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 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. This network of preclinical and clinical teams helps realize the ultimate goals of the research: the basic understanding of human pathophysiology and the improvement of prevention, diagnosis and treatment of disease. The research of most of the 120 Preclinical faculty members, from four schools of the Sackler Faculty of Medicine, are featured in this research brochure. These schools are 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.

The Faculty of Medicine engages in joint teaching and research programs with nearly every faculty at Tel Aviv University 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 Sacker affiliated departments and institutes in 17 hospitals hold academic appointments at Tel Aviv University. 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 regular 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 62 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 Yosef Mekori; Vice Deans Prof. Karen Avraham, Prof. Leonard Leibovici, Prof. Moshe Phillip, Prof. Anat Lowenstein, and Prof. Ehud Grossman; and Assistant to the Dean, Ms. Yael Keilin.

Cover credits
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Nurit Azouz - Ronit Sagii-Eisenberg  Mattan Levi - Ruth Shalgi
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Investigating the Molecular Basis of Visual System Development

Positions
Associate 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


**Review**


**Grants**

2010-2014, Roles of Pax6 in retinal development, Israel Science Foundation

2012-2015, Roles for microRNA in RPE differentiation, Morasha, Israel Science Foundation

2012-2015, Roles for Pax6 in neurons of the olfactory bulb, midbrain and retina, German Israeli Foundation (Co-PI with Magdalena Goetz).
**Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders and Cancer**

**Positions**
Professor, Sackler Faculty of Medicine  
Chair, Adelson Graduate School of Medicine

**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.

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.

**Publications**


Reviews


Grants

2009-2013 ISF, Israel Science Foundation, How chromatin organization affect alternative splicing
2010-2013 ISF, Bikura, How alternative splicing affect miRNA biogenesis (with Sebastian Kadener)
2012-2013 FD Consortium, Studying FD disease
2011-2013 Ministry of Health, Studying Drug Therapy in FD
2009-2013 DIP Program - German Israeli Project Cooperation Program, Alternative Splicing
Normal and Diseased Potassium Channels in Human Brain and Heart

Position
Professor, Sackler Faculty of Medicine

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

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.
Publications

Manuscripts


Reviews


Grants


2009-2013: Israel Academy of Science, (ISF). The Kv7.1 C-terminus of the IKS potassium channel complex: a multi-modular structure for channel gating and assembly, PI
Genomic Analysis of Hereditary Hearing Loss

Positions
Professor, Sackler Faculty of Medicine
Vice Dean for Preclinical Affairs, Sackler Faculty of Medicine
Board Member, I-CORE for Gene Regulation in Complex Human Disease
President, Israel Society of Auditory Research

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 encompassed the prevalence of connexin 26 mutations in these populations, the most common form of deafness, 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. Most recently, 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.

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 (out of 86)


Reviews and Chapters (out of 49)


Grants

2011 – 2015  Gene Expression and microRNA Regulation in Hair and Supporting Cells of Mouse, Israel Science Foundation

2011 – 2016  Gene Discovery for Hearing Loss in Middle East by Massively Parallel Sequencing, National Institutes of Health, Co-PI: Moien Kanaan


2012 – 2016  The Regulation and Cellular Activities of the Arl2 GTPase, National Institutes of Health – R01, Co-PIs: Richard Kahn, Saima Riazuddin
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 psycho-moral 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. Jewish bioethics: rabbinic law and theology in their social and historical contexts. Cambridge University Press. In press.

Publications


Barilan YM. From hope in palliative care to hope as a virtue and a life skill. (An original keynote article with a response to commentators) Philosophy, Psychiatry and Psychology. 2012; 19:165-181.


Barilan YM, Brusa M. Deliberation at the hub of medical education: beyond virtue ethics and code of practice. Medicine, Health Care and Philosophy 2012 (Published online first)


Barilan YM. Informed consent: between waiver and excellence in responsible deliberation. Medicine, Health Care and Philosophy 2010; 13:89-95.

Brusa M, Barilan YM. Cultural circumcision in EU public hospitals: an ethical discussion.

Grants

2010-2014, ISF, Responsibility in medical education.
2012-2015 COST (EU join collaborative grant), Ethics in Disaster Medicine.
Prof. Dafna Benayahu, Ph.D.
Department of Cell and Developmental Biology
Sackler Faculty of Medicine

Tel Aviv University
Email: dafnab@post.tau.ac.il

Musculoskeletal – Stem cells and Nanotechnology

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

Research
Our primary interest is the differentiation of skeletal stem cells and their fate. The research includes characterization of the muscle and bone stem cells at the cellular and molecular biology level. Bioinformatics is used along with gene profiling and identification of biomarkers networks to identify markers for stem cells. The ultimate goal of the research is to study how to improve stem cell functionality. Such knowledge will provide novel approaches to combat skeletal changes due to aging or metabolic disease. The use of stem cells is used also for tissue regeneration.

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


Shefer G, Rauner G., Yablonka-Reuveni, Z, Benayahu D, 2010. Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. PloS One 5:e13307


Review
Shefer G and Benayahu D. 2010. SVEP1 is a novel marker of activated pre-determined skeletal muscle satellite cells. Stem Cell Rev. 6:42-49
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 are 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


Grants

2011 - 2013, Effects of SUMO protease on developmental pathways with oncogenic potential, Israel Cancer Research Fund (ICRF)
Epidemiology of Infectious Diseases

Positions
Professor of Epidemiology and Preventive Medicine
Head, School of Public Health, Sackler Faculty of Medicine
Incumbent of Diana & Stanley Steyer Chair of Cancer Prevention and Control
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


Bisharat, N, A. Bialik, E. Paz, C. Amaro, D. Cohen. Serum antibodies to Vibrio vulnificus biotype 3 lipopolysaccharide and susceptibility to disease caused by the homologous V. vulnificus biotype. Epidemiol Infect. 2011;139:472-81.


Reviews


Grants

2011-2015 European Union, Development of vaccines against Shigella and enterotoxigenic E. coli enteric diseases. Leader of 2 WPs.
PARP Proteins in Health and Disease

Position
Associate Professor, Sackler Faculty of Medicine

Research
The general focus of our research is on signal transduction mechanisms implicating PARP (polyADP-ribose polymerase) proteins. PARPs are highly conserved proteins that are involved in a variety of processes, including epigenetic mechanisms, DNA repair, cell cycle and gene expression. PARP-1, the most abundant PARP protein, is activated by binding to single strand DNA breaks. Activated PARP-1 recruits ligases to the lesion, promoting DNA repair.

One of our contributions to this field was the discovery of alternative mechanisms activating PARP-1 in the absence of DNA breaks. This unveiled a variety of extra-nuclear signals activating PARP proteins in a variety of processes regulating gene expression.

We found that PARP-1 is a target of signal transduction mechanisms activated by intracellular Ca^{2+} mobilization or by the MEK-ERK phosphorylation cascade. Moreover, we found that ERK activity in the nucleus is highly up-regulated by activated PARP-1, implicating PARP-1 in ERK-dependent gene expression. Up-regulation of immediate early genes underlying long-term memory formation may underlie the pivotal role of PARP-1 in long-term memory formation during learning. Regulation of gene expression, controlling cell growth and development, may underlie the role of PARP-1 in neuronal remodeling and cardiomyocytes growth.

Recently, we found that a phenanthrene derived PARP inhibitor acts as an extra-centrosomes de-clustering agent, exclusively and efficiently eradicating human cancer cells by ‘mitotic catastrophe’ cell death, without impairing normal cells. Since many human cancer cells depend on extra-centrosomes clustering for their survival, this molecule is now used for developing a novel cancer targeting therapy.

Cell death by extra-centrosomes de-clustering in mitosis

http://www.biomedcentral.com/content/supplementary/1471-2407-11-412-s1.m4v

A depicted experiment describing ‘mitotic catastrophe’ cell death detected by overnight confocal imaging in multi-centrosomes human mammary cancer cells MDA-MB-231 treated with PARP inhibitor PJ-34. Cells were transfected by vectors encoding for g-tubulin-GFP (for labeling of centrosomes; green) and for histone H2B-RED (for labeling of chromosomes; red).

Publications


**Review**


**Grants**

2012-2014 ICRF- Human cancer cells exclusively eradicated by extra-centrosomes de-clustering.
Prof. Jiska Cohen-Mansfield, Ph.D.
Department of Health Promotion
Sackler Faculty of Medicine
Tel Aviv University
Email: jiska@post.tau.ac.il

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

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. (2013) Even with regular use of an observational scale to assess pain among nursing home residents with dementia, pain-relieving interventions are not frequently used. *Evid Based Nurs*. 2013 May 1. [Epub ahead of print]


**Chapters**


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

Position
Professor of Physiology, Sackler Faculty of Medicine

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

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, G\(\alpha\) and G\(\beta\)\(\gamma\) synergistically alter the conformation of GIRK1 subunit.
Publications


a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA* 110, E1685-1694.


**Grants**


2013-2016: Mechanisms of isoform-specific regulation of L-type Ca\(^{2+}\) channels by protein kinases. German-Israel Foundation (GIF), With S. Weiss and E. Klussmann.
Cell Replacement Therapy for Diabetes

Position
Professor, Sackler Faculty of Medicine
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.

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.

Publications


Reviews


Grants
2009-2013 Ex vivo expansion and redifferentiation of insulin-producing cells from human pancreatic islets, Israel Science Foundation (ISF)
2011-2014 Insulin-producing cells from iPS cells derived from human beta cells, Juvenile Diabetes Research Foundation (JDRF)
2011-2014 Beta-cell replacement by human islet beta cells expanded in vitro, Israel Science Foundation (ISF)
2012-2017 Stem cells for biological assays of novel drugs and predictive toxicology, Innovative Medicines Initiative (IMI)
2013 Development of diabetes cell replacement therapy, Grodman Cure Foundation:
2013-2017 Generation of human insulin-producing cells by redifferentiation of cells expanded from pancreatic islet beta cells through inhibition of the NOTCH pathway, Israel Science Foundation (ISF)
Cancer Related Inflammation in Tumor Progression and Metastasis

Position
Senior Lecturer, Sackler Faculty of Medicine

Research
Tumors are more than just cancer cells— the tumor microenvironment plays a crucial role in all stages of tumorigenesis. One of the hallmarks of all tumors is inflammation; chronic inflammation is highly correlated with many types of human cancer. The main interests of our lab are cancer-related inflammation and the role of the tumor microenvironment, and in particular, Cancer-Associated Fibroblasts (CAFs) in facilitating tumor initiation, progression and metastasis. We study these crucial aspects of cancer using genetically engineered mouse models of human cancer. Our aim is to uncover stromal pathways that contribute to tumorigenesis and metastasis in breast and ovarian cancer, and to identify novel targets for CAF-directed therapies.

Methodologies used include transgenic mouse tumor models, in vivo imaging, expression profiling, cell culture models, and immunohistochemistry.

![CXCL1, Cox-2, IL-6, H&E](image)

Tumor tissue sections from breast cancer patients were immunostained with antibodies for the pro-inflammatory factors CXCL1, COX-2, IL-6 or with Hematoxylin & Eosin, as indicated. Arrows indicate stained CAFs in the tumor stroma. T=tumor. S=stroma. Scale bar=50μM.

Publications


Reviews


Grants

2011-2014 The Marie Curie International Reintegration Grant (IRG), EU
2011-2014 Israel Cancer Research Fund (ICRF)
2012-2016 Israel Science Foundation (ISF) Grant: Characterizing Fibroblast-Mediated Inflammation in Breast Cancer Metastasis
Prof. Hagit Eldar-Finkelman, Ph.D.
Department of Human Molecular Genetics and Biochemistry
Sackler Faculty of Medicine
Tel Aviv University
Email: heladr@post.tau.ac.il
URL: http://www.tau.ac.il/~heldar/

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 inhibitor, L803-mts, produces anti-diabetic and anti-depressive effects in animal models. A recent work further indicated that L803-mts lowers beta amyloid burdens and improves cognitive deficits in an Alzheimer’s mouse model. Research methods employ cell biology, molecular biology and biochemistry disciplines, combined with bioinformatics, computational biology and drug design.

Treatment with L803-mts reduces beta amyloid burden in brain of an Alzheimer’s mouse model (Left). Computational model of L803-mts interaction with the catalytic core of GSK-3 (right).

Publications


Reviews


Grants

2010-2014, Exploring the distinct functions of the mammalian GSK-3 isoforms, Israel Science Foundation (ISF)
Modeling the Nervous System in Development and Disease Using Pluripotent Stem Cells

Position
Lecturer, Sackler Faculty of Medicine

Research
Our lab makes use of human embryonic stem cells in order to elucidate developmental programs in the human nervous system, with particular interest in neural stem cells (NSCs).

The NSC ontogeny dogma predicts that early developing NSCs are highly potent and can yield all nervous system cell types, but they rapidly lose this potential as development proceeds. Because NSCs behave similarly in culture, they are almost useless for studying differentiation to most neuronal cell types—a major impediment for understanding basic development and application to regenerative medicine.

Our main goal is to learn the biology of early neural stem cells in the lab in order to develop strategies for standardizing their growth in culture without loss of differentiation potential. Such continuously self-renewing cells will serve as a gold standard NSCs for studying nervous system development and disease, making cells for therapy and discovering novel drugs.

We use a variety of techniques in mouse and human embryonic stem cells and NSCs cells including transgenics (genetic labeling), viral expression of coding genes and microRNAs, classic stem cell assays, FACS-sorting and stem cell differentiation, and two-photon/confocal live cell imaging.

Human embryonic stem cells (Left panel) differentiate into NSCs (Middle and tight panels), which organize in a shape of rosettes. Neural rosettes have strong tight and adherens junctions, and are the earliest and most potent NSCs.
Publications


Grants

2011-2014  Fate Potential and plasticity of human embryonic stem cell derived neural stem cells. Israel Science Foundation (ISF).

2011-2014  Confocal/2-photon microscope system for 3D live cell imaging of neural stem cells. Israel Science Foundation (ISF).

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.

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 (2 left panels). Electron microscopy analysis demonstrates elevated formation of caveosomes in K562 cells responding to an ongoing immune attack (right).

Publications


Sexual dimorphism skeletal remodeling is well-established, although not completely understood. Recently, we have characterized two pathways with sex-specific influence on the skeleton. (1) Moderate fluctuations in Wnt signaling, a ubiquitous pathway with critical roles in bone formation and resorption, affect preferentially the female skeleton. (2) Deficiency in Krox20 in the monocytic/osteoclastic lineage results in a low bone mass phenotype in females only. The goal of my research group is to investigate the putative role of these pathways, as mediators of the sex-specific skeletal response to sex hormone signaling in osteoblasts (the bone forming cells) and in osteoclasts (the bone resorbing cells).

Figure 1: Low bone mass in Krox20-haploinsufficient females. μCT images of representative distal femoral trabecular bone of female and male Krox20+/+ (left) and Krox20+/− (right) mice.

Figure 2. Effect of haploinsufficiency in Lef1, a Wnt transcription factor. μCT analysis of the vertebral trabecular bone of female (left) and male (right) Lef1+/+ (black) and Lef1−/− (white) mice. AR<sup>tfm</sup> males have no functional AR, while AR<sup>tfm</sup> females are carriers for the defective AR allele. Data represent mean±SEM, * = p< 0.05. Note that only males carrying a functional AR are protected against Lef1 gene dosage.

Publications


Chapter

Grants
2012-2017 Israel Science Foundation (ISF) Grant
2013 Turnheim Foundation Research Grant, “Biomechanical evaluation of thermoplastic aligners by way of von Mises strains and stereolithography layers”, Co-PI
Proteomics of Breast Cancer Progression

Position
Senior Lecturer, Sackler Faculty of Medicine

Research
Our main interest is to understand the mechanisms of breast cancer progression. We are using state-of-the-art mass spectrometry-based proteomics to obtain a system-wide view of the tumor proteins. Analysis of the changes in protein levels and modifications that occur during tumor development is aimed to discover novel regulators of transformation. Combination of the proteomics technology with biochemical and genetic methods will show the significance of these candidates to cancer development and may suggest novel drug targets and tumor markers. Our laboratory opened at Tel Aviv University in October 2011.

Publications


<table>
<thead>
<tr>
<th>Year</th>
<th>Sponsor/Program</th>
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<tr>
<td>2013</td>
<td><strong>Stolz Foundation:</strong> Characterization of the proteomic changes that occur during breast cancer progression.</td>
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<td>2013</td>
<td><strong>Israel Cancer Association:</strong> Proteomic analysis of intratumoral heterogeneity in breast cancer.</td>
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<td>2012-2015</td>
<td><strong>Israel Cancer Research Fund (ICRF):</strong> Elucidation of regulatory networks in triple-negative breast</td>
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<td>2012-2016</td>
<td><strong>Israeli Center for Research Excellence (I-CORE):</strong> Gene Regulation in Complex Human Disease</td>
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<td>2012-2017</td>
<td><strong>Israel Science Foundation (ISF) Grant:</strong> The role of metabolic pathways in the regulation of breast cancer progression.</td>
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Neuronal Plasticity and Nerve Cell Protection in Disease

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 Alzheimer's disease and related neurodegeneration and utilizing a multidisciplinary approach, our group investigates 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). Small ADNF and ADNP derivatives are in clinical development. The lead compound, davunetide is being tested in a Phase II/III clinical trial targeting progressive supranuclear palsy, a fatal neurodegenerative disorder often misdiagnosed as Parkinson disease (www.allontherapeutics.com).

Publications


Dresner E, Agam G, Gozes I. Activity-dependent neuroprotective protein (ADNP) expression level is correlated with the expression of the sister protein ADNP2: deregulation in schizophrenia. *Eur Neuropsychopharmacol* 21:355-361.


Reviews


Grants
2007-2014 AMN Foundation
2011-2014 Muscular Dystrophy Association, Inc (together with Maria Pennuto) - consultant
2012-2015 Israeli Ministry of Science and Technology – New Models for ALS with Rivka Ofir
Pathobiology of Secretory Granule Packaging and Growth

Positions
Professor, Sackler Faculty of Medicine
Chair, Department of Pathology, Tel Aviv University
Academic Advisory Committee, ISEF Foundation
Academic Advisory Committee, Gazit-Globe Foundation

Research topics
Unit Granule formation

The classical model of secretory granule formation holds that proteins are transported from the RER to the Golgi zone where they can undergo post-transitional modification. They are then packaged for secretion by concentration within membrane-bound condensing vacuoles. The transportation of secretory proteins occurs in a vectorial way. The newly synthesized proteins in the RER are moved, probably via a vesicular transport, to the proximal side of the Golgi cisternae, the cis Golgi side. While moving through the Golgi cisternae the proteins undergo many modifications; most of the steps of which have not yet been resolved. The processed proteins are packed into vesicles that bud off the Golgi cisternae. The elucidation of this sequence of protein synthesis, packaging and secretion constitutes a major contribution to cell biology. It is well documented that granules in various cellular systems increase in size as time passes. For example, after degranulation is induced in either mast cells or mouse pancreatic acinar cells, granules start to accumulate. If the cell is not re-sensitized, the granule size distribution becomes broader and the mean granule size is increased. We have demonstrated that the unit granule volume is conserved; indicating that the granule size increase is probably due to homotypic fusion. The mechanism of polymerization is theoretically and experimentally investigated by us. It is found that two major mechanisms may lead to polymerization. The first one is defined as unit addition mechanism, while the second one is defined as a random addition process. In the unit addition mechanism polymer size may be increased only by the addition of a basic monomer $M_1 + M_n \rightarrow M_{1+n}$. Such a mechanism has a Poisson-like distribution. The alternative process, random addition mechanism, assumes that polymer of any size may react with any other polymer $M_m + M_n \rightarrow M_{m+n}$. The random polymerization has a geometric distribution and its main characteristic is that the smaller the polymer unit, the more frequent it is [$P(n)>P(n+1)$]. The monomer is the most frequent unit, whereas in a Poisson distribution the mean polymer size defines the value of the most frequent polymer as well. Using such an approach we have demonstrated that the pancreatic acinar cell and mast cell granule size distribution is better fitted to the unit addition model rather than the random addition model. The Chediak-Higashi syndrome is an example of a random mechanism of granule growth.
Protein movement within pancreatic acinar cells

Publications


Chapters


Brain Mechanisms of Human Emotion Generation & Regulation

Positions
Professor, Tel Aviv University
Director, Functional Brain Center, Cooperation of Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center and Levi-Edersheim-Gitter Institute for Human Neuroimaging, TAU
Steering Committee, I-CORE in Advanced Cognitive Science

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.

A frame from Intra- and inter-Network Cohesion Index (NCI) mapping, obtained from 16 healthy individuals while viewing a sad inducing movie clip (Stepmom). The trace on top presents continuous reported sadness intensity indicating that the frame depicts a moment of enhanced sadness (adapted from Raz et al Neuroimage 2012).
Publications


Chapters and Reviews


Grants
2011-2014 Euro-Active. Pre and intraoperative surgical advanced brain mapping capabilities, including multi-scale measurements of brain structure and function (consortium partner).
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

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 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.
Publications


Reviews


Grants

2010 The Bircher Benner Foundation: Identifying demographical and biological characteristics of historical populations via ancient DNA analysis

2011 Dan David Foundation: Qesem Cave Project
Intracellular Membrane Trafficking

Position
Senior Lecturer, 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 later, 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 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


Grants

2011-2013 Israel Cancer Association
2012-2015 German Israel Foundation (GIF)
2012-2016 Israel Science Foundation (ISF) Grant. Surface expression of proteins is regulated by sorting and selection in endoplasmic reticulum exit sites and in the Golgi apparatus
**Immunotherapy of Hematologic Malignancies**

**Positions**
Associate Professor, Sackler Faculty of Medicine
Associate Editor, *Frontiers in Immunotherapies and Vaccines*
Editorial Board, *Immunotherapy*

**Research**
Our research focuses on immunotherapy of hematologic cancers, particularly lymphoma and multiple myeloma. Its goal is to design personalized treatments that combine passive and active immunotherapy. To this end, we generate monoclonal antibodies and vaccines against tumor-specific antigens. We also generate novel bispecific antibodies against tumor antigens and adhesion molecules, antibodies that selectively block tumor metastasis. The effects of combined antibody treatment and vaccination on anti-tumor responsiveness (induction of immune responses and tumor rejection) are analyzed in vivo and in vitro, using methods such as fluorescence imaging of tumor-bearing mice, immunohistochemistry, antibody- and cell-mediated cytotoxicity assays, cell proliferation assays, cell migration assays, enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunospot assay (ELISPOT), and fluorescence-activated cell sorting (FACS).

Schematic presentation of our novel bispecific antibodies
Publications


Review


Grants

2012-2013 The Carol and Leonora Fingerhut Fund
Genetic Bases of Host Response to Infections and Chronic Diseases

Position
Associate Professor, Sackler Faculty of Medicine

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 involved of making some people resistant to a diseases 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 Peumonia.
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


Grants

2009-2013, European Systems Genetics Network for the study of complex genetic human diseases using mouse genetic reference populations, European Council, Co-PI: Klaus Schugart
Prof. Shai Izraeli, M.D
Functional Genomics and Childhood Leukemia Research
Cancer Research Center, Sheba Medical Center and Department of Human Molecular Genetics & Biochemistry
Sackler Faculty of Medicine

Tel Aviv University
Email: shai.izraeli@sheba.health.gov.il
http://eng.sheba.co.il/Research_and_Development/Research_Center_of_Leukemia/

**Basic and Translational and Research of Childhood Malignancies and Leukemia**

**Position**
Professor, Sackler Faculty of Medicine
Chair, MD-PhD program

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

Our research is divided into two major topics:
1. Basic, translational and clinical research of leukemia.
2. The role of SIL (STIL) protein in mitosis, centrosomal biology and cancer.

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

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

Publications


**Reviews**


**Grants**

2010-2013 National Institutes of Health (NIH)
2010-2013 Children with Cancer UK
2010-2013 USA Department of Defence (DOD)
2010-2013 Israel Cancer Research Foundation (ICRF)
2012-2015 Israel Science Foundation (ISF)
2012-2014 Swiss Bridge Foundation
Dr. Orit Karnieli-Miller, Ph.D.
Department of Medical Education
Sackler Faculty of Medicine

Tel Aviv University
Email: oritkm@post.tau.ac.il

**Studying Doctor-Patient Relationships, Communication and Medical Professionalism**

**Positions**
Senior Lecturer, Sackler Faculty of Medicine
Adjunct Assistant Research Professor of Medicine, Department of Internal Medicine, Indiana University, Indianapolis, USA

**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**


Reviews


Grants

Translational Research on the Development of Cancer Treatment Modalities

Positions
 Professor, Sackler Faculty of Medicine
 Roberts-Guthman Chair in Immunopharmacology
 Secretary, Israeli Society for Cancer Research

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 immunostimulatory 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 and 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 and Astronomy), is based on insertion into the tumor of radioactive wires which spread in the tumor alpha emitting atoms (Diffusing Alpha-emitters Radiation Treatment – DaRT). This treatment 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. It is postulated that the immunological response can be further amplified by the use of immune response modifiers.

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).
Publications


Grants

2011-2014, In situ ablation of primary tumors to induce anti-tumor T-cell reactions and neutralize immunosuppressive tumor microenvironment. German-Israeli Foundation (GIF), Co-PI, Viktor Umansky.
Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

Positions
Associate Professor, Sackler Faculty of Medicine
Chair, Department of Physiology and Pharmacology

Research
Calcium (Ca\(^{2+}\)) is a major regulator in the living cell. In many cell-types the Na\(^{+}/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 biogenesis, 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 dysfunction. 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


Reviews


Grants
Fields Center of Molecular Cardiology 2013-2017
Israel Science Foundation 2010-2014
USA-Israel Binational Science Foundation 2010-2014
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.

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.

Publications


Reviews

Prof. Rafi Korenstein, Ph.D.
Department of Physiology and Pharmacology
Sackler Faculty of Medicine
Tel Aviv University
Email: korens@post.tau.ac.il

Interaction of Nanomaterials and Electromagnetic Fields with Cells

Positions
Professor, 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
Director, Marian Gertner Institute for Medical Nanosystems, Tel Aviv University

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).

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

Publications


Grants
Theoretical Biophysics of Membranes and Cytoskeleton

Position
Professor of Biophysics, Sackler Faculty of Medicine

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 Endoplasmaic 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.

Figure legend: Computational results for membrane curvature generation by amphipathic N-terminal helices of N-BAR domains, ENTH domains and small G-proteins.

Figure legend: 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

Reviews

Grants
2011-2015 The Israel Science Foundation (ISF), Membrane Shaping by Proteins
2009-2013 Marie Curie (EC), Virus Entry
Pancreas Development and Function: 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 another pancreatic cell population, the mesenchymal cells. Our results indicate the pivotal role of mesenchymal cells in the regulation of insulin secretion, and blood glucose levels. Using transgenic mouse models, we study how mesenchymal cells and insulin-producing cells communicate with one another, 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 mesenchymal and other pancreatic cell types in both healthy and diseased mouse models.

Mesenchymal cells in the embryonic and adult pancreas. A) Mesenchymal cells (green) surround the developing pancreatic bud (red and blue) and support normal organogenesis. B) Mesenchymal cells (green) form a network around the Islet of Langerhans (gray) in the adult pancreas. The islets organize pancreatic endocrine cells, including insulin-producing beta-cells.
Publications


Grants
2012 - 2016 Marie Curie Career Integration grant (CIG), *Cellular composition of the pancreas: elucidating the role of mesenchymal signaling pathways*

2013 - 2018 European Research Council (ERC), *β-cell Dysfunction in Diabetes: Elucidating the Role of Islet-Associated Mesenchymal Cells*
microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position
Senior Lecturer, 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


Reviews


Grants

2011-2013 ICRF grant, US
2011-2014 Marie Curie CIG Reintegration Grant, EU
<table>
<thead>
<tr>
<th>Year</th>
<th>Award/Grant</th>
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<tr>
<td>2012-2013</td>
<td>Carol Award</td>
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<td>2012-2014</td>
<td>BSF grant: Identifying novel miRNA signatures that contribute to melanomagenesis and developing associated targeted delivery systems (with Dr. Michael Goldberg, Harvard)</td>
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<td>2012-2014</td>
<td>Israel Cancer Association Award (ICA)</td>
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<td>2012-2015</td>
<td>Fritz Thyssen Stiftung</td>
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<td>2012-2016</td>
<td>Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease</td>
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Genetic and Metabolic Research of Age-Dependent Chronic Degenerative Disease

Positions
Professor, Sackler Faculty of Medicine
Chair, Department of Anatomy and Anthropology
Director, Yoran Institute for Human Genome Research, Sackler Faculty of Medicine
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 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.

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 Livshists et al 2011, Ann Rheumat Dis.
Publications


Yulia Vistoropsky, Sergey Ermakov, Mohammed Toliat, Svetlana Trofimov, Janine Altmüller, Ida Malkin, Peter Nürnberg, Gregory Livshits. Genetic determinants of circulating levels of Tumor Necrosis Factor Receptor II and their association with TNFRII gene variants. Cytokine 2010; 51: 28-34.


Anna Leonov, Svetlana Trofimov, Sergey Ermakov, Gregory Livshits. Quantitative genetic study of amphiregulin and fractalkine circulating levels - potential markers of arthropathies. Osteoarthr & Carti, 2011; 19:737-742

Gregory Livshits, Maria Popham, Ida Malkin, Philip N. Sambrook, Alex J MacGregor, Timothy Spector, Frances M.K Williams. Degenerative disc disease and genetic predisposition are the main risk factors for low back pain in women: The UK Twin Spine Study (TUTSS). Ann Rheumat Dis 2011; 70:1740-1745


Liran Franco, Frances MK Williams, Svetlana Trofimov, Tim D Spector, Gregory Livshits. Contribution of putative genetic factors and candidate gene variants to inter-individual variation of circulating fractalkine (CX3CL1) levels in a large UK twins' sample. Human Immunology, 2013; 74:358-63.

Liran Franco, Frances MK Williams, Svetlana Trofimov, Tim D Spector, Gregory Livshits. Elevated plasma fractalkine levels are associated with higher levels of IL-6, Apo-B, LDL-C and insulin, but not with body composition. Metabolism, 2013; 62:1081-87.


Grants

2010-2013 Genetic Epidemiological Study of Sarcopenia Associated Phenotypes in the General Human Population, Israel Science Foundation (ISF)
Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

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 $\beta$ 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.

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.

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

Review

Grants
2010-2013 United States-Israel Binational Foundation (BSF) - Role of the Kv2.1 potassium channel cytoplasmic C-terminus in insulin secretion (Co-PI with Professor Louis Phillipson, USA).
2010-2013 The Israel Academy of Sciences and Humanities - Enhancement of exocytosis by the Kv2.1 potassium channel.
Dr. Chen Luxenburg, Ph.D.
Department of Cell & Developmental Biology
Sackler Faculty of Medicine

E-mail: ilotan@post.tau.ac.il
Brain@tau: neuroscience.tau.ac.il/

**The Mechanobiology of Tissue Development Homeostasis and Disease**

**Position**
Senior Lecturer, Sackler Faculty of Medicine

**Research**

Many biological processes such as cell migration and division require mechanical forces. However, similar to chemical cues, mechanical forces also play a key regulatory role that affect many additional key biological processes. Therefore, it is not surprising that changes in the mechanical properties of tissues contribute to the development of common diseases.

Our lab uses the mouse skin epidermis as a model system to study how mechanical and geometrical cues regulate morphogenesis, affect gene expression and contribute to cell fate determination during development, homeostasis and disease. The skin is an ideal model system for these studies for the following reasons: 1) the skin is a mechano-sensitive organ, capable of sensing and responding to mechanical signals. 2) Defects in the mechanical and geometrical properties of epidermal cells are among the hallmarks of common skin diseases including cancer and psoriasis. 3) The epidermis can easily and rapidly be manipulated genetically *in vivo*, making it a tractable model system to discover novel genes and study their function.

Left hand side: On top of classic mouse genetic tools 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.

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 \textit{in vivo} and \textit{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.

\textbf{Publications}

\textbf{Luxenburg C}, Heller E, Pasolli HA, Chai S, Stokes N, and Fuchs E Wdr1 mediated cell shape dynamics and cortical tension are essential for epidermal planar cell polarity (submitted)


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


**Review**


**Grants**

2013-2015  FP7-PEOPLE-2012- MARIE CURIE CAREER INTEGRATION GRANTS (CIG)
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.

Publications


Reviews


Grants

2013 – 2018 I-CORE Cognitive Neuroscience
Human Mold Infections

Positions
Associate Professor, Sackler Faculty of Medicine
Chair, Department of Human Microbiology and Immunology
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.


Levdansky E, Kashi O, Sharon H, Shadkchan Y, Osherov N. The *Aspergillus fumigatus* cspA gene encoding a repeat-rich cell wall protein is important for normal conidial cell wall architecture and interaction with host cells. Eukaryot Cell. 2010, 1403-15


Reviews


Grants
ISF 2009-2013 Israel Science Foundation
BSF 2012- 2016 Binational Science Foundation
Host-Virus Interactions in Bacterial Systems

Position
Senior Lecturer, 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


**Grants**

2010-2013  Israel Science Foundation Grant

2010-2014  ERC Marie Curie IRG Grant

2012-2013  Sackler Research Funds Award

2012-2014  KAMIN – Ministry of Industry and Commerce, Grant for Novel Innovations

2013-2018  ERC Starting Grant
Prof. Drorit Neumann, Ph.D.
Department of Cell and Developmental Biology
Sackler Faculty of Medicine

Tel Aviv University
Email: histo6@post.tau.ac.il
http://neumann.mytau.org/

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

Positions
Professor, Sackler Faculty of Medicine
Chair, M.Sc. Studies, 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 we made a novel, original discovery, together with Prof. Mittelman from the Sourasky Medical Center, 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. The studies are based on a variety of in-vitro and murine experimental models, and include also an avenue of elucidating the relevance and possible clinical application of the results.

Publications
Liron T., T. Nahari, M. C. Souroujon and D. Neumann. Insertion of an NPVY sequence into the cytosolic domain of erythropoietin receptor selectively affects erythropoietin mediated signaling.
and function. Biochem. J. 427:305-312 (2010) *Selected by Faculty of 1000:
http://www.f1000biology.com/article/id/3771958/evaluation

nitrogenous macrolides from the madagascar sponge Fascaplysinopsis sp. Tetrahedron 66, 4339–
4345 (2010)

Lifshitz L., G. Tabak, M. Gassmann, M. Mittelman, and D. Neumann. Macrophages as novel

Ben-Califa N., A. Bishara, Y. Kashman and D. Neumann. Salarin C, a member of the salarin
superfamily of marine compounds, is a potent inducer of apoptosis. Invest. New Drugs 30:98-104
(2012)

Yosha L., O. Ravid, N. Ben-Califa, and D. Neumann. Cytosolic lysine residues enhance
anterograde transport and activation of the erythropoietin receptor. Biochem. J. 435:509-518
(2011)

Inbar D., M. Cohen-Armon and D. Neumann. Erythropoietin driven signaling and cell migration

Erythropoietin treatment is associated with an augmented immune response to the influenza

Chapters and Reviews

Mittelman M., H. S. Oster, M. Hoffman and D. Neumann. The lower risk MDS Patient a risk of
rapid progression Leukemia Research 34:1551-555 (2010)


Grants

2010 – 2013, Israel Science Foundation, Molecular mechanisms regulating erythropoietin receptor
metabolism and function

2010 – 2014, Bi-National Science Foundation, together with Constantinos Koumenis U. Penn.
Erythropoietin Receptor Metabolism and Function Guided by Hypoxia and by the Unfolded Protein
Response

2011 - 2012, Multiple Myeloma Foundation, Erythropoietin as an anti-Multiple Myeloma
Immunomodulating Agent

sage on the Epoetins’ saga: assessing long term risks and advancing towards better Epoetin driven
treatment modalities – Acronym: EpoCan, Proposal No: 282551
Regulatory Mechanisms in Mucosal Inflammation

Position
Senior Lecturer, Sackler Faculty of Medicine

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.

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).

Publications


Reviews and Chapters


Stein M, Munitz A. Targeting interleukin 5 in asthma and hypereosinophilic syndromes. Recent Pat Inflamm Allergy Drug Discov. 2010:4:201-209.


Grants

2013-2016, Fritz Thyssen Stiftung, The role of IL-13Rα1 in pulmonary fibrosis

2012-2013, Djerassi-Elias Institute of Oncology Dream Ideas Grant, Paired Immunoglobulin like-receptor B regulates macrophage activation in colorectal cancer

2012-2016, The US-Israel Binational Scientific Foundation (BSF), The expression and function of paired immunoglobulin-like receptor B in eosinophils

2011-2015, The Israel Science Foundation (ISF), Expression and function of CLM-1 in eosinophils

2011-2013, The Israel Cancer Research Fund (ICRF), The Role of Paired Immunoglobulin-Like Receptor B (PIR-B) in Colorectal Cancer

2010-2014, The Marie Curie FP7 Reintegration Grant, Resistin-like molecules in lung inflammation
Dr. Chava Peretz, Ph.D.
Department of Epidemiology
School of Public Health
Sackler Faculty of Medicine
Tel Aviv University
E-mail: cperetz@post.tau.ac.il

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


**Grants**

2010 - 2013 Ministry of Environmental Protection

2012 - 2013 Maccabi Healthcare Services

2013 - 2014 Teva National Network of Excellence (NNE) in Neurosciences, Student Scholarship
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 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.

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.

In-vitro microfluidic platform with motor neuron cell bodies on one side and muscle cells on the other, creating a powerful system to study neurodegeneration mechanisms.
Publications

Reviews

Grants
2010-2014 Retrograde signaling, Marie Curie International Reintegration Grants (IRG)
2011-2015 ISF (Israel Science Foundation), The dual role of dynein in GDNF signaling
2011-2014 Molecular Mechanisms of Neurodegeneration in ALS, Legacy Heritage Biomedical Science Partnership
2011-2014 Molecular Mechanisms of Rabies Virus Transport, GIF, (German-Israeli Foundation).
2012-2014 Young BSF grant, Novel Screen for Axonal Transcriptomes and non-coding RNAomes along the process of Motor Neuron Death, Axon Degeneration and Neuromuscular Junction Disruption Occurring in Amyotrophic Lateral Sclerosis, with Dr. Dianna Willis, Burke Medical Research Institute, Weill Medical College, Cornell University
2012-2015 Small molecule screen for neuromuscular junction maintenance, Rosetrees Trust
2012-2017 Molecular Communication Mechanism of Motor Neuron Survival and Synapse Maintenance, European Research Council (ERC) Starting Grant
Brain Injuries: Cognitive, Behavioral and Cellular Outcome

Position
Professor, Sackler Faculty of Medicine

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


Edut S., Rubovitch, V., Schreiber, S., Pick C.G. The intriguing effects of ecstasy (MDMA) on cognitive function in mice subjected to a minimal traumatic brain injury (mTBI). *Psychopharmacology* 214: 877-889 (2011).


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

Position
Professor Emeritus, Sackler Faculty of Medicine

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; the development of the first cell-free system of ROS production; the discovery of the cytosolic oxidase components; the discovery of the role of the small GTPase Rac in oxidase activation; the introduction of "peptide walking" to identify sites of protein-protein interaction, and the construction of chimeric cytosolic oxidase activators. The laboratory is fully 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 p67phox. 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 p67phox. This finding is based on a novel methodology, designed by us, in which we measure the binding of recombinant p67phox to an array of synthetic overlapping peptides covering the sequence of the dehydrogenase region of Nox2. Two Nox2 peptides which share the CGC triad, at their C- and N-termini, respectively, were found to bind p67phox. "Mutating" either C369 or C371 to R resulted in loss of p67phox 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 p67phox to the catalytic component of the NADPH oxidase complex is redox regulated and involves the establishment of disulfide bonds between p67phox and Nox2. The CGC triad might have a double role by acting both as a protein disulfide isomerase (PDI) and by providing the cysteines for the establishment of disulfide bonds with p67phox. This novel hypothesis rests on the evidence that the CGC motif mimics functionally and structurally the CGPC catalytic site of members of the PDI family. 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.
Schematic representation of the stabilization of binding of “activated” p67\textsubscript{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.

Publications

**Pick, E.** When charge is in charge - "Millikan" for leukocyte biologists. *J. Leukoc. Biol.* 87, 537-540, 2010

Mizrahi, A., Berdichevsky, Y., Casey, P. J., and **Pick, E.** A prenylated p47\textsubscript{phox}-p67\textsubscript{phox}-Rac1 chimera is a quintessential NADPH oxidase activator. Membrane association and functional capacity. *J. Biol. Chem.* 285, 25485-25499, 2010


**Pick, E.**, and Dahan, I. Strategies for identifying synthetic peptides to act as inhibitors of NADPH oxidases, or "All that you did and did not want to know about Nox inhibitory peptides". *Cell. Mol. Life Sci.* 69:2283-2305, 2012


Dahan, I., Molshanski-Mor, S., and **Pick, E.** Inhibition of NADPH oxidase activation by peptides mapping within the dehydrogenase region of Nox2-A “peptide walking” study. *J. Leukoc. Biol.*, 91:501-515, 2012

Dahan, I., and **Pick, E.** Strategies for identifying synthetic peptides to act as inhibitors of NADPH oxidases, or "All that you did and did not want to know about Nox inhibitory peptides". *Cell. Mol. Life Sci.* 69, 2283-2305, 2012

Chapters and reviews


Grants

2009-2014 The pivotal encounter in NADPH oxidase activation – The molecular mechanisms of Nox2 – p67\textsubscript{phox} interaction, Israel Science Foundation

2013-2017 Assembly of the phagocyte NADPH oxidase complex, Israel Science Foundation

2008-2013 The molecular mechanisms of NADPH oxidase assembly, The David and Natalie Roberts Fund
Investigating Normal and Deficient Visual Functions

Position
Associate Professor, Sackler Faculty of Medicine

Research
Our research focuses on function, development and plasticity of perceptual interactions in normal and abnormal visual cortex. In our research, we have revealed a unique pattern of neural interactions, both excitatory and inhibitory, underlying global behavior involved in contour integration and texture segmentation. Specifically, a network of long-range intra-cortical connections supporting integration of collinear elements of the visual input is characterized beyond its spatial properties, especially emphasizing the temporal dynamics. Using of training protocols based on spatial and temporal masking paradigms is another area of interest. Studies on the effects of perceptual learning on visual function are conducted, including cases of abnormal visual development, considered as untreatable, such as amblyopia.

The laboratory combines techniques such as psychophysics, visual evoked potentials (VEP), event-related potentials (ERP) and eye movement recording. Computational modeling of neural networks of long-range interactions provides theoretical framework for our empirical findings.

Ongoing studies:

Clinical: Amblyopia, Major depression, ADHD, Pharmacological effects on vision, Vision in eye diseases

Development: Visual acuity, Contrast sensitivity, Lateral interactions, Visual crowding, Contour integration, Visual grouping

Learning: Learning to see faster, Improvement of normal vision, Improvement of impaired vision, Adaptation vs. learning, Visual rehabilitation, Refraction plasticity, Visual Performance


Publications


**Grants**

2010-2013 USA-DOD A Behavioral Treatment for Traumatic Brain Injury – Associated Visual Dysfunction Based on Adult Cortical Plasticity

2010-2014 ISF From local to global: a spatio-temporal theory for visual integration
Molecular Mechanisms of Drugs for Neuropsychiatric Disorders

Positions

Professor, Sackler Faculty of Medicine
Dr. Miriam and Sheldon G. Adelson Chair in Biology of Addictive Diseases
Head, Varda and Shalom Yoram Institute for Human Genome Research

Research

Main projects in the lab include:

1. Presynaptic monoamine transportes and the vesicular monoamine transporter as targets for neuropsychiatric drugs.
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.

(A) Six representative coronal slices of T2-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.

**Publications**


**Grants**

2011-2015 Novel herbal treatment for anxiety disorder, Israel Science Foundation
Dr. Laura (Leah) J. Rosen, Ph. D.
Department of Health Promotion
School of Public Health
Sackler Faculty of Medicine

Tel Aviv University
Email: rosenl@post.tau.ac.il

Improving Public Health, and Control Tobacco Use and Exposure

Positions
Senior Lecturer, Sackler Faculty of Medicine
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,
Chair, Tobacco Control Subcommittee, Healthy Israel 2020 (Ministry of Health initiative)

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, 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.

Publications

Rosen L, Ben Noach M, Rosenberg E. Missing the forest (plot) for the trees? A critique of the systematic review in tobacco control. BMC Medical Research Methodology 2010, 10:34.


Grants

2008-2013. Intervention to prevent young child exposure to tobacco smoke. Flight Attendant Medical Research Institute. (PI)
Dr. Rina Rosin-Arbesfeld, Ph.D.
Department of Clinical Microbiology and Immunology
Sackler Faculty of Medicine

Tel Aviv University
E-mail: arina@post.tau.ac.il

The Wnt Signaling Pathway and Colorectal Cancer

Position
Senior Lecturer, Sackler Faculty of Medicine

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.

Publications


**Grants**

2009 – 2013 The Israel Science Foundation (ISF)

2011 – 2013 German-Israeli Foundation (GIF)

2011 – 2013 The Israel Ministry of Science

2011 – 2013 Israel Cancer Association (ICA)

2011 – 2015 The US-Israel Binational Scientific Foundation (BSF)

2012 – 2013 The Singer Norbert Research Fund
Computational Analysis of Metabolic Alterations in Cancer and Aging

Positions
Professor, Sackler Faculty of Medicine
Co-chair, TAU Bioinformatics Training Program
Joint appointment, Blavatnik School of Computer Science

Research
Our research focuses on computational biology with an emphasis on metabolic modeling. Our lab is currently working on the development and study of large-scale models of metabolism in a variety of human tissues, in both healthy and disease states. Our efforts are focused on two main subjects: (1) We have generated the first model of cancer metabolism. This development has paved the way for the first large-scale computational search for new and selective metabolic drug targets in cancer (Nature/MSB 2011) – some which are already under various stages of further experimental testing and validation (Nature 2011). (2) We have recently developed a new approach for inferring drug target for extending life span in humans (anti-aging), which are currently under experimental investigation. Taken together, these studies and others ongoing in the lab offer new ways for harnessing computers to advance our understanding of metabolically-related human disorders, and further our ability to diagnose and treat them in a rationale-designed manner.

Metabolic drug targets (x-axis) that are predicted to selectively kill cancer cells of different types (y-axis).
Publications

Y. Waldman, T. Geiger, **E. Ruppin**. A genome-wide systematic analysis reveals different and predictive proliferation expression signatures of cancerous vs. non-cancerous cells. PLoS Genetics, in press.


Metabolic modeling of endosymbiont genome reduction on a temporal scale.(K. Yizhak, T. Tuller, B. Papp, E. Ruppin), Molecular Systems Biology (MSB), 7, article number 479, 2011.


Reconstructing ancestral genomic sequences by co-evolution: formal definitions, computational issues and biological examples. (T. Tuller, H. Birin, M. Kupiec, E. Ruppin), Journal of Computational Biology (JCB), 17(9), 1327-1344, 2010.


Translation efficiency is determined by both codon bias and folding energy. (T. Tuller, Y. Waldman, M. Kupiec, E. Ruppin), Proceedings of the National Academy of Sciences, 2010.


Review


Grants

2009-2013 Microme EU grant for modeling microbial metabolism
2009-2013 Israeli Science Foundation (ISF) grant for studying liver metabolism
2011-2014 Ministry of Science and Technology (MOST) grant for studying plant metabolism
2011-2015 US-Israeli Binational Science Foundation (BSF) for studying human host-pathogen metabolic interactions in the gut
Molecular Basis of Allergic Diseases: Genomic and Functional Analyses

Positions
Professor, Sackler Faculty of Medicine
Chair, Scholarship Committee, Graduate School of Medicine

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.

Publications


Review


Grants

2012-2013 Tel Aviv University- Faculty of Medicine, Systems analyses of mast cell activation patterns in response to tumor insults.

2012-2015 The Israel Science Foundation, Dissecting the molecular mechanisms underlying mast cell exocytosis; new insights provided by the small GTPase Rab5
Angiogenic Switch Using Rationally-Designed Theranostic Nanomedicines

Positions
Associate 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
Editorial board member, Advanced Drug Delivery Reviews
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, NMR, HPLC, in situ hybridization, bioinformatics, polymer chemistry, molecular imaging, angiogenesis assays, animal models of cancer (human xenografts in mice, syngeneic and transgenic mice models), pharmacokinetics and pharmacodynamics.

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.
Publications


Reviews


Chapters


Grants

2010-2014 Israel Science Foundation (ISF) grant (1309/10): “Anti-angiogenic polymer therapeutics to target bone neoplasms”.

Sackler Faculty of Medicine
2011-2014 Swiss Bridge Award: "Deciphering the molecular mechanism of tumor dormancy using bone-targeted polymer therapeutics".

2011-2014 The Association for International Cancer Research (AICR): "In vivo targeting of Akt1siRNA to tumors and their stroma".

2011-2014 German-Israel Foundation (GIF): siRNA delivery to brain tumors" (German collaborator: Rainer Haag, Frei University Berlin)

2012-2014 Sheba Medical Center - Tel Aviv University Grant: "Targeting NCAM-expressing cancer stem cells with nano-scaled polyglutamic acid-doxorubicin-peptide conjugate". (Co-PI: Benjamin Dekel, Sheba Medical Center)

2012-2016 MAGNET Rimonim Consortium, Office of the Chief Scientist of the Ministry of Industry, Trade & Labor: "siRNA delivery to ovarian cancer".

2012-2017 Israel National Nanotechnology Initiative (INNI), Focal Technology Area in nanotechnology, "Theranostic Nanomedicines for Personalized Medicine"
Novel Antioxidant and Stem Cells for Treatment of Degenerative Diseases

Positions

Professor, Sackler Faculty of Medicine
Director, Goldschleger Eye Research Institute
Chair, Maratier Institute for the Study of Blindness & Visual Disorders

Research

We are developing treatments for degenerative diseases of the eye and nerve system utilizing novel antioxidant and stem cells. The research involves cell biology tools and animal models.

The following specific subjects are studied:

- Development of a new reagent up-regulating the antioxidant cellular mechanisms that increases the protective capacity of cells against reactive oxygen species. The main target of this reagent is attenuation of neural system and retina degenerative diseases.

- Preparation of differentiated stem cells for the prevention of glaucoma induced retinal ganglion cell degeneration and age related macular degeneration (AMD).

Publications


**Grants**

2012 – 2013 Mordechai Ofer Fund for Medical Research, Sackler Faculty of Medicine.

2013 – 2014 Baharv Fund for Glaucoma Research, Sackler Faculty of Medicine.
Prof. Ruth Shalgi, Ph.D.
Department of Cell and Developmental Biology
Sackler Faculty of Medicine

Reproduction in Animal Models and in Humans

Positions
Professor, Sackler Faculty of Medicine
Gabriel Pinkas Chair for the Prevention and Diagnosis of Congenital Anomalies
Chair, Faculty Search Committee
Executive Committee, Open University, Member

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.
- The role of Interleukin-1alpha in reproductive aging and in chemotherapy-induced exhaustion of ovarian follicular pool.

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.

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.
Publications


Reviews


**Grants**

2009-2013  Israel Science Foundation (ISF) - Role of Fyn kinase in meiosis of mammalian oocytes

2010-2014  Binational Science Foundation (BSF) - Does acid Ceramidase regulate the fate of female germ cells and somatic cells?


2011-2013  Israel Cancer Foundation (ICA) - Chemotherapy-induced gonadal toxicity - the role of vascular impairment

2013-2014  Bayer Healthcare Pharmaceuticals - A physiological approach for treating endometriosis by recombinant pigment epithelium-derived factor (PEDF)
Position
Professor, Sackler Faculty of Medicine

Research
The main subject of interest currently in my laboratory is the subject of neuroprotection, finding the means to protect the brain against all kinds of injurious events such as stroke, ischemia and neurodegenerative diseases. Our laboratory is focusing on deciphering the mechanism of activation of endogenous protective mechanisms. Of special interest is the mechanism of the phenomenon termed “preconditioning”. By this mechanism, exposure of the brain to low, sublethal dose of injurious conditions or substances preconditions the brain to resist a subsequent lethal exposure to damaging conditions. The preconditioned brain activates signal transduction pathways leading to enhanced synthesis of protective proteins. Understanding the preconditioning mechanism will enhance the development of drugs that will activate when necessary neuroprotection against stroke and other similar devastating injurious conditions. Presently our research is focused on the phenomenon of NMDA preconditioning. NMDA activates specifically one type of the ionotropic glutamate receptors (NMDA receptors). In presence of excessive glutamate concentration, these receptors mediate much of the neuronal damage, due to excitotoxicity, but at moderately elevated, yet sublethal glutamate concentration, glutamate stimulates the NMDA receptors inducing the activation of the protective NMDA preconditioning mechanism. NMDA preconditioning is one of the most important neuroprotective preconditioning mechanisms. This protective mechanism is involved in many of the various other preconditioning mechanisms, such as the ischemic preconditioning. We are now in the midst of deciphering the involvement of several signal transducing proteins in the protective mechanism.

Publications

Navon, H., Bromberg, Y., Sperling, O., Shani, E., Neuroprotection by NMDA preconditioning against glutamate cytotoxicity is mediated through activation of ERK 1/2, inactivation of JNK and by prevention of glutamate-induced CREB inactivation. J Mol Neurosci, 2012; 46:100-8.

Grants
2011-2012 The Herman Shouder Research Fund, Sackler Faculty of Medicine, Tel Aviv University.
Transforming Functions of Human Papillomaviruses

Position
Professor, Sackler Faculty of Medicine

Research

Research in my laboratory focuses on the study of human papillomaviruses (HPVs) and their role in the development of anogenital and skin cancer. Employing various biochemical and molecular biology tools, epithelial cell culture models and immunofluorescence techniques, our studies aim at elucidating the molecular mechanism(s) by which HPVs contribute to epithelial cell transformation. The major topics under investigation are: 1. Inhibition of human keratinocyte terminal differentiation by the E6 oncoprotein. 2. Role of HPV polymorphism in cervical carcinogenesis. 3. Augmentation of the Wnt/β-catenin signaling pathway by the E6 oncoprotein. 4. Transforming activities of the E6 and E7 genes of cutaneous human papillomavirus. 5. Novel anticancer agents for cervical cancer and modulation of their activity by the HPV oncoproteins.

1. HPV16 E6 variants differ in their ability to induce differentiation resistant colonies in human keratinocytes.
2. HPV 16 E6 dysregulates keratinocyte differentiation induced in organotypic cultures. Immunofluorescence for basal cell keratinocyte marker, K5, suprabasal cell marker, K10, the overlay of both and H+E staining. 3. HPV16 E6 does not alter cellular localization of β-catenin.

Publications


Grants
2010-2014 Augmentation of the Wnt/β-catenin signaling by the E6 oncoprotein: Role of the ubiquitin ligase E6AP and biological significance, Israel Science Foundation
2011-2013 Alteration of keratinocyte differentiation by E6 and E7 proteins of cutaneous HPV types, Israel Ministry of Health
The ATM-Mediated DNA Damage Response

Positions
Professor, Sackler Faculty of Medicine
David and Inez Myers Chair in Cancer Genetics

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


Reviews


Book Chapter


Grants

2011-2015 Israel Science Foundation: The ATM and WRN Proteins at the Crossroads of Genomic Stability, Cancer and Aging

2011-2015 German-Israel Foundation for Scientific Research and Development: UBE4B: A New Player in the Interface between the Ubiquitin Arena and the DNA Damage response
Dr. Noam Shomron, Ph.D.  
Department of Cell and Developmental Biology  
Sackler Faculty of Medicine  
Tel Aviv University  
Email: nshomron@post.tau.ac.il  
URL: http://www.tau.ac.il/~nshomron

Gene Regulation by Small RNAs

Positions
Senior Lecturer, Sackler Faculty of Medicine  
Director, Functional Genomics Laboratory  
Academic Director, BioAbroad  
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


Reviews

Grants
Israel Cancer Research Foundation Earlier.org - for Early Detection of Breast Cancer
2011-2014 Wolfson Family Charitable Fund, Functional Genomics Center for Complex Diseases, Lead PI (representing 20 co-PIs)
**Prof. Ella Sklan, Ph.D.**  
Department of Clinical Microbiology and Immunology  
Sackler Faculty of Medicine

Tel Aviv University  
E-mail: sklan@post.tau.ac.il

**Viral Host Interactions of Positive Strand RNA Viruses**

**Position**  
Associate Professor, 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 Hepatitis C virus (HCV) and Dengue virus. 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 HCV assembly.

**Publications**


Grants
2012-2016 Israel Science Foundation (ISF) Grant
Dr. Inna Slutsky, Ph.D.
Department of Physiology and Pharmacology
Sackler Faculty of Medicine
Tel Aviv University
Email: islutsky@post.tau.ac.il

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

Positions
Senior Lecturer, Sackler Faculty of Medicine
Committee Member, IBRO
Scientific Advisory Council Member, American Federation for Aging Research (AFAR)
Organizing Committee Member, Israel Society for Physiology and Pharmacology
Committee Member, Sagol School of Neuroscience, TAU
Committee Member, Center for Nanoscience and Nanotechnology, TAU

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


Grants


2010 – 2014, Interactions Between Presynaptic GABA(B) and Muscarinic Receptors: From Multicomplex formation to Regulation of Synaptic Filter, Binational Science Foundation (BSF).
Prof. Arieh S Solomon, M.D., Ph.D.
Goldschleger Eye Research Institute
Department of Ophthalmology
Sackler Faculty of Medicine
Sagol School of Neuroscience
Tel Aviv University
E-mail: asolomon@post.tau.ac.il

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


Grants
2012-2013 Baharav Research Grant
2012-2014 WP7 EC VISION
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 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 orthotopically 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 reduce 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


Review


Grants (last 3 years)

2010 – 2014 BSF, The Interplay between Tumor Cell Glucose Metabolism and Met Tyrosine Kinase Growth Factor Receptor Signaling as a Target for Anti Tumor Therapy

2010 – 2015 Sackler Foundation, Establishment of the Tel Aviv University Sackler Cellular and Molecular Imaging Center (SCMIC)
**Molecular Biology of the Insulin-Like Growth Factor System**

**Positions**
Professor, Sackler Faculty of Medicine  
Lady Davis Chair in Biochemistry  
Chair, Department of Human Molecular Genetics and Biochemistry  
Vice Director, MD Graduate Program, Sackler School of Medicine

**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**


Reviews


Grants


2013-2014 “Genome-wide identification of cancer-protecting pathways in Laron syndrome: data mining a rare disease translates into new discoveries in oncology”. Cancer Biology Research Center, Tel Aviv University
Steyer School of Health Professions
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Sackler Faculty of Medicine

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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 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.

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.

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.
Publications


Grants

2012-2013, Tel Aviv University Internal Research Fund
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Sackler Faculty of Medicine

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Voice, Speaking Rate, Stuttering and Fluency Disorders

Positions
Senior Lecturer, 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 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.).

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

Publications


Investigating Sensory Modulation Disorder (SMD) Over Life Span

Positions
Lecturer, Sackler Faculty of Medicine

Research
SMD is a health condition in which abnormal responses to naturally occurring stimuli is demonstrated in a manner that interferes with daily life, affecting 13% of otherwise healthy individuals. Our research is aiming to better understand and expand the therapeutic modalities by identifying biomarkers that would specify this health condition, applying psychophysical and neurophysiological methodologies (see below) to characterize children and adults with SMD, suggesting a unique perspective associating SMD with pain.

Moreover in trying to understand the potential role of SMD in neurodevelopmental trajectory, we study this disorder in other health conditions such as chronic pain, mental health, substance abuse, and neurodevelopmental disorders.

EEG of resting state (5 min) in controls and SMD adults recorded from frontal and central cortical sites demonstrated lower power cortical oscillations at $\delta$ (orange), $\beta$ (yellow) and $\alpha$ (green)

Another area of research is embedded in occupational science: Leisure activities are usually perceived as promoting health and well-being. In recent years we're witness to such activities that are harmful, specifically substance abuse activities. This research is exploring substance abuse activities in Israeli adolescents applying an occupational perspective.

Publications
Manuscripts


Nursing Genetics and Information Technologies

Positions
Associate Professor, Sackler Faculty of Medicine
Chair, Department of Nursing, Stanley Steyer School of Health Professions

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 caregivers 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


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


Investigating Pain Perception and Mechanisms of Chronic Pain

Position
Associate Professor, Sackler Faculty of Medicine

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


Chapter


Grants

2012-2014, IRP- International Foundation for research in Paraplegia
2010-2013, National Insurance Association
Models and Rehabilitation of Grasping

Positions
Senior Lecturer, Sackler Faculty of Medicine
Associate Investigator, ARC Centre of Excellence in Cognition and its Disorders, Australia

Research
We study human movement in typical and clinical populations, with a focus on grasping and finger movements. Our approach is to construct mathematical models that describe movement and force generation by the hand, 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.

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).

Publications


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Cardiovascular Disease Epidemiology

Positions
Senior Lecturer, Sackler Faculty of Medicine
Adjunct Associate Professor of Epidemiology, College of Medicine, Mayo Clinic, Minnesota

Research
My 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. I 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, and clinical details obtained through medical records and examinations. I am also interested in methodological aspects involved in conducting and interpreting observational studies.

Osteoporotic fracture-free survival curves by time period adjusted for age, sex, and prior fracture among Olmsted County, Minnesota, residents with incident myocardial infarction in 1979–1989 (A), 1990–1999 (B), and 2000–2006 (C) versus community control subjects.

Publications


**Prof. Minka Hildesheimer, Ph.D.**
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**Hearing Science and Clinical Audiology**

**Position**
Professor, 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 brainstem 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.

Publications


Knowledge and Perceptions of Patients and Caregivers on Health and Illness Situations

Position
Guest Lecturer, Sackler Faculty of Medicine

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
Itzhaki M & Koton S. Knowledge, perceptions and thoughts of stroke among Arab-Muslim Israelis. European Journal of Cardiovascular Nursing 2013, DOI:10.1177/1474515113479721


Tabak N*Itzhaki M* Sharon D, Barnoy S. Intentions of nurses and nursing students to tell the whole truth to patients and family members. Journal of Clinical Nursing. 2013, 22:1434-41 (*Equally contributing authors)


**Chapter**

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Stanley Steyer School of Health Professions
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Quality of Care and Patient Safety

Positions
Lecturer, Sackler Faculty of Medicine
Head, Nursing Continuous Education Unit

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 biophysical 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


Grants

2013-2015  PI, study "Patient's and health caregivers' perception on quality, safety culture and patient involvement in medical care in general hospitals in Israel"  Research Board, The Israel National Institute for Health Policy and Health Services Research (NIHP), Israel
Prof. Liat Kishon-Rabin, Ph.D.
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‘Bottom-Up’ and ‘Top-Down’ Processes in Human Auditory Perception and Recognition

Position
Associate Professor, Sackler Faculty of Medicine
Committee Member, Israel Auditory Society of Research
Chairperson, Committee of Head of Communication Disorders Depts in Israel (CHE)

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 analogous 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.
Publications


Chapters in Books


Grants


2012 *Processing speech in autistic and typically developing adolescence: The meaning beyond words*. Fanny Fensteter Research Award, Sackler Faculty of Medicine, TAU (Co-researcher Osnat Segal, TAU).

2011-2013 *Is the underlying deficits of children with SLI specific to the language domain: The role of the procedural and declarative memory systems in learning of a linguistic and a non-linguistic auditory task*. Ministry of Health (Co-PI Sara Ferman TAU, Avi Karni Haifa U).
Epidemiology of Cardiovascular Diseases

Position
Senior Lecturer, Sackler Faculty of Medicine
Chair, Post Basic B.A. Program for Registered Nurses

Research
Our research focuses on the epidemiology of cardiovascular diseases with especial 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, 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, I carry out nationwide studies in collaboration with specialists in neurology and stroke research. Theses 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


**Koton S.** Risk factors for ischemic stroke and intracerebral hemorrhage: Updated review based on the INTERSTROKE study. *JINA* 2010;4:24-5. (Invited review in Hebrew)


**Koton S.** Tanne D, Bornstein NM, on behalf of the NASIS Investigators. Ischemic stroke on-awakening: Patients’ characteristics, outcomes and potential for reperfusion therapy. *Neuroepidemiology* 2012;39:149-53.


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**Spinal Form and Function**

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

**Research**
Clinical, diagnostic, therapeutic, kinematical, and anthropometric research 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 (see middle figure) and pathological conditions (see left and right figures for isthmic spondylolysis- ISP). 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 and therapeutic), kinematical and morphological:

**Clinical/kinematic:**
1. The efficiency of group exercising, in weight-bearing and non-weight-bearing, in individuals with non-specific chronic low back pain (NSCLBP).
2. The effect of community ballet classes on the thoracic and lumbar curves while standing in young girls.
3. Kinematical evaluation of lumbar rotation while sitting and standing in men with NSCLBP.
4. The effect of group exercising with directional specificity into rotation on sensorimotor and functional parameters in individuals with NSCLBP.
5. Kinematical evaluation of lumbar motions during functional lifting.

The effect of Pilate's group exercising on sensorimotor parameters in individuals with NSCLBP.

**Morphological/Anatomical/Biomechanical:**
1. A morphometric analysis of the normal thoracic and lumbar vertebrae in the human spine.
2. A morphometric analysis of the lumbar spine in spondylolysis and degenerative spondylolisthesis.
3. A morphological characterization of the cervical spine in spinal stenosis and cervical headaches.
4. Genetic determinants of LBP and lumbar disc degeneration in complex Arab pedigrees in Israel. The relationship between the sacroiliac joint form, function, and nerve entrapment with NSCLBP.

**Biomechanical:**
Mechanical aspects in the normal and pathological human spine. A finite element analysis research.

**Publications**


Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

Position
Senior Lecturer, Sackler Faculty of Medicine
Chair, Department of Physical Therapy

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.

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.

Publications


Krasovsky T., Berman S., Liebermann D.G., Kinematic features of continuous hand reaching movements under simple and complex rhythmical constraints. J. Electromyography & Kinesiology 2010, 20, 636-641


Grants

2011-2013
Necht Foundation– in collaboration with S. Frenkel-Toledo, Dr. N. Soroker (TAU), Prof. Sh. Bentin, RIP, (HUIJ)
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**Hearing Science and Clinical Audiology**

**Position**  
Associate Professor, Sackler Faculty of Medicine and School of Education

**Research**

- Speech perception and production by the hearing impaired  
- The implications of hearing loss on communication, cognitive and socio-emotional functionning 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.

   Our research activities relate, on the one hand, to a wide range of age groups and, on the other, to the effectiveness of various hearing devices (hearing aids, cochlear implants). Our research on the production and perception of emotions among young children with normal hearing and children with hearing loss makes a significant contribution to understanding the development of interpersonal communication.

   In our research we examine the unique contribution of each of the various sensory channels (auditory and visual) as well as the contribution of integrated (audio-visual) perception of this information. We also research the relationship between perception of the speaker's emotional state, the social awareness of the child with a hearing loss and his/her social competency.

   From a rehabilitation point of view, we examine the contribution of the various types of hearing devices to the perception of suprasegmental and paralinguistic features. We examine how people/children function in order to receive this important information, comparing those who have received cochlear implants at different stages of life with those with different levels of hearing loss who are using hearing aids. Our research focuses on investigating the contribution of hearing aids.
in the contra-lateral side, in understanding these features by unilateral cochlear implant users (bimodal users). In other words, we examine the complementary information received by bimodal rehabilitation, that is, a cochlear implant in one ear (electric information) and a hearing aid in the other ear (acoustic information).

We also relate in my research to the relationship between rehabilitation with the various sensory aids and the pragmatic functioning of the child with a hearing loss during interactive communication through spoken language.

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.

My research focuses on the relationship between the hearing loss and the communication functioning through the use of spoken language in general and the speech intelligibility in particular. I study the effect of these variables on the social and emotional functioning in various life environments of the population. I also study the ramifications of the hearing and communication difficulties on the individual's environment (at home, at the educational system or at work). This research is carried out on a wide range of ages from kindergarten to young adults. The research shows that already from kindergarten age, children with a hearing loss whose speech is less intelligible, and are integrated into regular kindergartens with hearing children, feel more alone than their friends who are easily understood.

Looking at these ramifications of a hearing loss on the daily functioning of the individual, I also research population with a mild and unilateral hearing loss. The findings show evidence of the harmful effect of a hearing loss on academic and social functioning, even with a mild or unilateral hearing loss.

With the current trend to integrate children with a hearing loss into regular educational frameworks either individually or in a group, I 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, I 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

**Most, T. & Kozlovski, L.** (2010). Academic and social functioning of adolescents with hearing loss who are included individually in regular classrooms. *DASH-Dibur, Safa & Shmia*, 29, 103-122 (Hebrew)


Prof. Chava Muchnik, Ph.D.
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Hearing Science and Clinical Audiology

Position
Professor, Sackler Faculty of Medicine
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


Attitudes Toward Organ/Tissues Donation and Transplantation

Position
Guest Lecturer, Sackler Faculty of Medicine

Research
Patients on organ transplant waiting lists continue to far exceed donor rates. Our research seeks to understand the barriers preventing people in Israel from donating organs/tissues for transplantation. The study tries to elucidate attitudes and perceptions regarding different sides of organ/tissues donation and transplantation. The research attempts to expound the understanding of emotional and ethical issues to which the transplant patients, organ donors and their family and health care professionals are exposed.

Publications


Computational Biomechanics in Motor Rehabilitation

Position
Lecturer, Sackler Faculty of Medicine

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.

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

3D kinematics of daily activities acquired using a passive-marker-based motion capture system

Publications


Chapter

Dr. Debbie Rand, Ph.D., O.T.
Department of Occupational Therapy
Stanley Steyer School of Health Professions
Sackler Faculty of Medicine

Tel Aviv University
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Motor Recovery, Cognition, Physical Activity in Neurological and Geriatric Populations

Position
Senior Lecturer, Sackler Faculty of Medicine

Research
Our research focuses on achieving a better understanding of the factors hindering and facilitating recovery posts-troke. We have developed interventions aimed to improve the motor recovery and executive functions deficits that these individuals experience, in order to enhance function in daily living. The effectiveness of these novel interventions is assessed by conducting clinical trials.

Our current research project aims to assess the effectiveness of a ‘Community’ and ‘Home’ based VR therapy (using video games) as opposed to traditional therapy for enhancing daily function and participation of individuals with chronic stroke living in the community. The daily physical activity (daily walking and arm use) of these individuals is quantified by an innovative form of instrumentation technology (accelerometers). We are also investigating the use of Apps that run on Tablets for self-training of the impaired hand during rehabilitation of individuals following acquired brain injury.

Publications


Rand D, Eng JJ. Disparity between functional recovery and daily use of the upper and lower extremities during subacute stroke rehabilitation. Neurorehabil Neural Repair, 2012, 26:76-84.


Book Chapters


Grants
2011-2015 EU, Marie Curie International Reintegration Grant (FP7-PEOPLE-2010-IRG) -
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


Ratzon, N., Ben Ari (Shevil), E., Froom, P., Friedman, S., Amit, Y. (2013). Functional capacity evaluation of work performance among individuals with pelvic injuries following motor vehicle


**Grants**

2009-2013 National Road Safety Authority Grant

2012-2014 Office of Senior Citizens Grant

2013-2014 National Insurance Institute Grant

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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