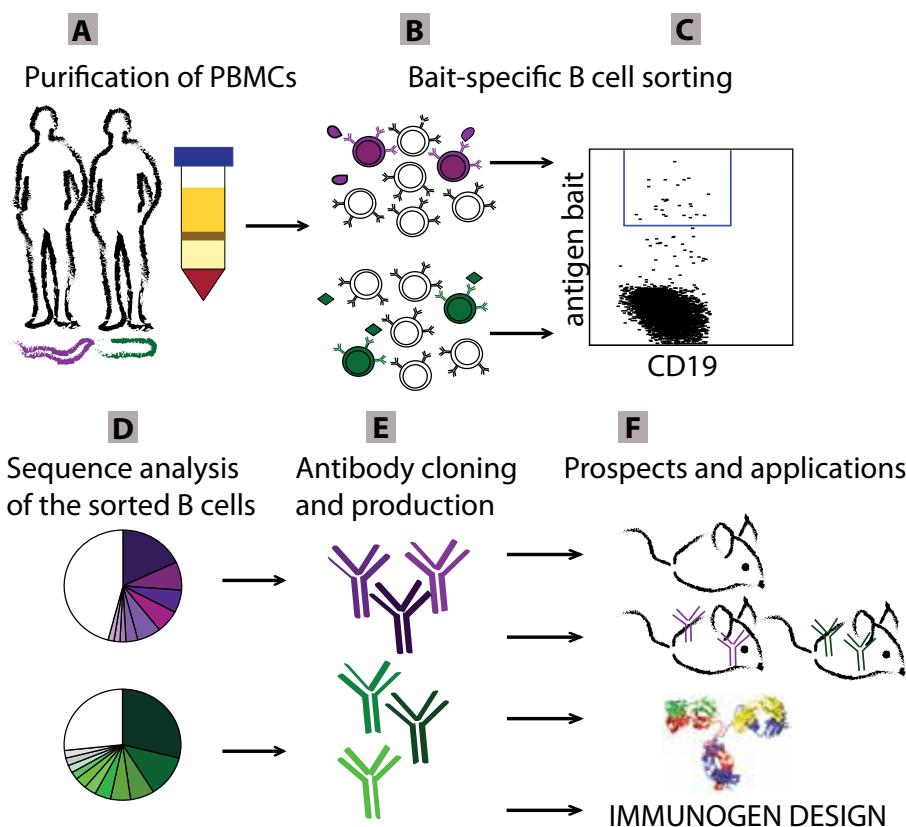
Research

Antibodies are major players of the immune system and are the basis of most vaccines. Despite their important role, the mechanism by which they contribute to protection during disease, and how to elicit them, remains a mystery.

Each one of us possesses a diverse repertoire of naïve B cells, expressing one type of membrane antibody on each cell. This diversity allows us to respond to a variety of different invaders. When a naïve B cell encounters an antigen, it migrates to the secondary lymph organs, where it interacts

with other cells of the immune system. There, B cells undergo affinity maturation, which is one of the most remarkable phenomena in nature. During affinity maturation, somatic mutations are introduced in antibody genes, and subsequently both antibody strength and affinity are improved, while weak and autoimmune antibodies are deleted. B cells then differentiate into antibody-secreting plasma cells and long-lived memory B cells.

We use molecular immunology and genetics, combined with innovative single cell methods, to isolate high-affinity disease-specific antibodies from memory B cells of infected patients. The ultimate goal of our lab is to study pathogen:host interactions, as well discover novel antibody-based drugs and vaccines.



ANTI-PATHOGEN ANTIBODY PURIFICATION FROM PATIENTS. (A) Whole blood will be collected from infected patients. (B) B cells are enriched and (C) stained with pathogen-specific antigens-baits. The positive cells are single cell sorted. (D) The heavy and light chain genes of the sorted cells will be amplified by PCR and the sequences analyzed for clonality. (E) Antibodies that are part of expanded clones of antigen-specific B cells are cloned into expression vectors and produced recombinantly. (F) The antibodies are used in a variety of downstream applications.

Publications

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Freund NT, Haoqing H, Scharf L, Noguiera L, Horwitz JA, Sievers S, Sok D, Golijanin J, Halper-Stromberg A, West A, Lorenzi JC, Toth I, Piechocka-Torcha A, Wang LX, Seaman MS, Burton D, Gazumyan A, Walker BD, Bjorkman PJ; Nussenzweig MC. Co-existence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic controller. *Science Trans. Med.* 2017, 18;9(373).

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Dosenovic P, von Boehmer L, Escolano A, Jardine J, **Freund NT**, Gitlin AD, McGuire AT, Kulp DW, Oliveira T, Scharf L, Pietzsch J, Gray MD, Cupo A, van Gils MJ, Yao KH, Liu C, Gazumyan A, Seaman MS, Björkman PJ, Sanders RW, Moore JP, Stamatatos L, Schief WR, Nussenzweig MC. Immunization for HIV-1 Broadly Neutralizing Antibodies in Human Ig Knockin Mice. *Cell.* 2015, 18;161(7):1505-15.



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Genetic Bases of Host Response to Infections and Chronic Diseases

Position

Professor, Sackler Faculty of Medicine
Chair, Department of Clinical Microbiology and Immunology

Research

The research in my laboratory is focused on understanding the genetic bases of host response to infections and chronic diseases, which are important for human health. My team uses mouse model for speeding up the process of identifying such genes, which may involve of making some people resistant to a disease while others are not. After finding the genes in mouse, it will be possible to identify the homologous genes in human. The product of our research can be used in developing new prevention and treatment tools for these diseases.

The main ongoing research projects at his lab are:
Identifying and characterizing genes involved in host response to bacterial infection by *Klebsiella Pneumoniae*.

Identifying and characterizing genes involved in host response to fungal infection by *Aspergillus Fumigatus* (Aspergillosis)

Identifying and characterizing genes involved in host response to bacterial that causes dental infection (periodontitis)

Identifying and characterizing genes involved in development of type-2 diabetes (T2D) in humans as a result of obesity and high fat-diet.

Identifying and characterizing genes involved in host immune response to infectious and chronic diseases.

Identifying and characterizing genes involved in development of colon cancer.

Publications

Shusterman A, Durrant C, Mott R, Schaefer A, Weiss EI, **Iraqi FA*** and Houri-Haddad Y* (2013) Host susceptibility to periodontitis: Mapping murine genomic regions. *J Dent Res* 92: 438-443.

Shusterman A, Salaymeh Y, Nashef A, Soller M, Wilensky A, Mott R, Weiss EI, Houri-Haddad Y and. **Iraqi FA** (2013) Genotype is an important determinant factor of host susceptibility to periodontitis in the Collaborative Cross and inbred mouse populations. *BMC Genet* 14: 68-79.

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De Simone M, Spagnuolo L, Ivan Lorè N, Rossi G, De Fino I, Cigana C, **Iraqi FA** and Bragonzi A (2014) Host genetic background influences the response to the opportunistic *Pseudomonas aeruginosa* infection altering cell-mediated immunity and bacterial replication. *PLOS One* 9: e106873, 1-10.

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Schaefer A, Bochenek G, Jochen As, Ellinghaus D, Dommisch H, Guzeldemir E, Graetz C, Harks I, Jockel-Schneide Y, Staufenbiel I, Eberhard J, Meyle J, Eickholz P, Linden G, Cine N, Nohutcu R, Yilmaz E, Weiss E, Houri-Haddad Y, Iraqi FA, Folwaczny M, Noack B, Strauch K, Gieger C, Waldenberger M, Peters A, Wijmenga C, Lieb W, Franke A, Rosenstiel P, Doerfer C, Bruckmann C, CARDIoGENICS, König I, Bruno G, Loos GB, Schreiber S (2014) Genetic evidence for PLASMINOGEN as a shared genetic risk factor of coronary artery disease and periodontitis. *Circ Cardio Genet* 8:159-67.

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Lore' NI, **Iraqi FA** and Bragonzi A (2015) Host genotype an important determinant factor of *Pseudomonas aeruginosa* susceptibility in the Collaborative Cross mice. *BMC Genetics* 16 (106).

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Review and editorials

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Rajilić-Stojanović M, Daisy M, Raes J, Hanevik K, Salonen A, Jalanka J, de Vos WM, Manichanh C, Golic N, Enck P, Philippou E, **Iraqi FA**, Clarke G, Spiller RC and Penders J. (2015) Intestinal microbiota and diet in IBS: causes, consequences or epiphenomena. *Am J Gastroenterol* doi: 10.1038/ajg.2014.427.

Abu-Hussein M, Watted N, Yehia M, Proff P and **Iraqi FA** (2015) Clinical genetic basis of tooth agenesis. *J Dent Med Sci* 14: 1-10.

Grants

2014-2018	German Research Foundation (DFG-TRIO)
2015-2018	Israeli-Science Foundations (ISF)
2016-2020	United States-Israel Binational Science Foundation (BSF)



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Investigating Viral Genetic Diversity

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our research is focused on understanding how viruses generate and maintain genetic diversity. All virus populations display high genomic diversity, which provides opportunities for survival in the constantly changing environment. In many cases, such diversity results in failure of antiviral treatment (resistance to vaccines and antiviral drugs) and the emergence of zoonotic viral pathogens. DNA viruses and segmented RNA viruses exploit recombination and reassortment as mechanisms for diversity creation. We are interested in the mechanisms allowing DNA viral recombination and finding ways to inhibit these mechanisms.

Yamin D., Jones F.K., DeVincenzo J.P., Gertler S., **Kobiler O.**, Townsend J.P. and Galvani A.P. (2016). Vaccination strategies against RSV. *Proc Natl Acad Sci USA*. 113 (46), 13239-44

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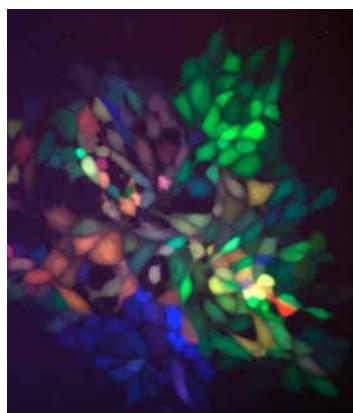
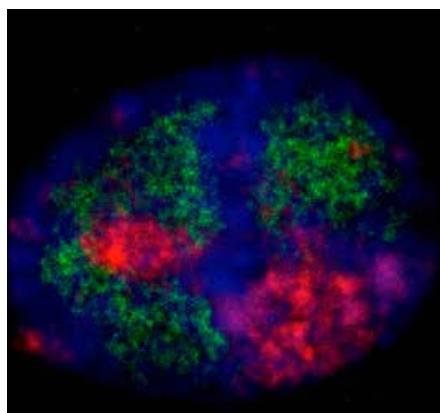
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Publications

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Grants

2014-2019 Grant, Israel Science Foundation (ISF)
2014-2019 Equipment Grant, Israel Science Foundation (ISF)
2016-2020 BSF, co-PI Dr. Weitzman Matthew



A. Spread of three alpha herpesviruses (each expressing a different XFP) from a single infected cell suggests that only a limited number of viral genomes are able to be expressed and replicated inside a single cell. B. Replication compartments in a single nucleus infected with two alphaherpesviruses suggest that genomes remain in separate territories in the nucleus.



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Human Mold Infections

Positions

Associate Professor, Sackler Faculty of Medicine
Chair, M.Sc. Committee, Sackler School of Medicine
Director, Ella Kodesz Institute of Host Defense against
Infectious Diseases

Research

Aspergillus fumigatus is the most common mold pathogen of human beings, causing invasive diseases in immunocompromised (cancer after chemotherapy, bone marrow transplant etc) patients. Poor diagnostic tools and the ineffectiveness of antifungal drugs against established *Aspergillus* infections combine to result in high mortality following *A. fumigatus* infection. Left untreated, mortality rates from invasive pulmonary aspergillosis (IPA) exceed 90% and even following aggressive antifungal treatment fatality rates of 50-70% are common.

The goals of my lab are:

To understand what enables this mold to be such an effective and dangerous pathogen of immunocompromised patients

To develop novel modes of treatment including new antifungal compounds, targeted antibodies and nano medicines.

Publications

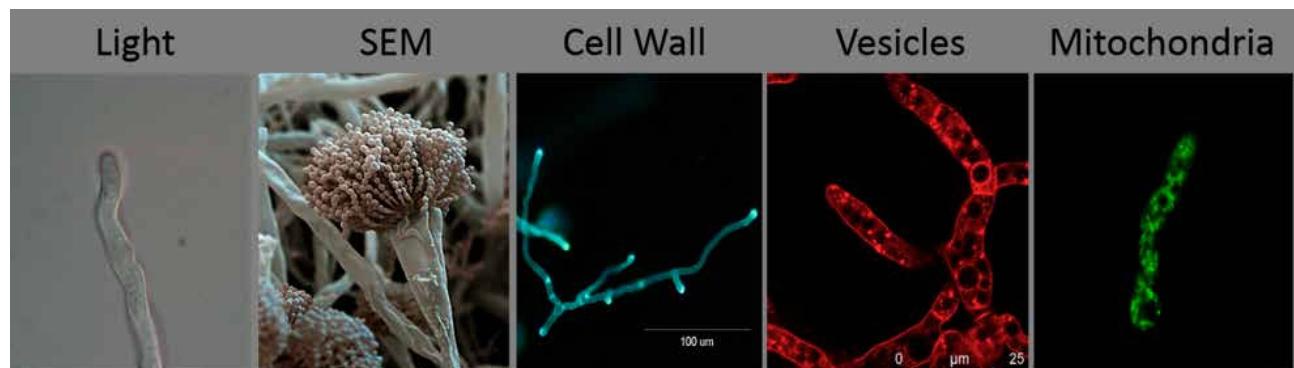
Wiemann P, Perevitsky A, Lim FY, Shadkchan Y, Knox BP, Landero Figueora JA, Choera T, Niu M, Steinberger AJ, Wüthrich M, Idol RA, Klein BS, Dinauer MC, Huttenlocher A, **Osherov N**, Keller NP. *Aspergillus fumigatus* copper export machinery and reactive oxygen intermediate defense counter host copper-mediated oxidative antimicrobial offense. *Cell Rep.* 2017;19:2174-2176.

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The pathogenic mold *Aspergillus fumigatus*

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Ben Yaakov D, Rivkin A, Mircus G, Albert N, Dietl AM, Kovalerchick D, Carmeli S, Haas H, Kontoyiannis DP, **Osherov N.** Identification and characterization of haemofungin, a novel antifungal compound that inhibits the final step of haem biosynthesis. *J Antimicrob Chemother.* 2016;71:946-52.

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Identification and characterization of a novel family of selective antifungal compounds (CANBEFs) that interfere with fungal protein synthesis. *Antimicrob Agents Chemother.* 2015;59:5631-40.

Kroll K, Pähtz V, Hillmann F, Vaknin Y, Schmidt-Heck W, Roth M, Jacobsen ID, **Osherov N.**, Brakhage AA, Kniemeyer O. Identification of hypoxia-inducible target genes of *Aspergillus fumigatus* by transcriptome analysis reveals cellular respiration as an important contributor to hypoxic survival. *Eukaryot Cell.* 2014;13:1241-53.

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Grants

2014–2017 Infect-ERA Net Joint European Grant



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Host-Virus Interactions in Bacterial Systems

Position

Professor, Sackler Faculty of Medicine

Research

Our laboratory studies basic aspects of bacteriophage growth with emphasis on phage interactions with their bacterial hosts, and particularly, the recently identified bacterial defense system, the CRISPR. Our ultimate objective is to identify novel phage products and strategies that will assist in overcoming drug resistant pathogens.

We combine genetic and biochemical approaches to identify and characterize interactions of phage proteins with other phage or host proteins. Specifically, we employ the T7 phage and its *Escherichia coli* host as models. We use high throughput screening systems, transposon mutagenesis, tandem affinity purification, mass spectrometry, and classical as well as modern bacterial genetic methods to identify and characterize these viral-host interactions.

Publications

Sberro H*, Leavitt A*, Kiro R*, Koh E, Peleg Y, **Qimron U**, and Sorek R. Novel families of toxin/immunity modules confer phage resistance in bacteria. *Molec Cell*, 50:136-48, 2013. *contributed equally. *Recommended by F1000*

Kiro R, Goren MG, Yosef I, and **Qimron U**. CRISPR adaptation in *Escherichia coli* type I-E system. *Biochem Soc Trans*, 41:1412-5, 2013.

Yosef I, Shitrit D, Goren MG, Burstein D, Pupko T, and **Qimron U**. DNA motifs determining the efficiency of adaptation into the *Escherichia coli* CRISPR array. *Proc Natl Acad Sci USA*, 110:14396-401, 2013. *Recommended by F1000*

Kiro R, Molshanski-Mor S, Yosef I, Milam SL, Erickson HP, and **Qimron U**. Gene-product 0.4 increases phage competitiveness by inhibiting host cell division. *Proc Natl Acad Sci USA*, 2013. 110:19549-54; *Recommended by F1000*.



Kiro R, Shitrit D, and **Qimron U**. Efficient engineering of a bacteriophage genome using the type I-E CRISPR-Cas system. *RNA Biol*, 11:42-4, 2014.

Yosef I, Kiro R, Molshanski-Mor S, Edgar E, and **Qimron U**. Different approaches for using bacteriophages against antibiotic-resistant bacteria. *Bacteriophage*, 4:e2849, 2014.

Molshanski-Mor S, Yosef I, Kiro R, Edgar R, Manor M, Gershovits M, Laserson M, Pupko T, and **Qimron U**. Revealing bacterial targets of growth inhibitors encoded by bacteriophage T7. *Proc Natl Acad Sci USA*, 111:18715-20, 2014.

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Yosef I, Manor M, Kiro R and **Qimron U**. Temperate and lytic bacteriophages programmed to sensitize and kill antibiotic-resistant bacteria. *Proc Natl Acad Sci USA*, 112, 7267-7272, 2015.

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* Goren MG, Doron S, Globus R, Amitai G, Sorek R , and **Qimron U** #. Repeat size determination by two molecular rulers in the type I-E CRISPR array. *Cell Reports*, 16(11):2811-8, 2016.

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Manor M. and **Qimron U**. Selection of Genetically Modified Bacteriophages Using the CRISPR-Cas System. *Bio-Protocol*, in press.

Reviews

Yosef I and Qimron U. Microbiology News and Views: How bacteria get spacers from invaders. *Nature*, 519, 166-167, 2015.

Yosef I, Manor M, and Qimron U. Counteracting selection for antibiotic-resistant bacteria. *Bacteriophage*, in press.

Goren MG, Yosef I, and Qimron U. Programming bacteriophages by swapping their specificity determinants. *Trends Microbiol*, 23, 744-746, 2015.

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Yosef I, Edgar R, and **Qimron U**. Phenotypic heterogeneity in a bacteriophage population only appears as stress-induced mutagenesis. *Curr Genet*, 62(4):771-773.

Goren MG, Yosef I, and **Qimron U**. Sensitizing pathogens to antibiotics using the CRISPR-Cas system. *Drug Res Updates*, 30:1-6, 2017.

Globus R, and **Qimron U**. A Technological and Regulatory Outlook on CRISPR Crop Editing. *J Cell Biochem*, in press.

Grants

2014-2017 Israeli Ministry of Health Grant

2013-2018 ERC Starting Grant

2014-2019 Israel Science Foundation Grant

2016-2017 Momentum Fund



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Bacterial Protein Secretion Systems and Toxins

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our lab is interested in the recently discovered Type VI Secretion Systems (T6SSs) and the toxins they deliver. We are pursuing discovery-driven research and translational approaches to utilize the T6SS and its toxins as platforms for the development of novel antibacterial treatments.

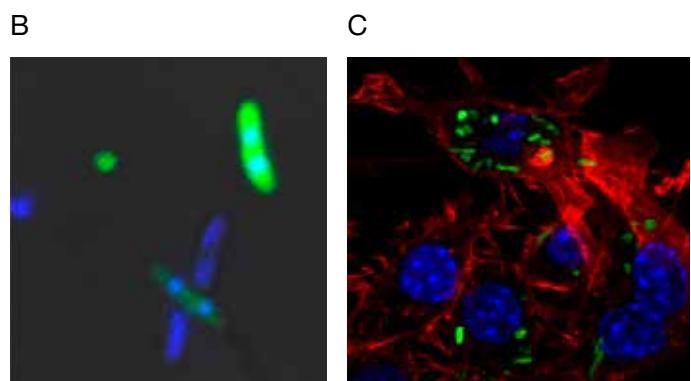
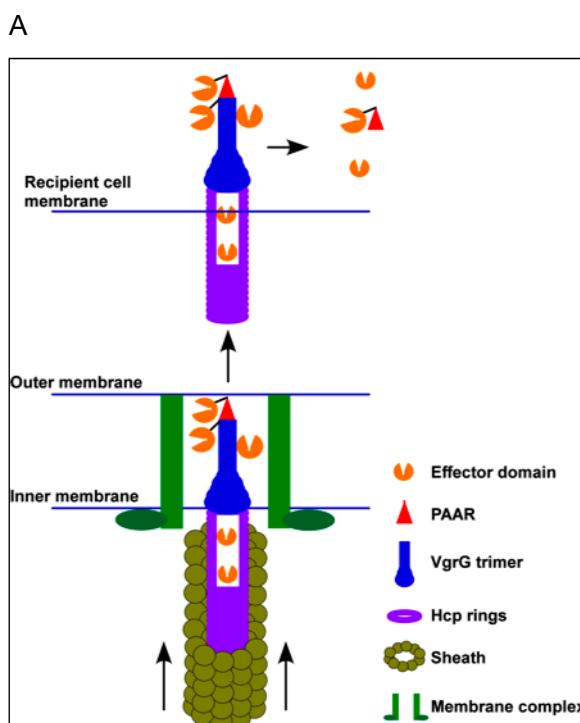
The T6SS is a contact-dependent protein delivery system that is found in many Gram-negative bacteria. It uses a contractile apparatus to propel an inner-tube, which is decorated with toxic effector proteins, outside of the bacterial cell and into an adjacent recipient cell, where effectors are deployed. The T6SS is unique as it can deliver toxins directly into eukaryotic host cells as well as into competing

bacterial cells, and thus mediates both virulence and antibacterial toxicities.

We employ a multi-disciplinary approach to identify T6SSs activities and toxins in various bacterial pathogens. Using molecular biology, genetics, microbiology, biochemistry, microscopy, proteomics, and bioinformatic tools, we are identifying novel virulent and antibacterial toxins and determine their mechanism of action and their targets. In addition, we study T6SSs in pathogenic bacteria and determine their contribution to pathogenicity, inter-bacterial competition, and dissemination in the environment.

Publications

Ray A, Schwartz N, de Souza Santos M, Zhang J, Orth K, **Salomon D**. Type VI secretion system MIX-effectors carry both anti-bacterial and anti-eukaryotic activities. *EMBO Reports*. 2017, in press.



Type VI secretion systems (T6SSs) deliver effectors mediating antibacterial and virulence toxic activities. (A) A scheme of the T6SS. (B) Bacterial attackers (blue) using a T6SS with nuclease effectors to kill prey bacteria (green). (C) Bacteria (green) using a T6SS to allow survival and replication within a macrophage (red=actin cytoskeleton, blue=DNA).

Li P, Kinch LN, Ray A, Dalia AB, Cong Q, Nunen LM, Camilli A, Grishin NV, **Salomon D** #, Orth K #. Acute Hepatopancreatic Necrosis Disease (AHPND)-causing *Vibrio parahaemolyticus* strains maintain an antibacterial Type VI Secretion system with versatile effector repertoires. *Appl Environ Microbiol.* 2017, 83(13): e00737-17. # Corresponding authors

Ray A, Kinch LN, de Souza Santos M, Grishin NV, Orth K #, **Salomon D** #. Proteomics analysis reveals previously uncharacterized virulence factors in *Vibrio proteolyticus* *mBio.* 2016, 7(4):e01077-16. # Corresponding authors

Salomon D. MIX and match: mobile T6SS MIX-effectors enhance bacterial fitness. *Mob Genet Elements.* 2016, 6:e1123796.

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Salomon D, Klimko JA, Orth K. H-NS regulates the *Vibrio parahaemolyticus* type VI secretion system 1. *Microbiology.* 2014, 160:1867-73.

Salomon D, Kinch LN, Trudgian DC, Guo X, Klimko JA, Grishin NV, Mirzaei H, Orth K. Marker for type VI secretion system effectors. *Proc Natl Acad Sci USA.* 2014, 111:9271-6.

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Salomon D, Orth K. What pathogens have taught us about posttranslational modifications. *Cell Host Microbe.* 2013, 14:269-79.

Grants

2016-2019	Alon Fellowship
2017-2022	European Research Council (ERC) Starting Grant
2017-2021	Israeli Science Foundation (ISF) Grant



Prof. Esther Segal, Ph.D.

Department of Clinical Microbiology and Immunology



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Investigating the Pathogenesis of Candidiasis, Epidemiology of Dermatophytosis and Experimental Antifungal Drugs

Positions

Professor (Emeritus), Sackler Faculty of Medicine

President, Israel Society of Medical Mycology (ISMM)

Board Member (Treasurer), European Confederation of Medical Mycology (ECMM)

FECMM, Fellow of ECMM

Honorary Member of International Society of Human and Animal Mycology (ISHAM)

Research

We focus on studying phenotypic and genotypic characteristics of clinical *Candida albicans* strains from systemic and mucosal candidiasis in vitro and in vivo in experimental animal models, mice and *Galleria mellonella*.

We developed experimental antifungal drugs: the polyenes Amphotericin B (AMB) and Nystatin (NYT) associated with Intralipid (IL): AMB-IL and NYT-IL. Currently we assess susceptibility of the *C. albicans* clinical strains to AMB-IL and NYT-IL.

We investigate the epidemiology of dermatophytoses in Israel, in the general population and in the military.

Publications

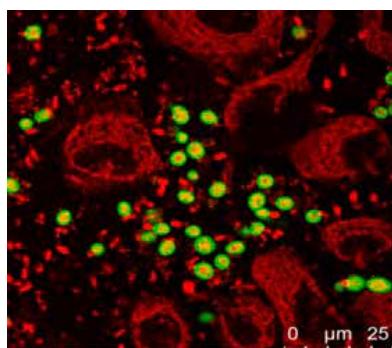
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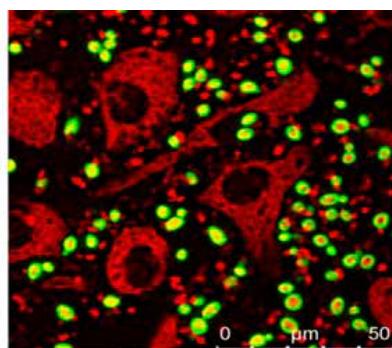
Segal E, Frenkel M. Dermatophyte infections in environmental contexts. *Res. Microbiol.* 2015; 166:564-9

Semis R, Nahmias M, Lev S, Frenkel M, **Segal E**. Evaluation of antifungal combinations of nystatin-intralipid against *Aspergillus terreus* using checkerboard and disk diffusion methods. *J Mycol Med*. 2015;25:63-70

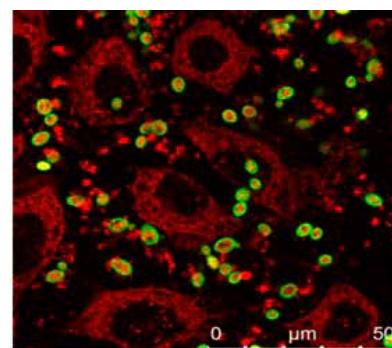
Segal R, Shemer A, Hochberg M, Keness Y, Shwarzman R, Mandelblat M, Frenkel M, **Segal E**.



CBS strain



S strain



M strain

Confocal microscopy of *C. albicans* strains adhering to HACAT cells showing strongly adherent strain from *Candida* blood-stream infection and weakly adherent strain from vaginal infection.

Onychomycosis in Israel: epidemiological aspects.
Mycoses. 2015; 58: 133-9

Frenkel M, Mandelblat M, Alastruey-Izquierdo A, Mendlovic S, Semis R, **Segal E**. Pathogenicity of *Candida albicans* isolates from bloodstream and mucosal candidiasis assessed in mice and *Galleria mellonella*. *J Mycol Med*. 2016; 261-8

Mandelblat M, Frenkel M, Abbey D, Ben Ami R, Berman J, **Segal E**. Phenotypic and genotypic characteristics of *Candida albicans* isolates from bloodstream and mucosal infections. *Mycoses*. 2017 60:534-545

Segal E. Testing antifungal vaccines in an animal model of invasive candidiasis and in human mucosal candidiasis. *Methods Mol Biol*. 2017;1625:343-353

Grants

2018-2019 Maratier Fund



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Viral Host Interactions of RNA Viruses

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our long-term goal is identification and characterization of the interactions of viruses with their host cells. Our current model systems include Ebola virus, Dengue virus and Hepatitis C and D viruses.

Current projects in the lab include:

1. Development of systems for the identification and characterization of new interactions between viral and host cell proteins.

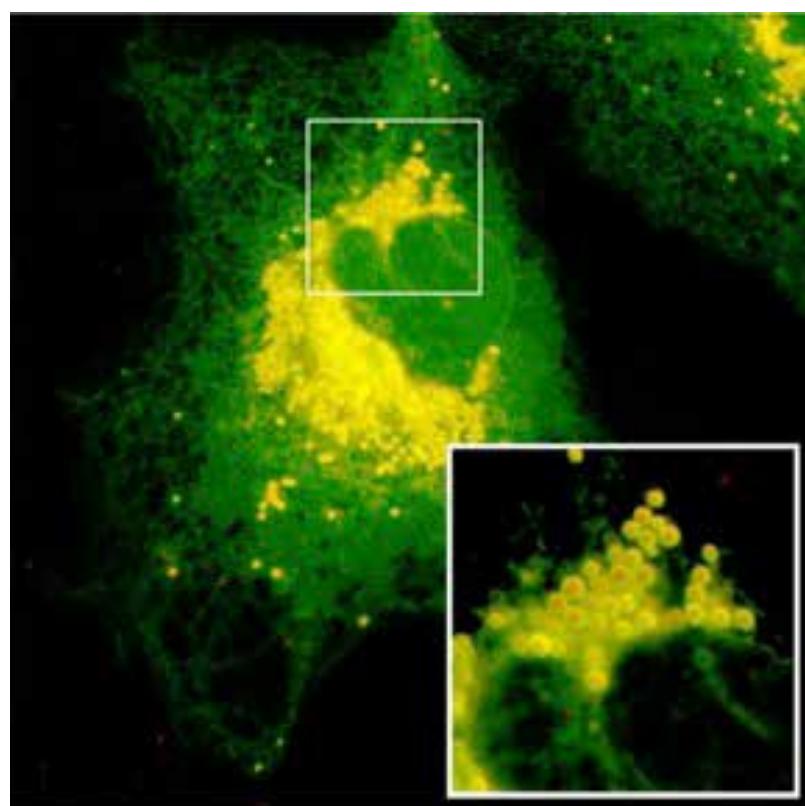
2. Using live cell imaging techniques to study viral-host interactions.

3. Identification of the mechanism of action of antiviral interferon stimulated genes.

Publications

Stern O, Hung YF, Valdau O, Yaffe Y, Harris E, Hoffmann S, Willbold D, **Sklan EH**. An N-terminal amphipathic helix in dengue virus nonstructural protein 4A mediates oligomerization and is essential for replication. (2013) *J Virol.* 87:4080-5.

Hanin G, Shenhar-Tsarfaty S, Yayon N, Hoe YY, Bennett ER, **Sklan EH**, Rao DC, Rankinen T, Bouchard



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C, Geifman-Shochat S, Shifman S, Greenberg DS, Soreq H. Competing targets of microRNA-608 affect anxiety and hypertension. (2014) *Hum Mol Genet*. 23:4569-80

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Hung Y, Schwartena M, Schünkea S, Thiagarajan-Rosenkranza P, Hoffmann S, **Skian EH**, Willbold D, Koenig B. (2015) Dengue virus NS4A cytoplasmic domain binding to liposomes stabilizes membrane curvature. *BBA – Biomembranes*. 184:8 1119-1126.

Yaffe Y, Hagger I, Nevo Yassaf I, Shepshelovitch J, **Skian EH**, Elkabetz Y, Yeheskel A, Pasmanik-Chor M, Benzing C, Macmillan A, Gaus K, Eshed-Eisenbach Y, Peles E, Hirschberg K. (2015) The myelin proteolipid Plasmolipin, forms oligomers and induces liquid ordered membranes in the Golgi apparatus. *J Cell Sci*, 128:2293-302.

Hung Y, Schwartena M, Hoffmann S, Willbold D, **Skian EH**, Koenig B. (2015) Amino terminal region of Dengue virus NS4A cytosolic domain binds to highly curved liposome. *Viruses*, 7, 4119-4130.

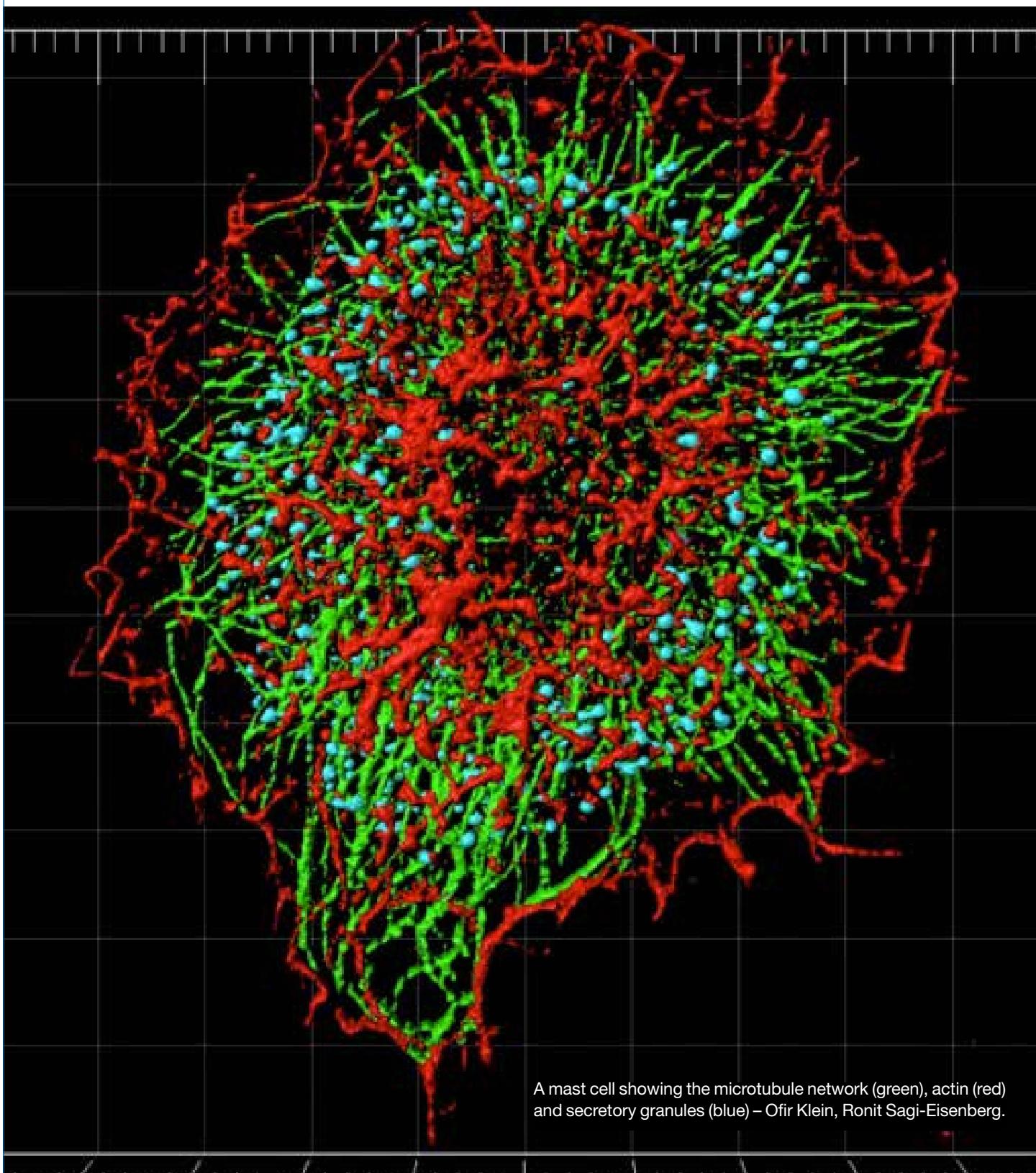
Levy G, Bomze D, Heinz S, Ramachandran SD, Noerenberg A, Cohen M, Shibolet O, **Skian E**, Braspenning J, Nahmias Y. (2015) Long-term culture and expansion of primary human hepatocytes. *Nat Biotechnol*. 33:1264-1271.

Feldman M, Hershkovitz I, **Skian EH**, Kahila Bar-Gal G, Pap I, Szikossy I, Rosin-Arbesfeld R. (2016). Detection of a tumor suppressor gene variant predisposing to colorectal cancer in an 18th century Hungarian mummy. *PLoS One*.11:e0147217.

Levy G, Habib N, Guzzardi M.A, Kitsberg D, Bomze D, Ezra E, Uygun B.E, Uygun K, Trippler M, Schlaak, J.F, Shibolet O, **Skian EH**, Cohen M, Timm J, Friedman N, Nahmias Y. (2016) Nuclear receptors control pro- and anti-viral metabolic response to HCV infection. *Nature Chem Biol*. 12:1037-1045.

Nevo-Yassaf I, Lovelle M, Nahmias Y, Hirschberg K, **Skian EH**. (2017) Live cell imaging and analysis of lipid droplets biogenesis in hepatitis C virus infected cells. *Methods*. 127:30-36.

Inflammatory and Autoimmune Diseases





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Regulatory Mechanisms in Mucosal Inflammation

Position

Associate Professor Sackler Faculty of Medicine

Associate Editor, *Journal of Allergy and Clinical Immunology*

Research

The gastrointestinal, respiratory and urogenital tracts are primary entry points of numerous pathogens and antigens. Therefore, complex immunological mechanisms evolved to efficiently and potently respond to such antigens. Notably, exaggerated immune responses such as those observed in asthma and inflammatory bowel disease are often harmful and may lead to substantial morbidity.

Our goal is to identify immunological mechanisms that can be pharmacologically targeted in diseases affecting the lung and gastrointestinal tract. We are specifically interested in defining the roles of immune inhibitory receptors in these mucosal sites. To achieve this goal we use a combination of novel in-vivo (unique gene targeted mice) and in-vitro approaches combining genomics, proteomics, molecular biology and biochemistry.

Publications

Reichman H, Moshkovits I, Itan M, Pasmanik-Chor M, Vogl T, Roth J, **Munitz A**. Transcriptome profiling of mouse colonic eosinophils reveals a key role for eosinophils in the induction of s100a8 and s100a9 in mucosal healing. *Sci Rep.* 2017;7:7117.

Rozenberg P, Reichman H, Zab-Bar I, Itan M, Pasmanik-Chor M, Bouffi C, Qimron U, Bachelet I, Fulkerson PC, Rothenberg ME, **Munitz A**. CD300f:IL-5 cross-talk inhibits adipose tissue eosinophil homing and subsequent IL-4 production. *Sci Rep.* 2017;7(1):5922.

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Amit U, Kain D, Wagner A, Sahu A, Nevo-Caspi Y, Gonon 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, Leor J. New role for Interleukin-13 Receptor 1 in myocardial homeostasis and heart failure. *J Am Heart Assoc.* 2017;6(5).

Elhaik Goldman S, Moshkovits I, Shemesh A, Filiba A, Tsirulsky Y, Vronov E, Shagan M, Apte RN, Benharroch DA, Karo-Atar D, Dagan R, **Munitz A**, Mizrachi Nebenzahl Y, Porgador A. Natural Killer Receptor

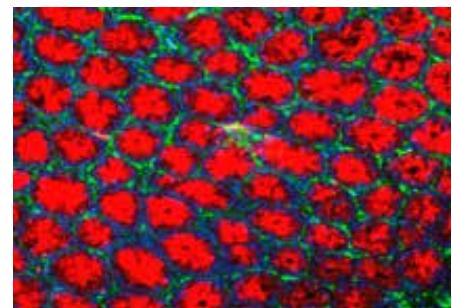
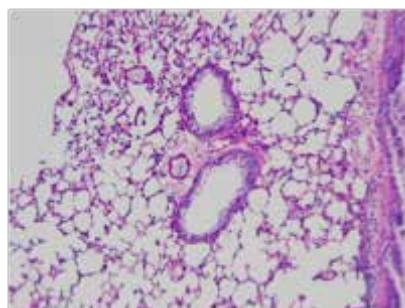
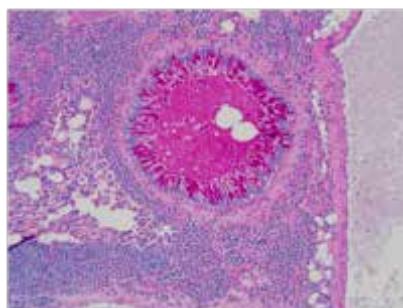


Figure legend: A photomicrograph of a normal lung displaying two large airways and a blood vessel (left). In many inflammatory conditions such as asthma and COPD, the airway is filled with mucus plugs (middle, pink stain). Right – an immunofluorescent stain of resistin-like molecule alpha (red), a proinflammatory, immunoregulatory molecule that is highly upregulated in gastrointestinal epithelial in conditions such as inflammatory bowel disease (IBD).

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Grants

2014-2017	Israel Ministry of Health
2016-2017	The Teva Research Fund for Breakthroughs in Biomedicine; Title: Role of CD300f in eosinophils
2015-2020	The Israel Science Foundation Individual Research grant #95/11; Title: Regulation of GI eosinophils by CLM-1
2015-2018	The Israel Cancer Research Fund; Title: Molecular regulation of eosinophil activation in colorectal cancer



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Cell Death and Immune Response: the Role of Necroptosis and Pyroptosis in Inflammation

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Cell death is an essential cellular process during development, but also facilitates the removal of damaged or infected cells, and is required for the resolution of innate and adaptive immune responses.

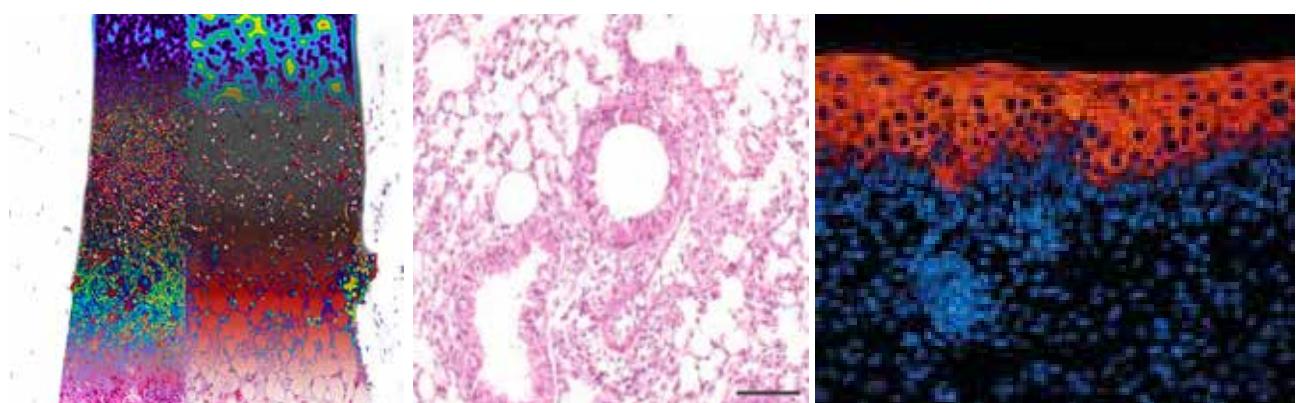
Our research focus is the understanding of the inflammatory response, with particular emphasis on novel NLRs (Nucleotide-binding domain and Leucine-rich repeat containing Receptors), and the non-apoptotic forms of cell death during infection. In particular we are interested in how pathogens (viruses and bacteria) are recognized by the innate immune system to facilitate these signals and how some pathogens evolve to target these mechanisms and prevent the host inflammatory response.

Recently, we discovered a physiological role for NLRP1 in driving a lethal, systemic inflammatory disease that is triggered by Caspase-1 activation and IL-1 β production. Remarkably, active NLRP1 triggered a Caspase-1-dependent form of cell death, known as pyroptosis. This cell death affected

hematopoietic stem and progenitor cells (HSPC), resulting in leukopenia at steady state, and cytopenia, bone marrow hypoplasia and immunosuppression, during periods of hematopoietic stress induced by chemotherapy or viral infection. Our recent research into how pathogens modulate complexes such as the NLRP1 inflammasome has defined mechanism by which *Vaccinia Virus* protein, F1L, target inflammasomes directly by binding and inhibiting the NLRP1 inflammasome formation. These findings reveal novel mechanism for viruses to evade host innate immune responses. Furthermore, we recently changed the thinking of necroptosis, which was thought to be RIPK1-dependent. We found the opposite, namely, that RIPK1 acts as a negative regulator of necroptosis, and loss of RIPK1 results in a lethal multi-organ systemic inflammatory response.

Publications

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Non-apoptotic induce inflammation. Inflammasome dependent lung inflammation during *vaccinia virus* infection (Left panel); Pyroptotic dependent bone marrow failure after chemotherapy treatment (Middle panel); Necroptotic dependent skin inflammation (Right panel).

harbouring vesicles activate cytosolic immune sensors. *Nat Comm*, in press, Oct, 2017.

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Grants

2016-2018 Israel Society Foundation (ISF), Individual Research grant, *Mechanisms and physiological consequences of necroptosis*

2016-2018 Alpha-1 Foundation, Research grant, *The role of Necroptosis and IL-33 in lung pathology of A1AT deficiency*



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Molecular Basis of Allergic Diseases: Genomic and Functional Analyses

Positions

Professor, Sackler Faculty of Medicine
Chair, Department of Cell and Developmental Biology

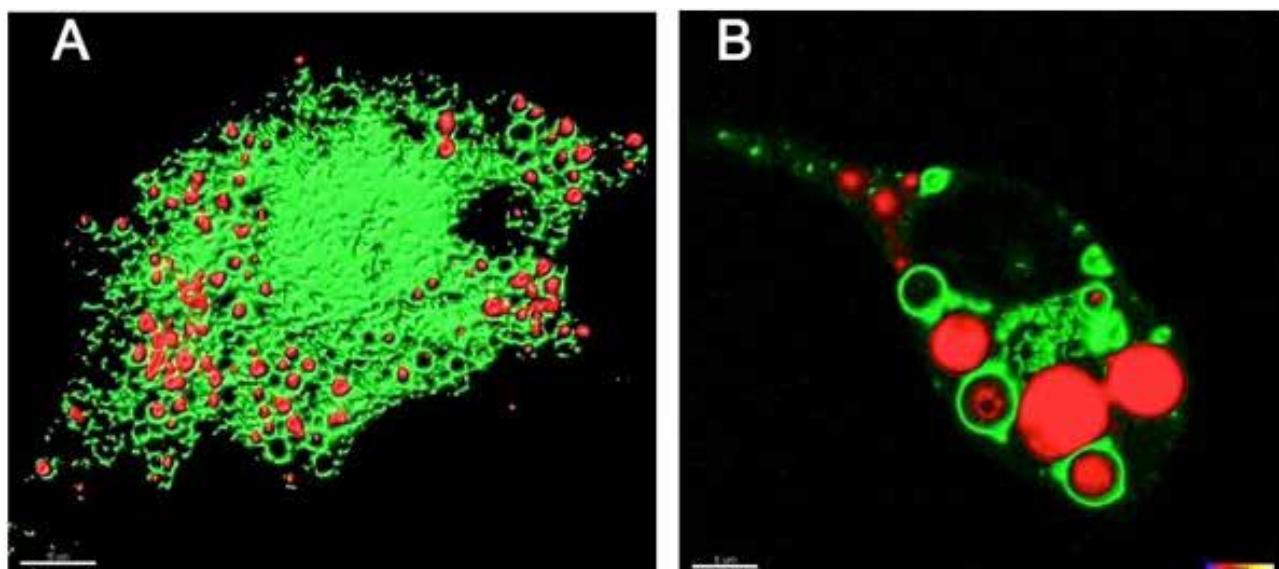
Research

Our primary interest is the molecular basis of allergic and allergy related diseases, including skin allergy and asthma. Specifically, we explore the mechanisms underlying release of allergic (i.e. histamine) and inflammatory (i.e. cytokines) mediators from activated mast cells. Our research focuses on deciphering the signaling networks that link mast cell activation with mediator release and characterization of genes that could serve as cellular targets for the future development of anti allergic and asthma drugs. To this end, we combine functional genomics and

phenotype driven screens of mast cells, activated by multiple stimuli, in order to recapitulate human pathophysiologic conditions. Research methods used include confocal microscopy in live and fixed cells; gene cloning; quantitative RT-PCR, pull down-assay; mass spectrometry, and bioinformatics.

Current projects in the lab include:

1. Revealing the secrets of mast cell secretion.
2. Mast cells and cancer – the good, the bad and the ugly.
3. Decoding the Rab networks that control mast cell function.



Cell imaging of mast cells (RBL-2H3 mast cell line), which were co-transfected with NPY-mRFP (red), as reporter for the secretory granules, and GFP-tagged wild type (A) or active mutant (B) of the small GTPase Rab5A (green) reveals a dramatic effect of this Rab active mutant on the secretory granules size.

Publications

Klein O, Roded A, Zur N, Azouz NP, Pasternak O, Hirschberg K, Hammel I, Roche PA, Yatsu A, Fukuda M, Galli SJ, **Sagi-Eisenberg R.** Rab5 is critical for SNAP23 regulated granule-granule fusion during compound exocytosis. *Sci Rep.* 2017;7:15315.

Gaudenzio, N., Sibilano, R., Marichal, T., Starkl, P., Reber, L.L., Cenac, N., McNeil, B.D., Dong, X., Hernandez, J.D., **Sagi-Eisenberg, R.**, Hammel, I., Roers, A., Valitutti, S., Tsai, M., Espinosa. E., and Galli, S.J. Different activation signals induce distinct mast cell degranulation strategies. *J Clin Invest.* 2016; 196, 3981-3998.

Gorzalczany, Y., Akiva E, Klein, O., Merimsky, O., and **Sagi-Eisenberg, R.** Mast cells are directly activated by contact with cancer cells by a mechanism involving autocrine formation of adenosine and autocrine/paracrine signaling of the adenosine A3 receptor. *Cancer Lett.* 2017; 397, 23-32.

Efergan A, Azouz NP, Klein O, Noguchi K, Rothenberg ME, Fukuda M, **Sagi-Eisenberg R.** Rab12 regulates retrograde transport of mast cell secretory granules by interacting with the rilp-dynein complex. *J Immunol.* 2016;196:1091-101.

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Reviews

Rudich N, Ravid K, and **Sagi-Eisenberg R.** Mast cell adenosine receptors function: a focus on the A3 adenosine receptor and inflammation. *Front Immunol.* 3:134. (2012).

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Medical Education and Ethics





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Bioethics, Biolaw and Medical Humanities

Position

Associate Professor, Sackler Faculty of Medicine

Research

The research area of our group is Medical Humanities, relying on theoretical methods with the occasional excursion to qualitative research.

My own personal interests encompass moral theory and the intersections among bioethics, social history and related normative domains, such as law and religion, especially Halakhah (Jewish religious law). I explore human rights law and international humanitarian law in the light of the contemporary ethical and meta-ethical discourse. Another aspect of my work aims at developing better understanding and tools of deliberation in bioethics as a psychomoral process and as socially constructed events of legitimization and education. I am intrigued by the incorporation of the history and philosophy of ideas such as conscience, responsibility, hope and doubt in clinical reality and medical education.

Another branch of research is the socio-historical and moral ideas in the representation of illness and medicine in Western visual art, since the late middle ages through contemporary and experimental art.

Ongoing research projects are:

1. Moral psychology and the notion of ethical expertise in medical education.
2. The history of karyotyping exams in questions of gender (e.g. gender verification in sport).
3. Ethics and law of military, humanitarian and disaster medicine.
4. The regulation of cloning in international law.
5. New born screening and the regulation of large, public-health data banks.
6. Human rights and international humanitarian law.

Our group's chief aim is to integrate deep theoretical knowledge and creativity with applied problems, contextualizing their ethical dimensions historically and socially. Efforts are made in the direction of cross-disciplinary work, especially through participation in the activities of the new **Edmund J. Safra Center for Ethics**, Tel Aviv University.

Monographs

Barilan, YM. Human dignity, human rights and responsibility: the new language of global bioethics ad biolaw. Cambridge (MA): MIT Press. 2012.

Barilan, YM. Jewish bioethics: rabbinic law and theology in their social and historical contexts. Cambridge University Press. 2017

Publications

Barilan YM. Bedside rationing or rational planning: in search for perspective on medical need and safety. In: Masin M, Fleck L, Hurst S. (eds.) Towards fair rationing at the bedside. Oxford: Oxford University Press, 2013.

Barilan YM, Barnea R. Routine medical care in the military. In: Siegal G, Kasher A. (eds.) Bioethics blue and white. Ha'kibbutz Ha'Me'uhad Press, 2014. [Hebrew]

Barilan YM. Rethinking the withholding / withdrawing distinction" the cultural construction of "life support" and the framing of end-of-life decisions". Multidisciplinary Respiratory Medicine 2015; 10:10

Barilan YM. Moral enhancement, gnosticism and some philosophical paradoxes. Cambridge Quarterly of Healthcare Ethics 2015; 24:75-85.

Lehmann J, Barilan YM. De-constructing de-mentia: a personal and person oriented perspective of de-personalization and moral status. Medicine Healthcare and Philosophy 2015; 18:153-158.

Barilan YM. and Brusa M. Triage. Encyclopedia of Global Bioethics. H. Ten Have (ed.) New York: Springer. Forthcoming 2016.

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Barilan YM. Terror and the Leviathan. Pragmatics and Cognition. 2016; 23:461-472.

Asman O and **Barilan YM.** The songs of the sirens and the wax in the ears: an autonomy-based tool for DBS device users. AJOB Neuroscience 2017; 8:120-122

Barilan YM. The role of doctors in hunger strikes. Kennedy Institute of Ethics Journal. 2017; 27:341-369.

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Chapters

Brusa M and **Barilan YM.** Newborn screening on the cusp of genetic screening. From solidarity in public health to personal counseling. In Peterman HI, Harper PS, and Doetz S. (eds). History of Human Genetics: Aspects of its Development in Global Perspectives. New York: Springer, 2017. pp. 503-522.

Brusa M. and **Barilan YM.** Childbirth in Israel with special attention to home birth and newborn screening. In Lavi. S. and Boas H. (eds.) Bio-Israel. Cambridge University Press. 2017. pp. 180-201.



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Studying Doctor-Patient Relationships, Communication and Medical Professionalism

Positions

Senior Lecturer, Sackler Faculty of Medicine

Board of Directors member, American Academy of Communication in Healthcare – AACH

Member, Research Committee, European Association of Communication in Healthcare (rEACH)

Member, Founding Committee, Society of Medical Education in Israel (Healer)

Research

Our primary research and teaching interests are focused on:

- Professionalism and humanism in medical schools. Understanding what students experience, how they interpret it and what we should do to help their development as humanistic professionals.
- Developing communication skills for handling and assessing multi-participant conversations (triadic communication) physician-patient-companion. Understanding how we should and could involve family members.
- Teaching medical students and professionals how to break bad news, including assessing how their personal difficulties and biases affect their communication.
- Enhancing medical students self-awareness (e.g., by using reflective diaries and narratives in medical education).
- Defining and applying Shared Decision Making in healthcare.

Publications

Bril-Barniv, S., Moran, G. S., Naaman, A., Roe, D., **Karnieli-Miller, O.** (2017). A qualitative study examining experiences and dilemmas in concealment

and disclosure of people living with serious mental illness. *Qualitative Health Research*, 27(4) 573–583.

Naaman, A., Roe, D., Karni-Weiser, N., & **Karnieli-Miller, O.** (2017). Exploring the process of self-disclosure from the perspective of people coping with Schizophrenia. *Society and Welfare*, 37 (Hebrew).

Goldberg, M., Hadas-Lidor, N., & **Karnieli-Miller, O.** (2017). Professional development of social work students coping with mental illness. *Society and Welfare*, 37 (Hebrew).

Karnieli-Miller, O., Miron-Shatz, T., Siegal, G., & Zisman-Ilani, Y. (2017). On the verge of implementing shared decision making in Israel: An overview and future directions. *Z. Evid. Fortbild. Qual. Gesundh. Wesen (ZEFQ)*, <http://dx.doi.org/10.1016/j.zefq.2017.05.007>

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Zisman-Ilani, Y., Roe, D., Scholl, I., Härtter, M., **Karnieli-Miller, O.** (2016). Shared decision-making during active psychiatric hospitalization: assessment and psychometric properties. *Health Communication*. 32(1), 126-130 .

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Goldberg, M., Hadas-Lidor, N., **Karnieli-Miller, O.** (2015). From patient to Therapatient: Social work students coping with mental illness. *Qualitative Health Research*. 25, 887–898. 2015

Zisman-Ilani, Y., Roe, D., **Karnieli-Miller, O.** (2015) Involving patients in decision making: understanding

the past and planning the future. *Quality in Medicine*, 3, 10-12. 2015 (Hebrew)

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Moran, G., Oz, G., & **Karnieli-Miller, O.** (2014) Psychiatrists' challenges in considering disclosure or schizophrenia diagnosis in Israel. *Qualitative Health Research*. 24, 1368-1380.

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Karnieli-Miller, O., Perlick, D. A., Nelson, A., Mattias, K., Corrigan, P., & Roe, D. (2013). Family members' of persons living with a serious mental illness: Experiences and efforts to cope with stigma. *Journal of Mental Health*, 22, 254-262.

Reviews

Yamin, A., Roe, D., **Karnieli-Miller, O.** (2017). Re-viewing from the inside and out – the processes of parents of people coping with a mental illness enrolled

in a group intervention to reduce self-stigma. In A. Shalev and N. Lidor-Hadass (Eds.,) *From Invisibility to Partnership: Paths to Recovery and Coping with Mental Illness in the Family* (Hebrew). Kiryat Ono: Ono Academic College, pp 117-130 (vol 2).

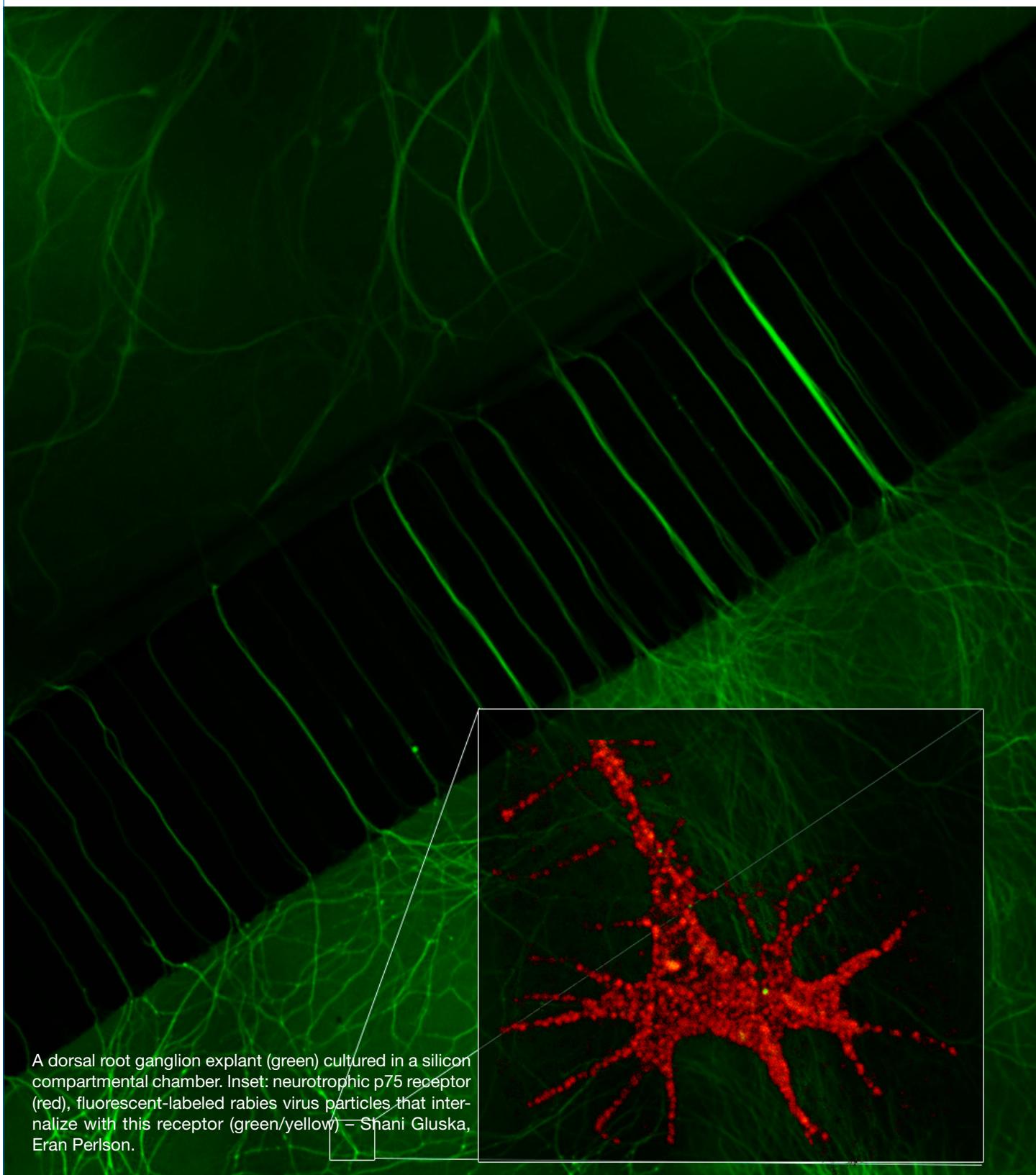
Shalev, A. Goldberg M., & **Karnieli-Miller O.** (2017). Building relationships, promoting communication and partnership with families of people coping with a mental illness. In A. Shalev and N. Lidor-Hadass (Eds.,) *From Invisibility to Partnership: Paths to Recovery and Coping with Mental Illness in the Family* (Hebrew). Kiryat Ono: Ono Academic College, pp 235-272 (vol 2).

Werner, P., **Karnieli-Miller, O.**, Eidelman, S. (2013). Current knowledge and future directions about the diagnostic disclosure of dementia: A systematic review of the first decade of the 21st century. *Alzheimer's & Dementia*, 9, e74-e88.

Grants and Chapters

2016-2018	Preventing burnout and enhancing professionalism in the surgical unit care and medical teams
2017-2019	<i>Israel National Institute for Health Policy Research</i> , Enhancing Patient Centered Care through Understanding Barriers and Promotors to Implementing Shared Decision Process in Diabetes

Nervous System and Brain Disorders



A dorsal root ganglion explant (green) cultured in a silicon compartmental chamber. Inset: neurotrophic p75 receptor (red), fluorescent-labeled rabies virus particles that internalize with this receptor (green/yellow) – Shani Gluska, Eran Perlson.



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Investigating the Molecular Basis of Visual System Development

Positions

Professor, Sackler Faculty of Medicine

Committee Member, Israel Society of Developmental Biology

Research

We study the gene networks that transform the embryonic cells into a complex, differentiated organ. We focus on exploring this question by studying the process of eye development as a model for organogenesis. We apply cutting-edge technologies including mouse genetic tools (Cre/loxP), molecular biology, and microarray analysis to identify and functionally characterize genes that regulate the development of the eye in mammals. Understanding the normal developmental regulation of the different eye structures is essential for understanding visual disorders and designing treatments for ocular phenotypes including retinal degeneration, glaucoma

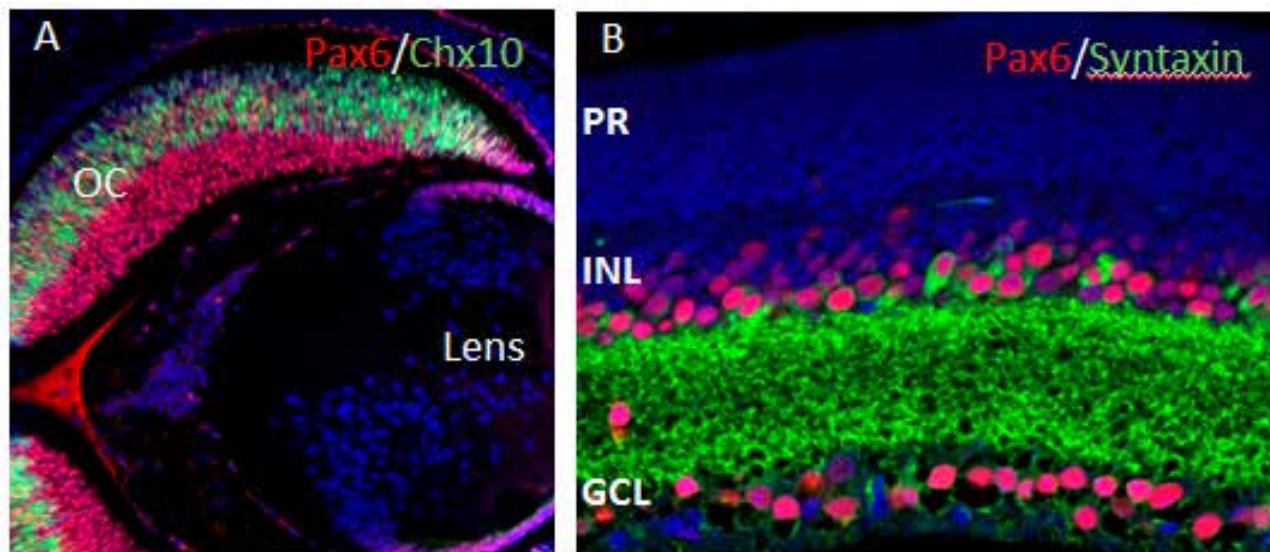
and cataracts, all of which are leading causes of blindness.

Publications

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Developmental genes play role in adult neurons. Immunofluorescence analysis reveals the expression pattern of developmental transcription factors (A) in the retinal progenitor cells located in the embryonic mouse optic cup (OC). (C) In the adult retina the developmental gene Pax6 is expressed in subtypes of retinal interneurons that co-express the synaptic protein syntaxin.

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and the differentiation kinetics of retinal progenitor cells. *PLoS One*, 2013. 8:e76489.

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Shaham O, Gueta K, Mor E, Oren-Giladi P, Grinberg D, Xie Q, Cvekl A, Shomron N, Davis N, Keydar-Prizant M, Raviv S, Pasmanik-Chor M, Bell R, **Levy C**, Avellino R, Banfi S, Conte I, Ashery-Padan R. Pax6 regulates gene expression in the vertebrate lens through miR-204. *PLoS Genet*, 2013, 9:e1003357.

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Grants

2014-2018	Binational Science Foundation (with Ales Cveki, Albert Einstein School of Medicine)
2014-2019	Israel Science Foundation
2016-2018	ISF-China (with Naihe Jing, Chinese Academy of Sciences, Shanghai)



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GSK-3 Signaling in Health and Disease

Position

Professor, Sackler Faculty of Medicine
Chair, Sackler Committee for Ph.D. Graduate Studies

Research

Our research is focused on the molecular mechanisms regulating the protein kinase GSK-3 and their implications in human disease. GSK-3 is a central player in diabetes, neurodegenerative and psychiatric disorders, and recently emerged as a promising drug discovery target. We propose that inhibition of GSK-3 should produce therapeutic benefits in treating these disorders. We develop selective substrate competitive GSK-3 inhibitors and evaluate their efficacy and therapeutic effects in relevant *in vitro* and *in vivo* systems. So far we could show that our leading compound inhibitors had therapeutic efficacy in CNS disorders models for Alzheimer's disease, mood disorders, and multiple sclerosis.

In recent work we identified the lysosome as a GSK-3 target. This implicated GSK-3 as a key player in protein degradation pathways, particularly autophagy and endocytosis. Research methods combine cell biology, molecular biology and biochemistry disciplines together with bioinformatics and computational biology.

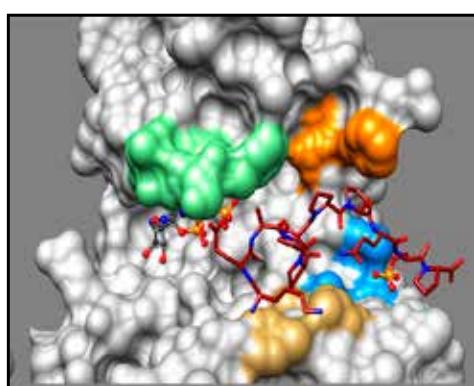
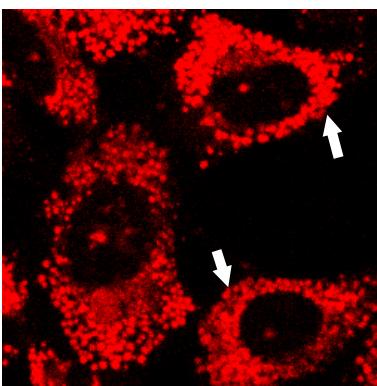
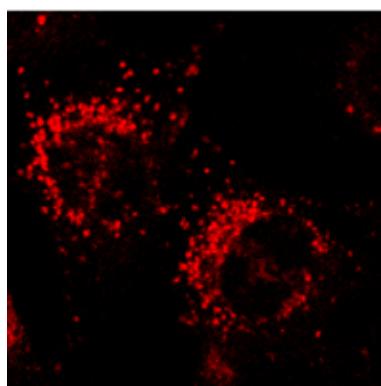
Publications

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Avrahami, L., Farfara, D., Shaham-Kol, M., Vassar, R., Frenkel, D., **Eldar-Finkelman, H.** 2013, Inhibition of GSK-3 ameliorates β -amyloid (Ab) pathology and restores lysosomal acidification and mtor activity in the alzheimers disease mouse model. *In vivo* and *In vitro* studies. *J Biol Chem* 288:1295-1306.

Beurel, E., Kaidanovich-Beilin, O., Yeh, W., Song, L., Palomo, V., Michalek, SM., Woodgett, JR, Harrington, LE, **Eldar-Finkelman, H.**, Martinez, A., Jope, RS. 2013, Regulation of Th1 cells and experimental autoimmune encephalomyelitis (EAE) by GSK-3. *J. Immunol.* 190:5000-5011.

La Pietra V., La Regina, G., Coluccia, A., Famiglini, V., Pelliccia, S., Plotkin, B., **Eldar-Finkelman, H.**, Brancale, A., Ballatore, C., Crowe, A., Brunden, KR., Marinelli, L., Novellino, E., Silvestri R. 2013. Design, synthesis, and biological evaluation of 1-Phenylpyrazolo[3,4-e]pyrrolo[3,4-g]indolizine-4,6(1H,5H)-diones as new glycogen synthase kinase-3 β inhibitors. *J. Med Chem.* 56: 10066-10078.



Treatment with GSK-3 inhibitor restores lysosomal activity, lysosomes shown as red dots (left). Computational model of GSK-3 inhibitor -L803-mts-binding with the substrate binding site (right).

Azoulay-Alfaguter I, Elya R, Avrahami L, Katz A, **Eldar-Finkelman H.** 2014, Combined regulation of mTORC1 and lysosomal acidification by GSK-3 suppresses autophagy and contributes to cancer cells growth. *Oncogene*. 34:4613-23.

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Licht-Murava A, Paz R, Vaks L, Avrahami L, Plotkin B, Eisenstein M, **Eldar-Finkelman H.** (2016) A unique type of GSK-3 inhibitor brings new opportunities to the clinic. *Sci Signal*. 9:ra110.

Pardo M, Cheng Y, Velmeshev D, Magistri M, **Eldar-Finkelman H**, Martinez A, Faghihi MA, Jope RS, Beurel E. (2017) Intranasal siRNA administration reveals IGF2 deficiency contributes to impaired cognition in Fragile X syndrome mice. *JCI Insight*. 2:e91782.

Reviews

Avrahami, L., **Eldar-Finkelman, H.** 2013, GSK-3 and lysosomes meet in Alzheimer's disease. *Comm Integrat Biology*. 6:e251789.

Grants

2017-2020 Israel Science Foundation



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Models and Rehabilitation of Grasping

Positions

Senior Lecturer, Sackler Faculty of Medicine

Associate Investigator, ARC Centre of Excellence in Cognition and its Disorders, Australia

Member, Sagol School of Neuroscience

Research

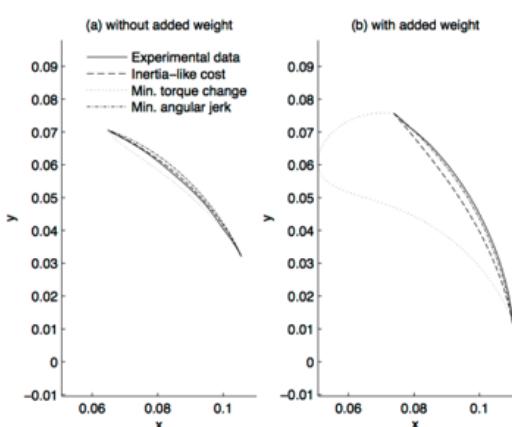
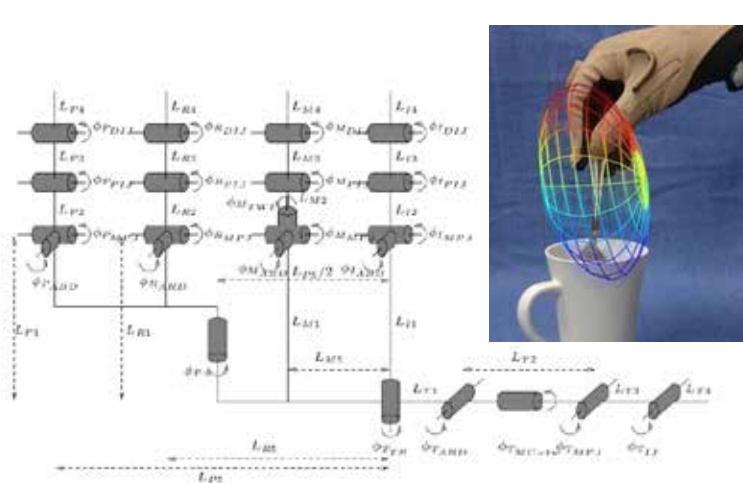
We study human movement in typical and clinical populations, with a focus on grasping and finger movements. We are interested in fundamental questions such as how we learn to make new movements, how children develop motor skills during development, and how our motor function is affected by disorders such as stroke, dystonia or cerebral palsy. We also study the interconnection between decision making and human movements. Our approach is to construct models that describe movement and force generation by the hand and arm, taking into account the biomechanics of the hand and the neural processes leading up to making

movements. This approach gives us insights into the strategies behind the complex movements and force coordination required to successfully perform grasping and manipulation, as well as a greater understanding of the causes of differences in performance in individuals with motor disorders. A goal of this research is to improve rehabilitation of hand function through improving our knowledge of these strategies.

Publications

Shaklai S, Mirmouni-Bloch A, Levin M, **Friedman J.** (2017) Development of finger force coordination in children. *Exp Brain Res.* 235:3709-3720.

Raveh E, **Friedman J.**, Portnoy S. (2017) Visuomotor behaviors and performance in a dual-task paradigm with and without vibrotactile feedback when using a myoelectric controlled hand. *Assist Technol.* 1-7.



Left: We use a model of the hand with the finger joints modelled as revolute joints, with twenty degrees of freedom. **Middle:** Based on models such as these, we can determine the properties of grasps subjects select, for example, when stirring with a spoon, to determine what are the important factors used when generating these grasps. The ellipsoid shows that the subject selected the grasp to maximize the angular velocity about the up-down axis (i.e., to stir the coffee!). Figure from the cover of *Cortex*, 2007. **Right:** Comparing different models of finger movement to experimental data allowed us to adjudicate between different theoretical models of movement generation (from Friedman and Flash, *Exp. Brain Res.* 2009).

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Awasthi, B., Sowman, P., **Friedman, J.** and Williams, M.A. (2013) Distinct spatial scale sensitivities for early categorisation of Faces and Places: Neuromagnetic and Behavioural Findings. *Frontiers in Neuroscience*, 7:91.



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Neuronal Plasticity and Nerve Cell Protection in Disease

Positions

Professor Emeritus of Clinical Biochemistry, Sackler Faculty of Medicine

Lily and Avraham Gildor Chair for the Investigation of Growth Factors

Director, Dr. Diana and Zelman Elton Laboratory for Molecular Neuroendocrinology

Editor-in-Chief, *Journal of Molecular Neuroscience*

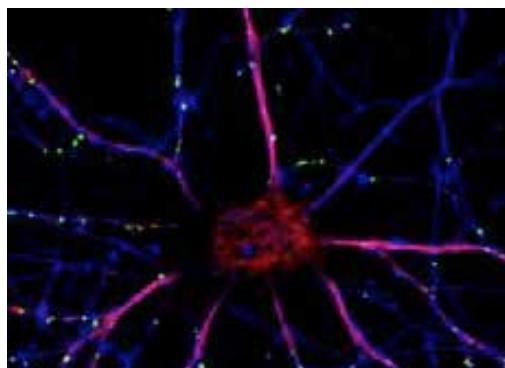
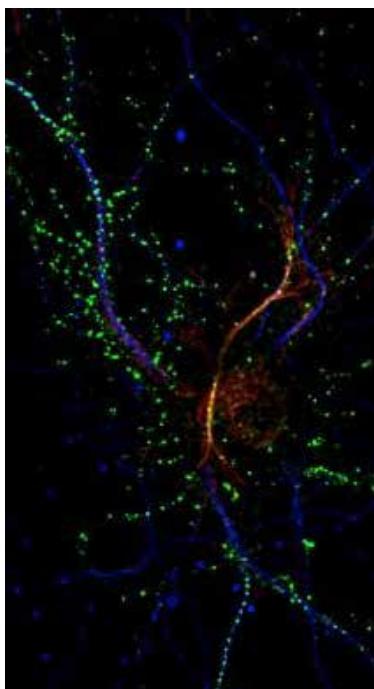
Member, MALAG (Israeli Council of Higher Education)

different aspects of neuronal plasticity and nerve cell protection, at the molecular, cellular and system level. A major focus in the laboratory is on nerve structure and transport mechanisms. We have discovered novel families of proteins associated with cross talk among nerve cells and their support cells, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective proteins (ADNPs, with ADNP being a major gene mutated in autism). Small ADNF and ADNP derivatives are in clinical development. The lead compound, davunetide is planned for an advanced Phase II clinical trial with the biotech industry.

Davunetide has previously shown efficacy in several Phase II clinical trials (i.e. in patients suffering from mild cognitive impairment, preceding Alzheimer's disease and in schizophrenia patients, protecting activities of daily living).

Research

Our research is characterized by a multi-level approach to the study of brain function, behavior, memory and drug discovery, from molecules to cures. Targeting autism, schizophrenia as well as Alzheimer's disease and related neurodegeneration and utilizing a multidisciplinary approach, our group investigates



The NAP-motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through Microtubule End Binding (EB) proteins.

Publications

Jouroukhin Y, Ostritsky R, Assaf Y, Pelleg G, Giladi E, **Gozes I.** NAP (davunetide) modifies disease progression in a mouse model of severe neurodegeneration: Protection against impairments in axonal transport. *Neurobiol Dis.* 56C:79-94, 2013.

Esteves AR, **Gozes I.**, Cardoso SM. The rescue of microtubule-dependent traffic recovers mitochondrial function in Parkinson's disease. *Biochim Biophys Acta.* 1842:7-21, 2014.

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Heimesaat MM, Fischer A, Kühl AA, Göbel UB, **Gozes I.**, Bereswill S. Anti-Inflammatory properties of NAP in acute toxoplasma gondii-induced colitis in mice. *Eur J Microbiol Immunol (Bp).* 5: 210-220, 2015.

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Malishkevich A, Marshall GA, Schultz AP, Sperling RA, Aharon-Peretz J, **Gozes I.** Blood-borne activity-dependent neuroprotective protein (ADNP) is correlated with premorbid intelligence, clinical stage and Alzheimer's disease biomarkers *J Alzheimers Dis.* 2015;50:249-60.

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Reviews

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Gozes I. Sexual Divergence in Activity-Dependent Neuroprotective Protein (ADNP) Impacting Autism, Schizophrenia and Alzheimer's Disease. *J Neurosci Res*. 2016, In press.

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Grants

2014-2018	Israel Science Foundation – Deciphering beta-amyloid and tau neurotoxicity: Genome-wide RNA sequencing for sensitivity biomarkers- with Dr. David Gurwitz
2016-2019	ERA-NET NEURON – Modelling syndromic autism caused by mutations in the ADNP gene (with Frank Kooy, Pierre-Luc Germain, Christopher E. Pearson)



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The Molecular Basis of the Regulation of Immune and Cancer Cells by Ion Channels

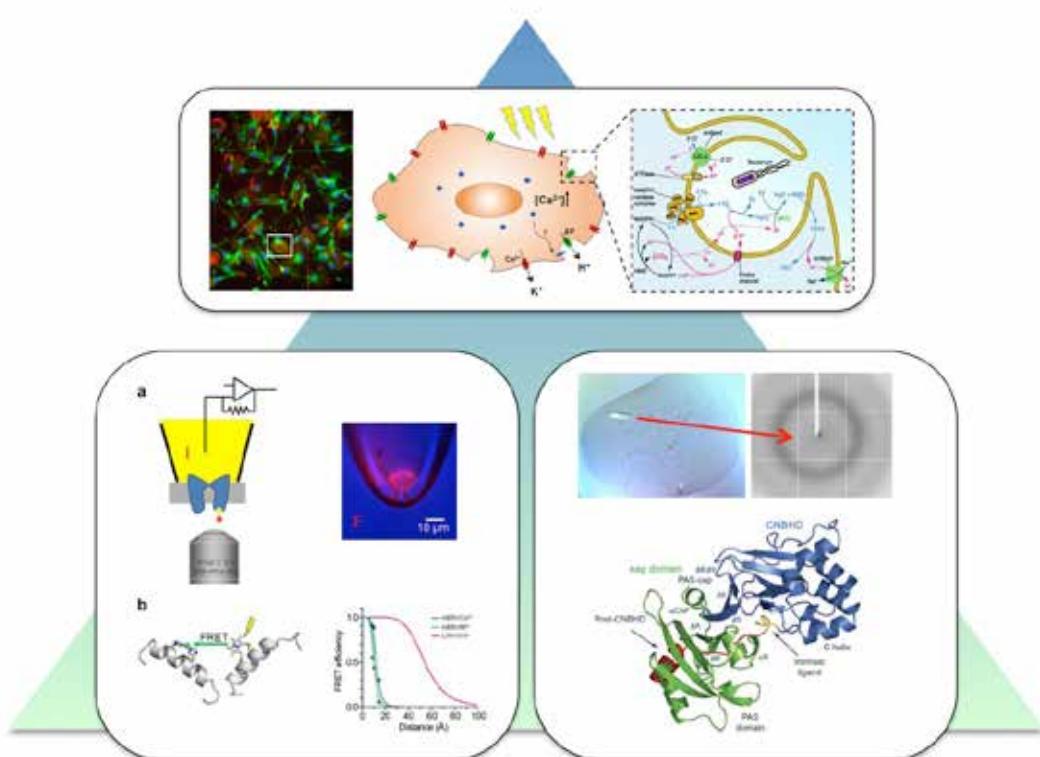
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Ion channels are membrane-embedded molecular machines that enable cells to communicate with their extracellular environment. Ion channels regulate a host of physiological processes such as neuronal excitability and immune cells activation. Consequently, genetic mutations that hamper their function can lead to severe pathologies, which include epilepsies, cardiac arrhythmias and transformation of cancer cells.

Our lab is interested in the utmost basic molecular and structural aspects of the emerging roles ion channels play in microglia, the resident immune cells of the brain. Any disturbance to brain homeostasis evokes rapid microglial transformation from a resting to an activated, phagocytic state. Ion channels, and other signalling cascades, orchestrate this activation. However, immune response in a central and delicate organ such as the brain can be a double-edged sword, exacerbating both acute conditions such as stroke and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.



Our efforts for elucidating how ion channels contribute to microglial activity are equally supported by combining electrophysiological and fluorescence, which enable the characterization of ion channel dynamics, with x-ray crystallography for structural analysis at the atomic level.

Using a combined multidisciplinary approach, which includes fluorescence, x-ray crystallography, and electrophysiology, we pursue better understanding of the molecular mechanisms and protein dynamics governing the regulation of these channels and, in turn, elucidate how they contribute to microglial activity. Ultimately, unveiling the molecular basis of microglial ion channels modulation may prove beneficial for microglial-related brain pathologies.

Publications

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Grants

2015 – 2019 Israeli Center for Research Excellence (I-CORE): Structural Biology of the Cell – Biophysics and medical technology

2016 – 2018 Recanati Foundation for Biomedical Research

2017 – 2018 German-Israeli Foundation for Scientific Research and Development (GIF), Young Scientists Program

2017 – 2020 Israel Science Foundation (ISF), Personal Grant

2017 – 2019 Israel Cancer Research Fund (ICRF), Research Career Development Award (RCDA)

2017 – 2018 INSTRUCT Pilot R&D Grant



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Brain Mechanisms of Human Emotion Generation & Regulation

Laboratory for Brain and Emotion Experience

Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center

Positions

Professor of Psychiatry and Psychology, Department of Physiology and Pharmacology, Sackler Faculty of Medicine, School of Psychological Sciences and Sagol School of Neuroscience

Director, The Sagol Center for Brain Functions, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center

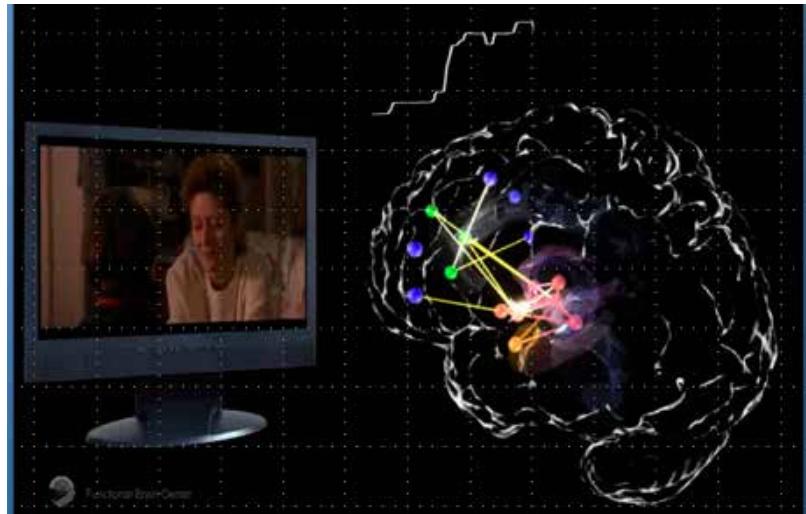
Research

Investigating brain mechanisms underlie generation and regulation of the human emotional experience, in healthy and pathological states. The research is based on measuring indices of brain structure and functional dynamics via MRI (functional-MRI, DTI and Volumetric-MRI) and separate or simultaneous recording of electrical signals (scalp-EEG and intracranial-EEG). The characterization of individual brain response is based on correlating neural activity

and connectivity with behavioral and physiological measurements of emotionality (e.g. heart rate, hormone secretion, genetic expression, skin conductance, eye movements and verbal output). Induction of emotional states is achieved via film and music media, inter-personal interactions, and interactive social games. Regulation of emotions is modulated via on-line feedback protocols from brain signals in a closed loop set-up (i.e. *NeuroFeedback*). The lab is also involved in studies aim to advance translation while focusing on neural markers of vulnerability and recovery with regard to post traumatic disorders (e.g. anxiety and depression), developmental disorders (e.g. schizophrenia and personality) and neurodegenerative disorders (e.g. parkinson disease). An essential part of this aspect of our work is the development of advanced new tools for acquiring and analyzing whole brain neural measurements; including applying multi-scale mapping for capturing dynamics of brain networks.

Publications

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Y. Jacob, D. Papo, **T. Hendler** and E. Ben-Jacob (2012). Functional Holography and Cliques in Brain Activation Patterns, *Advances in Brain Imaging*, Dr. Vikas Chaudhary (Ed.), ISBN: 978-953-307-955-4, InTech, (pp.101-126).

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Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

Position

Professor, Sackler Faculty of Medicine

Movement Science Lab., Department of Physical Therapy

Associate Editor, Journal of Electromyography & Kinesiology

Research

Behavioral and computational motor control is our field of research. This is a main venue for understanding the motor system and its organization, in healthy and clinical populations. In the last years, we have dedicated major efforts in investigating methods and technologies (virtual reality, robot-based rehabilitation, neuro-stimulation) that can potentially enhance motor recovery and functional performance in clinical populations with a focus on upper-limb motion in stroke survivors. Mathematical model-based, as well as empirical neuromotor approaches, are used in our research for studying

and understanding laws of motor control and sensorimotor integration.

Publications

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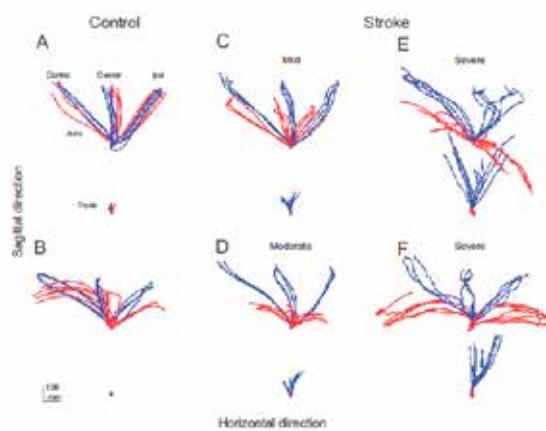
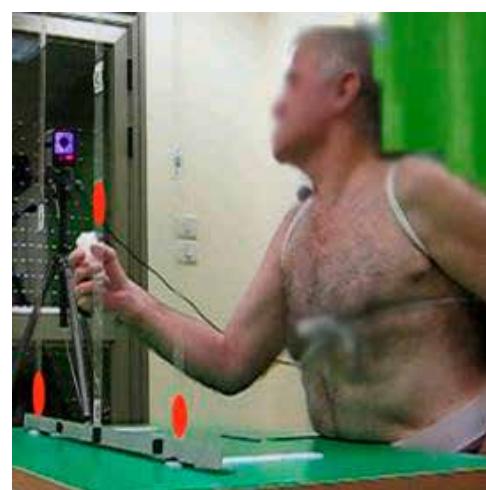


Fig. 2



Top: Schematic view of arm and trunk rotation used in modeling arm-trunk coordination based on a geometric algebra approach. **Right:** Arm endpoint and trunk paths (horizontal plane view; i.e., from the above) during reaching movements to contra-, center and ipsilateral visual targets for two healthy controls (A, B) and four stroke patients with mild (C), moderate (D) and severe (E-F) hemiparesis. Center-out paths to targets in the physical environment are depicted in blue traces and 2D virtual environment in red traces.

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Grants

2015-2017	Israeli Defense Forces
2015-2017	Nelly Horwitz Foundation
2015-2018	CIHR – ISF-Canada-Israel



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Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

Position

Professor, Sackler Faculty of Medicine

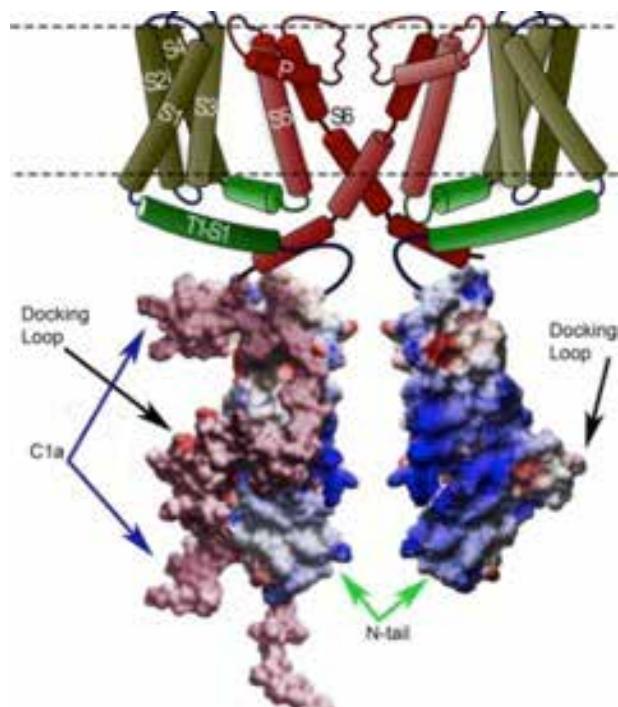
Research

We have a long standing interest in the study the molecular mechanisms of modulation of voltage gated K⁺ (Kv) channels by interaction with signaling molecules. We were first to describe modulation of a brain Kv channel by major protein components of the exocytotic machinery. Since then our main focus is the role of Kv channels in transmitter release, finding that it may be far more than just repolarizing the membrane potential: independent of K⁺ currents but mediated by protein-protein interactions with the

exocytic SNARE proteins. The dual actions of the channel, through its currents and via its interaction with SNAREs, in combination, may reinforce the known activity dependence of dense core vesicle exocytosis.

Main research projects currently in the lab:

- 1) Study of the novel role of Kv2.1 potassium channel in insulin secretion from pancreatic islet β cells, as a target for novel drug design for the treatment of type-2 diabetes;
- 2) Study of structure-function and modulations by presynaptic modulators of Kv2.1 and other Kv channels, specifically KCNQ2 and KCNQ3, important in axonal and synaptic excitability.



Kv2.1-C terminal domain, C1a, wraps around the N terminus and is accessible for protein-protein interactions. Using biophysical and FRET analyses, combined with computational biology approach dealing with homology and ab initio modeling of protein structures, proteins docking simulations and molecular dynamics.

Kv2.1 (Lvov et al., J. Biol. Chem. (2009)

Research methods:

Biophysical: 1) Two-electrode voltage clamp and patch clamp techniques for the study of whole cell and single channel currents. 2) Membrane capacitance and amperometry measurements for the study of exocytosis.

Biochemical: co-immunoprecipitation, immunohistochemistry, recombinant protein purification, etc, for the study of *in vivo* and *in vitro* protein-protein interactions.

Imaging: 1) Fluorescence Resonance Energy Transfer (FRET) for the study of protein-protein interactions. 2) Total Internal Reflection Fluorescence Microscopy (TIRFM) for the study of neurotransmitter vesicles behavior.

Publications

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Grants

2014-2018 Israel Science Foundation



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Sleep and Its Relation to Cognition

Position

Senior Lecturer, Sackler Faculty of Medicine

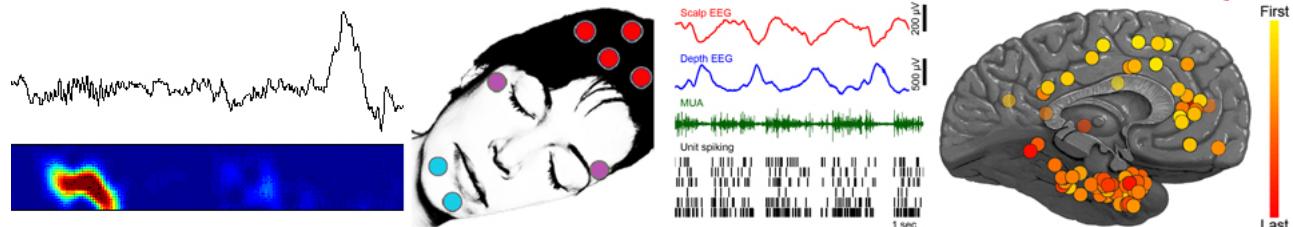
Research

Sleep is a universal behavior that is present across the animal kingdom. We spend a third of our lives sleeping, disconnected from the world around us. Our sleep is closely regulated so that when we are sleep deprived, we ultimately compensate with longer, deeper sleep. Sleep helps our cognitive performance, promoting learning and memory consolidation. Lack of sleep immediately affects our cognition, mood, and health. All this suggests that sleep is essential, but what exactly is it about brain activity during sleep that is so crucial for restoring our normal cognition?

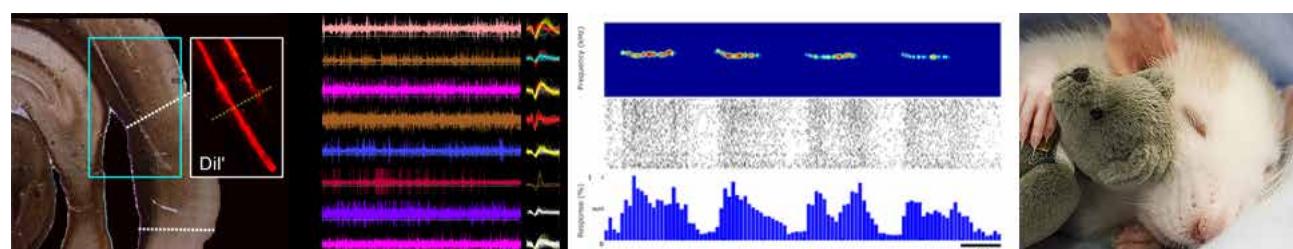
Sleep also involves dramatic changes to our perceptual awareness. Sometimes our consciousness fades altogether while at other times we experience vivid dreams. Although our brain continues to be

active, we are mostly disconnected from sensory signals such as sounds, which would otherwise be perceived, trigger plasticity and result in behavior. How does the internal state of brain activity during sleep affect brain responsiveness and perceptual awareness?

Our goal is to understand how sleep relates to cognition and perception. Our research is guided by a belief that such studies require a combination of human and animal models. We therefore use multiple experimental techniques, focusing on the strengths of each setup to investigate the same key questions synergistically. Animal models are used to investigate underlying mechanisms, by performing detailed recordings of electrical activity and by manipulating neuronal activity with optogenetic, electrical and sensory stimulation. Human studies are carried out for careful investigation of cognitive factors and for studying large-scale brain activity (with fMRI, EEG, recordings in neurosurgical patients, and behavioral tests).



Intracranial sleep recordings in neurosurgical patients reveal that slow waves and sleep spindles – the hallmark EEG oscillations of sleep – occur mostly locally and have a tendency to propagate from medial prefrontal cortex to the medial temporal lobe. Therefore, intracerebral communication during sleep is constrained as sleep oscillations often occur out-of phase in different brain regions.



A comparison of single-unit and LFP responses in rat auditory across wakefulness and sleep states reveals comparable selectivity and response magnitudes of auditory-evoked responses across vigilance states.

Publications

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Grants

2014 – 2018 EU Marie Curie Career Integration Grant (CIG)

2013 – 2018 I-CORE Cognitive Neuroscience

2015-2020 Israel Science Foundation grant



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Neural Circuits and Olfactory Perception in *Drosophila*

Position

Senior Lecturer, Sackler Faculty of Medicine and
Sagol School of Neuroscience

Research

We are exploring the various mechanisms by which neural circuits encode information and support behaviour, learning and memory. In addition, we are studying how the connectivity and activity of such circuits and neural networks are affected by molecular mechanisms underlying brain disorders. We use a multidisciplinary approach, with the *Drosophila* olfaction system as our model system. Our studies incorporate *in vivo* whole cell patch recordings, *in vivo* functional imaging, behaviour experiments, molecular biology, mathematical modelling and genetics.

Projects in the lab include:

1. Intensity and identity coding in a multidimensional sensory system – the *Drosophila* olfactory system.
2. Neuropeptidergic modulation of olfaction and its effect on odour perception.

3. The role of deregulated channel proteins and altered neuronal function in Frontotemporal Dementia.
4. A novel multifaceted approach to study the mechanisms underlying the effects of human genes associated with schizophrenia using *Drosophila*.

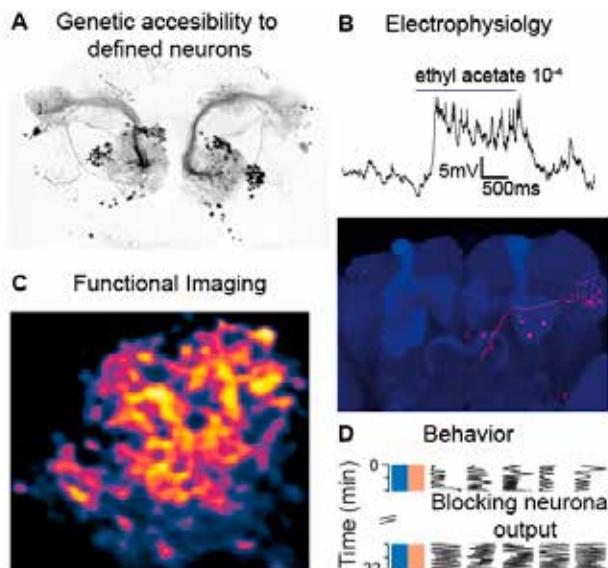
Publications

Manuscripts

Parnas, M., Lin, A.C., Huetteroth, W., and Miesenböck, G. (2013). Odor discrimination in *Drosophila*: From neural population code to behavior. *Neuron*, 79:932-944.

Grants

2016	NIPI – National Institute of Psychobiology in Israel
2017-2019	United States-Israel Binational Science Foundation
2016-2020	ERC Starting Grant



Drosophila as a model system for systems neuroscience. **A.** Using the genetic tools available for *Drosophila* there is accessibility for defined neurons. **B.** *In vivo* whole cell patch recording in awake behaving animals. **C.** *In vivo* functional imaging using genetically encoded sensors in awake behaving animals. **D.** Genetic access to defined neurons allows manipulation of the activity of neural circuits in behaving animals.



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Molecular Mechanisms of Neurodegeneration

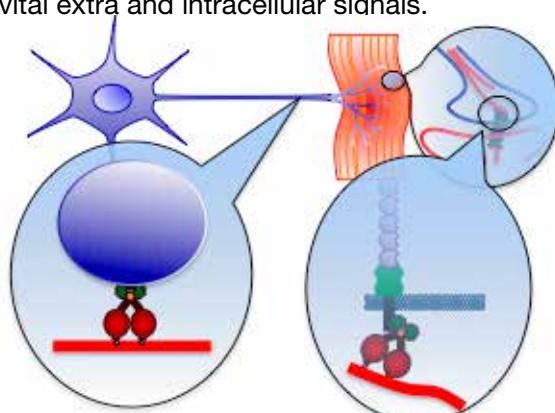
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

The lab is a new multi-disciplinary molecular and cellular neurobiology lab. The lab uses state-of-the-art single molecule live imaging techniques on neuronal cultures, as well as biochemistry, cell biology and biophysics approaches on mouse model systems to study the role of axonal transport in neurodegenerative diseases, with an initial focus on ALS.

Neuronal survival and proper function depends on cell-cell communication mediated by ligand-receptor mechanisms. During neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), there is considerable synapse/neuromuscular junction (NMJ) disruption and neuronal cell death. It is non-autonomous processes involve interactions between the neurons to its diverse extracellular microenvironments. The molecular basis for this neuronal dysfunction and death is still poorly understood. One possible reason is alterations in the nature, directed movement and spatial localization of vital extra and intracellular signals.



The dual role of dynein in spatiotemporal signaling. Dynein serve as a motor protein conducting long distance signaling process (left callout) or may play a role in receptors clustering and lateral movement in and out of membrane microdomain (right callout) for example in the neuromuscular junction. Alterations in its function leads to neurodegeneration.

The long-term research goal of the lab is to understand the vital molecular communications mechanisms between the neurons and its environment. More specifically, we seek to understand the role that retrograde signaling plays in (1) neuronal survival and (2) synapse stability.

We believe that our research will generate novel insights into neurodegenerative mechanisms and ultimately, provide a molecular basis for new drugs as well as delivery methods to treat a range of neurodegenerative diseases.

Publications

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Gluska S, Finke S, **Perlson, E.** (2015) Rabies Express: Receptor-Mediated Increase in Rabies Virus Axonal Transport. *Neuronal Regeneration Research*. 10:883-4.

Grants

2013-2018 Molecular Communication Mechanism of Motor Neuron Survival and Synapse Maintenance, European Research Council (ERC) Starter Grant



Prof. Chaim G. (Chagi) Pick, Ph.D.

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Brain Injuries: Cognitive, Behavioral and Cellular Outcome

Position

Professor, Sackler Faculty of Medicine
Chair, Department of Anatomy and Anthropology
Sagol School of Neuroscience faculty member
Dr Miriam and Sheldon G Adelson Chair in Biology of Addictive Diseases

Research

My group has a long history in mTBI research, not only in characterizing behavioral and biochemical sequelae of blunt head trauma, but also in developing preclinical models of mTBI of translational relevance to support the development of new treatment strategies and drugs. In order to look for answers regarding the blast induced traumatic brain injury, we have developed a blast injury model for mice that resembles, as much as possible, the conditions on the battlefield or at a terror-attack site. As such, the outcomes of the “real-life-like” exposure to the blast in our model may vary from severe to mild brain injury under controlled conditions for each mouse.

Publications

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Tweedie, D., Rachmany, L. Kim D.S., Rubovitch, V., Lehrmann, E., Zhang, Y., Becker, K.G., Perez, E., Hoffer, B.J., Pick C.G* and Greig, N.H. Mild traumatic brain injury-induced hippocampal gene expressions: the identification of target cellular processes for drug development. *J Neurosci Meth.* (2016). doi: 10.1016/j.jneumeth.2016.02.003. [Epub ahead of print]

Tweedie, D., Fukui, K., Li, Y., Barak, S., Tamargo, I., Rubovitch, V., Holloway, H.W., Hoffer, B.J. Becker, R.E., **Pick, C.G.** Greig, N.H. Cognitive impairments induced by concussive mild traumatic brain injury in mouse are ameliorated by treatment with pheneserine via multiple non-cholinergic mechanisms. *PLoS One.* (2016). 11(6):e0156493.

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Reviews

Hoffer BJ, **Pick CG**, Hoffer ME, Becker RE, Chiang YH, Greig NH. Repositioning drugs for traumatic brain injury - N-acetyl cysteine and Phenserine. *J Biomed Sci.* 24:71 (2017).



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Molecular Mechanisms of Drugs for Neuropsychiatric Disorders

Positions

Professor Emeritus, Sackler Faculty of Medicine

Research

Main projects in the lab include:

1. Presynaptic monoamine transporters and the vesicular monoamine transporter as targets for neuropsychiatric drugs.
2. Anxiolytic effects of new herbal treatment: mice models of anxiety and biochemical studies.
3. Quaternary serotonin-reuptake inhibitors as novel anti-platelet drugs.
4. Methylphenidate (Ritalin): abuse potential and long-term effects.
5. Neuronal rescue by Rasagiline (MAO-B inhibitor) in thiamine deficiency.

Publications

Oved K, Morag A, Pasmanik-Chor M, **Rehavi M**, Shomron N*, Gurwitz D*. (2013) Genome-wide

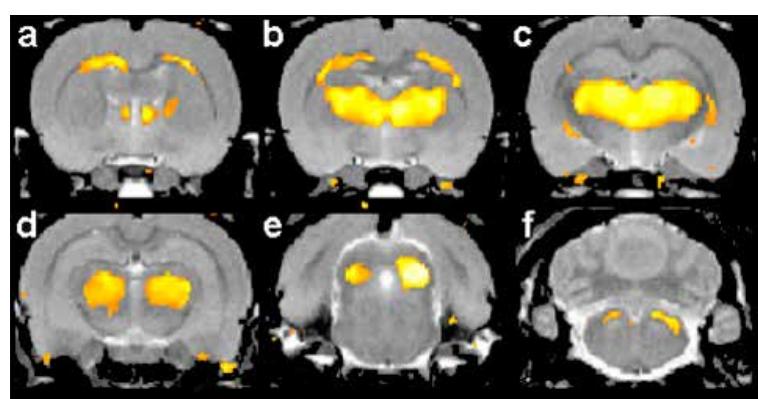
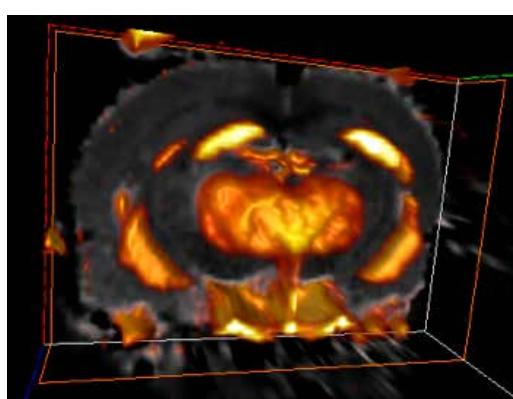
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Doron R, Lotan D, Einat N, Yaffe R, Winer A, Marom I, Meron G, Kately N, **Rehavi M** (2014) A novel herbal treatment reduces depressive-like behaviors and increases BDNF levels in the brain of stressed mice. *Life Sci.* 94:151-7

Dror V, **Rehavi M**, Biton IE, Eliash S. (2014) Rasagiline prevents neurodegeneration in thiamine deficient rats-A longitudinal MRI study. *Brain Res.* 1557:43-54

Kornilov P, Peretz A, Lee Y, Son K, Lee JH, Refaeli B, Roz N, **Rehavi M**, Choi S, Attali B. (2014) Promiscuous gating modifiers target the voltage sensor of Kv7.2, TRPV1, and Hv1 cation channels. *FASEB J.* 28:2591-602

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(A) Six representative coronal slices of T_2 -weighted MR images from untreated thiamine-deficient rats on day 14. The yellow areas represent abnormalities characterized by a significant increase in signal intensity that occurred on day 14 as compared to day 0 (ANOVA, $p < 0.01$). (a,b) thalamus and corpus callosum; (c,d) thalamus; (e) inferior colliculi; (f) superior cerebellar peduncle. (B) A Three-dimensional Maximum intensity projection (MIP) image of the T_2 maps, demonstrating the damaged thiamine-deficient areas on day 14.

Edut S, Rubovitch V, **Rehavi M**, Schreiber S, Pick CG. (2014) A study on the mechanism by which MDMA protects against dopaminergic dysfunction after minimal traumatic brain injury (mTBI) in mice. *J Mol Neurosci.* 54:684-97.

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Simchon-Tenenbaum Y, Weizman A, **Rehavi M**. (2015) Alterations in brain neurotrophic and glial factors following early age chronic methylphenidate and cocaine administration. *Behav Brain Res.* 282:125-32.

Hadar A, Milanesi E, Squassina A, Niola P, Chillotti C, Pasmanik-Chor M, Yaron O, Martásek P, **Rehavi M**, Weissglas-Volkov D, Shomron N, Gozes I, Gurwitz D. (2016) RGS2 expression predicts amyloid-sensitivity, MCI and Alzheimer's disease: genome-wide transcriptomic profiling and bioinformatics data mining. *Transl Psychiatry* 6:e909.



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The Molecular Basis of Epileptic Encephalopathies and Autism

Position

Senior Lecturer, Sackler School of Medicine

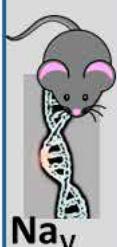
Research

We study the neuronal and molecular basis of visual system abnormalities in severe epilepsy and autism. One out of every 68 children is diagnosed with an autism spectrum disorder, characterized by impaired social skills. Moreover, autistic features are observed in people suffering from epileptic encephalopathies, a group of severe disorders characterized by refractory

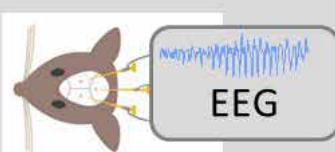
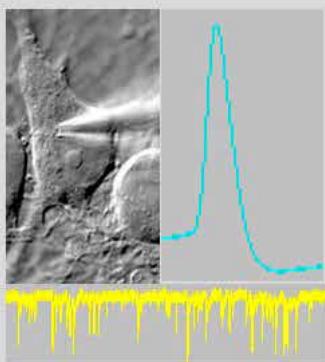
seizures and cognitive deficit with limited treatment options and poor prognosis.

Visual system abnormalities are often observed in both disorders, ranging from lack of eye contact, through abnormal visual processing, to photosensitive seizures. The tremendous advancement in genetic studies helped to identify the involvement of many genes in the etiology of epilepsy and autism. However, our understanding of the pathways leading from a genetic mutation to abnormal brain function is still in its infancy.

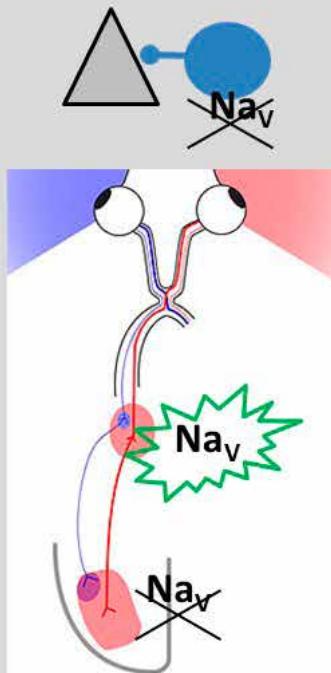
Mouse model



Electrophysiology



Selective and localized deletions and restored expression



Behavioral experiments

- Epilepsy
- Social behavior
- Visual system function

Ion channels are molecular machines, crucial for transforming synaptic inputs into electrical response, controlling neuronal firing and neurotransmitter release. One of the pivotal families of ion channels are the voltage-gated sodium channels (Na_v). Indeed, mutations in multiple types of Na_v channels were identified in epilepsy and autism patients. However, connecting the dots between Na_v dysfunction and the resulting diseases have proven to be a formidable task.

In order to bridge this gap we harness the strength of mouse genetics, combined with electrophysiological recordings, to elucidate the molecular and neuronal basis of epilepsy and autism and to understand how genetic mutations in ion channels leads to these disorders. We use mouse models mimicking the human genetic mutation and unveil perturbations of neuronal function on cellular, network and behaving animal levels. Moreover, the contribution of different classes of neurons and different brain regions is tested using global and viral mediated localized selective genetic deletions. Finally, behavioral experiments are used to examine epilepsy, sociability and the function of the visual system.

Publications

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Yakubovich, D., Berlin, S., Kahanovitch, U., **Rubinstein, M.**, Farhy-Tselnicker, I., Styr, B., Keren-Raifman, T., Dessauer, C.W., and Dascal, N. (2015). A quantitative model of the GIRK1/2 channel reveals that its basal and evoked activities are controlled by

unequal stoichiometry of G α and G $\beta\gamma$. *PLoS Comp Biol* 11, e1004598.

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Grants

2017 - 2022 ISF. Deciphering the neuronal and molecular basis of epileptogenesis and compensatory mechanisms in Dravet Syndrome

2017 - 2019 Fritz Thyssen Foundation. Unveiling the neuronal and network basis for visual system dysfunction in Dravet Syndrome

2017 - 2018 Jerome Lejeune Foundation. Unveiling the connection between epilepsy and intellectual disability in Dravet Syndrome.



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Novel Antioxidant and Stem Cells for Treatment of Degenerative Diseases

Positions

Professor Emeritus, Sackler Faculty of Medicine

Director, Goldschleger Eye Research Institute

Chair, Maratier Institute for the Study of Blindness & Visual Disorders

Research

We are studying the potential of S-allylmercapto-N-acetylcysteine (ASSNAC) a newly developed derivative of allicin (the active component in garlic) to serve as a treatment for oxidative stress associated degenerative diseases. The research involves cell biology tools and animal models.

The following specific subjects are studied:

- Demonstrating the capacity of ASSNAC to activate the transcription factor Nrf2 resulting in up-regulation of the antioxidant cellular mechanisms that increases the protective capacity of cells against reactive oxygen species.
- Testing the potential of ASSNAC to modulate the bone marrow stem cells population and attenuate the clinical manifestations of neurodegenerative diseases, diabetes, and osteoporosis.
- Testing the potential of ASSNAC to attenuate ocular degenerative diseases such as cataract and light-induced retinal damage.

Publications

M. Tao, P. Yu, B.T. Nguyen, B. Mizrahi, **N. Savion**, G. Sukhova, F.D. Kolodgie, R. Virmani, C.K. Ozaki, J. Schneiderman. Locally applied leptin induces regional aortic wall degeneration in apoe deficient mice preceding aneurysm formation. *Arterioscler. Thromb. Vasc. Biol.* 33:311-20, 2013.

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E. Asher, P. Fefer, M. Shechter, R. Beigel, D. Varon, B. Shenkman, **N. Savion**, H. Hod, S. Matetzky. Increased Mean Platelet Volume is Associated with Non-responsiveness to Clopidogrel. *Thromb. Haemost.* 112: 137-141, 2014

P. Fefer, R. Beigel, N. Rozenberg, M. Shechter, S. Gannot, D. Varon, **N. Savion**, S. Matetzky. Evaluation of Platelet Response to Different Clopidogrel Dosing Regimens in Patients with Acute Coronary Syndrome in Clinical Practice. *Platelets*, 26:126-131, 2015.

N. Savion, N. Izigov, M. Morein, S. Pri-Chen, S. Kotev-Emeth. S-Allylmercapto-N-acetylcysteine (ASSNAC) protects cultured nerve cells from oxidative stress and attenuates experimental autoimmune encephalomyelitis. *Neurosci. Lett.* 583:108-113, 2014.

I. Budnik, B. Shenkman, **N. Savion**. Synergistic effect of signaling from receptors of soluble platelet agonists and outside-in signaling in formation of a stable fibrinogen–integrin α IIb β 3–actin cytoskeleton complex. *Thromb. Res.*, 135:114-120, 2015.

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A. Gertler, G. Solomon, E. Kachel, E. Raanani, J. Lavee, S. Kotev Emeth, R. Virmani, F.J. Schoen, J. Schneiderman. Local application of leptin antagonist attenuates Angiotensin II-induced ascending aortic aneurysm and cardiac remodeling. *J. Am. Heart Assoc.* 5:e003474; 2016.

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Regulation of Hippocampal Plasticity: Single Synapses to Alzheimer's Disease

Positions

Associate Professor, Sackler Faculty of Medicine

Editorial Board Member: *eLife*, *Scientific Reports*, *Frontiers in Cellular and Molecular Neuroscience*

Member, American Federation for Aging Research (AFAR) National Scientific Advisory Council

Member, Minerva grant committee

Member, Azrieli PhD fellowship committee;

Member, PhD program committee, Sagol School of Neuroscience

Member, Scientific Committee, Center of Nanoscience and Nanotechnology

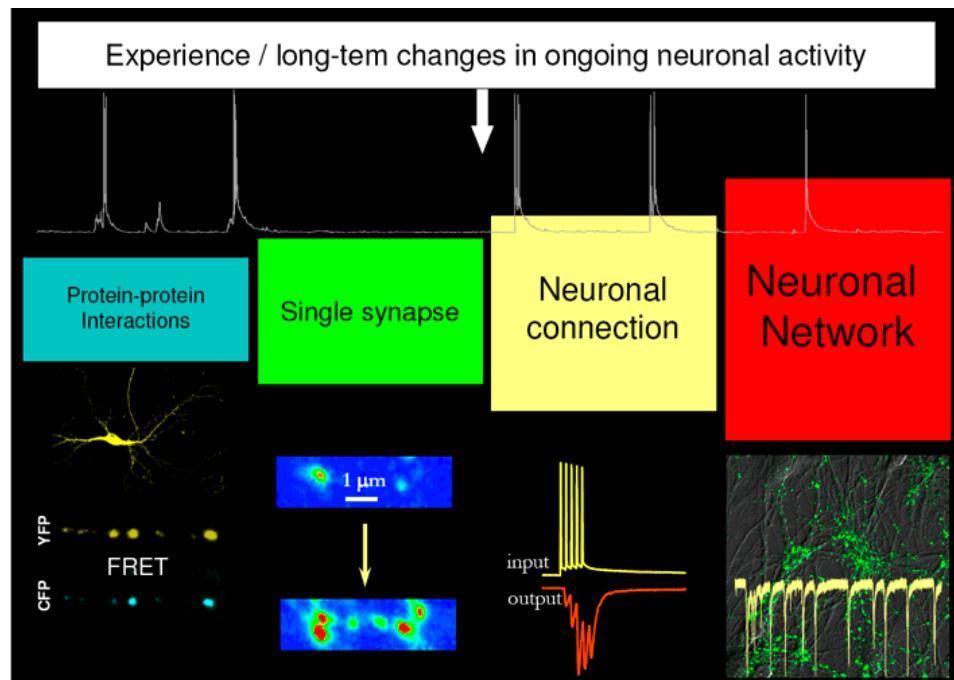
Research

The research in the laboratory is focused on understanding the basic mechanisms underlying synaptic function and primary mechanisms initiating

synaptic dysfunction at very early stages of Alzheimer's Disease. To achieve this goal, we developed an integrated system that enables simultaneous real-time visualization of structural reorganization in spatially-restricted signaling complexes and functional modifications of single synapses in brain circuits. Utilizing FRET spectroscopy, high-resolution optical imaging, electrophysiology, molecular biology, and biochemistry we explore experience-dependent mechanisms regulating the number and plasticity of hippocampal synapses under physiological and pathological conditions.

Publications

Wang Z, Jackson RJ, Hong W, Taylor WM, Corbett GT, Moreno A, Liu W, Li S, Frosch MP, **Slutsky I**, Young-Pearse T, Spires-Jones TL, Walsh DM. (2017) Human brain-derived A β oligomers bind to synapses and disrupt synaptic activity in a manner that requires APP. *J Neurosci*. pii: 2009-17.



Tao K, Xue B, Frere S, Slutsky I, Cao Y, Wang W, Gazit E. (2017) Multiporous supramolecular microspheres for artificial photosynthesis. *Chem Mater.* 29:4454-4460.

Milshtein-Parush H, Frere S, Regev L, Lahav C, Benbenisty A, Ben-Eliyahu S, Goshen I, **Slutsky I.** (2017) Sensory deprivation triggers synaptic and intrinsic plasticity in the hippocampus. *Cereb Cortex.* 27:3457-3470.

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. (2017) BDNF overexpression prevents cognitive deficit elicited by adolescent cannabis exposure and host susceptibility interaction. *Hum Mol Genet.* 26:2462-2471.

Gazit N, Vertkin I, Shapira I, Helm M, Slomowitz E, Sheiba M, Mor Y, Rizzoli S, **Slutsky I.** (2016) IGF-1 receptor differentially regulates spontaneous and evoked transmission via mitochondria at hippocampal synapses. *Neuron* 89, 583-597.

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Vertkin I, Styr B, Slomowitz E, Ofir N, Shapira I, Berner D, Fedorova T, Laviv T, Barak-Broner N, Greitzer-Antes D, Gassmann M, Bettler B, Lotan I, **Slutsky I.** (2015) GABAB receptor deficiency causes failure of neuronal homeostasis in hippocampal networks, *Proc Natl Acad Sci USA* 112, E3291-3299.

Slomowitz E, Styr B, Vertkin I, Milshtein-Parush H, Nelken I, Slutsky M, **Slutsky I.** (2015). Interplay between population firing stability and single neuron dynamics in hippocampal networks. *Elife* 4.

Fogel H, Frere S, Segev O, Bharill S, Shapira I, Gazit N, O'Malley T, Slomowitz E, Berdichevsky Y, Walsh Dominic M, Isacoff Ehud Y, Hirsch Joel A, **Slutsky I.** (2014) APP homodimers transduce an amyloid- β -mediated increase in release probability at excitatory synapses. *Cell Reports*, 7: 1560-1576.

Becker W, Shcheslavkiy V, Frere S, **Slutsky I.** (2014) Spatially resolved recording of transient fluorescence-lifetime effects by line-scanning TCSPC. *Microsc Res Tech.* 77:216-24

Dolev I*, Fogel H*, Milshtein H, Berdichevsky Y, Lipstein N, Brose N, Gazit N, **Slutsky I.** (2013) Spike bursts increase amyloid-beta 40/42 ratio by inducing a presenilin-1 conformational change. *Nature Neurosci.* 16: 587-595.

Review

Frere S, **Slutsky I.** (2016) Targeting PTEN interactions for Alzheimer's disease. *Nat Neurosci.* 19:416-8.

Grants

2013 – 2018 Israel Science Foundation

2014 – 2017 Heritage Legacy Fund and Israel Science Foundation

2014 – 2018 Binational US-Israel Science Foundation

2013 – 2018 Rosetrees Trust, UK



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Basic and Applicative Research of Eye Physiology, Diseases and Function

Positions

Associate Professor, Sackler Faculty of Medicine

Editorial Board, *Translational Vision Science & Technology (TVST)*

International Committee Member, ARVO

Research

The eye presents many challenges for research regarding unsolved conditions such as retinal and optic nerve assaults, damage to eye by surrounding conditions of work and every day activity.

The following specific subjects are studied:

- Optic nerve research: creating models of trauma and disease to investigate the mechanisms of degeneration and regeneration
- Investigate ways to treat corneal injury and diseases
- Ultraviolet light damage to the eye
- Research on the neovascular process in the eye and search ways to prevent it
- Occupational and environmental factors affecting eye and vision

Publications

Dvashi Z, Sar Shalom H, Shohat M, Ben-Meir D, Ferber S, Satchi-Fainaro R, Ashery-Padan R, Rosner M, **Solomon AS**, Lavi S. (2014) Protein phosphatase magnesium dependent 1a governs the wound healing-inflammation-angiogenesis cross talk on injury. *Am J Pathol*. 184:2936-2950.

Ohana R., Weiman-Kelman B., Shaul R., Tamm E., Pasmanik-Chor M., Rinon A., Netanely D., Shamir R., **Solomon AS**, Ashery-Padan R. MicroRNAs of the RPE are key for RPE differentiation and photoreceptor maturation. *Development*, 2015;142:2487-98.

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Yuval C, Ben-Mair E, Rosenzweig E, Shechter- Amir D, **Solomon AS**. The effect of nocturnal CPAP therapy on the intraocular pressure of patients with Sleep Apnea Syndrome. *Graephe's Arch Exp Clin Ophthal*, 2015, 253:2263-2271.

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Spiking Network Mechanisms Underlying Cognition

Position

Senior Lecturer, Sackler Faculty of Medicine and
Sagol School of Neuroscience

Research

We study the way neuronal networks give rise to function. There are many levels to approach this topic and we are interested at the spiking level, mainly in local circuits of free, behaving animals. We focus on short-term memory and spatial navigation in rodents. For this, we are continuously developing technologies to interface bi-directionally with the intact brain at the spatiotemporal resolution of a single neuron and a single spike. Our mechanistic approach involves high-density recording and manipulation of dozens to hundreds of neurons simultaneously, while freely moving rodents perform cognitive tasks. By erasing and writing individual spikes of multiple neurons in real time, we precisely modify network-spiking activity during specific epochs (for instance, short term memory maintenance), and study the effects on behavior (memory deterioration or boosting).

Publications

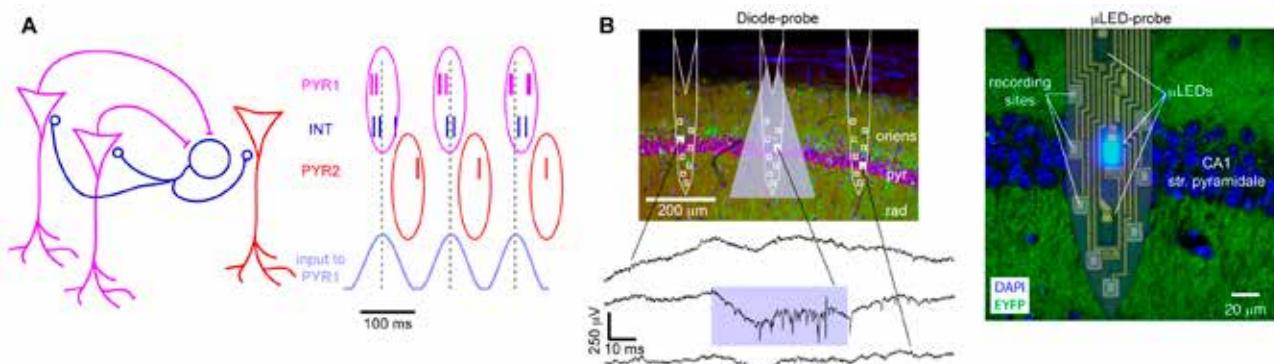
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A. Dynamic segregation of neuronal networks into cell assemblies. In the freely-moving mouse, external input is applied to one group of excitatory pyramidal cells (PYR1), which drive inhibitory cells (INT), which then inhibit a second group (PYR2). At certain input frequencies, inhibition actually *induces* spiking in PYR2. The activity of the PYR1 and PYR2 assemblies (each of which may represent a distinct memory) is thus linked and multiplexed in time. **B. Hardware for recording and manipulating circuit elements in freely moving animals.** A *diode-probe* device consists of multiple optical fibers, each coupled to a distinct light source and associated with a distinct electrode array. In animals that express light-sensitive ion channels (opsins), light applied at one site induces spiking of multiple cells only at that site. *μ LED-probes* take spatial resolution one step further by implanting neuron-sized diodes directly in the brain.

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Reviews

Buzsáki G, **Stark E**, Berényi A, Khodagholy D, Kipke DR, Yoon E, Wise K (2015) Tools for probing local circuits: high-density silicon probes combined with optogenetics. *Neuron* 86:92-105.

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Grants

2016-2021 ERC Starting Grant

2016-2020 CRCNS (NSF-BSF) Grant

2016-2020 ISF Grant

2017-2020 Rosetrees Grant

2017-2019 ISF Bikura Grant



Dr. Ido Tavor, Ph.D.

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Functional and Structural Brain Connectivity using MRI

Positions

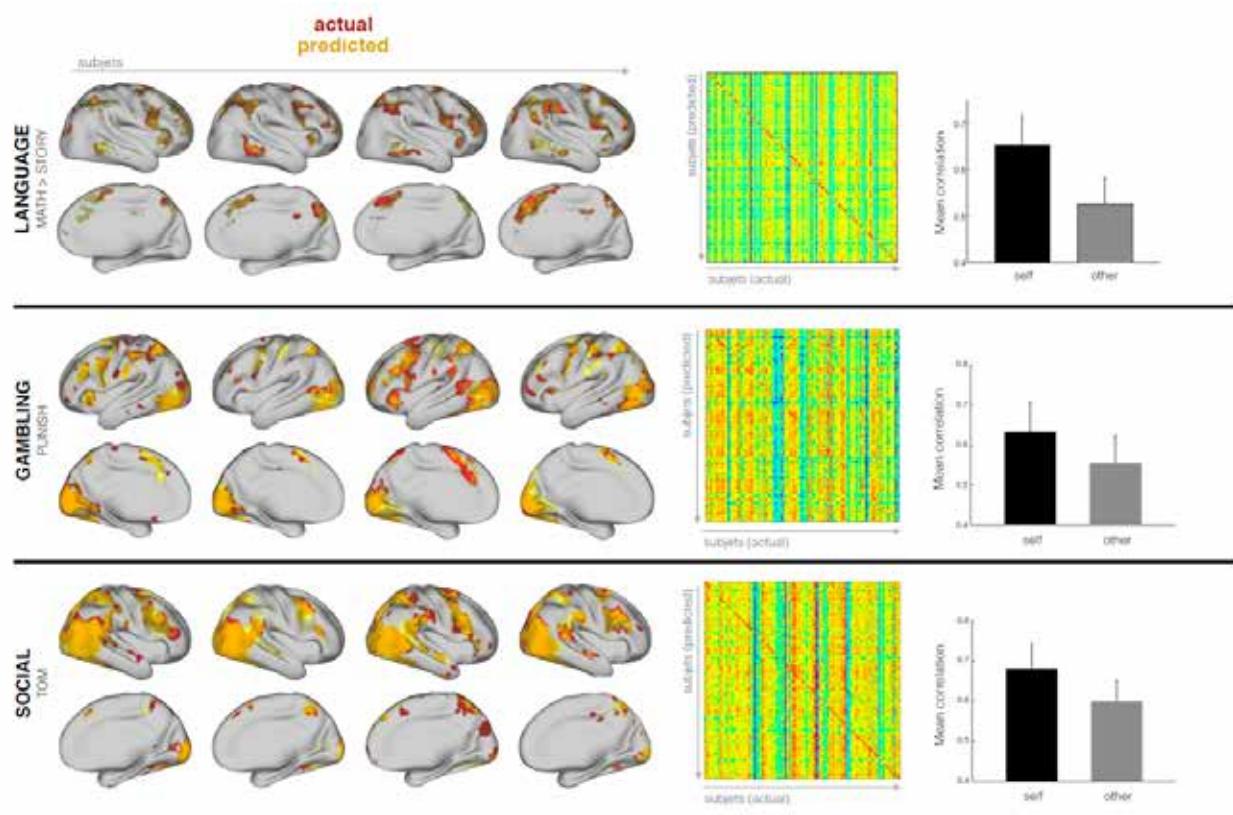
Senior Lecturer, Sackler Faculty of Medicine
Faculty member, Sagol School of Neuroscience

Research

Work in our lab is focused on exploring the relations between brain structure, function and behavior using magnetic resonance imaging (MRI). We're using state-of-the-art MRI methodologies to study inter- and intra- subject variability in brain connectivity and

use behavioral experiments to study whole-brain neuroplasticity.

Specifically, we develop models to predict individual differences in brain activity and human behavior from brain structure and connectivity measurements. We also study learning-related brain plasticity by developing behavioral tasks that induce functional and structural brain modifications and investigate the underline mechanisms of functional neuroplasticity as measured with fMRI. We also work on advanced statistical modeling of MRI data.



Predicting individual differences in brain activation in a variety of tasks: Examples for tasks in the language, decision making and social domains are shown for 4 representative subjects, where actual activation is shown in red and predicted activation in yellow. The specificity of prediction is demonstrated by the connectivity matrix between true and predicted activation maps of 100 subjects (note the pronounced diagonality of the correlation matrix).

Publications

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I. Tavor, M. Yablonski, A. Mezer. S. Rom, Y Assaf and G. Yovel. Separate parts of occipito-temporal white matter fibers are associated with recognition of faces and places. *NeuroImage* 86, 123-30, 2014

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I. Tavor, O. Parker Jones, R.B. Mars, S.M. Smith, T.E. Behrens, S. Jbabdi. Task-free MRI predicts individual differences in brain activity during task performance. *Science* 352, 216-220, 2016

Nursing, Occupational and Physical Therapy





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Steyer School of Health Professions



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Occupational Science: Investigating Occupations, Health and Well-Being Among Women

Positions

Lecturer, Sackler Faculty of Medicine

Committee Member, Occupational Science Europe Research Committee

Research

Occupational Science is the study of human participation. Research in this area focuses on specific populations and their unique challenges to engage in meaningful occupations. Our primary area of research is exploring the relationship between engagement in occupations, health and well-being among women, especially as related to the role of motherhood. We focus on the effect of occupational performance on life satisfaction and perceived physical and mental health in various life-changing situations. The populations that we study include women who experienced a major change in their lives (such as transgender women or becoming a caregiver), women diagnosed with illness or having a disability, mothers of children who were diagnosed with Autism Spectrum Disorder (ASD) or Attention Deficit Hyperactivity Disorder (ADHD), and healthy mothers from different cultures/religions.

Our second area of research is developing and evaluating advanced teaching methods in occupational therapy, specifically, testing the contribution of Problem-Based Learning (PBL) to the development of students' learning skills, knowledge, communication skills and success in clinical fieldwork studies.

Publications

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Investigating Sensory Modulation Disorder (SMD) Over Life Span

Positions

Lecturer, Sackler Faculty of Medicine

Research is performed in the Sensory Integration Laboratory at TAU and in hospitals.

Research

SMD is a health condition in which abnormal responses to naturally occurring stimuli are demonstrated in a manner that interferes with daily life, affecting 10% of otherwise healthy individuals. Our lab studies a unique perspective associating SMD with pain. Our research is aiming to better understand the underlying mechanisms by identifying biomarkers that would specify this health condition, applying psychophysical and neurophysiological methodologies in children and adults. New biomarkers found guide new therapeutic modalities for this population, ameliorating intervention opportunities: Specifically we are developing a neurofeedback system for treating SMD, based on our findings of EEG components that characterize individuals with SMD.

Moreover, in trying to understand the potential role of SMD in neurodevelopmental and other disorders trajectories, we study SMD as a risk factor in other health conditions such as chronic pain, mental health, substance abuse, and neurodevelopmental disorders.

Publications

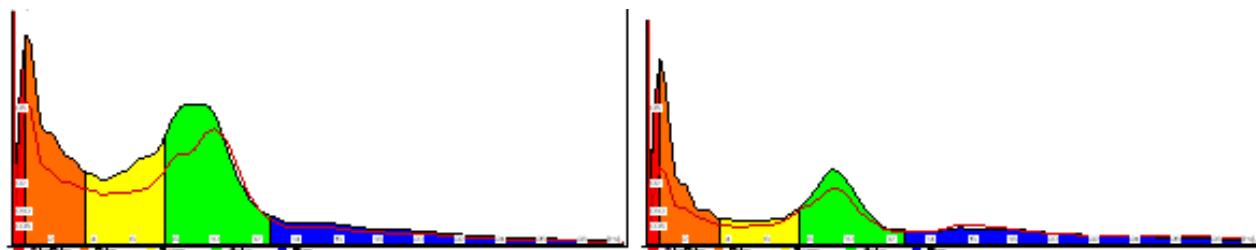
Weissman-Fogel I, Granovsky Y, **Bar-Shalita T.** Sensory over-responsiveness among healthy subjects is associated with a pronociceptive state. *Pain Pract.* 2017, doi: 10.1111/papr.12619.

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EEG of resting state (5 min) in controls and SMD adults recorded from frontal and central cortical sites demonstrated lower power cortical oscillations at δ (orange), β (yellow) and α (green)

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Nursing Genetics and Information Technologies

Positions

Associate Professor, Sackler Faculty of Medicine

Research

Our research focuses on two main fields: 1. Genetics
2. Nursing and Information Technologies

In genetics our interest is in factors influencing individual decision-making on taking genetic tests. The decision whether or not to take a test may be influenced by factors relating to the illness tested for such as its severity or how far it can be controlled, or by personality factors such as risk-perception and optimism, or by the identity of the agent recommending the test (doctor or nurse) and their perceived epistemic authority. In a series of studies we are currently conducting we are trying to find linkages between these factors and the decision whether or not to take genetic tests.

Another issue being studied is the question “to whom does genetic information belong?” Genetic information is of importance to the tested individual’s family as well as to them self. However, not all test subjects share the findings with their relatives. In a large-scale study, conducted together with Dr. Roy Gilbar of the Leicester University and funded by the Israel Cancer Association we examined the attitudes, opinions and behavioral intentions of genetic counselees regarding the disclosure of their genetic information to their families. We are planning a qualitative study to examine views of genetic counselors on this topic.

Information Technologies: Due to the rise of internet technology, medical information is no longer the exclusive property of medical service givers – it is now accessible to everybody—and this new situation has an effect on patient-caregiver relations. Among the research studies we are carrying out, we have investigated the attitudes of nurses towards patients who come forward with information found on the web, what affects those attitudes, and the

reactions of nursing teachers to students who bring such information to class. Up to now, most research into this issue has concentrated on the professional caregiver’s point of view. We wish to turn the spotlight onto the patient’s point of view, and on how they feel after bringing Internet information to an appointment with their doctor or nurse.

Publications

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Skirton, H., **Barnoy, S.** Erdem, Y., Ingvoldstad, C., Pestoff, R., Teksen, F. & Williams, J. (2012). Suggested components of the curriculum for nurses and midwives to enable them to develop essential knowledge and skills in genetics. *Journal of Genetic Counseling*, 3:323-9.

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Menshadi, N., Bar-Tal, Y. and **Barnoy, S.** (2013). The relationship between learned resourcefulness and cancer related fatigue in patients suffering from Non-Hodgkin's Lymphoma. *Oncology Nursing Forum*, 40, 133-138.

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Dr. Orit Bart, Ph.D., OTR

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Co-Morbidity of Sensory-Motor and Cognitive Dysfunction and Psychosocial Problems

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Occupational Therapy

Member, Israeli National Board for Certification of Occupational Therapy – Ministry of Health

Member, National Advisory Committee on Services for Child Development – Ministry of Health

Research

Our research is focused on the association between sensory-motor function and psychological aspects (anxiety, sense of coherence, hope, loneliness, etc.) of typically developed children and children with developmental problems such as Developmental coordination disorder (DCD), Attention Deficit Hyperactive Disorder (ADHD), and Sensory Processing Disorder (SPD). In the studies I conduct I try to learn and understand more about the mechanism behind the co-morbidity of sensory-motor dysfunctions and psychosocial problems. Further more, there are some studies where we assess the efficacy of sensory-motor intervention and its influence on the psychological behavior of the treated children.

Another related topic that is in the focus of my research is children's participation. According to the International Classification of Functioning, Disability and Health (ICF, 2001), Participation is relatively a new concept that reflects a new approach to functioning and serves as an outcome measure. Therefore we developed a questionnaire to assess pre-school children's participation. We are now developing additional questionnaires to assess infants, preschoolers and school age participation. We are running a few studies to assess differences in participation patterns of children with various developmental problems. Moreover I have started to investigate the influence of Occupational Therapy

(OT) intervention and sensory-motor approaches on children's satisfaction and participation.

Publications

O. Bart, D. Tzafrir, S. Averbuch. Validation of the Israeli version of the rivermead behavioral memory test for children following acquired brain injury. *Journal of Head Trauma Rehabilitation*. 28, 419-425, 2013.

L. Rosenberg, **O. Bart**, N. Ratzon, T. Jarus. Personal and environmental factors predict participation of children with and without mild developmental disabilities. *Journal of Child and Family Studies*, 22, 658-671, 2013.

O. Bart, L. Liberman, N. Ratzon. The profile of performance skills and emotional factors in the context of participation among young children with Developmental Coordination Disorder. *Research in Developmental Disabilities*, 34, 87-94, 2013.

O. Bart, L. Daniel, Y. Bar-Haim. Influence of methylphenidate on motor performance in children with Developmental Coordination Disorder and Attention Deficit Hyperactive Disorder. *Research in Developmental Disabilities*, 34, 1922-1927, 2013.

I. Morag, **O. Bart**, R. Raz, S. Shayevitz, T. Strauss, S. Zangen, J. Kuint, L. Gabis. Developmental characteristics of late preterm infants at six and twelve months: a prospective study. *Infant Behavior & Development*, 36, 451– 456, 2013.

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O. Bart, S. Raz, O. Dan. Reliability and validity of the online continuous performance test among children. *Assessment*. 21, 637-643, 2014.

L. Gabis, K. Hacham- Pilosof, O. Bar Yosef, G. Rabinovitz, G. Leshem, A. Shilon- Hadassa, Y. Biran, B. Reichman, J. Kuint, **O. Bart**. The influence of a multi-sensory intervention for preterm infants, provided by parents, on developmental abilities and on parental stress levels. *Journal of Child Neurology*. 30, 896-903, 2015.

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A. Mimouni Bloch, M. Tsadok-Cohen, **O. Bart**. Motor difficulties and their effect on participation in school-aged children. *Journal of Child Neurology*, 2016.

L. Rosenberg, A. Moran, **O. Bart**. The associations among motor ability, social-communication skills, and participation in daily life activities in children with low-functioning autism spectrum disorder. *Journal of Occupational Therapy, Schools & Early Intervention*, 2017.

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Bart O, Bar-Shalita T, Mansour H, Dar R. Relationships among sensory responsiveness, anxiety, and ritual behaviors in children with and without atypical sensory responsiveness. *Phys Occup Ther Pediatr*. 2017, 37:322-331.



Prof. Ruth Defrin, Ph.D.

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Investigating Pain Perception and Mechanisms of Chronic Pain

Position

Professor, Sackler Faculty of Medicine
Director, Biomed@TAU Pain Research Hub

Research

We study the perception of pain among healthy subjects as well as among individuals with mental disorders and cognitive impairments. We are interested in the manner with which the brain processes various temporal and spatial aspects of painful events and in inter-personal differences in pain perception.

We are also interested in the underlying mechanisms of chronic pain that develops after traumatic events. These include physical injuries such as spinal cord injury, brain injury and brain stroke as well as psychological traumas such as shell shock, captivity and torture. We are particularly interested in the effects of stress on the function of the pain system in these conditions and in healthy subjects.

We use state of the art devices such as computerized thermal stimulators, mechanical and electrical stimulators and a recording system for event related brain potentials. We perform experiments in the pain laboratory at TAU and in hospitals.

Publications

Levy D, Abdian L, Dekel-Steinkeller M, **Defrin R.** Experimental evidence for weaker endogenous inhibition of trigeminal pain than extra-trigeminal pain in healthy individuals. *Cephalgia*. 2017;333102417735851.

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Grants

2014-2017	National Insurance Association
2015-2017	IRP- International Foundation for research in Paraplegia
2015-2019	ISF-Israel Science Foundation



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Emotional Management, Cultural Competence and Decision-Making

Positions

Lecturer, Sackler Faculty of Medicine

Head, Generic BA Nursing Program

Research

Qualitative and quantitative research methods are used to study nurses' and patients' attempts to structure their emotions through the process of emotional management. We focus on self-care research: understanding the interventions, correlates and outcomes of nurses' self care by International research on caritas as healing. Our research involves studying cultural competence, which enables nurses to care for and to communicate with patients from different cultural and ethnic backgrounds. Furthermore, the focus is on acculturation and job satisfaction among immigrant nurses from different countries. The theory of family-centered care is studied: the preferences of lay people regarding family involvement in medical decisions. Moreover, we research the attitudes of lay people and staff members to family presence during resuscitations and invasive procedures. Understanding these aspects is essential for creating caring environments for nurses, patients and families within today's complex health care organizations.

Publications

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Quality of Care and Patient Safety

Positions

Lecturer, Sackler Faculty of Medicine

Head, Accelerated Program for Non-Nursing B.A. Graduates

Research

Peri-operative Factors and Their Impact on Post-operative Recovery

Our research area is developing in two tracks: a) discovering the factors that affect quality and safety behavior of healthcare workers (HCWs) and b) examination of psycho-social and bio-physiological factors before and after surgery and their impact on short-/long-term recovery and rehabilitation. The first research track focuses on both the "human element" variables and the systemic approach to the quality improvement, clinical risk management and patient safety issues such as medical error-reporting, safety culture, disclosure errors to patients, patient empowerment and more. The studies highlight the barriers that have to be addressed when planning and implementing changes to improve quality and patient safety in healthcare. The second track addresses the influence of variables such as personal self-efficacy, situational anxiety, health literacy, subjective readiness to surgery, gender, ethnicity etc., on post-operative recovery. These studies aim to identify variables that could have a positive or negative effect on readiness to leave hospital after surgery, to comply with the recommendations on discharge from hospital, to adhere rehabilitation programs and more.

Publications

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Epidemiology of Cardiovascular Diseases & Risk Factors

Position

Associate Professor, Sackler Faculty of Medicine
Chair, Department of Nursing
Adjunct Associate Professor of Epidemiology, Johns Hopkins University

Research

Our research focuses on the epidemiology of cardiovascular diseases with a special interest in epidemiology of stroke. During the last years, our studies have covered diverse subjects including trends in stroke morbidity and mortality among different population groups in Israel and in the United States, strategies for primary and secondary prevention of stroke, determinants of stroke outcomes and novel risk factors acting long-term and as immediate triggering factors. Taking advantage of our knowledge and skills in the environmental and occupational health area, we also study the health effects of pollution mainly among survivors of cardiovascular diseases.

Since the establishment of the ongoing triennial National Acute Stroke Israeli (NASIS) registry in 2004, as a member of the registry's steering committee, We carry out nationwide studies in collaboration with specialists in neurology and stroke research. These studies are aimed at characterizing management and outcomes of acute stroke patients and are an important means for providing both clinicians and health policy makers with data required for optimizing prevention strategies and care of stroke patients in Israel.

Publications

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Participation in Everyday Life and Occupational Therapy Practice for People with Psychiatric Disorders

Positions

Lecturer, Sackler Faculty of Medicine

Research

Participation in meaningful activities according to personal values and choices is one of the central components of health and well-being. Moreover, it is one of the ultimate goals of health services delivery, as suggested by the WHO vision. Today, psychiatric disorders still remain one of the main reasons for disability payments all over the world due to the functional disability they cause. Our research is focused on exploring everyday functioning and participation patterns of people with psychiatric disorders that were found to be both unique and similar to those of the general population; and detecting factors affecting the everyday functioning such as functional capacity, motor abilities, sense of belonging and sensory modulation over the more conventional ones (psychiatric symptoms and cognition). In addition, we investigate efficacy of Occupational Therapy (OT) evaluation and intervention process and develop new tools and techniques for practice. Since Occupational Therapy services are provided in different settings, including in mental health hospitals, one of our particular areas of interest is investigation of the OT practices in acute settings to promote successful transition to everyday life after discharge and reintegration into community.

Publications

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Lipskaya-Velikovsky, L., Avrech- Bar, M., & Bart, O. (2014). Context and psychosocial intervention in mental health. *Scandinavian Journal of Occupational Therapy*, 21, 136-144.

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Physical Activity, Gait and Posture in People with Neurological Diseases

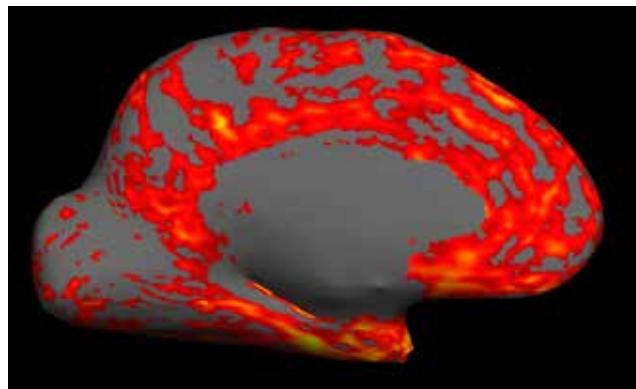
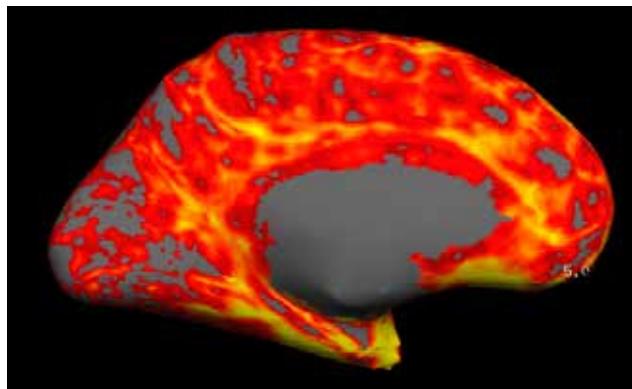
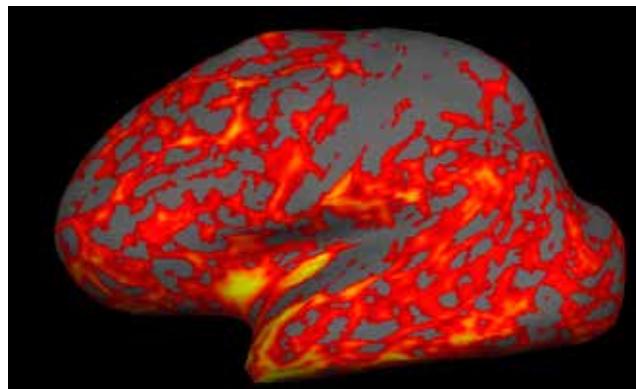
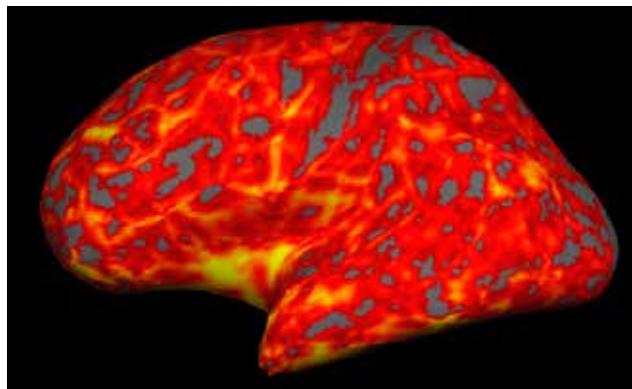
Position

Lecturer, Sackler Faculty of Medicine

Research

Our main research focuses on physical activity, gait and balance measurements, predictors, and outcomes in persons with neurological diseases, specifically multiple sclerosis (MS). Currently we are examining the relationship between various physical and mobility parameters with brain damage, determined by MRI methods in different neurological patient groups. Special interest is placed

on aerobic function capabilities during various daily and challenging situations. We anticipate that our research will result in quantifying differences in physical activity, particularly in the rates of moderate-to-vigorous physical activity in several neurological patient groups vs. non-diseased controls. The interest in this research is based on the rationale that a better understanding of these mechanisms will facilitate the development of practical interventions, thus minimizing the negative aspects of the disease process. Overall, the research questions range from theoretical exploration to clinical application and are often multi-disciplinary in nature.



Freesurfer results showing the inflated lateral hemispheres view of two MS participants with similar age, EDSS and disease duration. Slow walker images are on the left row, normal walker images are presented on the right row. Cortical thickness is determined according to color; yellow – thick, grey- thin.

Publications

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Kalron A, Bar-Sela S. A systematic review of the effectiveness of Kinesio taping® – fact or fashion? *Eur J Phys Rehabil Med*, 49:699-709; 2013.

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Grants

2017-2018 European Network in Rehabilitation in MS



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Spinal Form and Function

Position

Senior Lecturer, Sackler Faculty of Medicine
Member, Associate Board, Spine Journal

Research

Clinical, diagnostic, therapeutic, epidemiological, kinematical, and anthropometric investigations of the normal and pathological human spine.

During the last decade, we have focused our research on studying the form and function of the human spine in normal and pathological conditions. We proposed some unique models for the pathogenesis and biomechanics of several spinal pathologies. Specifically, the following research projects were investigated and categorized as clinical (diagnostic, therapeutic and clinical reasoning), kinematical and morphological:

- **Clinical/kinematic:** a. Directional and positional preference of group exercising in individuals with chronic low back pain and osteoporosis; b. Clinical reasoning and decision making; c. Kinematical evaluation of lumbar rotations in erected and fully flexed standing and sitting positions in patients with chronic low back pain.
- **Morphological/Anatomical:** a. A morphometric analysis of the normal and pathological human

spine; b. Spinal shape variation and postural changes during growth.

- **Epidemiological:** An epidemiological study on spinal osteoporosis in females and sport related back injuries in children.

Publications

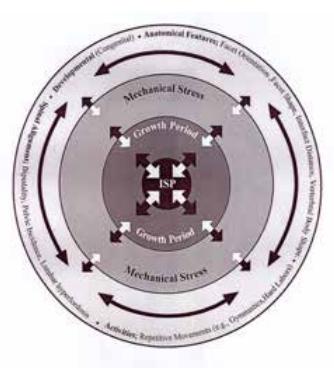
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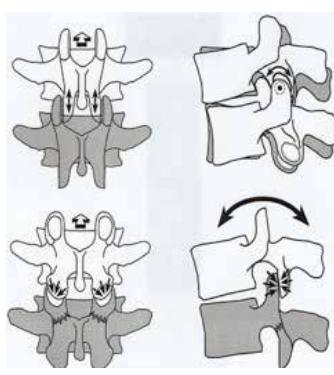
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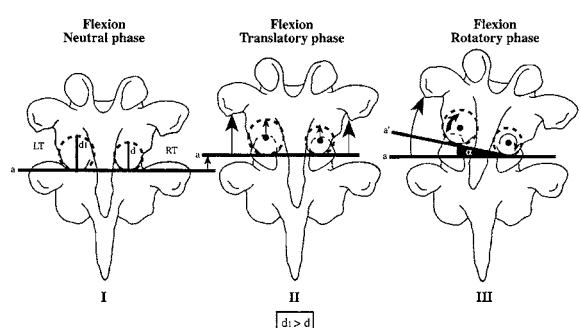
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Reviews

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Health Maintenance Among Immigrants from the Former USSR, Ethiopia and Arab Citizens of Israel

Position

Head, Short-day studies BA Nursing Program
Lecturer, Sackler Faculty of Medicine

Research

Health maintenance among immigrants from the former USSR, Ethiopia and among Arab citizens of Israel.

The rates of chronic illness such as ischemic heart disease and hypertension among immigrants from the former USSR (FUSSR) and among Arab citizens of Israel, and of diabetes among Ethiopian immigrants are higher than those in the general Israeli population. In my research, I focus on the study of behaviors aimed at health maintenance among immigrants from the FUSSR and Ethiopia, and Arab citizens of Israel according to Bandura's Reciprocal Determinism (1983) model. I will examine how the immigrants' and ethnic minorities members' personal characteristics, such as knowledge and attitudes toward chronic disease, together with environmental effects, are linked to behaviors aimed at maintaining health among immigrants from the FUSSR and Ethiopia, and among Arab citizens of Israel.

Publications

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Computational Biomechanics in Motor Rehabilitation

Position

Lecturer, Sackler Faculty of Medicine

The work in the laboratory is highly interdisciplinary, combining aspects of biomedical engineering, rehabilitation medicine, physiotherapy, and occupational therapy.

Research

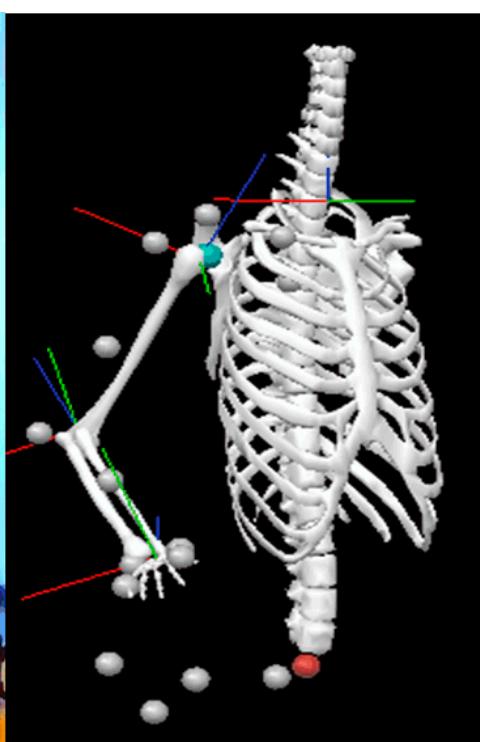
The motor function and rehabilitation lab is dedicated to the study of motor mechanisms and rehabilitation strategies. The major research themes of the laboratory are:

1. Design of new evaluation and treatment tools for clinicians, based on state-of-the-art technologies.
2. Quantification, evaluation and feedback, provided to the motor-impaired patient by utilizing real-time data of the kinematics, kinetics and muscular activity patterns.
3. Development of innovative assistive technology and out-of-clinic rehabilitation solutions.

Publications

Portnoy S, Schwartz I. Gait characteristics of post-polio-myelitis patients: standardization of quantitative data report, *Annals of Physical and Rehabilitation Medicine*. S1877-0657(13)00103-6. 2013.

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Chapter

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Gaming for Rehabilitation of Neurological and Geriatric Populations

Position

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Occupational Therapy

Research

Our research focuses on achieving a better understanding of the factors hindering and facilitating recovery post-stroke. We have developed interventions aimed to improve the motor recovery and executive functions deficits of these individuals, in order to enhance function in daily living. The effectiveness of these novel interventions is assessed by conducting randomized clinical trials, the highest level of clinical research. We have researched the effectiveness of a 'Community' and a 'Home' based intervention using video-games compared to traditional therapy for enhancing daily function and participation of individuals with chronic stroke. We are currently collaborating to investigate the use of touchscreen tablets for self-training of the weaker upper extremity to improve dexterity of individuals with acquired brain injury and to improve cognitive abilities of older adults with Mild Cognitive Impairments.

Publications

Rand D, Ben-Chaim KL, Malka R, Portnoy S. Development of internet-based tasks for the executive function performance test. *Am J Occup Ther*, in press.

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Agmon M, Zisberg A, Gil E, **Rand D**, Gur-Yaish N, Azriel M. (2017). association between 900 steps a day and functional decline in older hospitalized patients. *JAMA Int Med*, 1;177:272-274.

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Ratzon NZ, Friedman S, Zamir S, Amit Y, **Rand D**. Functional capacity evaluation; does it change the determination of the degree of work disability? *Disabil Health J*. 2015, 8:80-85.

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Book Chapters

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Grants

2017-2019 Maccabi Healthcare Services Research Fund

2017-2019 Israel National Institute for Health Policy Research



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Investigating the Ergonomics of Occupational Tasks and Driving Rehabilitation

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our research focuses on the ergonomics of occupational tasks such as typing and playing musical instruments. Our current research integrates the usage of 3-dimensional advanced technologies to evaluate the movement of hands, specific devices to evaluate force, computerized technologies to evaluate sitting which enable to refer to dynamic situations and the change in risk factors while performing different tasks. These studies have provided essential information concerning risk factors for musculoskeletal disorders and have led to more recent investigations of the determinants of postural patterns amongst children that may contribute to risks in adolescence and adulthood. The anticipated outcomes of these programs of research are to develop training programs and/or contribute to workspace design to minimize these risks.

Driving rehabilitation is another major area of research. Research explores the impact of disease and disorder on driving with the aim of developing appropriate rehabilitation programs, reflecting the importance of 'driving' as a factor in independence as well as a marker of function for variety of populations.

Publications

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Grants

2016-2019 Insurance Research Fund, The Israeli Association of Insurance Company



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The Role of Glutamate Excitotoxicity in Neurodegenerative and Malignant Diseases

Position

Lecturer, Sackler Faculty of Medicine

Research

Glutamate (Glu) has been shown to play a role not only in neural processes, such as learning and memory, but in bioenergetics, biosynthetic and metabolic oncogenic pathways as well. High extracellular Glu concentrations, such as those found in numerous CNS pathological conditions, ultimately cause the excitotoxic death of the exposed neurons and entail irreversible neurological deficits. Our research focuses on the mechanisms that maintain the Glu homeostasis in brain extracellular fluids and their role in the pathogenesis of neurodegenerative and malignant diseases. Our aim is to determine the impact of excess extracellular Glu levels and the various antiglutamatergic therapeutic strategies on the progression of the malignant and neurodegenerative diseases. We believe that a profound understanding of the glutamate signaling pathways may provide novel therapeutic opportunities for various CNS diseases.

Publications

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Grants

2016 – 2019 Israel Science Foundation (ISF)

2016 – 2018 Cancer League, University of California (UCSF)



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The Effect of Fish Oil Enriched Diet on Wound Healing Processes in ICU Patients

Positions

Lecturer, Sackler Faculty of Medicine

Research

Wound healing is the complex, multi-stage response to tissue injury. This physiologic repair response requires a dynamic temporal and spatial interplay of several cell types, including local parenchymal and mesenchymal cells as well as resident and recruited inflammatory cells. N-3 Fatty acids are recognized as influencing both wound healing and immunity. Our group studies the impact and the specific role of fish oil- and micronutrient enriched formulae on the healing of pressure ulcers and on immune function mediated through a modulation of expression of adhesion molecules in critically ill patients.

Our results show a reduction in inflammation levels of C – reactive protein concentrations and increasing levels of adhesion molecules preceding the subsequent reduction in ulcer severity of critically ill patients.

The formulae may ameliorate the inflammatory response, both in magnitude and duration, probably mediated by an effect on adhesion molecule expression. by promoting the transition from an inflammatory to reparative stage of wound healing.

Publications

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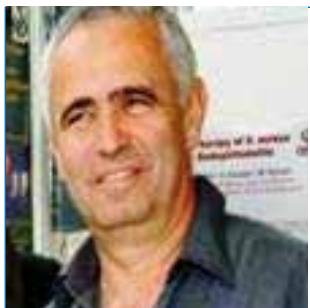
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Kagan I, **Theilla M**, Singer P. Is total parenteral nutrition (TPN) an evil in trauma patients? *Curr Trauma*, 2016.

Public Health





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Epidemiology of Infectious Diseases

Positions

Professor of Epidemiology and Preventive Medicine

Head, School of Public Health, Sackler Faculty of Medicine

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Director, Stanley Steyer Institute for Cancer Epidemiology and Research

Director, Tel Aviv University Center for the Study of Bioterrorism

Research

Emerging Infectious Diseases, Vaccinology

(1) The study of risk and protective host factors against enteric diseases; identification of correlates of protection related to the immune response and host microbiota; development of enteric vaccines
(2) Development of laboratory-based surveillance methods for enteric diseases
(3) Seroepidemiology of vaccine-preventable diseases to monitor the immune status of the Israeli population
(4) The study of the association between selected infectious agents (e.g. Helicobacter pylori, Human Papilloma Virus) and cancer.

Publications

Di giovine P, Kafatos G, Nardone A, Andrews N, Olander, Alfarone G, Broughton K, **Cohen D**, Kriz B, Mikova I, O'flanagan D, Schneider F, Selga I, Valinsky I, Velicko I, Karacs I, Pebody R, Von hunolstein C. Comparative seroepidemiology of diphtheria in six European countries and Israel. *Epidemiol Infect.* 2013, 141:132-42.

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Grants

2011-2017	European Union: “Development of vaccines against Shigella and enterotoxigenic <i>E. coli</i> enteric diseases” (Leader 2 WPs)
2017-2019	Ministry of Agriculture, Development of a New vaccine Against Brucellosis
2017	Nuclear Threat Initiative, Advanced Training in Epidemiology of Israeli, Palestinian and Jordanian Students and Health Professionals

Reviews

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Aging and End of Life

Positions

Professor, Department of Health Promotion, Sackler Faculty of Medicine
Director, Minerva Center for the Interdisciplinary Study of End of Life
Dr Igor Orshstein Chair for Research in Aging

Research

Health and Mental Health Promotion in older persons:

- Preventing loneliness and social isolation in older persons
- Promoting physical activity in old age
- Age segregation and integration in society
- Methodologies for alleviating memory difficulties

End of Life

- Delineating end of life as a life stage
- Encountering the gap between the good death and the usual death
- Dementia
 - Understanding symptoms and behaviors in dementia
 - Improving dementia care
- Promoting dignity at the end of life

Publications

Cohen-Mansfield J, Juravel-Jaffe A, Cohen A, Rasooly I, Golander H. (2013) Physicians' practice and familiarity with treatment for agitation associated with dementia in Israeli nursing homes. *Int Psychogeriatr*, 25:236-44.

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Chapters

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Grants

2016-2019 Israel Ministry of Science. Enhancing quality of care at the end of life.



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Cardiovascular Disease Epidemiology

Positions

Professor, Sackler Faculty of Medicine
Adjunct Faculty, Health Sciences Research, College of Medicine, Mayo Clinic, Minnesota
Chair, Dept. of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine

Research

Our research covers a wide array of topics related to the epidemiology of cardiovascular diseases. These include risk factor and biomarker evaluation, secular trend analysis, and outcomes research. We have a particular interest in assessing long-term prognosis after acute myocardial infarction. This type of investigation usually combines data from multiple sources, including interviews and

questionnaires, laboratory measurements involving blood specimens, GIS-derived environmental data, interviews and questionnaires. We are also interested in methodological aspects involved in conducting and interpreting observational studies.

Publications

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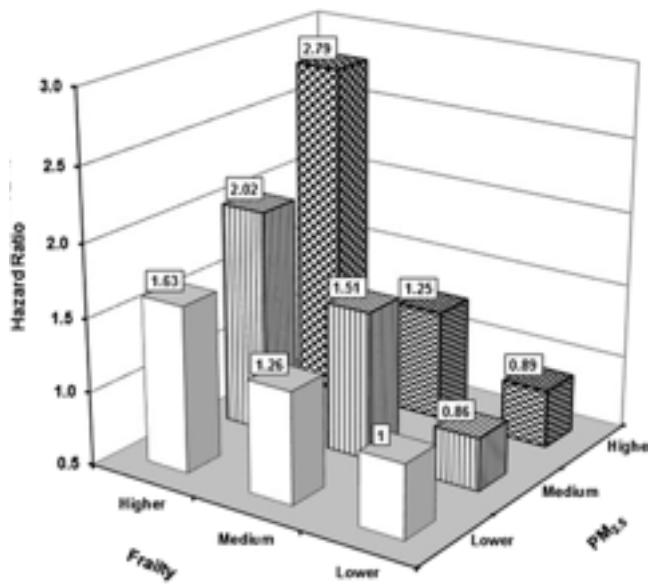
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Cohen G, **Gerber Y**. Air pollution and successful aging: recent evidence and new perspectives. *Curr Environ Health Rep* 2017;4(1):1-11.

Grants

2016-2017	The Israel Cancer Association (ICA), Chronic residential exposure to outdoor air pollution and cancer incidence in a high-risk population: A cohort study.
2016-2018	Bircher-Benner Foundation: Development of a frailty evaluation tool in a high-risk Israeli population.
2017-2020	Chief Scientist Office, Ministry of Health: A prospective study of dietary patterns in relation to healthy aging.



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Investigating Cardiovascular Risk Factors and Outcomes, Predictors of Frailty and Declining Cognitive Function

Positions

Professor Emeritus, Sackler Faculty of Medicine

Honorary Member, Israeli Heart Society

Founding Chairman, Israel Heart Society Working Group on Epidemiology and Prevention

Research

The pioneering large scale epidemiological study named "The Israeli Ischemic Heart Disease project" (IIHD project) was initiated in the Jerusalem, Tel Aviv and Haifa areas in 1963. Over the years three stages of extended mortality follow up, in 1978, 1986 and 2011, as well as a "dementia phase" among survivors in 2000, Charlson morbidity index as of 2002 and cancer follow up though 2011 were added. Results of IIHD laid the foundation for the teaching of epidemiology of CVD in Israel. BIP (Bezafibrate Infarction Prevention) was the most extensive locally planned and executed in Israeli Cardiology, involving over 15,000 screened patients and 3090 original participants with coronary heart disease (CHD)

Current involvement:

Dementia and multiple morbidity, over the last years of life, in the above mentioned cohort (IIHD) and several research groups.

Epidemiology of stroke.

Epidemiology of cognitive decline and frailty among the BIP survivors (two recurrent examinations)

Cancer incidence in the IIHD.

Vegan health profile, associated putative risk lowering and cost-benefit factors.

Diverse multinational meta-analytic collaborations (Oxford, Cambridge, Sydney, Harvard)

Publications

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Weinstein G, **Goldbourt U**, Tanne D. Body height and late-life cognition among patients with atherosclerotic disease. *Alzheimer Dis Assoc Disord.* 2013;27(2):145-52

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Helicobacter pylori, Enteric Infections and Their Role in Health and Disease

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Helicobacter pylori infection is acquired during early childhood. It causes chronic gastritis, which mostly remains asymptomatic; however in a small portion of the infected people *H. pylori* causes peptic ulcers and gastric cancer. Our research focuses on the role of *H. pylori* in extragastric diseases such as iron deficiency anemia, cognitive function, and diabetes mellitus. Epidemiology of enteric infections in various populations consists an additional main research area in our group.

Our research involves population-based studies in which we integrate various epidemiological and biostatistical methods, as well as biological markers assessed by immunological and microbiological tools.

Publications

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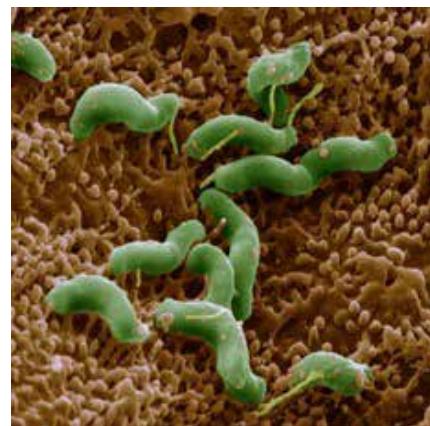
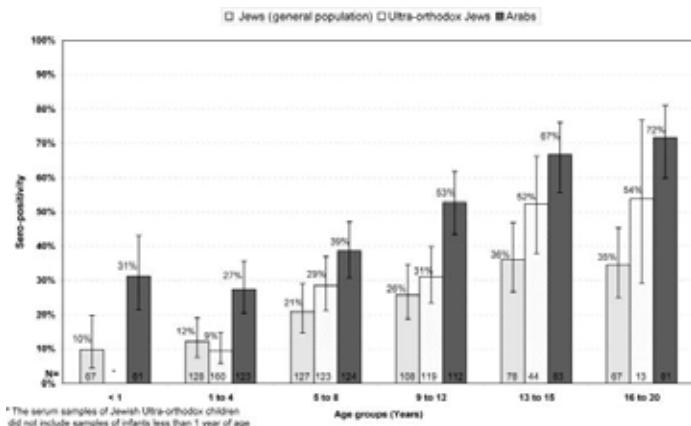
hospitalizations of children < 5 years of age in Israel. *Pediatr Infect Dis J*. 2013; 32:688-90.

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universal rotavirus vaccination in Israel. *Euro Surveill*. 2015;20(42).

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Sow SO, **Muhsen K**, Nasrin D, Blackwelder WC, Wu Y, Farag T, Panchalingham S, Sur S, Zaidi AKM, Faruque ASG, Saha D, Adegbola R, Alonso PL, Breiman RF, Q, Tamboura B, Sanogo D, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Ahmed S, Qureshi S, Quadri F, Hossain A, Das SK, Antonio M, Hossain MJ, Mandomando I, Nhampossa T, Acácio S, Omole R, Ochieng JB, Oundo JO, Mintz ED, O'Reilly CE, Berkeley LY, Livio S, Tennant SM, Sommerfelt H, Nataro JP, Ziv-Baran T, Robins-Browne RM, Liu J, Houpt E, Kotloff KL, Levine MM. The burden of *Cryptosporidium* diarrhea disease among children <24 months of age in moderate/high mortality regions of sub-Saharan Africa and South Asia, utilizing data from the Global Enteric Multicenter Study (GEMS). *PLoS Negl Trop Dis*. 2016;10(5):e0004729.

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Grants

2015-2017	Israel National Institute for Health Policy and Health Services Research (PI)
2016-2018	Israel Ministry of Health (PI)
2016-2018	BSF (PI with Prof. MM Levine, USA)
2018-2021	Israel National Institute for Health Policy and Health Services Research



Dr. Chava Peretz, Ph.D.

Department of Epidemiology
School of Public Health
Sackler Faculty of Medicine



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Epidemiology of Parkinson's Disease and Environmental Epidemiology

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, School of Public Health Seminars

Research

Our research focuses on two main fields: 1. Neuro-epidemiology, and 2. Environmental epidemiology, with a special interest in methodological issues.

In neuro-epidemiology, we study the epidemiology of neuro-generative diseases. Specifically, we follow up and investigate a large cohort of patients with Parkinson's disease on disease burden, etiology, early-markers and co-morbidity. The cohort was derived through a drugs-purchased dataset that was linked to clinical and administrative databases.

In the area of environmental epidemiology, we study the short term effects of air pollution on adverse health outcomes such as birth-defects, emergency-room visits and mortality. We also evaluate vulnerability to air pollution hazards of specific sub-groups such as subjects with diabetes. In light of global climate changes, we study the short-term effects of ambient temperature on mortality and on the occurrence of food-borne diseases. These studies involve a temporal/spatial analysis.

Publications

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Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, **Peretz C**. Ambient temperature and congenital heart defects. *Hum Reprod.* 2013; 28:2289-97.

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Agay-Shay K, Peled A, Crespo AV, **Peretz C**, Amitai Y, Linn S, Friger M, Nieuwenhuijsen MJ. Green spaces and adverse pregnancy outcomes. *Occup Environ Med.* 2014;71(8):562-9.

Gurevich T, Balash Y, Merims D, **Peretz C**, Herman T, Hausdorff JM, Giladi N. Effect of rivastigmine on mobility of patients with higher-level gait disorder: a pilot exploratory study. *Drugs R D.* 2014;14(2):57-62.

Zuk L, Tlumek H, Katz-Leurer M, **Peretz C**, Carmeli E. A new tool for identifying children with motor problems: reliability and validity study. *J Child Neurol.* 2014;29(5):592-8.

Sade M, Zlotnik Y, Kloog I, Novack V, **Peretz C**, Ifergane G. Parkinson's Disease Prevalence and Proximity to Agricultural Cultivated Fields. *Yitshak. Parkinsons Dis.* 2015;2015:576564.

Khamis S, Dar G, **Peretz C**, Yizhar Z. The Relationship Between Foot and Pelvic Alignment While Standing. *J Hum Kinet.* 2015;46:85-97.

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-yr time-window around disease onset: A large-scale cohort study. *Parkinsonism Relat Disord.* 2016;28:68-72.

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Zitser J, **Peretz C**, Ber David A, Shabtai H, Ezra A, Kestenbaum M, Brozgol M, Rosenberg A, Herman T, Balash Y, Gadoth A, Thaler A, Stebbins GT, Goetz CG, Tilley BC, Luo ST, Liu Y, Giladi N, Gurevich T. Validation of the Hebrew version of the Movement Disorder Society-Unified Parkinson's Disease Rating

Scale. *Parkinsonism Relat Disord.* 2017;pii: S1353-8020(17)30341-3.

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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.* 2017;12:e0175054.



Dr. Laura (Leah) J. Rosen, Ph.D.

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Improving Public Health, and Control Tobacco Use and Exposure

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, Dept. of Health Promotion, School of Public Health

Affiliated Faculty, Harvard Global Center for Tobacco Control

Appointed Member, Israel Public Committee for Reduction of Tobacco Use and Damage

Temporary Adviser, European Advisory Council on Health Research (EACHr), World Health Organization

External Steering Committee Member, World Health Organization EvipNet

including understanding and improving the evidence base for public health policy, systematic reviews, and rigorous evaluation of health promotion interventions.

Our main substantive research interest is tobacco, one of the major public health problems of our time. This includes the epidemiology of tobacco use, exposure, and harm, with a focus on the Israeli context; and development and evaluation of intervention programs and strategies to reduce tobacco use and exposure at the individual, local, and national levels. Specific research projects include: monitoring and evaluation of the recent governmentally-approved National Tobacco Control Plan; development of an intervention to protect young children from tobacco smoke exposure; understanding tobacco use initiation among youth; research on changes in tobacco use during Israeli military service, the study of smoking cessation among adults, research on the exposure of the Israeli public to tobacco smoke, and understanding public and policy-maker attitudes towards governmental intervention for tobacco control.

Research

Our primary goal is to contribute to public health, at the national and global levels, through conducting research, advancing public health research methods and evidence-based health policy, and teaching and mentoring students. We focus on methodological issues of public health and health promotion research,



Publications

Rosen L, Rier D, Connolly G, Oren A, Landau C, Schwartz R. Do health policy advisors know what the public wants? An empirical comparison of how health policy advisors assess public preferences regarding smoke-free air, and what the public actually prefers. *Israel Journal of Health Policy Research* 2013, 2:20.

Rosen L. An intuitive approach to understanding the attributable fraction of disease due to a risk factor: the case of smoking. *Int. J. Environ. Res. Public Health* 2013, 10, 2932-2943.

Ioscovich A, Davidson E, Orbach-Zinger S, Rudich Z, Ivry S, Rosen L, Avidan A Ginosar Y. Performance of aseptic technique during neuraxial analgesia for labor before and after the publication of international guidelines on aseptic technique. *IJHPR* 2014 3:9.

Rosen L, Rozhavski V, Levine H, Sela T, Bar-Ze'ev Y, Molina-Hazan V, Zarka S. Smoking initiation among Israeli adolescents: A 24-year time-to-event analysis. *Prev Med* (In Press)

Rosen LJ, Myers V, Hovell M, Zucker D, Ben Noach M. Meta-analysis of parental protection of children from tobacco smoke exposure. *Pediatrics*. 2014;133(4):698-714.

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Rosen L, Suhami R. The art and science of study identification: A comparative analysis of two systematic reviews. *BMC Med. Res. Methodol*. 2016;16:24

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Rosen LJ, Lev E, Guttman N, Tillinger E, Rosenblat S, Zucker DM, Myers V. Parental perceptions and misconceptions of child tobacco smoke exposure. *Nicotine Tob Res*. 2017;doi: 10.1093/ntr/ntx169

Zarka S, Levine H, Rozhavski V, Sela T, Bar-Ze'ev Y, Molina-Hazan V, **Rosen LJ**. Smoking behavior change during compulsory military service in Israel, 1987-2011. *Nicotine Tob Res*. 2017;19:1322-1329.

Reviews and Chapters

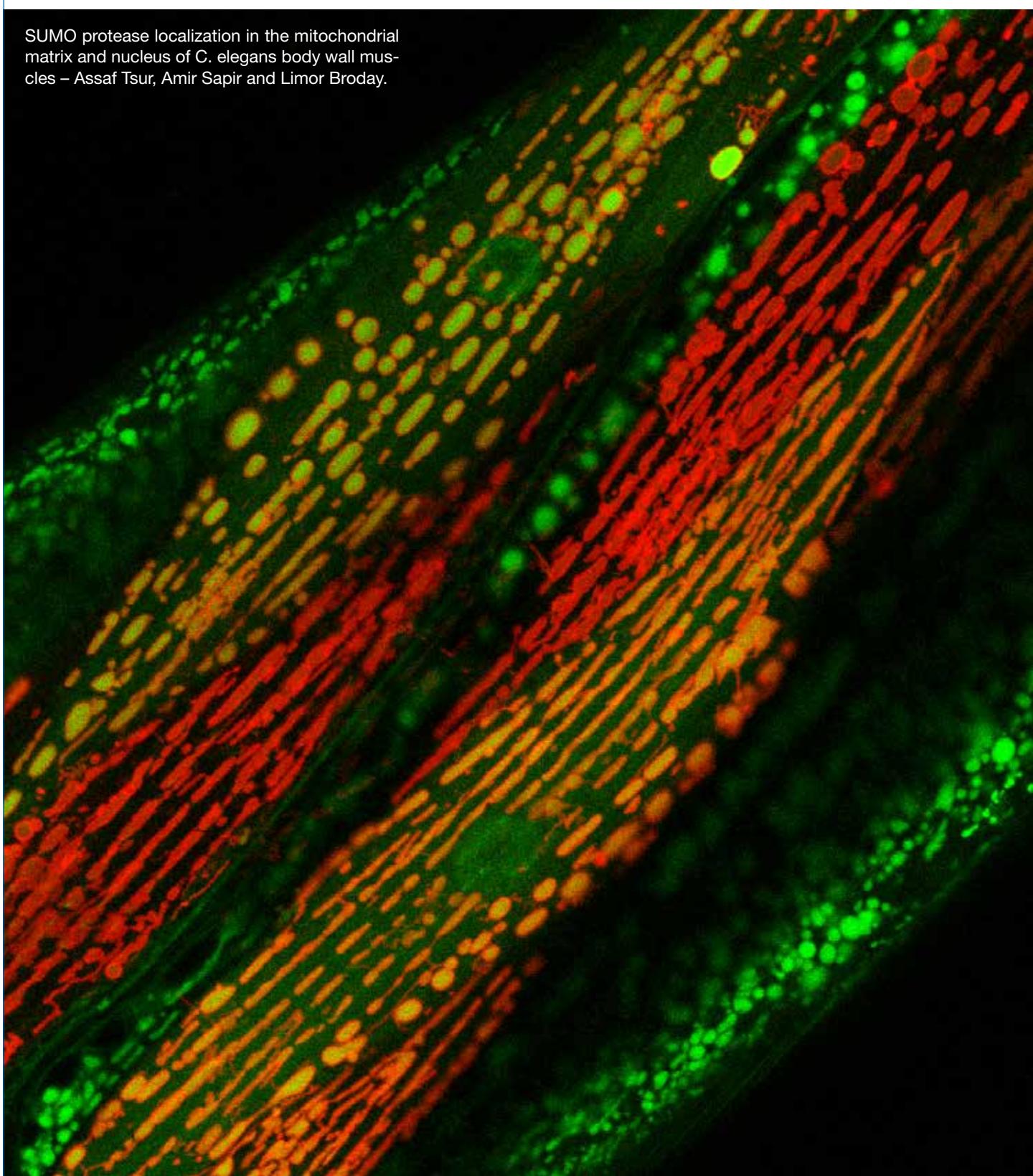
Rosen LJ, Peled-Raz M. Tobacco policy in Israel: 1948-2014 and beyond. *Isr J Health Policy Res*. 2015;4:12.

Grants

2012-2017 Flight Attendant Medical Research Institute (FAMRI).

Reproduction, Development and Evolution

SUMO protease localization in the mitochondrial matrix and nucleus of *C. elegans* body wall muscles – Assaf Tsur, Amir Sapir and Limor Broday.





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Molecular Analysis of Ubiquitin and SUMO Pathways in the *C. Elegans* Model

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Protein modifications by ubiquitin and ubiquitin-like proteins are essential for many cellular regulatory mechanisms. De-regulation of such processes is a cause for many human diseases. The main objective of our research is to understand, at a mechanistic and molecular level, how these processes are regulated. We use the nematode *C. elegans* as a model system to analyze various elements of the ubiquitin and ubiquitin-like system

Current lab projects:

Regulation of morphogenetic processes by SUMO (small ubiquitin-like modifier)

The role of E3 ubiquitin ligases in normal development and under cellular stress conditions

Publications

Linhart, E Halperin, Y. Darom, A. Kidron, S. **Broday, L.** and Shamir. R. 2012. A novel cis-regulatory motif pair in the promoters of germline and oogenesis genes in *C. elegans*. *Genome Res.* 22:76-83.

Kuang E, Okumura CY, Sheffy-Levin S, Varsano T, Shu VC, Qi J, Niesman IR, Yang HJ, López-Otín C, Yang WY, Reed JC, **Broday L.**, Nizet V, Ronai ZA. 2012. Regulation of ATG4B stability by RNF5 limits basal levels of autophagy and influences susceptibility to bacterial infection. *PLoS Genet.* 8:e1003007.

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Tsur, A., Bening Ab-Shach, U., and **Broday, L.** 2015. ULP-2 SUMO protease regulates E-cadherin recruitment to adherens junctions. *Developmental Cell.* 35:1-15, 2015. *Preview: Adhesion with a SUMO.* *Developmental Cell.* 35, 2015. *Featured in Research Highlight:* SUMO controls a tug of war at junctions. *Nature Rev. Mol. Cell. Biol.* 16:641, 2015.

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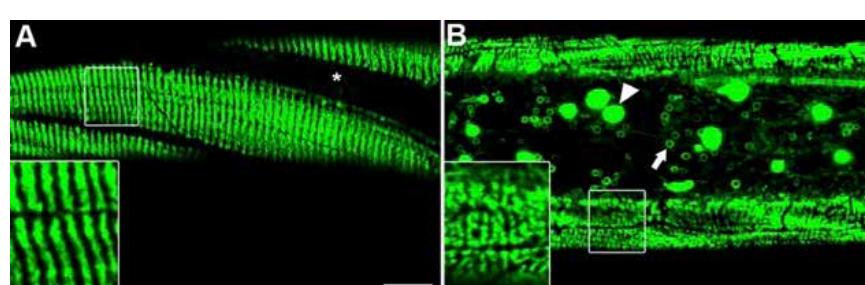
Reviews

Broday L. 2017. The SUMO system in *Caenorhabditis elegans* development. *Int J Dev Biol.* 6:159-164.

Grants

2015-2018 Israel Science Foundation (ISF)

2017-2018 Ministry of Defense, IDF



(A) Organization of the *C. elegans* epidermal intermediate filament protein IFB-1 in circumferential bands in wild-type animal.
(B) Abnormal filaments and formation of inclusions in *smo-1* deleted worms.



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Genetic and Hormonal Regulation of Bone Metabolism

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

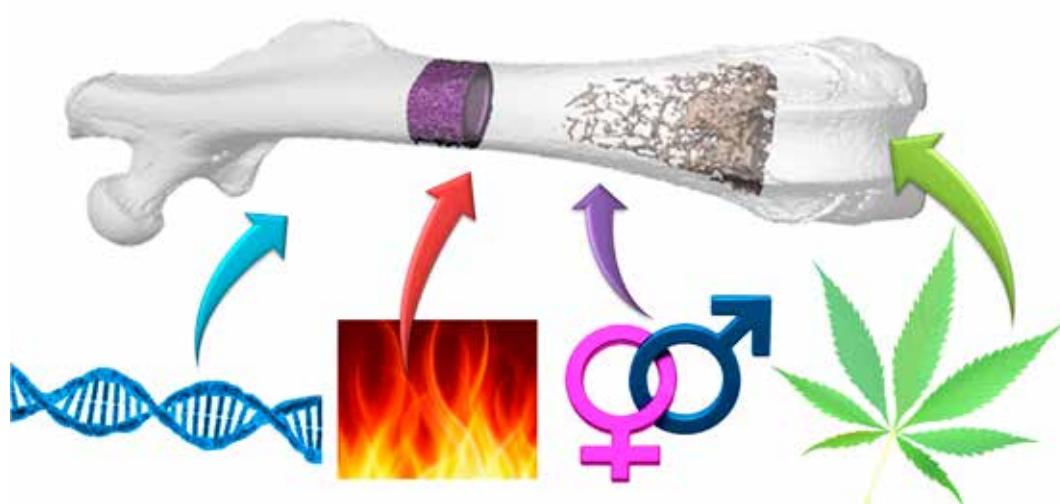
Genetics: Our laboratory focuses on the genetic and hormonal regulation of bone remodeling, microarchitecture and strength. These traits have a high degree of heritability, and one aspect of our research is to characterize new genetic determinants of bone remodeling as well as elucidate the mechanism of action of selected genes. Our GWAS confirmed the role of AVP (vasopressin) and OXT (precursor of oxytocin) in bone and identified for the first time Rhbdf2 as a significant determinant of bone structure.

Sex hormones: We investigate the actions of sex hormones with an emphasis on the skeletal dimorphism between males and females, and their interaction with other genes and transcription factors.

Erythropoietin: Epo is the main hormone that regulates blood cells production. We are investigating the role of Epo in bone remodeling in general and on the bone cells in particular.

Inflammation-induced osteolysis: Today, most dental implants undergo surface roughening to enhance osseointegration. However, ultrasonic scaling performed routinely for oral hygiene releases particles from titanium implants. We found that these particles stimulate the secretion of inflammatory cytokines and induce osteoclastogenesis in vitro and in vivo.

Cannabinoids: Cannabis-derived and endogenous cannabinoids are important regulators of bone cells. We investigate the beneficial actions of cannabinoids in bone fracture healing, osteoporosis, Osteogenesis Imperfecta, and inflammation-induced bone destruction.



Regulation of bone turnover and microstructure by genetic determinants, inflammation, sex hormones and cannabis/endocannabinoids.

Publications

Artsi A, Cohen-Kfir E, Gurt I, Shahar R, Bajayo A, Kalish N, Bellido T, **Gabet Y**, Dresner-Pollak R. (2014) The Sirtuin1 activator SRT3025 down-regulates sclerostin and rescues ovariectomy-induced bone loss and biomechanical deterioration in female mice. *Endocrinology* 155:3508-15.

Dolkart O, Liron T, Chechik O, Somjen D, Brosh T, Maman E, **Gabet Y**. (2014) Statins enhance Rotator Cuff healing by stimulating the COX2/PGE2/EP4 pathway in a rat model: an in vivo and in vitro study. *Am J Sports Med.* 42:2869-76.

Hiram-Bab S, Liron L, Deshet-Unger N, Mittelman M, Gassmann M, Rauner M, Franke K, Wielockx B, Neumann D, **Gabet Y**. (2015) Erythropoietin directly stimulates osteoclast precursors and induces bone loss. *FASEB J.* 29:1890-900.

Martin A, Xiong J, Koromila T, Chang S, Song YS, Krum SA, **Gabet Y**, Frenkel B. (2015) Estrogens antagonize RUNX2-mediated osteoblast-driven osteoclastogenesis through regulating RANKL membrane association. *Bone* 75:96-104

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Elsner JJ, Shemesh M, Shefy-Peleg A, **Gabet Y**, Zylberberg E, Linder-Ganz E. (2015) Quantification of in vitro wear of a synthetic meniscus implant using gravimetric and micro-CT measurements. *J Mech Behav Biomed Mater.*, 49:310-320.

Barak S, Iezzi G, Neuman M, Piattelli A, Perrotti V, **Gabet Y**. (2015) A new device for improving dental implants anchorage: a histological and microcomputed tomography study in the rabbit. *Clinical Oral Implants Research*, Epub.

Garfinkel BP, Arad S, Le PT, Bustin M, Rosen CJ, **Gabet Y***, Orly J*. (2015) Proportionate dwarfism in mice lacking heterochromatin protein 1 binding protein 3 (HP1BP3) is associated with alterations in the endocrine IGF-1 pathway. *Endocrinology*. Accepted, ePUB.

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Barak S, Iezzi G, Neuman M, Piattelli A, Perrotti V, **Gabet Y**. (2015) A new device for improving dental implants anchorage: a histological and microcomputed tomography study in the rabbit. *Clinical Oral Implants Research*, Epub.

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Bell RE, Golan T, Sheinboim D, Malcov H, Amar D, Salamon A, Liron T, Gelfman S, **Gabet Y**, Shamir R, Levy C. (2016) Enhancer methylation dynamics contribute to cancer plasticity and patient mortality. *Genome Research*; 26:601-11.

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

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Gabet Y, Bab I. A validated method for titanium implant anchorage analysis using microct and biomechanical testing biological sciences. *Adv Tech Biol Med.* Accepted June 6, 2016.

Deshet-Unger N, Hiram-Bab S, Haim-Ohana Y, Mittelman M, Gabet Y, Neumann D. Erythropoietin treatment in murine multiple myeloma: immune gain and bone loss. *Scientific Reports*, Accepted July 2016

Gilboa D, Haim-Ohana Y, Deshet-Unger N, Ben-Califa N, Hiram-Bab S, Reuveni D, Zigmund E, Gassmann M, Gabet Y, Varol C, Neumann D. (2017)

Erythropoietin enhances Kupffer cell number and activity in the challenged liver. *Sci Rep.* 7:10379.

Bar-Maisels M, Gabet Y, Shamir R, Hiram-Bab S, Pasmanik-Chor M, Phillip M, Bar-Yoseph F, Gat-Yablonski G. (2017) Beta palmitate improves bone length and quality during catch-up growth in young rats. *Nutrients.* 9(7).

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Martin A, Yu J, Xiong J, Khalid AB, Katzenellenbogen B, Kim SH, Katzenellenbogen JA, Malaivijitnond S, Gabet Y, Krum SA, Frenkel B. ((2017) Estrogens and androgens inhibit association of RANKL with the pre-osteoblast membrane through post-translational mechanisms. *J Cell Physiol.* 232:3798-3807.

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Grants

2012-2017	Israel Science Foundation (ISF) Grant
2015-2017	American Society for Bone and Mineral Research GAP Award
2015-2017	Kalytera Therapeutics Ltd
2016-2017	Israel Cancer Association (co-PI)
2018-2021	German-Israeli Foundation (GIF)



Prof. Israel Hershkovitz, Ph.D.

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Evolutionary Medicine, Paleopathology and Bio-history

Position

Professor, Sackler Faculty of Medicine
Head, Dan David Laboratory for the Search and Study of Modern Humans
Director, Tassia and Joseph Meychan Chair for the History and Philosophy of Medicine

in human evolutionary studies for over a century. New fossils excavated at Qesem, Misliya and Manot caves, may shed light on the above questions.

Evolutionary medicine: This section is divided into three topics: 1) Establishing valid methods for identifying diseases in ancient bones, 2) Identifying diseases in the fossil record, 3) Evolutionary perspective of current diseases.

Research

Biohistory: The social and biological impact the transition from foraging and hunting to farming had on human populations. Although a rapid event in human evolution, the 'agriculture revolution' was the most significant cultural process in human history, something that forever changed the face of humanity (culturally and biologically). Unlike many other paleoanthropological studies, we adopt an 'osteobiographic' approach, i.e., life history as recorded in bones. The study is based on several hundreds of Natufian and Neolithic skeletons (large portion of them were excavated by the team), housed at Tel Aviv University. The study, besides traditional methods, applies new methods and technologies as CT, Micro-CT, SEM, Histochemistry, aDNA, Isotope analyses.

Human evolution: Searching for the origin of anatomically modern humans. The origin of anatomically modern *Homo sapiens* and the fate of the Neanderthals have been fundamental questions

Publications

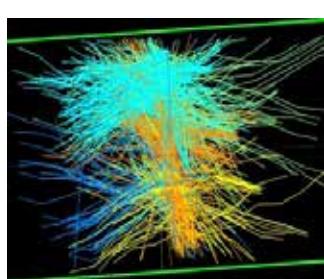
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N. Steinberg, **Hershkovitz I**, Peleg S, Dar G, Masharawi Y, Zeev A, Siev-Ner I. Morphological characteristics of the young scoliotic dancer. *Phys Ther Sport.* 2013, 14:213-20.

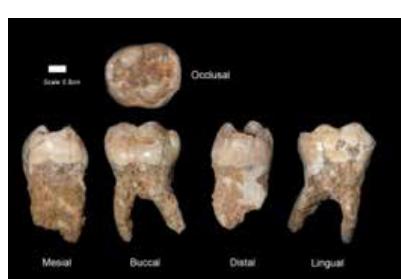
V. Slon, **Hershkovitz I**, May H. The value of cadaver CT scans in gross anatomy laboratory. *Anat Sci Educ.* 2014, 7:80-2.

N. Steinberg, Siev-Ner I, Peleg S, Dar G, Masharawi Y, Zeev A, **Hershkovitz I**. Injuries in female dancers aged 8 to 16 years. *J Athletic Training.* 2013, 48:118-123.

H. Cohen, V. Sloan, H. May, **I. Hershkovitz**, E. Peled, D. Norman. Musculoskeletal wounds characteristic



3D reconstruction of the anulus fibrosus, MRI study. Disc herniation project.



Teeth from Qesem cave 300,000 years. Modern human origin project.



Hyperostosis frontalis interna (HFI) identified via CT and direct observation (skeletal).

of the second Lebanon war. *Forensic Med Anat Res.* 2013, 1:14-17.

H. May, Cohen H, Medlej B, Kornreich L, Peled N, **Hershkovitz I.** Computed tomography-enhanced anatomy course using enterprise visualization. *Anat Sci Educ.* 2013, 6:332-41.

H. Valladas, Mercier N, **Hershkovitz I**, Zaidner Y, Tsatskin A, Yeshurun R, Vialettes L, Joron J-L, Reyss J-L, Weinstein-Evron M. Dating the Lower to Middle Paleolithic transition in the Levant: A view from Misliya Cave, Mount Carmel, Israel. *J Hum Evol.* 2013, X: 1-9.

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Prof. Michael M. Kozlov, Ph.D.

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Theoretical Biophysics of Membranes and Cytoskeleton

Position

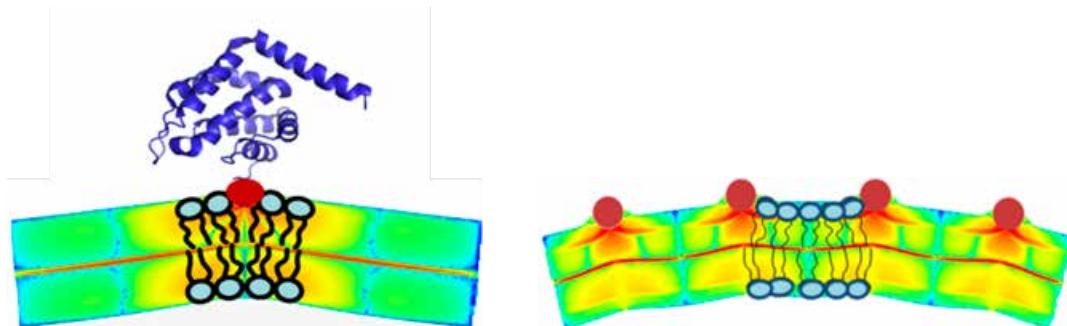
Professor, Sackler Faculty of Medicine
Joseph Klafter Chair in Biophysics

Research

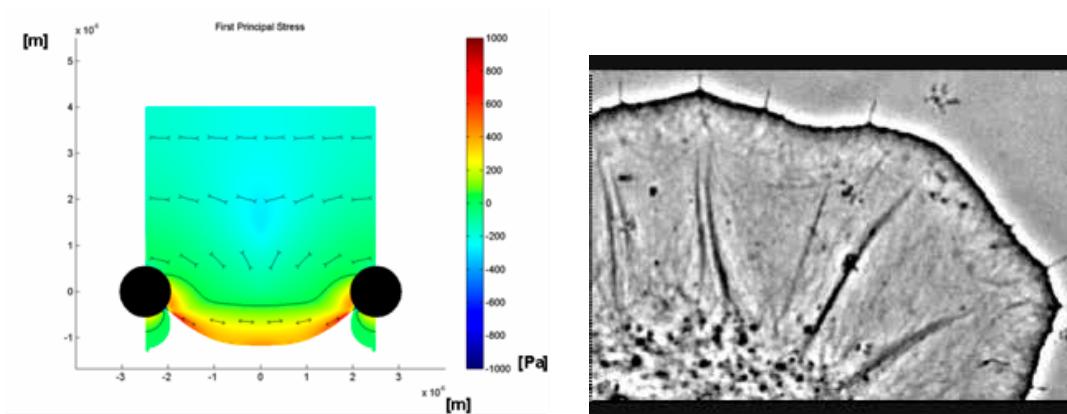
We model the mechanisms of shaping and remodeling of intracellular membranes by specialized proteins that includes generation of large membrane curvatures, membrane fission and fusion. Our goal is to reveal the common mechanistic themes in the function of membrane shaping proteins acting in different intracellular systems. In this way, we hope to be able to understand whether every stage of membrane

shaping needs a special protein or the same protein machinery can enable both membrane curvature generation and fission and/or fusion. Specifically, we model the action of BAR domain proteins, Epsins and Dynamins in endocytosis, Reticulons and their partners in shaping the Endoplasmic Reticulum, and ESCRT-III complexes in fission of cytokinetic tubes.

We model the mechanisms underlying the dynamic organization of the actin cytoskeleton and the system of cell adhesion in polarizing and moving cells. Our major goal is to understand the mechanosensitivity of the cytoskeletal systems and its role in the system temporal rearrangements and steady-state structures.



Computational results for membrane curvature generation by amphipathic N-terminal helices of N-BAR domains, ENTH domains and small G-proteins.



Computational modeling of lamellipodium boundary formation resulting from actin-focal adhesion interaction (left), the phenomenon observed in moving fibroblasts (right, courtesy of A. Verkhovsky).

Publications

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Grants

2017 EU-ITM

2015-2018 Israel Science Foundation



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Department of Anatomy and Anthropology
Sackler Faculty of Medicine



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Laboratory for Bio-History and Evolutionary Medicine

Position

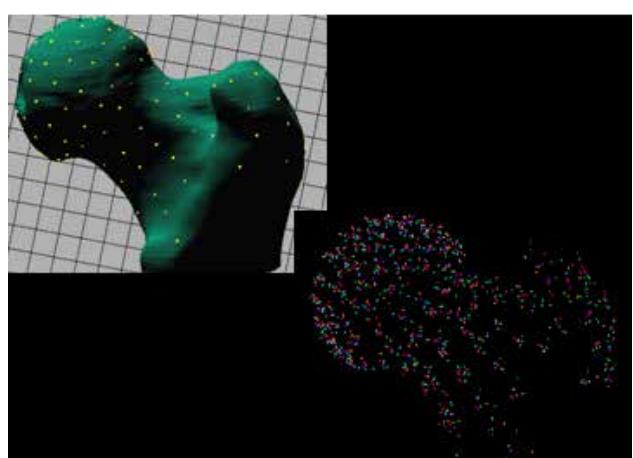
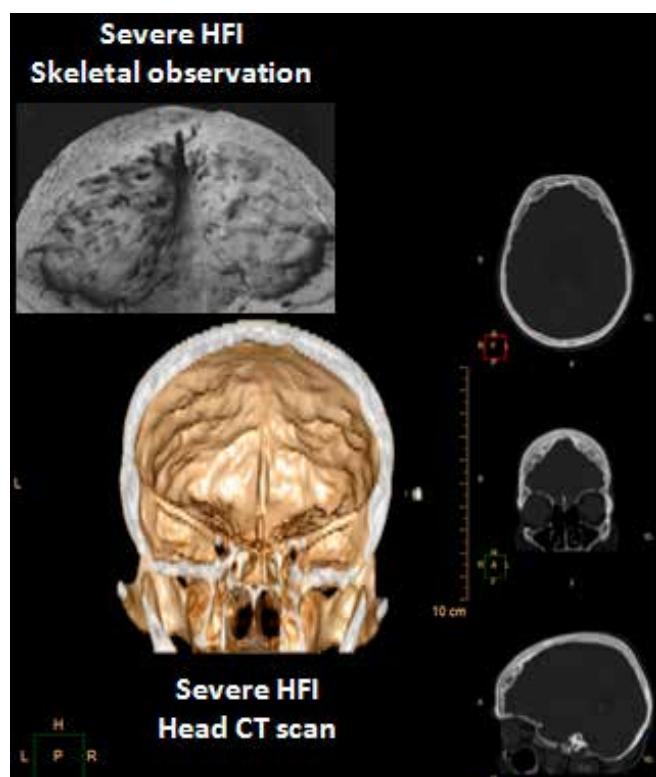
Lecturer

Research

Inter-disciplinary laboratory focusing on two major topics: evolutionary history of anatomical systems and their impact on current population health, and reconstruction of ancient populations' daily life, based on their skeletal remains, with emphasis on the interaction between genetic and socio-cultural factors.

The bio-history study of ancient populations is based on both morphological and molecular (aDNA) methods.

Reconstructing past population daily life: revealing daily activities of prehistoric and historic populations is a challenging task considering the evidence at hand (bones). Nevertheless, bones may furnish us with information otherwise not available, e.g., division of labor, social stratification, intensity of physical activities, health and nutrition, demography (sex ratio, mortality, family size, etc.). Beside traditional methods, the studies are being carried out utilizing advanced 3D analysis methods based on CT, micro-CT and 3D surface scans. The accompanied genetic studies, in addition to supporting and confirming observed pathologies in the bones, i.e., identifying pathogens suspected to cause diseases such as TB, leprosy, etc., also contribute to questions related to populations' migration from and to the Southern



Hyperostosis frontalis interna (HFI) identified via CT and direct observation (skeletal).

Levant, and questions related to population structure (e.g., extended family) and biological relationships between the local populations.

The evolutionary medicine studies focus on the quest for evolutionary explanations for common diseases found in modern human populations. We estimate the benefits and costs behind anatomical changes through evolution in order to better understand how compromised designs are being developed, and their outcomes (i.e., diseases).

Publications

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Grants

2016-2017 Israel Science Foundation (Equipment).

2016-2019 Israel Science Foundation: From Hunting to Farming: Exploring Micro-Evolutionary Trends in the Human Masticatory System and their Implications at the Terminal Pleistocene Levant



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Reproduction in Animal Models and in Humans

Positions

Professor Emeritus, Sackler Faculty of Medicine

Research

Our research focuses on Reproductive Physiology in animal models and in humans. The current research directions investigated in the laboratory are:

- The role of Fyn kinase, member of the Src family kinases, during meiosis and early events of oocyte activation, as well as in cancer cells (Figure-left panel).
- Fertility preservation – the signaling pathway leading to apoptosis in aging oocytes and in oocytes exposed to chemotherapeutic treatments and potential protectants (Figure -right panel).
- Regulation of angiogenesis in reproductive organs by Pigment epithelium derived factor (PEDF) and treatment of reproductive angiogenic-related pathologies.

Various research methods are routinely used in the laboratory, ranging from *in vivo* animal studies and cells cultures to an array of protein methodologies

such as western blotting, immunohistochemistry, molecular biology techniques as well as cellular and molecular imaging.

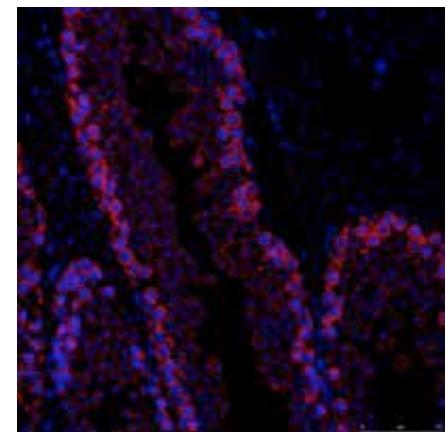
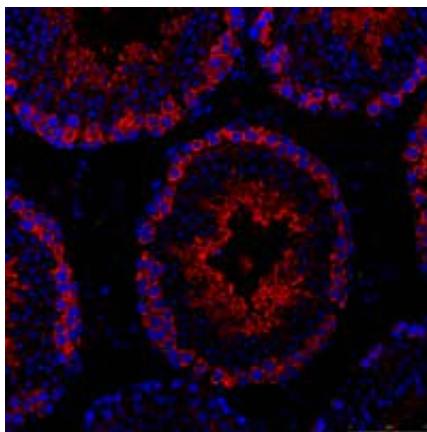
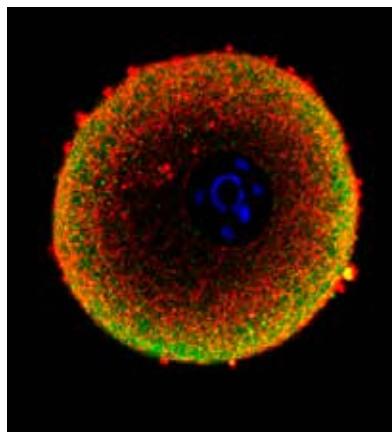
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Left panel- Human oocyte stained for DNA (blue); cytoskeleton (tubulin; red); protein (Fyn kinase; green). Arrow – Germinal vesicle (genetic material); C- Cytoplasm. Confocal microscopy. Right panels -Section of sperm producing tubules in mouse testis before (left) and after treatment with chemotherapy (right). The drug led to loss of sperm (S) production. DNA (blue); protein (DAZL; red). Immunofluorescent microscopy.

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Ninio-Many, L., **Shalgi, R.** and Ben-Aharon, I. miR-125a – Does the difference lie in the isoform? *Cell Cycle*.14:785-6. 2015.

Grossman, H. and **Shalgi, R.** A Role of microRNAs in cell differentiation during gonad development. *Results Probl Cell Differ.*;58:309-36;2016

Grants

2014-2018 Israel Science Foundation (ISF) – Post transcription regulation of Fyn kinase by miR-125a-3p in the ovary – potential relevance to ovarian function

2016-2017 Israel Cancer Association – miR-125a-induced cellular switch elicits a response to anti-HER2 targeted therapy in cancer cells

2016-2017 The Colton Foundation. PEDF for the treatment for uterine fibroids.



Prof. Ronen Zaidel Bar, Ph.D.

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Cellular Mechanics and Tissue Morphogenesis

Positions

Associate Professor, Sackler Faculty of Medicine

Visiting Professor, Mechanobiology Institute, Singapore

Research

Our main interest is in understanding how mechanical forces are generated by cells and how cells use these forces to change shape and move, as happens during cell division, cell migration and tissue morphogenesis. We focus on distinct cellular structures that mediate cell adhesion and contractility: cell-matrix and cell-cell junctions and the actomyosin cytoskeleton. Together, these structures are responsible for the dynamic control of cell and tissue shape during development and homeostasis and their misregulation is associated with various diseases.

We take a multi-scale approach in our investigations, from single proteins to an entire organism, and employ a variety of tools, including genetic engineering, proteomics, biochemistry and bioinformatics, but primarily relying on live imaging with fluorescence microscopy.

Our findings, both in mammalian cells and in the nematode *C. elegans*, are defining the protein

network regulating cell adhesion and contractility in vivo and elucidating molecular mechanisms of mechanosensing and mechanotransduction.

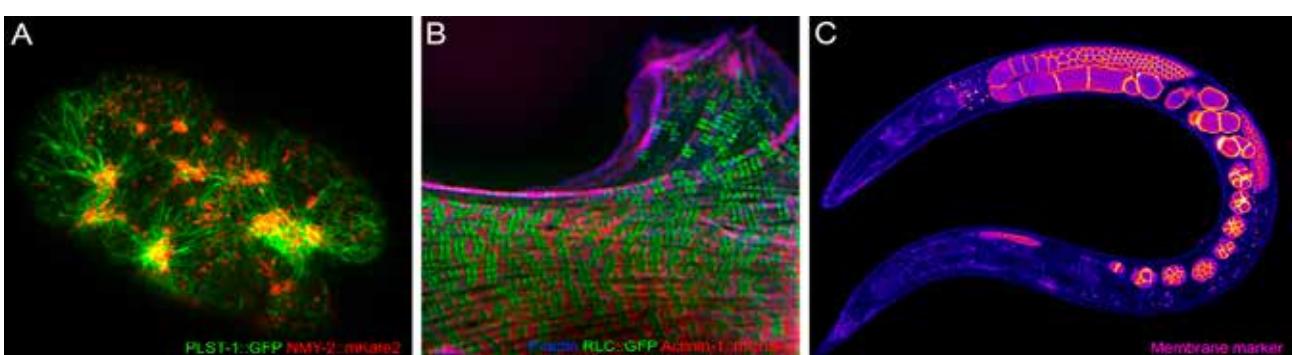
Publications

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Actomyosin-generated forces shape cells and tissues: **(A)** A contractile actomyosin network at the cortex of a *C. elegans* early embryo. It is essential for cell polarization and division. **(B)** Actin and myosin self-organize into arrays of parallel stress fibers in a REF52 fibroblast. They are required for cell spreading and adhesion. **(C)** The germline of *C. elegans*, highlighted by a membrane marker, is like an assembly line for embryos. Actomyosin contractility is essential for maintaining germline architecture and for moving oocytes and embryos along.

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Erami Z, Anannya O, Schwarz JP, Timpson P, Yao W, **Zaidel-Bar R**, and Anderson KI. There are four dynamically and functionally distinct populations of E-cadherin in cell junctions. *Biology Open* 4(11):1481-9. 2015.

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Budirahardja Y, Doan T, and **Zaidel-Bar R.** Glycosyl phosphatidylinositol anchor biosynthesis is essential for maintaining epithelial integrity during *Caenorhabditis elegans* embryogenesis. *PLoS Genetics* 11(3):e1005082. 2015.

Wu Y, Kanchanawong P, and **Zaidel-Bar R.** Actin-delimited adhesion-independent clustering of E-cadherin forms the nanoscale building blocks of adherens junctions. *Developmental Cell* 32(2):139-54. 2015.

Tan P-Y and **Zaidel-Bar R.** Transient membrane localization of SPV-1 drives cyclical actomyosin contractions in the *C. elegans* spermatheca. *Current Biology* 25(2):141-51. 2015.

Guo Z, Neilson LJ, Hang Z, Murray P, Zanivan S, and **Zaidel-Bar R.** E-cadherin adhesome complexity and robustness resolved by quantitative proteomics. *Science Signaling* 7(354), rs7. 2014.

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Reviews

Sethi K, Cram EJ, **Zaidel-Bar R.** Stretch-induced actomyosin contraction in epithelial tubes: Mechanotransduction pathways for tubular homeostasis. *Semin Cell Dev Biol*. 2017 pii: S1084-9521(17)30176-3. 2017.

Biswas KH, **Zaidel-Bar R.** Early events in the assembly of E-cadherin adhesions. *Experimental Cell Research*. pii: S0014-4827(17)30090-3. 2017.

Padmanabhan A, Vaman Rao M, Yao W, and **Zaidel-Bar R.** Jack of all trades: functional modularity in adherens junctions. *Current Opinion in Cell Biology* 36:32-40. 2015.

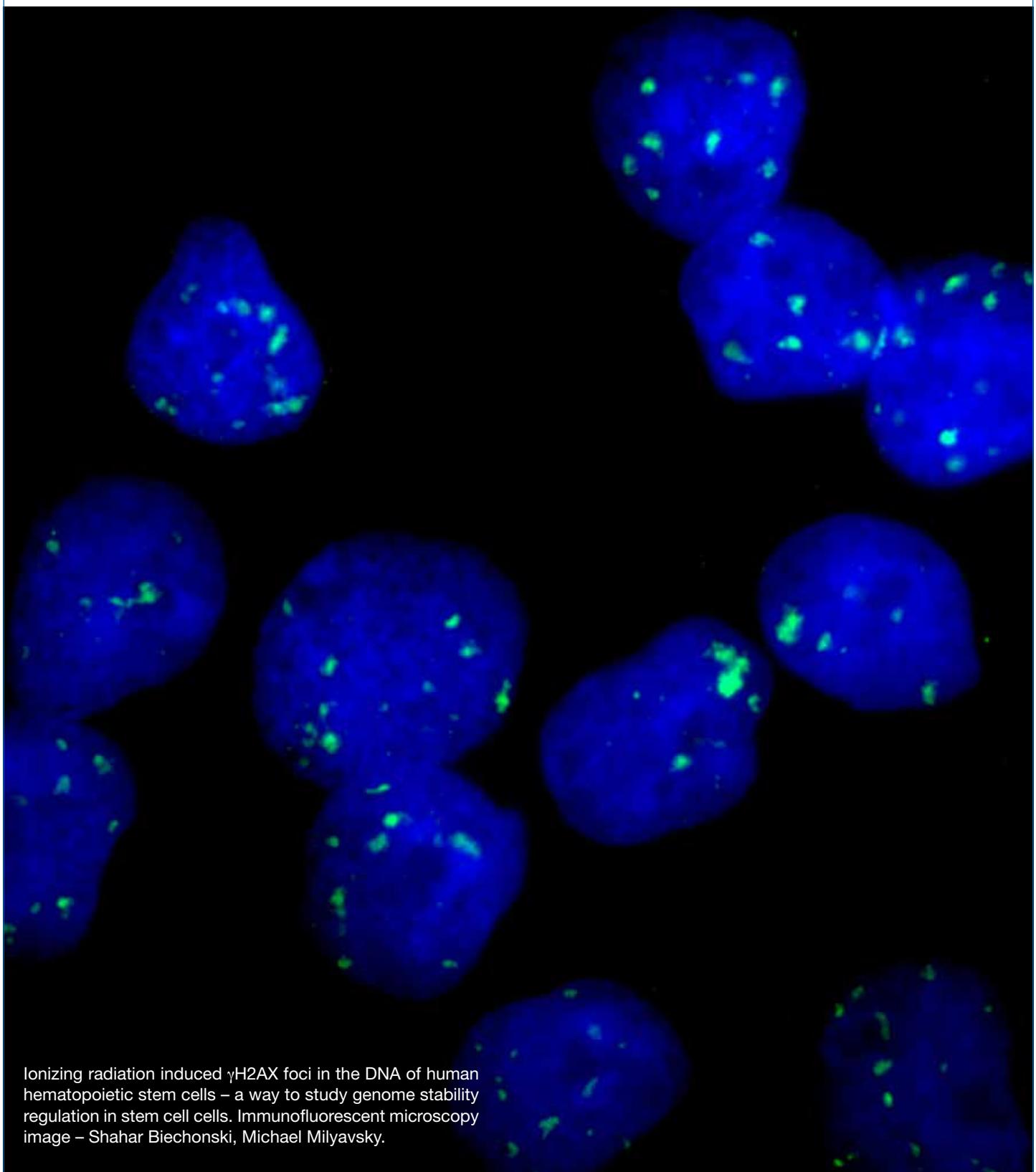
Zaidel-Bar R, Gou Z, and Luxenburg C. The contractome - a systems view of actomyosin contractility in non-muscle cells. *Journal of Cell Science* 128(12):2209-17. 2015.

Zaidel-Bar R. Cadherin adhesome components and interactions at a glance. *Journal of Cell Science* 126:373-378. 2013.

Grants

2014 –2018	National Research Foundation Singapore: Controlling cell-cell signaling using synthetic biometric interfaces
2015 –2017	Mechanobiology Institute Singapore: Unraveling the coupling between cell-cell and cell-matrix adhesions.
2016 –2018	Ministry of Education Tier2: Regulation of actomyosin cortex force generation by non-junctional E-cadherin.
2017 –2020	Israel Science Foundation Research grant: Mechanotransduction in contractile tubes: using the <i>C. elegans</i> spermatheca as a model to study the regulation of RHO-1- and Ca ²⁺ -dependent actomyosin contractility in response to stretching.
2017 –2020	Israel Science Foundation Equipment Grant

Stem Cells and Regenerative Medicine



Ionizing radiation induced γ H2AX foci in the DNA of human hematopoietic stem cells – a way to study genome stability regulation in stem cell cells. Immunofluorescent microscopy image – Shahar Biechonski, Michael Milyavsky.



Prof. Dafna Benayahu, Ph.D.

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Sackler Faculty of Medicine



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Musculoskeletal – Stem cells and Nanotechnology

Position

Professor, Sackler Faculty of Medicine

Research

Our interest is to follow the differentiation of skeletal stem cells and their lineage fate. The balance between skeletal stem cells and the adipose lineage is studied at the cellular and molecular biology levels. In silico characterization using bioinformatics of genes profiling and identification of biomarkers networks to identify markers for stem cells. Recent projects we have shown that biomechanics play a role in the stem cells activation and function under normal physiology and along aging. The ultimate goal of the research is to study how to improve the stem cells functionality. Such knowledge will provide novel approaches to combat skeletal changes due to aging or metabolic disease. The use of stem cell is also developed towards tissue regeneration along with development of novel collagen-based-scaffold.

Research methods used include bioinformatics, gene cloning, qRT-PCR, cell biology analysis including immunofluorescence, scanning electron microscopy and biochemistry. Nanotechnology combines the cell fate differentiation with multidisciplinary approaches for the development of new platforms for cell analysis.

Publications

Marcus Y, Shefer G, Sasson K, Kohen F, Limor R, Pappo O, Nevo N, Biton I, Bach M, Berkutzki T, Fridkin M, **Benayahu D**, Shechter Y, Stern N. 2013. Angiotensin 1-7 as a novel means to prevent the metabolic syndrome: lessons from the fructose-fed rat model. *Diabetic* 62(4):1121-1130.

Shefer G, Rauner G, Stuelsatz P, **Benayahu D**, Yablonka-Reuveni Z. 2013. Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. *FEBS J.* 280(17): 4063-4073.

Shoham N, Sasson A, Lin FH, **Benayahu D**, Haj-Ali R, Gefen A. 2013. Mechanics of hyaluronic acid/adipic acid dihydrazide hydrogel: towards developing a vessel for delivery of preadipocytes to native tissues *Journal of the Mechanical Behavior of Biomedical Materials. J Mech Behav Biomed Mater.* 22; 28C:320-331.

Shoham N, Girshovitz P, Katzengold R, Shaked NT, **Benayahu D**, Gefen A. 2014. Adipocyte Stiffness Increases with Accumulation of Lipid Droplets. *Biophysical J* 106: 1-11.

Ben-Or Frank M, Shoham N, **Benayahu D**, Gefen A. 2014 Effects of accumulation of Lipid Droplets on load transfer between and within Adipocytes. *Biomechanics and Modeling in Mechanobiology* (Accepted).

Sharabi M, Mandelberg Y, **Benayahu D**, Benayahu Y, Azem A, Haj-Ali R. A new class of bio-composite materials of unique collagen fibers. 2014. *Journal of the Mechanical Behavior of Biomedical Materials* 36:71-81.

Shkolyar A, Gefen A, **Benayahu D**, Greenspan H. Automatic detection of cell divisions (mitosis) in live-imaging microscopy images using Convolutional Neural Networks. *Conf Proc IEEE Eng Med Biol Soc.* 2015;2015:743-6.

Salomon-Kent R, Marom R, John S, Dundr M, Schiltz LR, Gutierrez J, Workman J, **Benayahu D**, Hager GL. New face for chromatin-related mesenchymal modulator: n-chd9 localizes to nucleoli and interacts with ribosomal genes. *J Cell Physiol.* 2015;230(9):2270-80.

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testing of adipocytes. *Biomech Model Mechanobiol.* 2015;14(3):537-47.

Katzengold R, **Benayahu D**, Gefen A. 2015 Simulating single cell experiments in mechanical testing of adipocytes. *Biomechanics and Modeling in Mechanobiology* 14: 537-547.

Yildirima C, **Benayahu D**, Adamovskia M, Wollenberger U. 2015. An electrochemical assay for differentiation of the osteoblastic cell line (MBA-15) on the sensor chip. *Electroanalysis* 27:1350-1358.

Sharabi M, **Benayahu D**, Benayahu Y, Issacs J, Haj-Ali R, 2015. Laminated Collagen-based bio-composites for tailor designed soft tissue mimetics. *Composites Science and Technology* 117:268-275.

Shoham N, Levy A, Shabshin N, **Benayahu D**, Gefen A. A multiscale modeling framework for studying the mechanobiology of sarcopenic obesity. 2016;16:275-295.

Mandelberg Y, **Benayahu D**, Benayahu Y. Octocoral Sarcophyton auritum Versteveldt & Benayahu, 1978: Microanatomy and Presence of Collagen Fibers. *Biol Bull.* 2016;230(1):68-77.

Yang X, Li Y, Liu X, Huang Q, He W, Zhang R, Feng Q, **Benayahu D**. The stimulatory effect of silica nanoparticles on osteogenic differentiation of human mesenchymal stem cells. *Biomed Mater.* 2016;12:015001.

Shemesh S, Sidon E, Kaisler E, Sheinis D, Velkes S, Ohana N, **Benayahu D**. Diabetes mellitus is associated with increased elastin fiber loss in ligamentum flavum of patients with lumbar spinal canal stenosis: results of a pilot histological study. *Eur Spine J.* 2017;doi: 10.1007/s00586-017-5315-0.

Yang X, Liu X, Li Y, Huang Q, He W, Zhang R, Feng Q, **Benayahu D**. The negative effect of silica nanoparticles on adipogenic differentiation of human mesenchymal stem cells. *Mater Sci Eng C Mater Biol Appl.* 2017;81:341-348.

Grants

2015-2017	Ministry of Science Cooperation , Israel-china
2016-2019	Ministry of Science Cooperation, Jointly with Prof. R. Haj-Ali
2016-2020	Israel Science Foundation, Jointly with Prof. A. Gefen



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Cytoskeletal Regulation of Epidermal Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our laboratory studies how cytoskeleton-derived signals control stem cell's ability to give rise to a functional tissue during development, to maintain it throughout life and repair it upon wounding.

The actomyosin cytoskeleton is a complex cellular structure that plays a role in many biological processes. Classic studies established its role in cell structural organization. However, new studies demonstrate that the cytoskeleton plays a major role in regulatory processes that control signal transduction, gene expression and stem cell lineage specification.

Our laboratory uses the skin epidermis as its main model system. Projects in the lab explore both skin development and skin common diseases such as

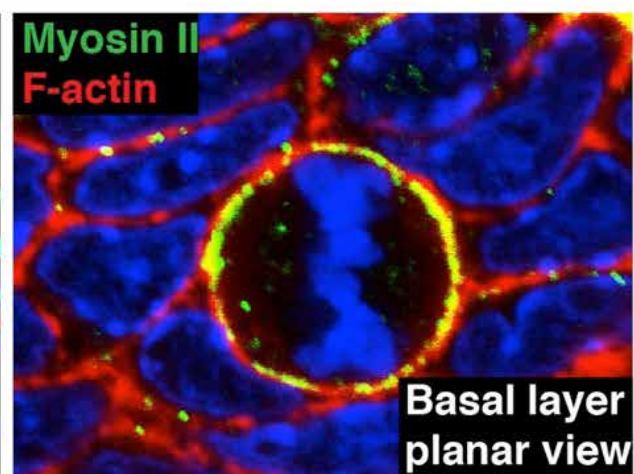
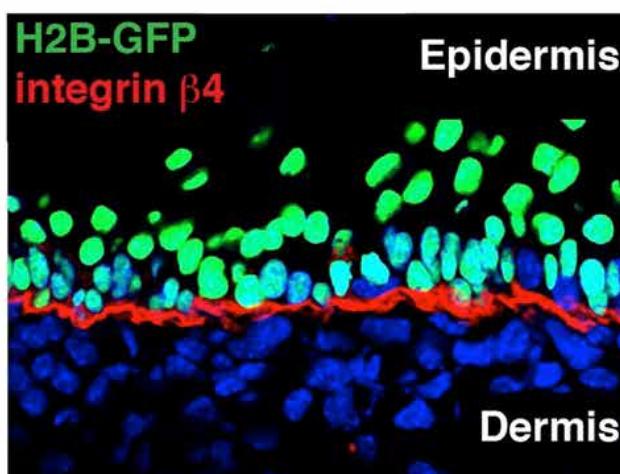
cancer and psoriasis. In addition to classic genetic tools and *in vivo* models we also use state of the art technology to manipulate stem cells *in utero*. Genome wide analysis of gene expression, quantitative digital microscopy and a variety of molecular and cellular methods are all commonly used in our lab.

Publications

Luxenburg C, Heller E, Pasolli HA, Chai S, Nikolova M, Stokes N, Fuchs E. Wdr1-mediated cell shape dynamics and cortical tension are essential for epidermal planar cell polarity. *Nat Cell Biol.* 2015;17:592-604.

Zaidel-Bar R, Zhenhuan G, **Luxenburg C**. The contractome--a systems view of actomyosin contractility in non-muscle cells. *J Cell Sci.* 2015;128:2209-17.

Peled A, Sarig O, Samuelov L, Bertolini M, Ziv L, Weissglas-Volkov D, Eskin-Schwartz M, Adase



Left hand side: We use state of the art *in utero* injections of lentivirus (H2B-GFP+ cells in the epidermis) to manipulate gene expression in epidermal stem cells/progenitors early in embryonic development, before cell fate specification.

Right hand side: Whole mount image of embryonic epidermis showing an early mitotic cell and its interphase neighbors in planar view. Note the dramatic differences in cell shape. We demonstrated that mitotic rounding is important for cells ability to orient their spindle and undergo asymmetric cell division.

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. (2016) Mutations in TSPEAR, encoding a regulator of Notch signaling, affect tooth and hair follicle morphogenesis. *PLoS Genet* 13;12:e1006369.

Dor-On E, Raviv S, Cohen Y, Adir O, Padmanabhan K, **Luxenburg C**. (2017) T-plastin is essential for basement membrane assembly and epidermal morphogenesis. *Sci Signal*. 2017;10(481).

Reviews

Luxenburg C, Geiger B. (2017) Multiscale view of cytoskeletal mechanoregulation of cell and tissue polarity. *Handb Exp Pharmacol*. 235:263-284

Grants

2014-2018 Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease

2015-2020 Israel Science Foundation (ISF) Grant



Dr. Michael Milyavsky, Ph.D.

Department of Pathology
Sackler Faculty of Medicine



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DNA Damage Response in Normal and Leukemia Hematopoietic Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

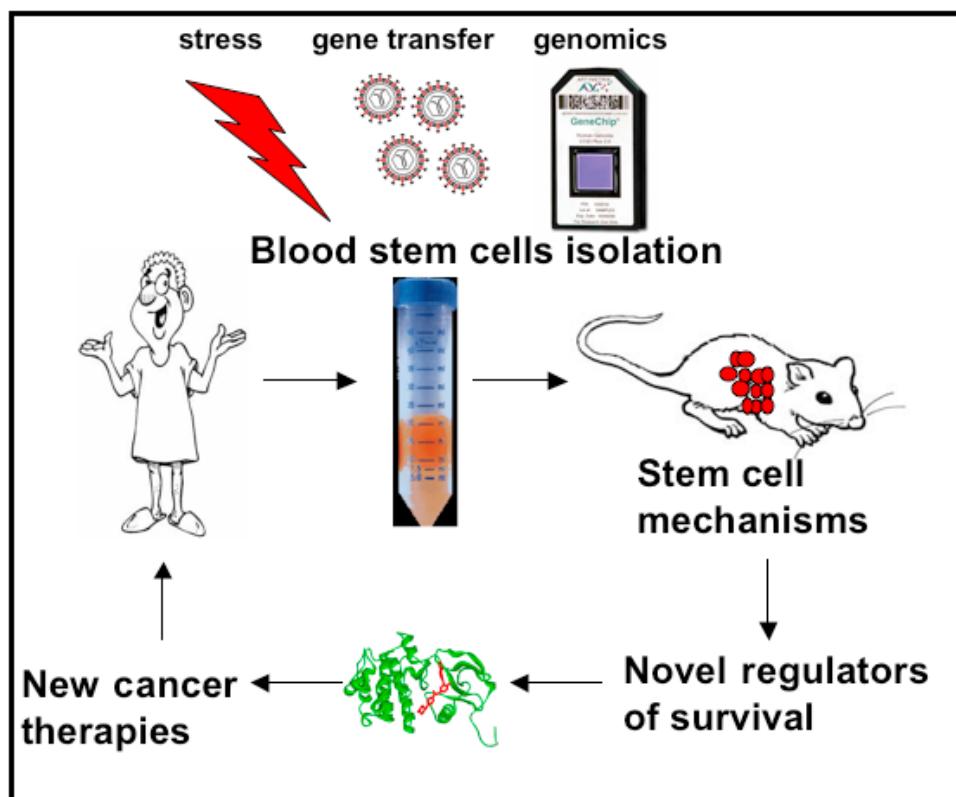
Research

Accumulation of unrepaired DNA damage in hematopoietic stem cells (HSC) is associated with bone marrow failure and accelerated leukemogenesis. Our laboratory aims to understand how HSC cope with DNA damage to preserve normal blood regeneration and to limit the risk of leukemogenesis. In addition, we strive to discover how leukemia stem cells escape therapy and try to devise strategies to prevent this from happening. To address these questions we study DNA damage signaling and its outcomes in highly purified human normal and leukemia cell subsets. We employ flow cytometry,

immunofluorescent and biochemical analyses, lentiviral gene transfer-mediated functional screens, expression/microRNA profiling, clonal *in vitro* assays and, most importantly, *in vivo* repopulation mouse assays of human normal HSC and leukemia-initiating cells.

Publications

Louria-Hayon I., Ruston J.C.F., Gish G., Jin J., Kofler M. M., Lambert J-P., Adissu H. A., **Milyavsky M.**, Herrington R., Minden M. D., Dick J. E., Gingras A-C., Iscove N. N., and T. Pawson. 2013. The Lnk adaptor suppresses radiation resistance and radiation-induced B-cell malignancies by inhibiting IL-11 signaling. *Proc Natl Acad Sci USA* 110: 20599-604.



Milyavsky M, Gole B, Wiesmüller L. Replication stress in MLL-rearrangements. *Oncoscience*. 2015;2:938-9.

Biechonski, S., Gourevich, D., Rall, M., Aqaqe, N., Yassin, M., Zipin-Roitman, A., Trakhtenbrot, L., Olender, L., Raz, Y., Wiesmuller, L., Jaffa, A. J., Grisaru, D., Elad, D., and **Milyavsky, M.** 2017. Quercetin alters DNA damage response in human hematopoietic cells via Topoll- and PI3K- dependent mechanisms that contribute to MLL rearrangements. *Int J Cancer*, 15; 140(4):864-876.

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Review

Biechonski, S., and M. Milyavsky. 2013. Differences between human and rodent dna-damage response in hematopoietic stem cells: at the crossroads of self-renewal, aging and leukemogenesis. *Transl Cancer Res* 2:372-383.

Grants

2014-2017	Israel Cancer Research Fund (ICRF)
2016-2018	German Israeli Foundation for Scientific Research and Development (GIF)
2014-2019	Israel Science Foundation (ISF) Grant: Elucidation of DNA damage response mechanisms in human normal and malignant hematopoietic stem cells.