

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine Research 2016

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Cover images (from bottom left, clockwise):

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

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

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

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

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

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

The Sackler Faculty of Medicine

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

The Faculty of Medicine engages in joint teaching and research programs with nearly every faculty at TAU, including the Wise Faculty of Life Sciences, the Sagol School of Neuroscience, the Edmond J. Safra Bioinformatics Center, the TAU Center for Nanoscience and Nanotechnology, and the Edmond J. Safra Center for Ethics, and multi-nationally with schools, hospitals and research centers throughout the world. The Sackler faculty is known for research

in the following areas: cancer biology, stem cells, diabetes, neurodegenerative diseases, infectious diseases and genetic diseases, including but not limited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians in 181 Sackler affiliated departments and institutes in 17 hospitals hold academic appointments at TAU. The Gitter-Smolarz Life Sciences and Medicine Library serves students and staff and is the center of a consortium of 15 hospital libraries.

The student body is made up of 750 Israeli students enrolled in the 6-year M.D. degree program, 300 American and Canadian students enrolled in a 4-year M.D. program chartered by the State of New York and accredited by the State of Israel, and a 4-year program for Israeli students for the M.D. degree, with 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 Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Meir Lahav, Prof. Ami Fishman, Prof. Moshe Kotler; and Assistant to the Dean, Ms. Yael Keilin.

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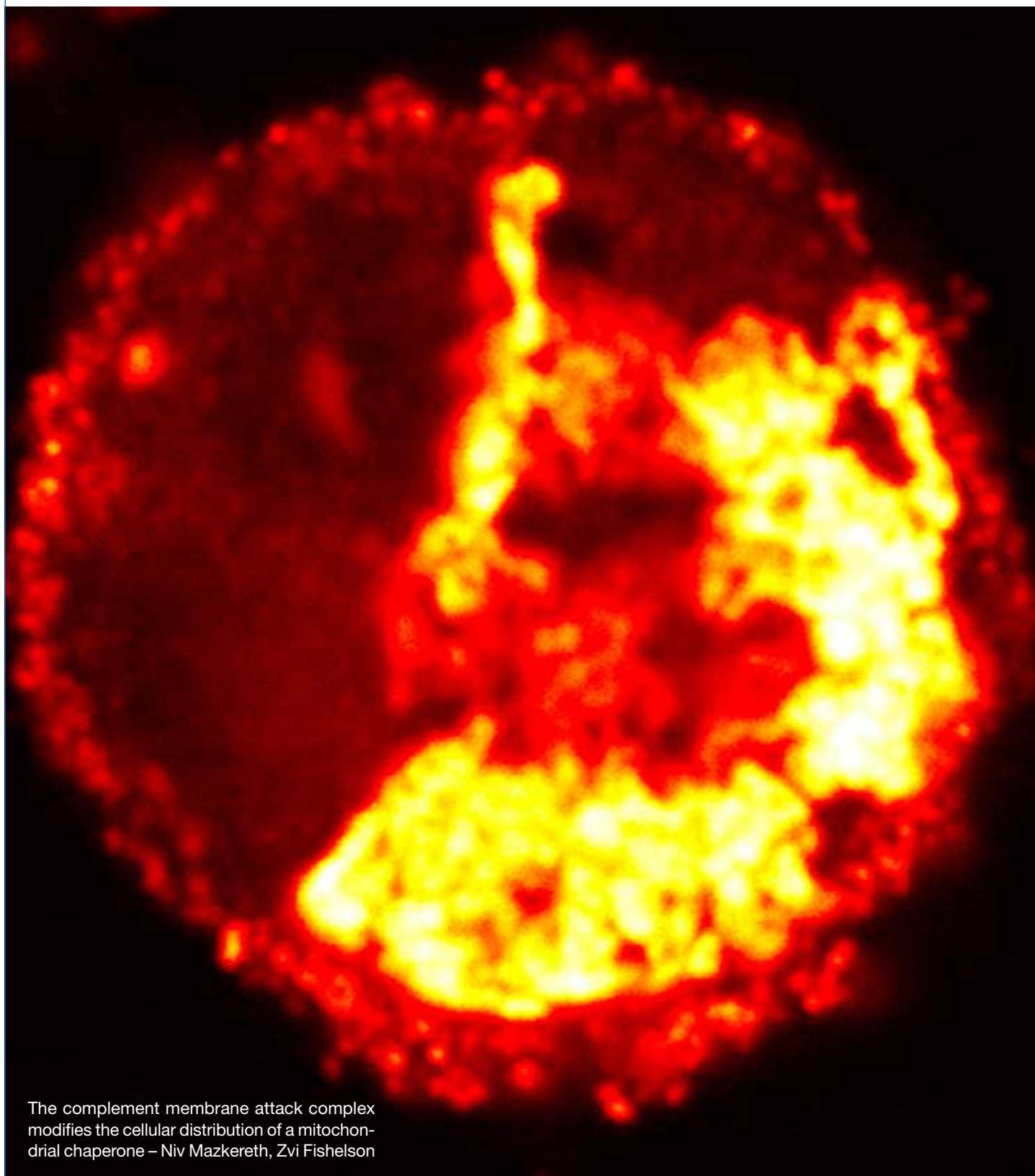
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Cancer and Molecular Therapies



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



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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.

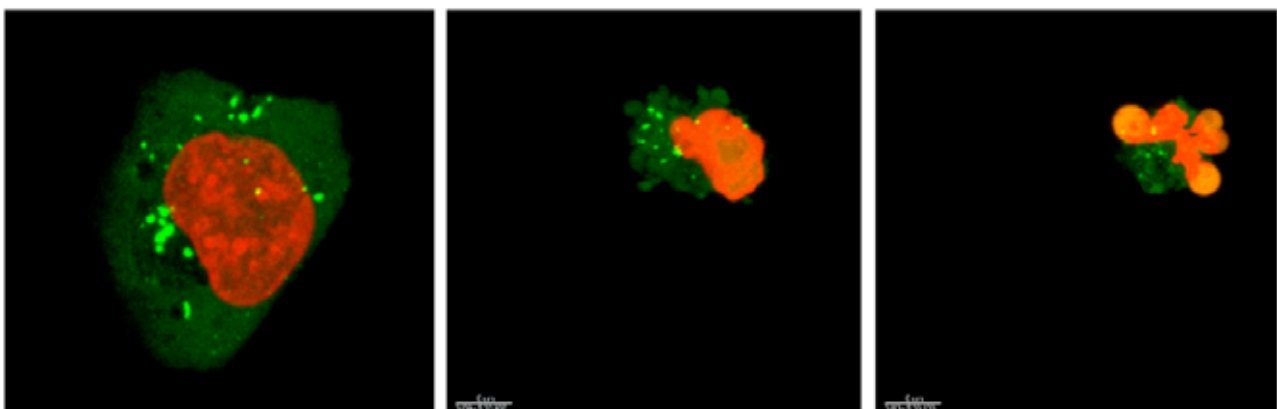
We found that PARP-1 is a target of signal transduction mechanisms activated by intracellular Ca^{2+} mobilization or by the MEK-ERK phosphorylation cascade. Moreover, we found that ERK activity in

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.

Publications

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Eradication of cancer cell treated with PJ-34 by mitotic catastrophe cell death. De-clustered extra-centrosomes and mitotic catastrophe cell death in MDA-MB-231 cells treated with PJJ-34 (20 mM) for 18 hours. Taken from Castiel et al., *JoVE* 2013.

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Review

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Patents

'Cancer Therapy'. US 8,729,080 B2

'Treatment of Addiction'. US 13,761,761 B1



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Department of Pathology
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Cancer Related Inflammation in Tumor Progression and Metastasis

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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

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

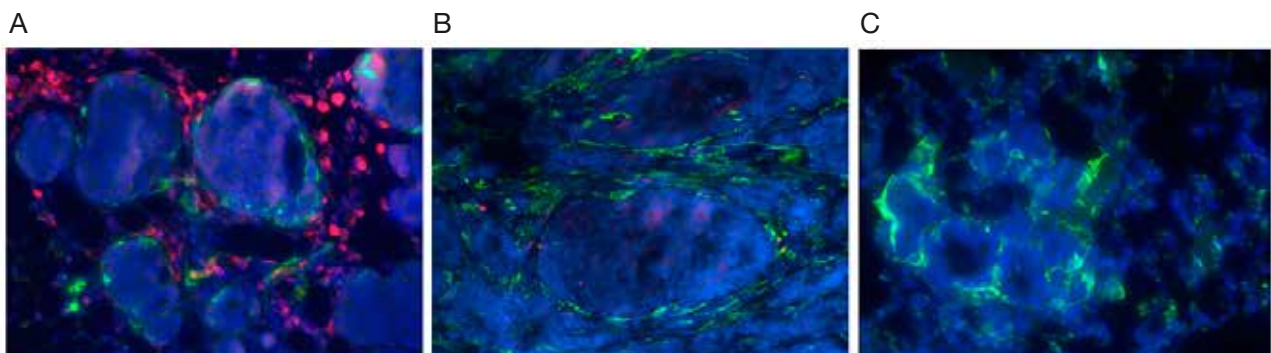
and unmet clinical need. Nevertheless, changes in the metastatic microenvironment that enable the growth of disseminated tumor cells are poorly characterized, and are the major focus of our research.

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

Publications

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

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Reviews

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Servais C. and **Erez N.** From sentinel cells to inflammatory culprits: cancer-associated fibroblasts in tumor-related inflammation. *J Pathol.* 2013; 229:198-207.

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Grants

2011 – 2015 European Union FP7, Marie Curie International Reintegration Grant

2012 – 2015 MOST-DKFZ (German Israeli Cooperation)

2012–2016 Israel Science Foundation (ISF) Grant

2014 – 2016 Israel Cancer Association (ICA)

2014 – 2016 The Eva and Henry Frænkel Mindefond-Denmark

2014–2017 Association for International Cancer Research (AICR)

2014 – 2017 Melanoma Research Alliance SABAN FAMILY FOUNDATION-TEAM SCIENCE AWARD

2014 – 2017 Israel Cancer Research Foundation (ICRF). Research Career Development Award

2015–2019 European Research Council (ERC) Starting Grant



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Molecular Analysis of Cancer Immunoresistance

Positions

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

Research

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

Publications

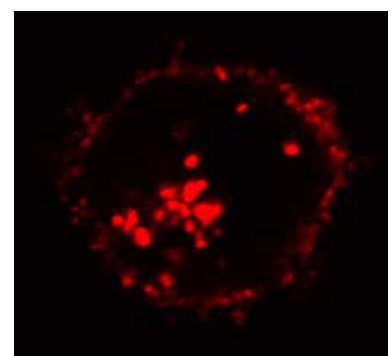
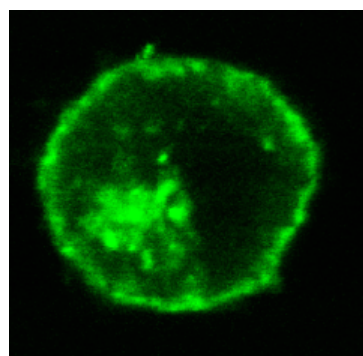
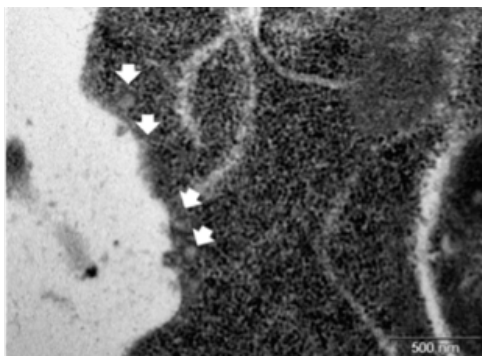
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Gancz D, Lusthaus M and **Fishelson Z**. A role for the NF- κ b pathway in cell protection from complement-dependent cytotoxicity, *J. Immunol.* 189: 860-866, 2012.



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

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Reviews

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Grants

2011 – 2015 Functional and molecular analysis of cancer cell resistance mechanisms to complement-dependent cytotoxicity, Israel Science Foundation (ISF)



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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.

Publications

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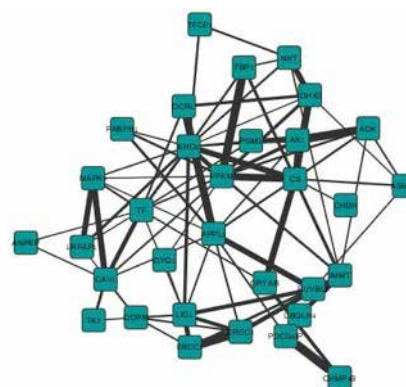
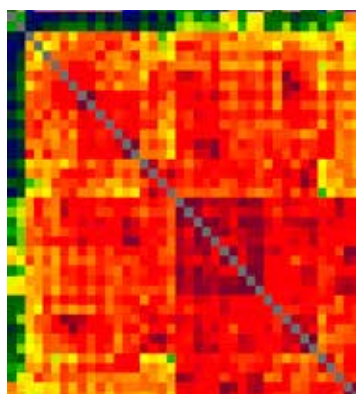
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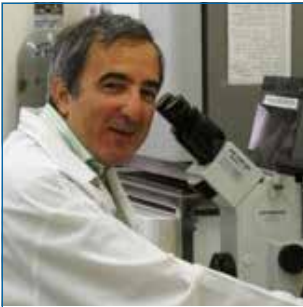
2014–2016 Israel Cancer Research Fund (ICRF): Novel approaches for early-detection biomarkers for ovarian cancer. Co-PI with Keren Levanon and Ariel Hourvitz.

2014–2016 Melanoma Research Alliance (MRA): Discovery of novel immune checkpoints in melanoma. Co-PI with Gal Markel and Noam Shomron

2012–2015 Israel Cancer Research Fund (ICRF): Elucidation of regulatory networks in triple-negative breast

2012-2016 Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease

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



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Functional Genomics and Childhood Leukemia
Research, Cancer Research Center,
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Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions

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

Research

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

Our research is divided into two major topics:

1. Basic, translational and clinical research of leukemia.
2. The role of SIL (STIL) protein in mitosis, centrosomal biology and cancer.

Cancer is the deadliest disease of children and leukemia is the most common childhood cancer. We are interested in the fundamental question how normal blood development is diverted into leukemia. What are the genetic and biochemical

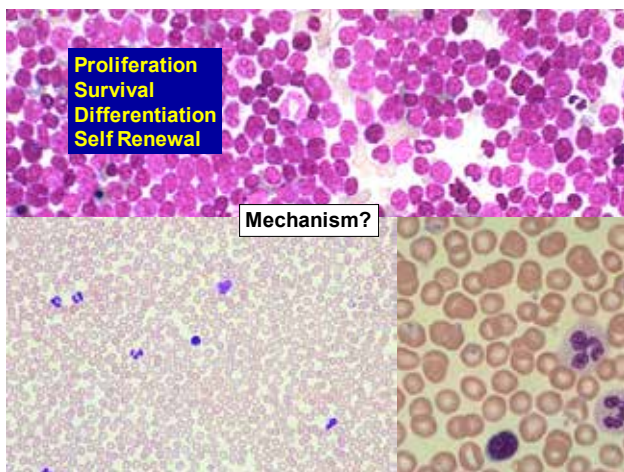
abnormalities that block cell differentiation, enhance proliferation and survival and confer the unique stem cell properties of self renewal to leukemia stem cells? We focus on chromosome 21 because of the mysterious association of leukemia with Down Syndrome. We utilize advanced genomic technologies, 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.

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Reviews

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Grants

2012-2015 Israel Science Foundation (ISF), The molecular pathogenesis of the acute lymphoblastic leukemia of Down Syndrome

2014-2017 EU ERA-NET TRANSCANCER "TRANSALL" Validation of biomarkers for the diagnosis and risk stratification of childhood ALL

2014-2018 BSF Functional analysis of ERG GATA1

2014-2018 ISF Modelling T-lympho-myeloid leukemia

2014-2017 ISF-NSFC Hematopoietic transcription factors in leukemia – mouse models and human leukemias

2014-2016 ICRF Modelling human acute lymphoblastic leukemia by activated cytokine receptors



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Development of Cancer Treatments Integrating Radiotherapy or Electrochemical Ablation and Immunotherapy

Positions

Professor, Sackler Faculty of Medicine
Roberts-Guthman Chair in Immunopharmacology
President, Israeli Society for Cancer Research
Associate Editor, *Mediators of Inflammation*

Research

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

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

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

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

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Books

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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*

Research

The research activity addresses the following lines of research:

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

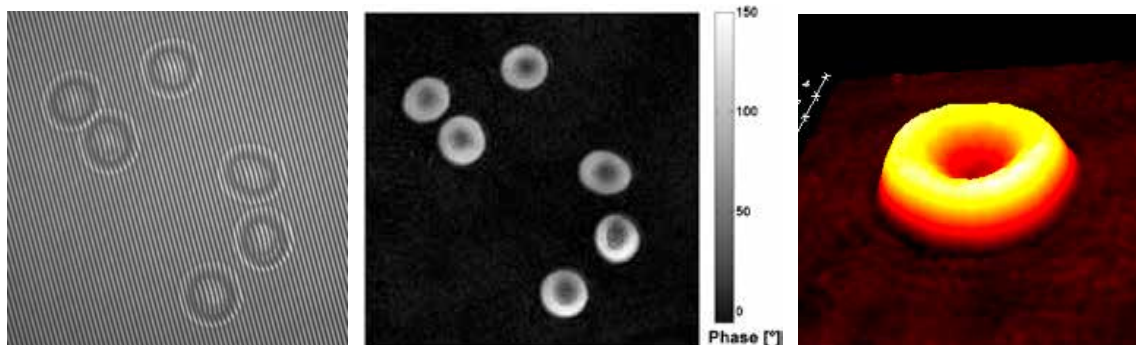
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Hologram image of red blood cells (left), reconstructed phase image (middle) and 3D reconstruction of a single red blood cell (right)

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Grants

2011-2015 European Commission – EP7 EC consortium on “*Research Infrastructures for processing, analysis and characterization of engineered nanomaterials*” (acronym – “QNano”, 27 partners)



Dr. Chen Luxenburg, Ph.D.

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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.

Publications

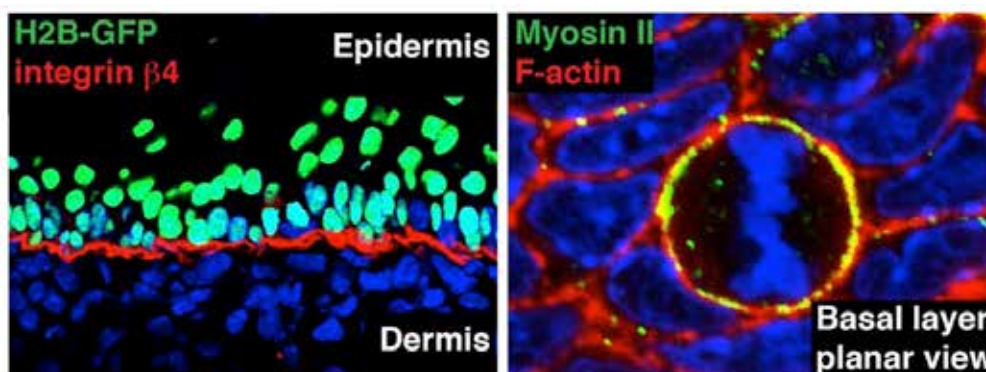
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Grants

2014–2015 Israel Cancer Research Fund (ICRF) Project Grant (co-PI Limor Broday)

2014–2018 Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease



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.



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The Wnt Signaling Pathway and Colorectal Cancer

Position

Senior Lecturer, Sackler Faculty of Medicine

Chair, Search Committee

Research

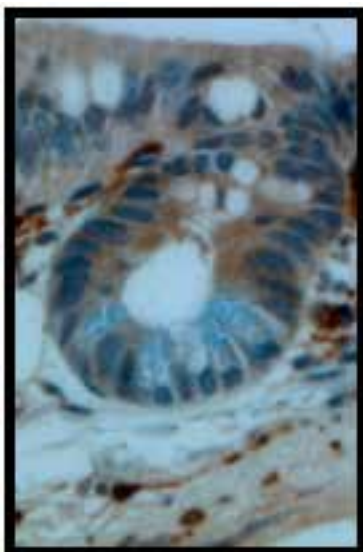
The Wnt signaling pathway is involved in virtually every aspect of human development, as well as in adult homeostasis. Hyperactivation of this pathway has been linked to a wide range of cancers and especially colorectal cancer. Our aim is to understand the molecular events underlying Wnt signal transduction,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

Current projects in the lab include:

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

Publications

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Grants

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



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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
Current location: University of Maryland, College Park, MD, USA

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,

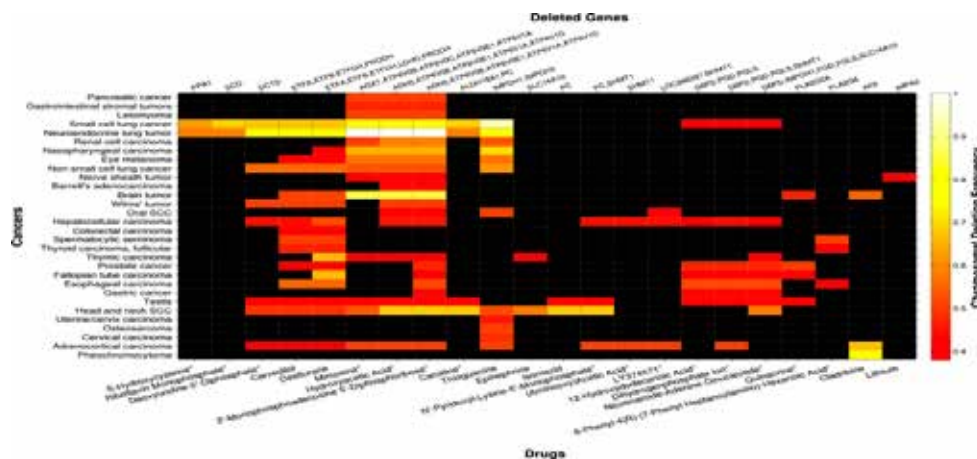
these studies and others ongoing in the lab offer new ways for harnessing computers to advance our understanding of metabolically-related human disorders, and further our ability to diagnose and treat them in a rationale-designed manner.

Publications

L. Zheng, S. Cardaci, L. Jerby, E.D. MacKenzie, M. Sciacovelli, T. Isaac Johnson, E. Gaude, A. King, J.D.G. Leach, R. Edrada-Ebel, A. Hedly, N.A. Morrice, G. Kalna, K. Blyth, **E. Ruppin**, C. Frezza, E. Gottlieb. Fumarate induces redox-dependent senescence by modifying glutathione metabolism. *Nature Communications*, 6, 6001, 2015.

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Decoupling environmental-dependent and independent genetic robustness across bacterial

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Grants

2011-2015 US-Israeli Binational Science Foundation (BSF) for studying human host-pathogen metabolic interactions in the gut



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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

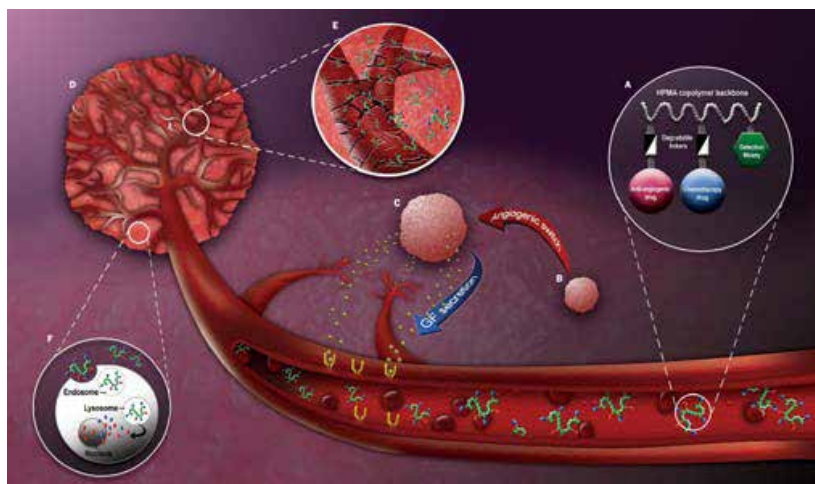
Editorial board member, *Advanced Drug Delivery Reviews*

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 nano-medicines 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.

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2012-2017 Israel National Nanotechnology Initiative (INNI), Focal Technology Area in nanotechnology, “Theranostic Nanomedicines for Personalized Medicine”

2014-2019 European Research Council (ERC) Consolidator Award. PolyDorm: “Uncovering the molecular and cellular mechanism of tumor dormancy for the rational design of theranostic nanomedicines”.



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The ATM-Mediated DNA Damage Response

Positions

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

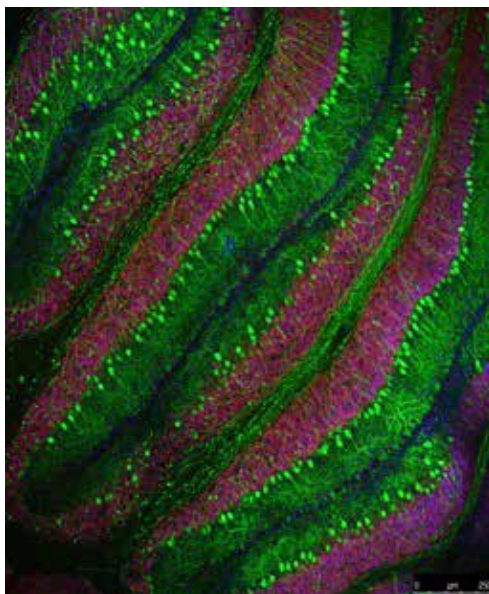
Research

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

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

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

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



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

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Book Chapter

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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



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

Position

Associate Professor, Sackler Faculty of Medicine

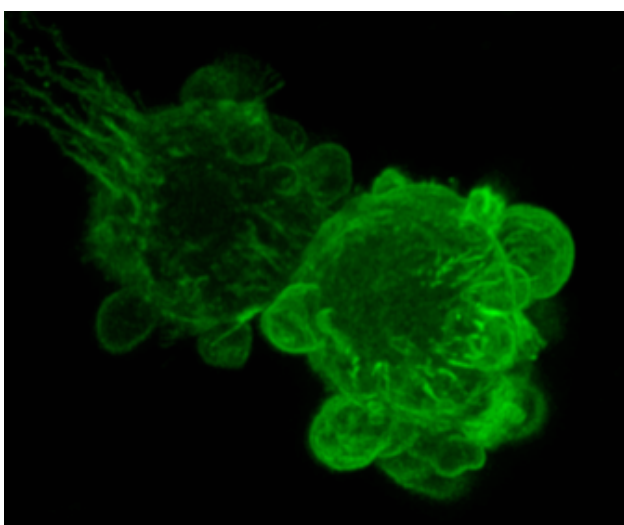
Director, Sackler Cellular and Molecular Imaging Center (SCMIC)

Research

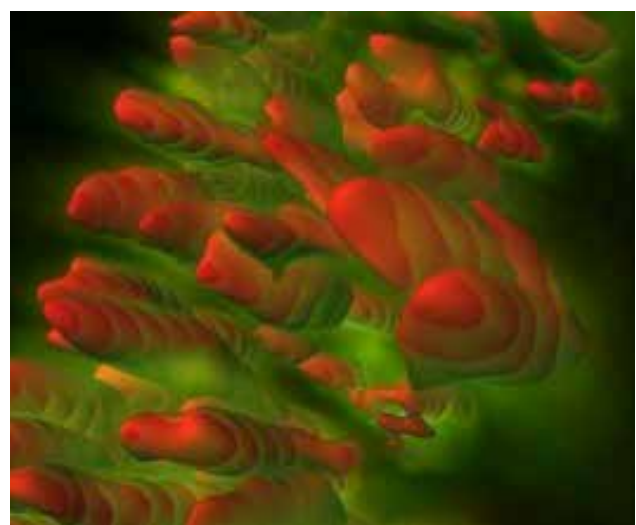
Breast cancer is the most common malignant disease in western women. In the majority of cases the cause of death in cancer patients is not the primary tumors, but complications derived from metastases at distant sites. The *met* proto-oncogene product (Met – a receptor tyrosine kinase) and its ligand,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

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

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



Met localization in blebbing cells



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

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

To study Met activation by HGF/SF *in vivo*, we used a xenograft mouse model in which DA3 cells expressing the fluorescent protein mCherry (DA3-mCherry) are injected 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 reduced upon inhibition of the receptor and its signaling pathway; Whole animal spectral imaging enabled detection of sub-millimeter metastases demonstrating fast developing micrometastatic spread of the tumor; Macro to Micro and two photon confocal imaging demonstrated HGF/SF-induced changes in blood flow at single vessel resolution, localization of metalloprotease and cathepsin activity at the tumor edge and increase in single cell motility.

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

Publications

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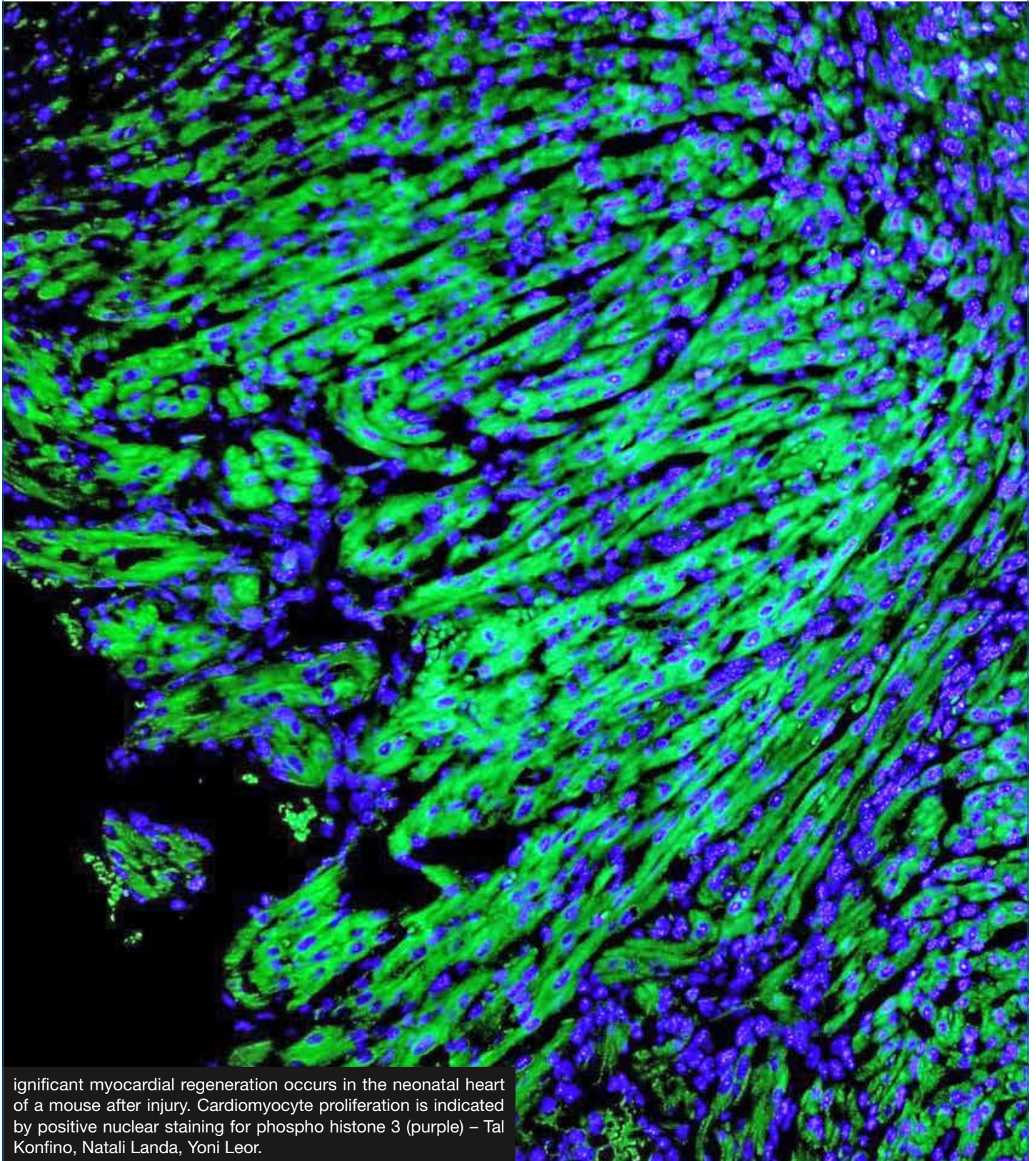
Review

Tsarfaty I, Ben-Jacob E. Secrets of tubule engineering by epithelial cells. *Proc Natl Acad Sci USA*. 2012. 109:6790-1.

Grants

2010 – 2015 Sackler Foundation, Establishment of the Tel Aviv University Sackler Cellular and Molecular Imaging Center (SCMIC)

Cardiovascular Research and Diseases



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



Prof. Bernard Attali, Ph.D.

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Sackler Faculty of Medicine



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Pursuing the Unknown

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Normal and Diseased Potassium Channels in Human Brain and Heart

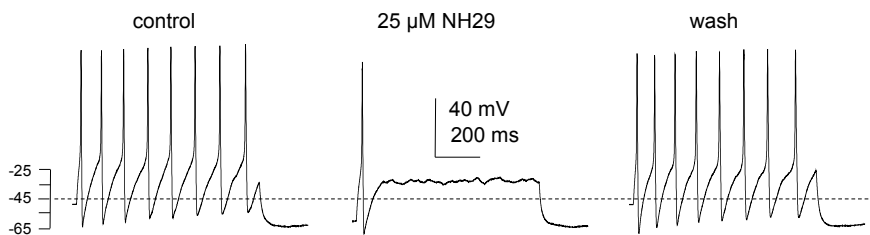
Position

Professor, Sackler Faculty of Medicine

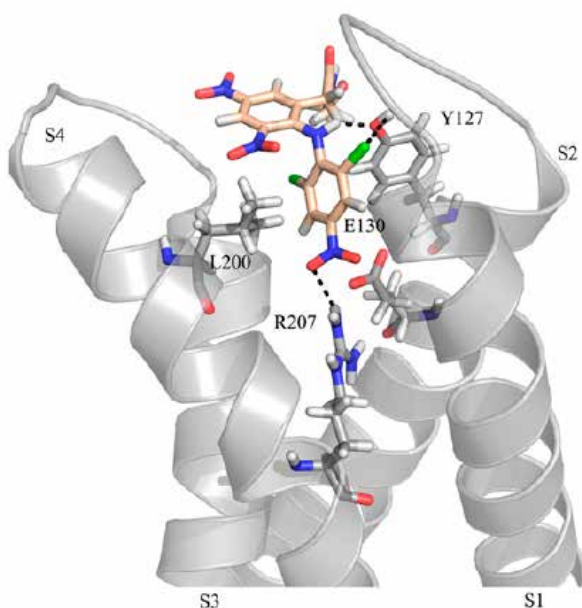
Research

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

Peretz A, Pell L, Gofman Y, Haitin Y, Shamgar L, Patrich E, Kornilov P, Gourgy-Hacohen O, Ben-Tal N, **Attali B.** (2010) Targeting the voltage sensor of Kv7.2 channels with a new gating-modifier. *Proc Natl Acad Sci USA.* 107:15637-15642.

Strutz-Seebohm N, Pusch M, Wolf S, Stoll R, Tapken D, Gerwert K, **Attali B,** Seebohm G. (2011) Structural basis of slow activation gating in the cardiac I_{Ks} channel complex. *Cell Physiol Biochem.* 27:443-452.

Ebner-Bennatan S, Patrich E, Peretz A, Kornilov P, Tiran Z, Elson A, **Attali B.** (2012) Multi-faceted modulation of K⁺ channels by protein tyrosine phosphatase epsilon tunes neuronal excitability. *J Biol Chem.* 287:27614-27628.

Weisbrod D, Peretz A, Ziskind A, Menaker N, Oz S, Barad L, Eliyahu S, Itskovitz-Eldor J, Dascal N, Khananshvil D, Binah O, **Attali B.** (2013) SK4 Ca²⁺ activated K⁺ channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA.* 110:E1685-94.

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

Reviews

Kornilov P, Peretz A, **Attali B.** (2013) Channel gating pore: a new therapeutic target. *Cell Res.* 23:1067-8.

Dvir M, Peretz A, Haitin Y, **Attali B.** (2014) Recent molecular insights from mutated I_{Ks} channels in cardiac arrhythmia. *Curr Opin Pharmacol.* 15:74-82.

Grants

2013-2017 Israel Academy of Science, (ISF:1215/13). Role of SK4 Ca²⁺-activated K⁺ channels in the developing human cardiac pacemaker using embryonic stem cell-derived cardiomyocytes as a model. (PI).

2013-2017 Fields Fund for Cardiovascular Research (Co-PI).



Prof. Nathan Dascal, Ph.D.
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Signal Transduction by Neurotransmitters in Brain and Heart in Health and Disease

Position

Professor of Physiology, Sackler Faculty of Medicine

Research

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

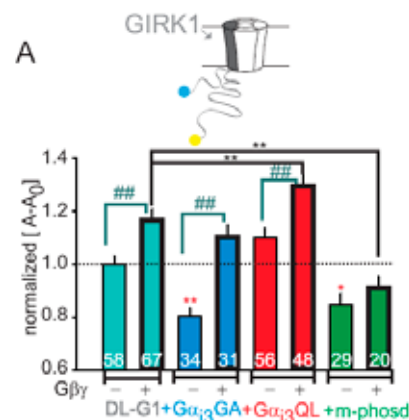
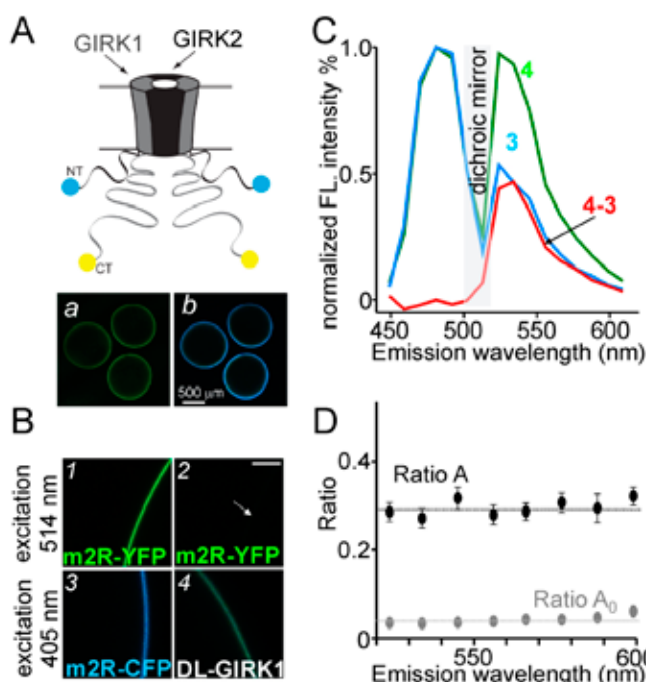
Function and regulation of receptors, G proteins, Ca^{2+} and K^+ channels in health and disease; Ion channel-related hereditary cardiac and neurological disorders (channelopathies); Mechanisms of coupling of G protein-coupled receptors with effectors; Molecular mechanisms of bipolar disorder.

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

Publications

Babai N, Kanevsky N, **Dascal N**, Rozanski GJ, Singh DP, Fatma N & Thoreson WB (2010). Anion sensitive regions of L-type $Ca_v1.2$ calcium channels expressed in HEK293 cells. *PLoS One*, 5, e8602.

Berlin S, Keren-Raifman T, Castel R, Rubinstein M, Dessauer CW, Ivanina T & **Dascal N** (2010). $G\alpha_i$ and $G\beta\gamma$ jointly regulate the conformations of a $G\beta\gamma$ effector, the neuronal G-protein activated K^+ channel (GIRK). *J Biol Chem*, 285, 6179-6185.



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.

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- Tselniker I, Tsemakhovich VA, Dessauer CW & **Dascal N**. (2010) Stargazin modulates neuronal voltage-dependent Ca^{2+} channel $\text{Ca}_v2.2$ by a $\text{G}\beta\gamma$ -dependent mechanism. *J Biol Chem* **285**, 20462-20471.
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- Almagor L, Chomsky-Hecht O, Ben-Mocha A, Hendin-Barak D, **Dascal N** & Hirsch JA. (2012). The role of a voltage-dependent Ca^{2+} channel intracellular linker: a structure-function analysis. *J Neurosci* **32**, 7602-7613.
- Pankonien I, Otto A, **Dascal N**, Morano I & Haase H. (2012). Ahnak1 interaction is affected by phosphorylation of Ser-296 on $\text{Ca}_v\beta2$. *Biochem Biophys Res Commun* **421**, 184-189.
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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. Klusmann.



Dr. Michal Katz-Leurer, Ph.D.

Department of Physical Therapy
Steyer School of Health Professions
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Investigating the Cardiac Autonomic System Among Brain Damaged Patients

Position

Senior Lecturer

Chair, Department of Physical Therapy

Research

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

Publications

Bartur G, Vatine J.J, Raphaely-Beer N, Peleg S, **Katz-Leurer M**. Heart rate autonomic regulation system at rest and during paced breathing among patients with CRPS as compared to age matched healthy controls. *Pain Med.* 2014;15:1569-74

Carmeli E, **Katz-Laureur M**, Scena S, Kodesh E, Steindler R. Functional reach test performance in distance and velocity – A pilot study. *European Journal of Physiotherapy.* 2014;16:168-172

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Amichai T, **Katz-Leurer M**. Heart rate variability in children with cerebral palsy: Review of the literature and meta-analysis. *NeuroRehabilitation* 2014;35:113-22.

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Cohen-Holzer M, **Katz-Leurer M**, Reinstein R, Rotem H, Meyer S. The effect of combining daily restraint with bimanual intensive therapy in children with hemiparetic cerebral palsy: a self-control study. *NeuroRehabilitation.* 2011;29(1):29-36.

Ginsburg P, Bartur G, Peleg S, Vatine JJ, **Katz-Leurer M**. Reproducibility of heart rate variability during rest, paced breathing and light-to-moderate intense exercise in patients one month after stroke. *Eur Neurol.* 2011;66:117-22.

Katz-Leurer M, Rotem H, Keren O, Meyer S. Effect of concurrent cognitive tasks on gait features among children post-severe traumatic brain injury and typically-developed controls. *Brain Inj.* 2011;25:581-6.

Toledano-Zarhi A, Tanne D, Carmeli E, **Katz-Leurer M**. Feasibility, safety and efficacy of an early aerobic rehabilitation program for patients after minor

ischemic stroke: A pilot randomized controlled trial. *NeuroRehabilitation.* 2011;28:85-90.

Alperovitch-Najenson D, **Katz-Leurer M**, Santo Y, Golman D, Kalichman L. Upper body quadrant pain in bus drivers. *Arch Environ Occup Health.* 2010;65:218-23.

Katz-Leurer M, Rotem H, Keren O, Meyer S. Recreational physical activities among children with a history of severe traumatic brain injury. *Brain Inj.* 2010;24:1561-7.

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Bezalel T, Carmeli E, **Katz-Leurer M**. The effect of a group education programme on pain and function through knowledge acquisition and home-based exercise among patients with knee osteoarthritis: a parallel randomised single-blind clinical trial. *Physiotherapy.* 2010 ;96:137-43.

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Prof. Daniel Khananshvili, Ph.D.

Department of Physiology and
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Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

Positions

Professor, Sackler Faculty of Medicine

Research

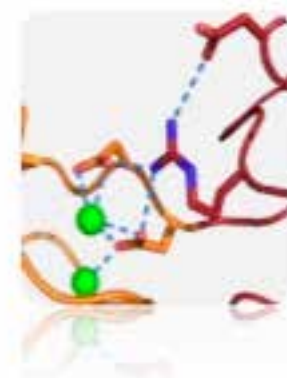
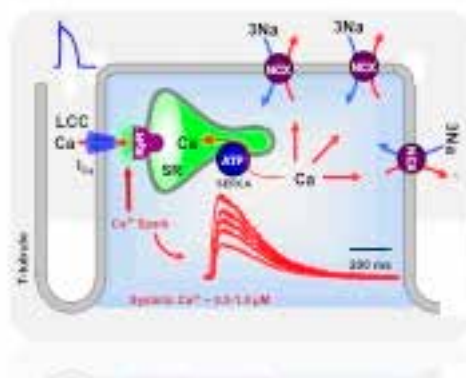
Calcium (Ca^{2+}) is a major regulator in the living cell. In many cell-types the $\text{Na}^+/\text{Ca}^{2+}$ exchanger proteins (NCX) represent a major Ca^{2+} extruding system and thus, play a key role in regulating the Ca^{2+} -dependent events in the cell. Three NCX genes form numerous splice variants,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

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

Publications

Marinelli F, Almagor L, Hiller R, Giladi M, **Khananshvili D***, and Faraldo-Gómez JD. Sodium recognition by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger in the outward-facing conformation. (*Corresponding Author). *Proc Natl Acad Sci USA*, 2014, doi:10.1073/pnas.1415751111

Giladi M, Lee S-Y, Hiller R, Chung K-Y, and **Khananshvili, D**. Structure-dynamic determinants



governing a mode of regulatory response and propagation of allosteric signal in splice variants of Na⁺/Ca²⁺ exchange (NCX) proteins. *Biochem J*, doi:10.1042/BJ20141036

Almagor L, Giladi M, van Dijk L, Buki T, Hiller R, and **Khananshvili D**. Functional asymmetry of bidirectional Ca²⁺-movements in an archaeal sodium-calcium exchanger (NCX_Mj). *Cell Calcium* 2014, 56:276-284.

Giladi M, Michaely L, Almagor A, Bar-On D, Buki T, Ashery U, **Khananshvili**, Hirsch JA. The C2B domain is the primary Ca²⁺ sensor in DOC2B: A structural and functional analysis. *J Mol Biol*, 2013, 425:4629-4641.

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Giladi, M. and **Khananshvili, D**. Molecular determinants of allosteric regulation in NCX proteins. *Adv Exp Med and Biol*, 2013, 961:35-48.

Khananshvili D, Binah O, Attali B. The Ca²⁺-activated K⁺ channel IKCa/SK4: a critical new player in human embryonic cardiac pacemaker. *Proc Natl Acad Sci USA*, 2013, 110:1685-1694.

Nita II, Hershinkel M, Fishman D, Ozeri E, Rutter GA, Sensi SL, **Khananshvili D**, Lewis EC, Sekler I. The mitochondrial Na⁺/Ca²⁺ exchanger upregulates glucose dependent Ca²⁺ signaling linked to insulin secretion. *PLoS One* 2012, 7:e46649.

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Giladi M, Sasson Y, Fang X, Hiller R, Buki T, Wang Y-X, Hirsch JA and **Khananshvili D**. A common Ca²⁺-driven interdomain module governs eukaryotic NCX regulation. *PLoS One*, 7:e39985. 2012

Boyman L, Hagen BM, Giladi M, Hiller R, WJ Lederer and **Khananshvili D**. Proton-Sensing Ca²⁺ Binding Domains Regulate the Cardiac Na⁺/Ca²⁺ Exchanger. *J Biol Chem*, 286:28811-28820, 2011.

Giladi M, Boyman L, Mikhasenko H, Hiller R and **Khananshvili D**. Essential role of the CBD1-CBD2 linker in slow dissociation of Ca²⁺ from the regulatory two-domain tandem of NCX1. *J Biol Chem* 285:28117-28125, 2010.

Palty R, Silverman WF, Hershinkel M, Caporale T, Sensi SL, Parnis J, Nolte C, Fishman, D., Shoshan-Barmatz V, Herrmann S, **Khananshvili D** and Sekler I. NCLX is an essential component of mitochondrial Na⁺/Ca²⁺ exchange. *Proc Natl Acad Sci USA* 107:436-441, 2010.

Reviews

Khananshvili, D. Sodium-Calcium Exchangers (NCX): Molecular Hallmarks Underlying Tissue-Specific and Systemic Functions, *Pflügers Arch* (in press)

Khananshvili, D. SLC8 gene family of sodium-calcium exchangers (NCX): Structure, function and regulation in health and disease. *Mol Asp Med* 34:220-35, 2013.

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Boyman L, GSB Williams, **Khananshvili D**, Sekler I, WJ Lederer. NCLX: The mitochondrial sodium calcium exchanger. *J Mol Cell Cardiology* 2013, 59:205-213.

Grants

2013-2017	Fields Center of Molecular Cardiology
2010-2015	USA-Israel Binational Science Foundation
2014-2018	Israeli Science Foundation



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Stanley Steyer School of Health Professions
Sackler Faculty of Medicine



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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. These studies are aimed at characterizing management and outcomes of acute stroke patients and are an important means for providing both clinicians and health policy makers with data required for optimizing prevention strategies and care of stroke patients in Israel.

Publications

Koton S, Tanne D, Green MS, Bornstein NM. Mortality and predictors of death one month and three years after first-ever ischemic stroke: data from the first National Acute Stroke Israeli Survey (NASIS 2004). *Neuroepidemiology* 2010;34:90-6.

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Reviews

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Prof. Jonathan Leor, Ph.D.

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



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Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions

Professor of Cardiology, Sackler Faculty of Medicine

Director, Neufeld Cardiac Research Institute, Tel Aviv University

Director, Tamman Cardiovascular Research Institute, Sheba Medical Center

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

Research

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

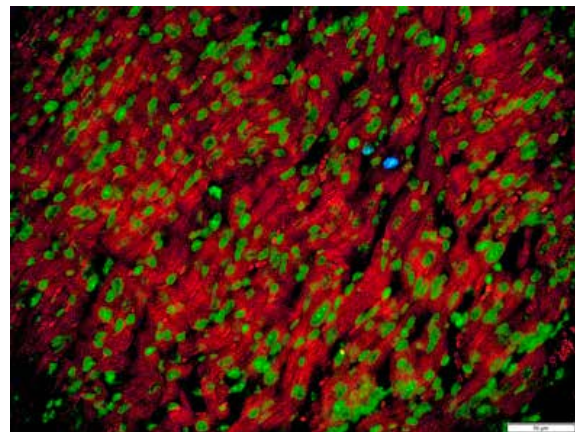
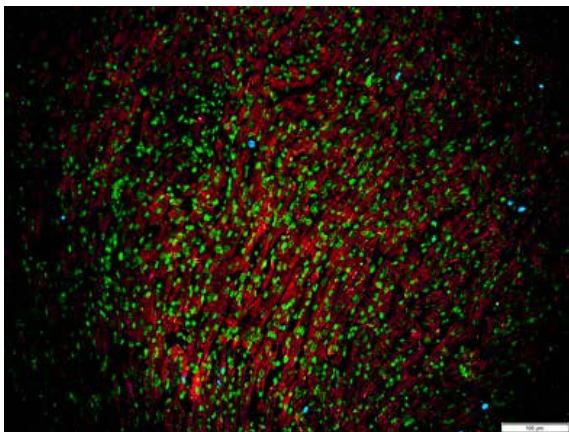
Publications

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Rinkevich-Shop S, Landa-Rouben N, Epstein FH, Holbova R, Feinberg MS, Goitein O, Kushnir T, Konen E and **Leor J**. Injectable collagen implant improves survival, cardiac remodeling, and function in the early period after myocarditis in rats. *J Cardiovasc Pharmacol Ther.* 2014;19:470-80.

Rinkevich-Shop S, Konen E, Kushnir T, Epstein FH, Landa-Rouben N, Goitein O, Ben Mordechai T, Feinberg MS, Afek A and **Leor J**. Non-invasive assessment of experimental autoimmune myocarditis in rats using a 3 T clinical MRI scanner. *Eur Heart J Cardiovasc Imaging.* 2013;14:1069-79.

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

Naftali-Shani N, Itzhaki-Alfia A, Landa-Rouben N, Kain D, Holbova R, Adutler-Lieber S, Molotski N, Asher E, Grupper A, Millet E, Tessone A, Winkler E, Kastrup J, Feinberg MS, Zipori D, Pevsner-Fischer M, Raanani E and **Leor J**. The origin of human mesenchymal stromal cells dictates their reparative properties. *J Am Heart Assoc*. 2013;2:e000253.

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Shachar M, Tsur-Gang O, Dvir T, **Leor J** and Cohen S. The effect of immobilized RGD peptide in alginate scaffolds on cardiac tissue engineering. *Acta Biomaterialia*. 2011;7:152-62.

Ruvinov E, **Leor J** and Cohen S. The promotion of myocardial repair by the sequential delivery of IGF-1 and HGF from an injectable alginate biomaterial in a model of acute myocardial infarction. *Biomaterials*. 2011;32:565-78.

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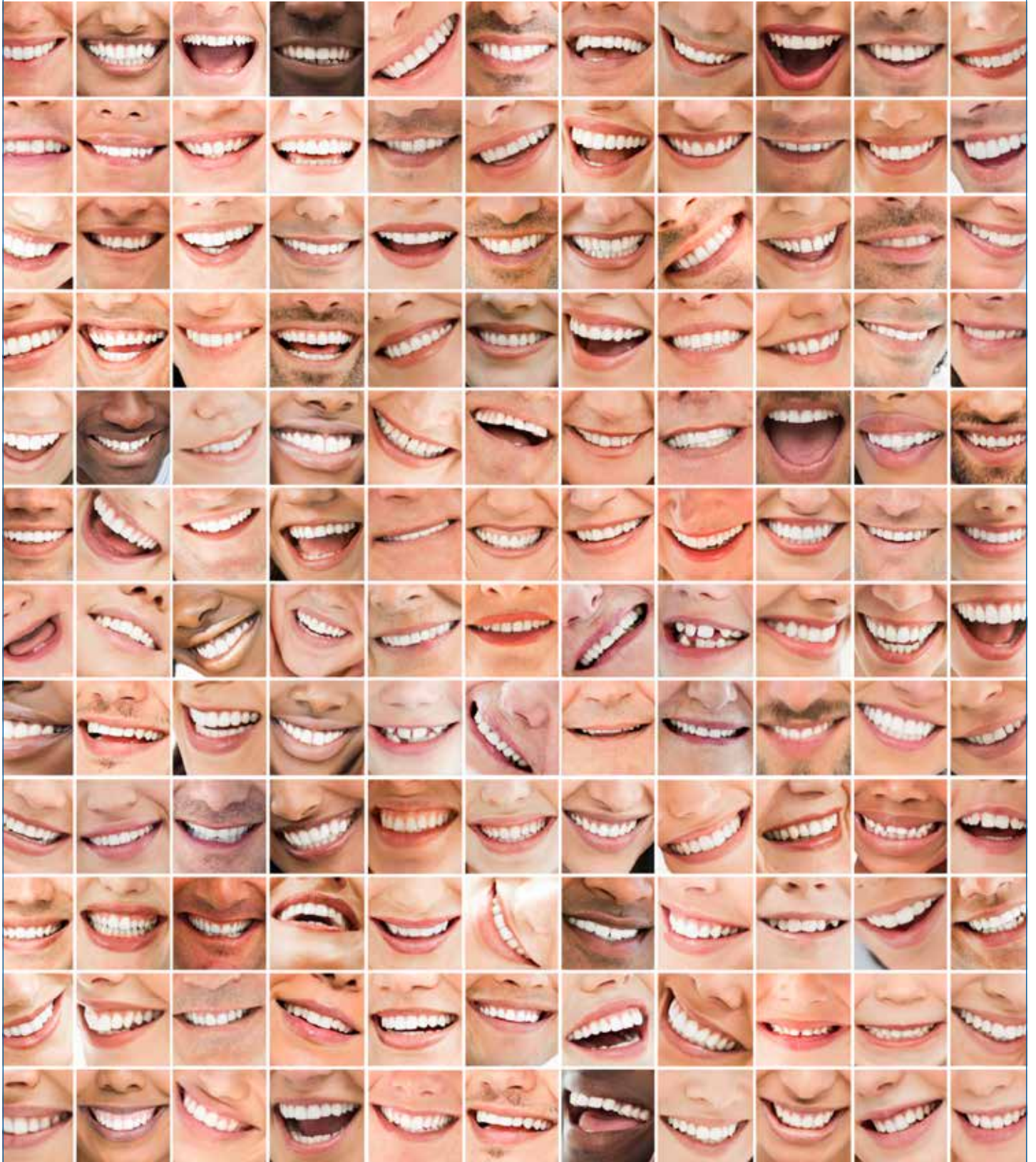
Grants

2012-2015 MRI imaging of infarct macrophage subset, Binational Science Foundation (BSF)

2012-2015 Israeli National Nanotechnology Initiative and Helmsley Charitable Trust for a focal technology area (FTA) on Nanomedicines for Personalized Theranostics

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

Dental Health and Medicine





Prof. Tamar Brosh, Ph.D.

Department of Oral Biology
Goldschleger School of Dental Medicine
Sackler Faculty of Medicine



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Biochemical Aspects of Dental Restorations and Orthodontic Tooth Movement

Positions

Associate Professor, Sackler Faculty of Medicine

Head, Department of Oral Biology

Research

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

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

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

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

Publications

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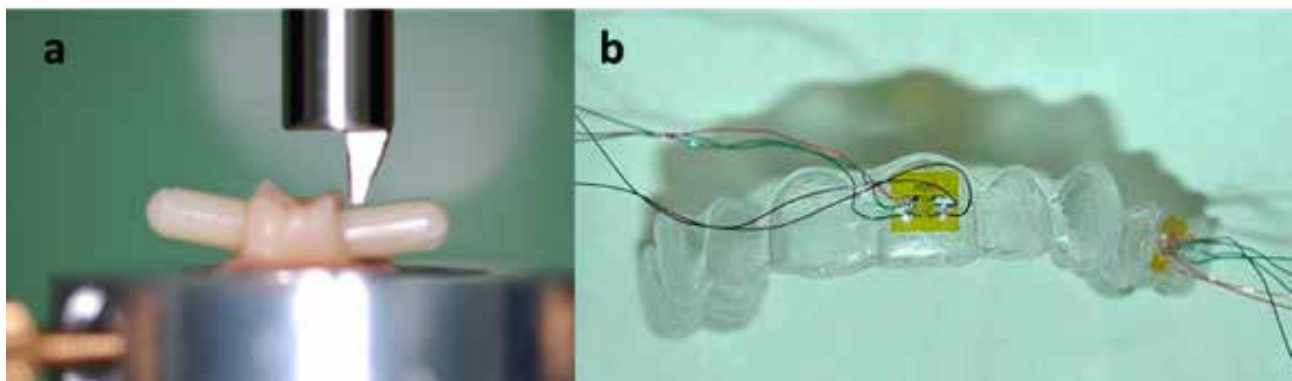
Vardimon AD, Shoshani K, Shpack N, Reimann S, Bourauel C, **Brosh T**. Incremental growth of the maxillary tuberosity from 6 to 20 years-A cross-sectional study. *Arch Oral Biol*. 2010; 59:655-62.

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

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Levartovsky S, Levy G, **Brosh T**, Harel N, Ganor Y, Pilo R. Dimensional stability of polyvinyl siloxane impression material reproducing the sulcular area. *Dent Mater J.* 2013; 32:25-31.

Heller S, **Brosh T**, Kosashvili Y, Velkes S, Burg A, Dudkiewicz I. Locking versus standard screw fixation for acetabular cups: is there a difference? *Arch Orthop Trauma Surg.* 2013; 133:701-5.

Herman A, Avivi E, **Brosh T**, Schwartz I, Liberman B. Biomechanical properties of bone treated by

magnetic resonance-guided focused ultrasound — an in vivo porcine model study. *Bone.* 2013; 92-97.

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Brosh T, Yekaterina BE, Pilo R, Shpack N, Geron S. Can cone beam CT predict the hardness of interradicular cortical bone? *Head & Face Medicine*, 2014, in press.

Grants

2013-2016 The use of peptide nanostructures for the reinforcement of dental materials, Kamin Fund



Prof. Ilana Eli, D.M.D.

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Behavioral Sciences in Dentistry

Positions

Professor, Sackler Faculty of Medicine

Head, School of Dental Medicine

Research

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

Research topics:

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

Publications

M. Ashkenazi, S. Blumer, **I. Eli**. Effect of computerized delivery intraligamental injection in primary molars on corresponding permanent tooth buds. *International Journal of Pediatric Dentistry*, 20, 270-275, 2010

I. Eli. Placebo/Nocebo: The "Biochemical" Power of Words and Suggestions (*Editorial*). *Journal of Orofacial Pain*, 24, 333-334, 2010

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R. Defrin, **I. Eli**, D. Pud. The interactions between sex, ethnicity and religion on gender role expectations of pain. *Gender Medicine* 8, 172-183, 2011

A. Emodi-Perlman, **I. Eli**, P. Friedman-Rubin, C. Goldsmith, S. Reiter, E. Winocur. Bruxism, oral

parafunctions, anamnestic and clinical findings of temporomandibular disorders in children. *Journal of Oral Rehabilitation*, 39, 126-135, 2012

N. Uziel, G. Bronner, E. Elran, **I. Eli**. Sexual correlates of gagging and dental anxiety. *Community Dental Health*, 29, 243-247, 2012

I. Eli. Clinical Decision Making – the Danger of Confirmation Bias (*Editorial*). *Journal of Orofacial Pain*, 26, 265-266, 2012

E. Elran, G. Bronner, N. Uziel, **I. Eli**, ND Kitrey, G. Raviv. Impact of vaginal penetration difficulties on sexual function of women and their male partners. *The European Journal of Contraception and Reproductive Health Care*, 2014 (in press)

Chapters

I. Eli and P. Svensson. The multidimensional nature of pain. In: *Textbook of Endodontology*, G. Bergenholz, P. Horsted-Bindslev, C. Reit, (Eds.), Wiley Blackwell Ltd., UK, 2nd edition, 2010, pp. 277-289

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I. Eli. Stress and anxiety in immediate implant insertion – the effect on cognition, pain and wound healing. In: *Ridge preservation & Immediate Implantation*, D. Swartz-Arad (Ed.), Quintessence Publishing Co., Ltd., New Malden, Surrey KT3 3AB, UK, 2012 (pp.239-241)

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



Prof. Sandu Pitaru, D.M.D.

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A Novel Primitive Stem Cell Population in Adult and Elderly Oral Mucosa – Basic Research and Clinical Translation

Position

Professor of Oral Biology, School of Dental Medicine

Research

Our research focuses on the biology of a new stem cell population recently discovered in our laboratory. We found, that in contrast to other tissues, the oral mucosa of the adult and elderly organism harbors a primitive neural crest-like stem cell population, which is capable of expressing embryonic associated markers and of differentiating into cell lineages of the 3 germ layers – ectoderm, mesoderm and endoderm. We term this population “oral mucosa derived stem cells – OMSC”. Using cutting edge technologies, we are investigating the genetic and epigenetic mechanisms that maintain such a fetal-like stem cell population in the adult and aging oral

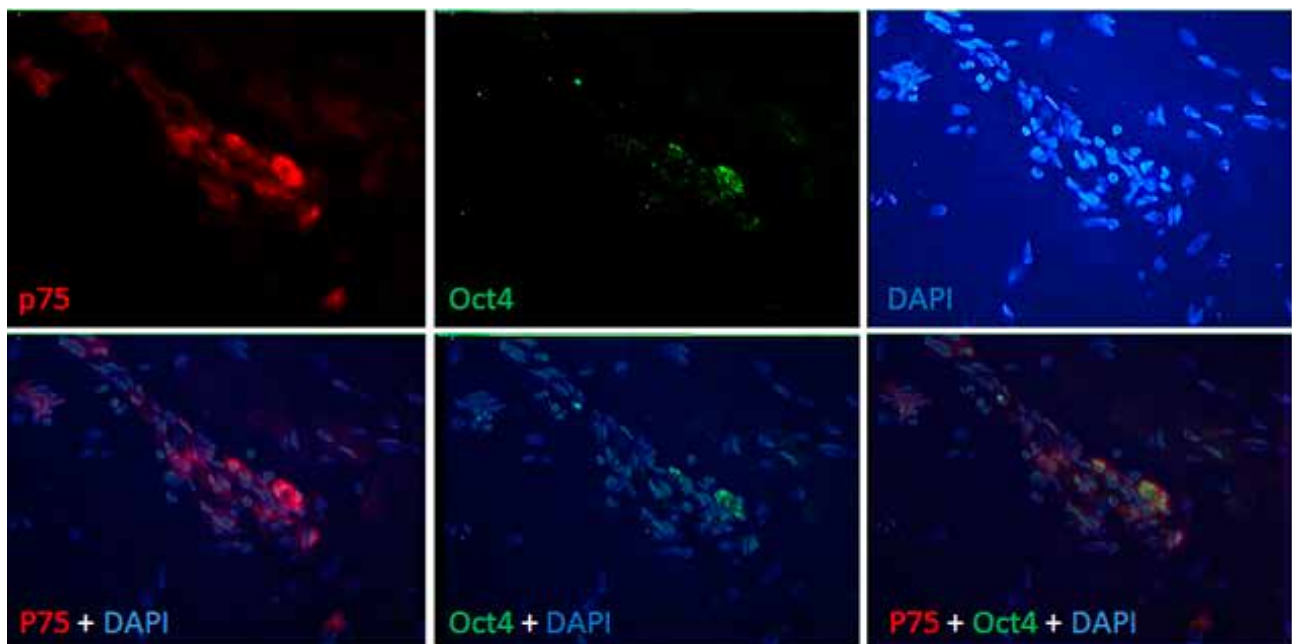
mucosa, and study how these mechanisms and OMSC are affected by chronic and neurodegenerative diseases as diabetes and Parkinson’s Disease. By elucidating these mechanisms, we aim to develop new therapeutic approaches for treating chronic diseases associated with ageing.

Based on OMSC plasticity and stemness we are currently testing their therapeutic potential for the treatment of diabetic chronic wounds, Parkinson’s disease, skeletal defects, inflammatory bowel disorders, retinal disorders and periodontal diseases.

We have developed unique fibrin-based matrices for OMSC delivery and tissue engineering purposes.

Publications

Friedmann A, Gissel K, Soudan M, Kleber BM, **Pitaru S**, Dietrich T. Randomized controlled



Human OMSC co-expressing neural crest markers – p75 (red) and pluripotency associated markers – Oct4 (green) are located in specific niches within the lamina the lamina propria of the adult human oral mucosa

trial on lateral augmentation using two collagen membranes: morphometric results on mineralized tissue compound. *J Clin Periodontol*. 2011;38:677-85.

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Treves-Manusevitz S, Hoz L, Rachima H, Montoya G, Tzur E, Vardimon A, Narayanan AS, Amar S, Arzate H, **Pitaru S**. Stem cells of the lamina propria of human oral mucosa and gingiva develop into mineralized tissues in vivo. *J Clin Periodontol* 2013;40:73-81.

Ganz J, Arie I, Ben Zur T, Dadon-Nachum M, Pour S, Araidy S, **Pitaru S**, Offen D. Astrocyte-like cells derived from human oral mucosa stem cells provide neuroprotection in vitro and in vivo. *Stem Cells Transl Med* 2014;3:375-86.

Grants

2012 – 2016 Oral mucosa stem cells for the generation of a primordial periodontium - The effect of aging and diabetes type 2. US-Israel Binational Science Foundation



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

Department of Orthodontic & Department of Oral Biology, Maurice and Gabriela Goldschleger School of Dental Medicine, Sackler Faculty of Medicine



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

Position

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

Research

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

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

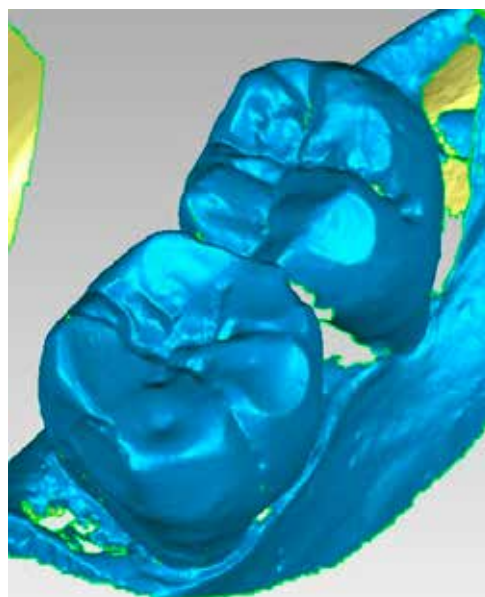
help us planning and establishing better treatment strategies. Long-term evolutionary processes such as decrease in jaws and teeth size, higher prevalence of impacted teeth and the loss of teeth in the arch, are all important factors that should be considered.

Publications

I. Hershkovitz, P. Smith, **R. Sarig**, R. Quam, L. Rodríguez, R. García, J.L. Arsuaga, R. Barkai, A. Gopher. Middle Pleistocene dental remains from Qesem Cave (Israel). *American Journal of Physical Anthropology*, 144, 575–592, 2011.

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

J. Abbas, K. Hamoud, H. May, N. Peled, **R. Sarig**, D. Stein, D. Alperovitch-Najenson, I. Hershkovitz. Socioeconomic and physical characteristics of



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

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N. Shpack, R.G. Bar-Ness, D. Gazit, **R. Sarig**, A.D. Vardimon. Efficacy of three hygienic protocols in reducing biofilm adherence to removable thermoplastic appliance. *Angle Orthodontics*, 84, 161-170, 2013.

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R. Sarig, A.M. Tillier. Reconstructing cultural behavior from dental wear studies: Is para-facets analysis approach scientifically valid? *HOMO-Journal of Comparative Human Biology*, 65, 181-186. 2014.

R. Sarig, I. Hershkovitz, N. Shvalb, T. Sella-Tunis, H. May, A.D. Vardimon. Proximal Attrition Facet: morphometric, demographic and aging characteristic. *European Journal of Oral Sciences*. 122, 271-278, 2014

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Shpack, N., Brosh, T., Mazor, Y., Shapinko, Y., Davidovitch, M., **Sarig, R.**, Reimann, S., Bourauel, C., Vardimon, A. D. Long-and short-term effects of headgear traction with and without the maxillary second molars. *American Journal of Orthodontics and Dentofacial Orthopedics*, 146, 467-476, 2014

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Sarig, R., Vardimon, A.D., Sussan, S., hhhBenny, L., Sarne, O., Hershkovitz I., Nir, S. Pattern of maxillary and mandibular proximal enamel thickness at the contact area of the permanent dentition from first molar to first molar. *American Journal of Orthodontics and Dentofacial Orthopedics* (accepted for publication) 2014.



Prof. Haim Tal, D.M.D., M.Dent., Ph.D.

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Sackler Faculty of Medicine



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Pursuing the Unknown



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Bone Regeneration in the Jaws

Positions

Professor

Chair, Department of Periodontology and Oral Implantology

Gerald Niznick Chair of Implantology

Research

Current research is focused on modification of techniques of bone regeneration, investigating the biological qualities of various bone substitute used to augment atrophic sites in the jaws and stabilizing collagen membrane used in guided bone regeneration procedures.

- Implant stability – histologic study.
- Use of synthetic materials in periodontal defects.
- Evaluation of novel implants – histologic study
- Grafting extraction sockets
- Stabilization of resorbable collagen membranes

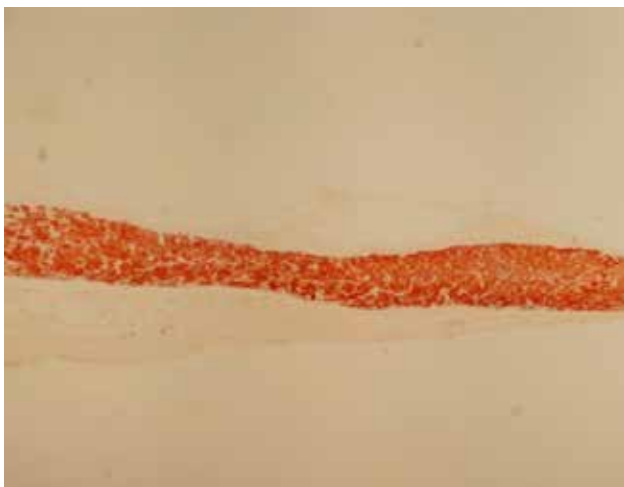
Publications

Moses O, Frenkel T, **Tal H**, Weinreb M, Bornstein M, Nemcovsky C. Effect of systemic Tetracycline (TTC) on the degradation of TTC-impregnated bi-layered collagen membranes. An animal study. *Clinical Implant Dentistry and Related Research* 2010;12:331-37

Simultaneous versus two-stage implant placement and guided bone regeneration in the canine: histomorphometry at 8 and 16 months. *Journal of Clinical Periodontology* 2010;37:1029-38.

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Stabilizing collagen membrane used in guided bone regeneration procedures.

a. Histological view (x40) of a native collagen membranes 21 days after implantation with phosphate buffered saline (0 mg/mL TTC); versus **b.** similar membrane after treatment with 50 mg/mL TTC. Collagen stained in red/brown with Avidin-Biotin-HRP reaction.

Artzi Z, Nemcovsky CE, **Tal H**, Weinberg E, Weinreb M, Prasad H, Rohrer MD, Kozlovsky A. Clinical and histomorphometric observations around dual acid-etched and calcium phosphate nanometer deposited-surface implants. *International Journal of Oral and Maxillofacial Implants*. 2011; 26:893-901.

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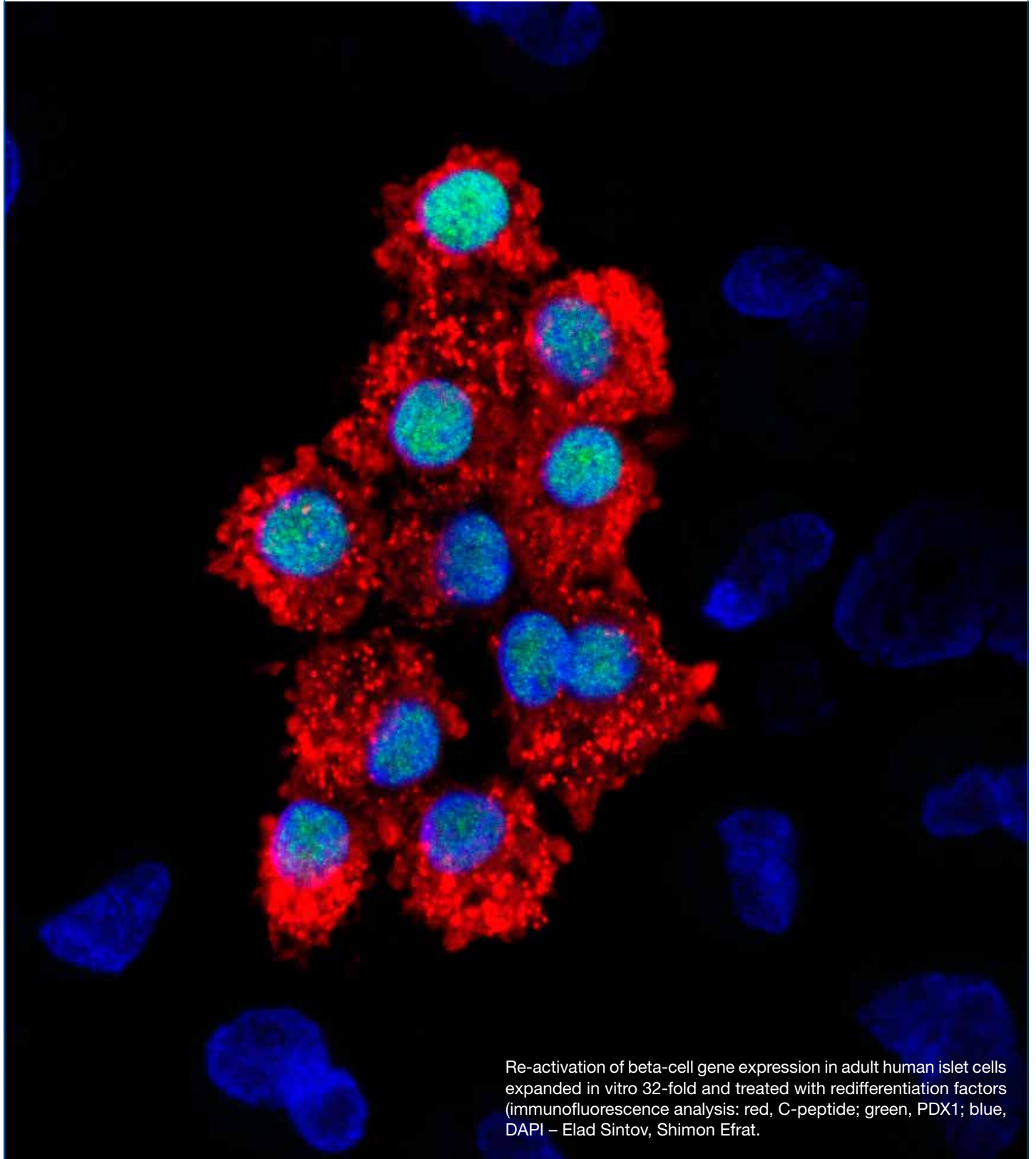
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Chapters

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Diabetes, Metabolic and Endocrine Diseases



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



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Cell Replacement Therapy for Diabetes

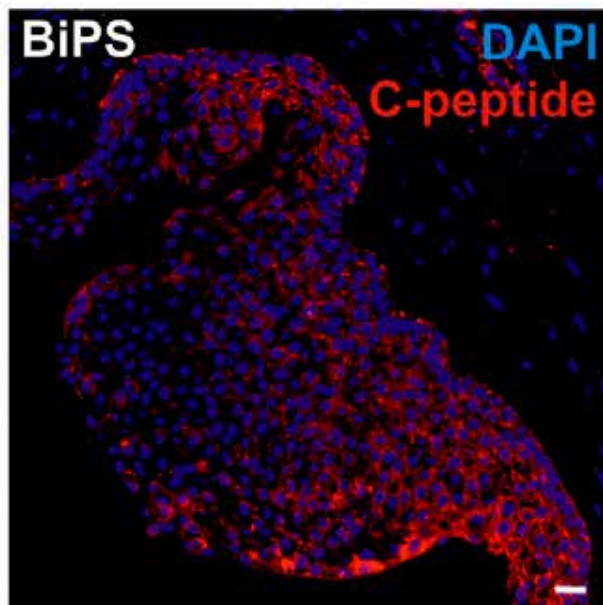
Position

Professor, Sackler Faculty of Medicine
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

Bar-Nur O, Russ HA, **Efrat S**, Benvenisty N (2011) Epigenetic memory and preferential lineage-specific differentiation in induced pluripotent stem cells derived from human pancreatic islet beta cells. *Cell Stem Cell* 9:17-23.

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Bar Y, Russ HA, Anker-Kitai L, Knoller S, **Efrat S** (2012) Redifferentiation of expanded human pancreatic beta-cell-derived cells by inhibition of the NOTCH pathway. *J Biol Chem* 287:17269-17280.

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Reviews

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N, Fox IJ (eds.), *Methods in Bioengineering*, Yarmush ML, Langer RS (eds.), Artech House, pp. 35-46.

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

Grants

2012-2017 Stem cells for biological assays of novel drugs and predictive toxicology, Innovative Medicines Initiative (IMI)

2013-2015 Redifferentiation of expanded human beta-cell-derived cells for cell therapy of diabetes, Israel Ministry of Industry, Trade, and Labor Kamin Program

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)



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Pathobiology of Secretory Granule Packaging and Growth

Positions

Professor, Sackler Faculty of Medicine

Chair, Department of Pathology

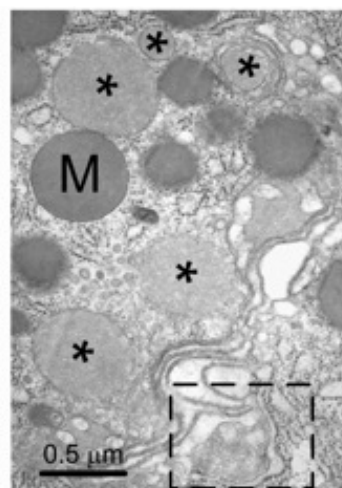
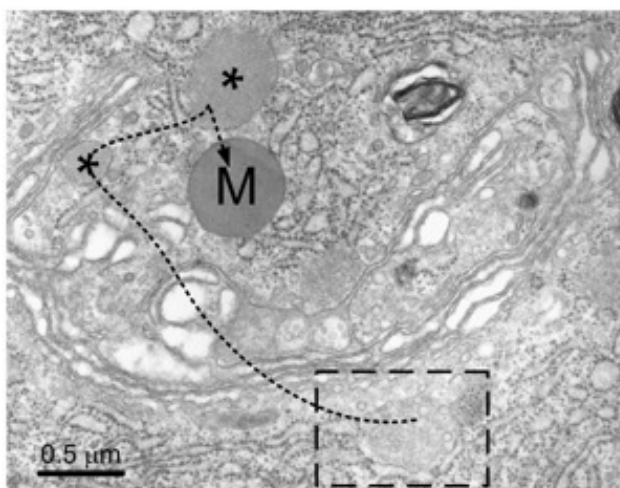
Academic Advisory Committee, ISEF Foundation

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-translational 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. 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

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Gorzalczany Y, Gilad Y, Amihai D, **Hammel I**, Sagi-Eisenberg R, Merimsky O, Combining an EGFR directed tyrosine kinase inhibitor with autophagy-inducing drugs; A beneficial strategy to combat non-small cell lung cancer. *Cancer Letters* 2011; 310:207-15.

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Reviews

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Chapters

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Hammel I, Meilijson I. The stealthy nano-machine behind mast cell granule size distribution. *Mol Immunol.* 2014. pii: S0161-5890(14)00032-7. doi: 10.1016/j.molimm.2014.02.005 [Epub ahead of print]

Grants

2014-2017 Bination Science Foundation (Co-PI, Ronit Sagi-Eisenberg)



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Pursuing the Unknown

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Intracellular Membrane Trafficking

Position

Senior Lecturer, Sackler Faculty of Medicine

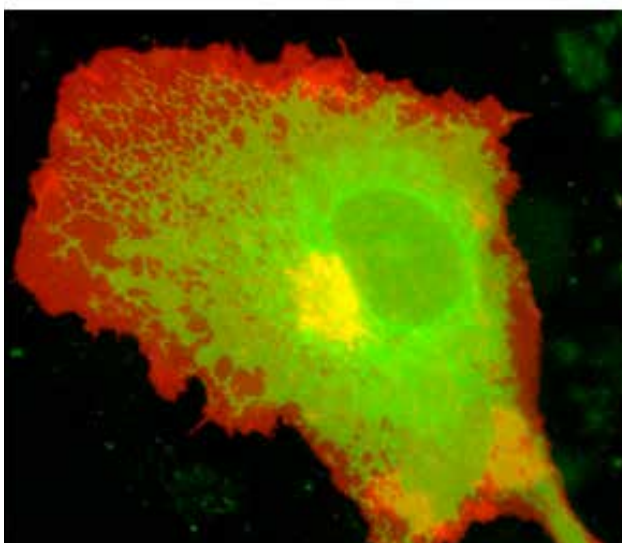
Research

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.



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

Publications

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from the plasma membrane by modulating Rac1 activity. *Biochemical J.* 439:433-42. 2011.

Yaffe Y, Shepshelovitch J, Yeheskel A, Shmerling H, Kwiatek JM, KaGaus K, Pasmanik-Chor M, **Hirschberg K**. The MARVEL transmembrane domain of Occludin mediates oligomerization and targeting to the basolateral surface in epithelia. *J Cell Sci.* 125:3545-56. 2012.

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David N, Yaffe Y, Hagoel L, Elazar M, Glenn JS, **Hirschberg K**, Sklan EH. The interaction between the Hepatitis C proteins NS4B and NS5A is involved in viral replication. *Virology.* 475C:139-149. 2014

Grants

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



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Pancreas Development and Function: the Role of Microenvironmental Cues

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

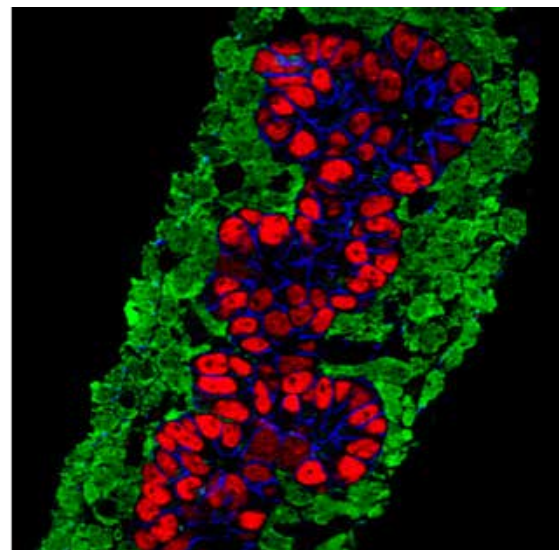
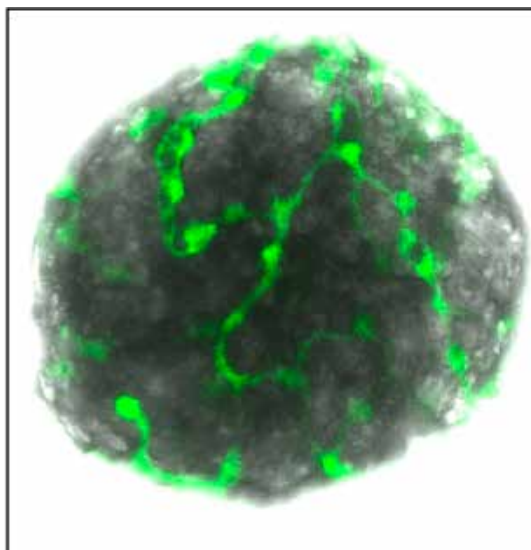
Maintenance of blood glucose levels is dependent upon the tight regulation of insulin secretion from pancreatic beta-cells. Insufficient insulin secretion, whether due to reduced beta-cell numbers, or impaired beta-cell function, leads to diabetes. Our group studies how insulin-producing beta-cells maintain 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.

Publications

Avraham-Davidi I, Yona S, Grunewald M, **Landsman L**, Cochain C, Silvestre JS, Mizrahi H, Faroja M, Strauss-Ayali D, Mack M, Jung S, Keshet E. (2013)



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

On-site education of VEGF-recruited monocytes improves their performance as angiogenic and arteriogenic accessory cells. *J Exp Med* 210, 2611-25.

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

Landsman L., Parent A. and Hebrok M. (2011) Elevated Hedgehog/Gli signaling causes b-cell dedifferentiation in mice. *Proc Natl Acad Sci USA* 108, 17010-17015.

Landsman L., Nijagal A., Whitchurch T.J., VanderLaan R.L., Zimmer W.E., MacKenzie T.C. and Hebrok M. (2011) Pancreatic mesenchyme regulates epithelial organogenesis throughout development. *PLoS Biol* 9, e1001143.

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) Starter Grant

β -cell dysfunction in diabetes: elucidating the role of islet-associated mesenchymal cells

2014-2017 Israel Ministry of Health

Elucidating the role of pancreatic mesenchyme secreted factors in beta-cell function and diabetes progression



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Brain@tau.neuroscience.tau.ac.il



Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

Position

Professor, Sackler Faculty of Medicine

Research

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

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

Main research projects currently in the lab:

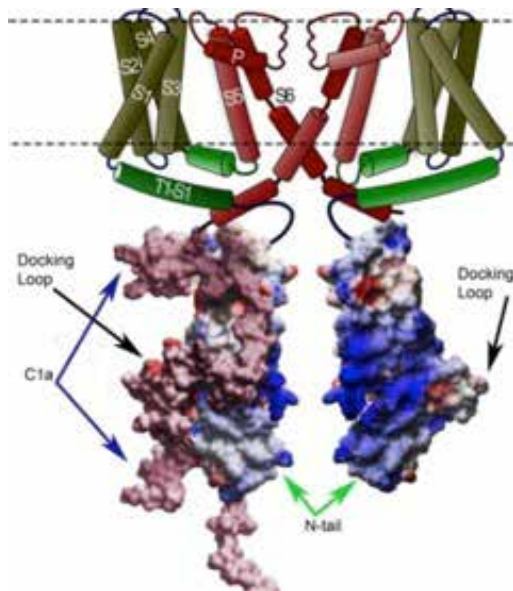
- 1) Study of the novel role of Kv2.1 potassium channel in insulin secretion from pancreatic islet β cells, as a target for novel drug design for the treatment of type-2 diabetes;
- 2) Study of structure-function and modulations by presynaptic modulators of Kv2.1 and other Kv channels, specifically KCNQ2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

Research methods:

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

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

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



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

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

Publications

Feinshreiber, L., Singer-Lahat, D., Friedrich, R., Matti, U, Sheinin, A., Yizhar, O., Nachman, R., Chikvashvili, D., Rettig, J., Ashery, U. and **Lotan, I.** Non-conducting function of the Kv2.1 channel enables it to recruit vesicles for release in neuroendocrine and nerve cells. *J Cell Sci.* 123:1940-7 (2010)

Etzioni, A., Siloni, S., Chikvashvili, D., Strulovich, R., Sachyani, D., Regev, N., Greitzer-Antes, D., Hirsch, J.A. and **Lotan, I.** Regulation of neuronal M channel gating in an isoform-specific manner; functional interplay between calmodulin and syntaxin 1A. *J Neurosci.* 31:14158-71 (2011).

Dai XQ, Manning Fox JE, Chikvashvili D, Casimir M, Plummer G, Hajmrle C, Spigelman AF, Kin T, Singer-Lahat D, Kang Y, Shapiro AM, Gaisano HY, **Lotan I**, Macdonald PE. The voltage-dependent potassium channel subunit Kv2.1 regulates insulin secretion from rodent and human islets independently of its electrical function. *Diabetologia.* 2012;55:1709-20.

Lotan I, Khlebtovsky A, Inbar E, Strenov J, Djaldetti R, Steiner I. Primary brain T-cell lymphoma in an HTLV-1 serologically positive male. *J Neurol Sci.* 2012;314:163-5.

Greitzer-Antes D, Barak-Broner N, Berlin S, Oron Y, Chikvashvili D, **Lotan I.** Tracking Ca²⁺-dependent and Ca²⁺-independent conformational transitions in syntaxin 1A during exocytosis in neuroendocrine cells. *J Cell Sci.* 2013;126:2914-23.

Hellmann MA, Mosberg-Galili R, **Lotan I**, Steiner I. Maintenance IVIg therapy in myasthenia gravis does not affect disease activity. *J Neurol Sci.* 2014;338:39-42.

Review

Michaevlevski, I. and **Lotan, I.** Role of neuronal potassium M-channels in sympathetic regulation of cardiac function. *J Physiol.* 589:2659-2660 (2011).



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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

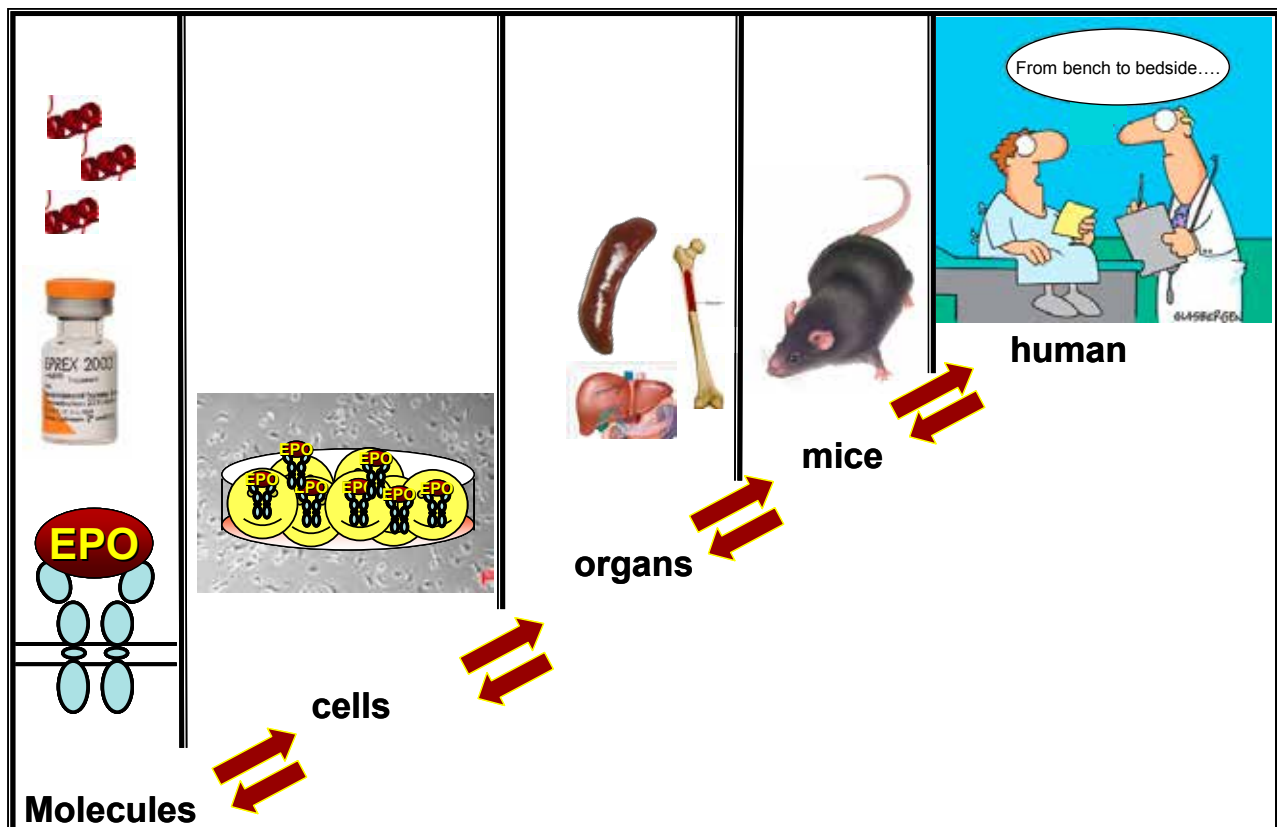
Research

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

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

Position

Professor Emeritus, Sackler Faculty of Medicine

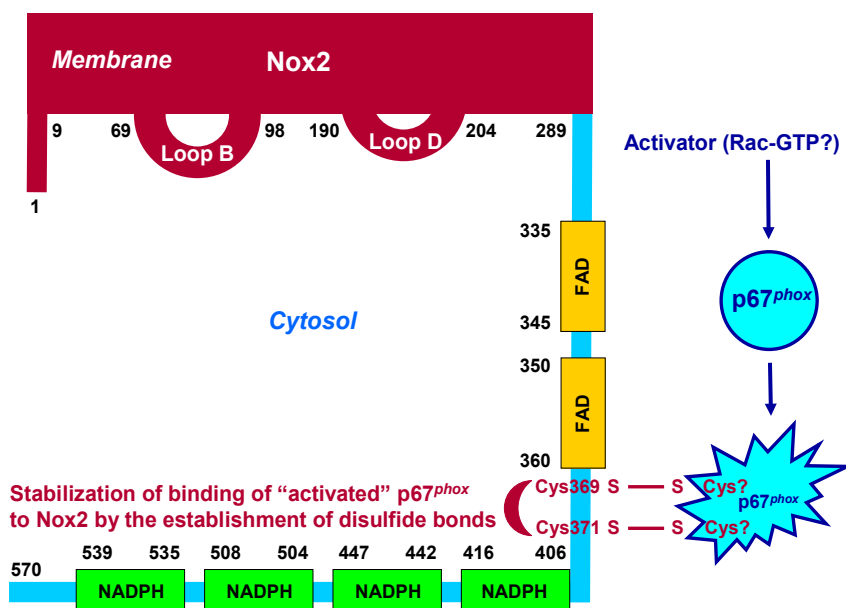
Julius Friedrich Cohnheim Laboratory of Phagocyte Research

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 (991 citations); the development of the first cell-free system of ROS production; the discovery of the cytosolic oxidase components (673 citations); the discovery of the role of the small GTPase Rac in oxidase activation (832 citations); the introduction of

“peptide walking” to identify sites of protein-protein interaction, and the construction of chimeric cytosolic oxidase activators. The laboratory is equipped for the performance of advanced biochemical and molecular biology techniques.

The most recent interest of our group is focused on the mapping of the hotspots of interaction between the catalytic oxidase component Nox2 and the cytosolic activator p67^{phox}. We found that the dehydrogenase region of Nox2 (residues 288-570) contains a Cys-Gly-Cys (CGC) triad (residues 369-371), which serves as a binding site for p67^{phox}. This finding is based on a novel methodology, designed by us, in which we measure the binding of recombinant p67^{phox} to an array of synthetic overlapping peptides covering the sequence of the dehydrogenase region of Nox2. Two Nox2 peptides that share the CGC triad, at their C- and N-termini, respectively, were found to bind p67^{phox}. “Mutating” either C369 or C371 to R resulted



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

in loss of p67^{phox} binding. Chemical reduction of CGC-containing peptides also led to loss of binding. Linking the two cysteines by a disulfide bond resulted in a marked increase in binding. We concluded that binding of p67^{phox} to the catalytic component of the NADPH oxidase complex is redox regulated and involves the establishment of disulfide bonds between p67^{phox} and Nox2. The CGC triad might have a dual role by acting both as a protein disulfide isomerase (PDI) and by providing the cysteines for the establishment of disulfide bonds with p67^{phox}. This novel hypothesis rests on the evidence that the CGC motif mimics functionally and structurally the CGHC catalytic site of members of the PDI family. Recently, we showed that a recombinant Nox2 construct possesses

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

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Molecular Biology of the Insulin-Like Growth Factor System

Positions

Professor, Sackler Faculty of Medicine

Head, Yoran Institute for Human Genome Research

Lady Davis Chair in Biochemistry

Chair, Department of Human Molecular Genetics and Biochemistry

Research

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

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

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Genomics & Personalized Medicine



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Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders & Cancer

Positions

Professor, Sackler Faculty 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.

Publications

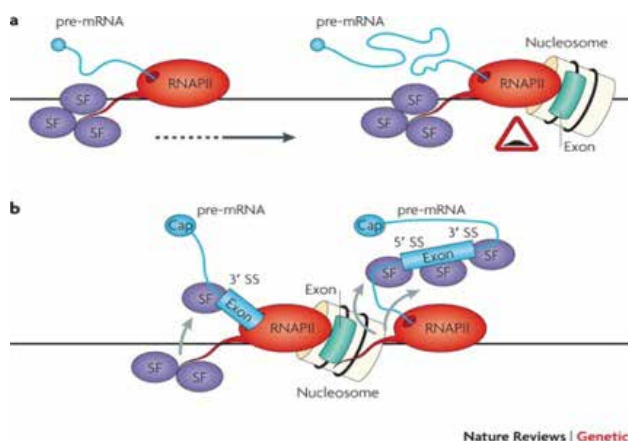
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Nucleosome occupancy marks exons and is coupled to transcription. **a**. RNA polymerase II (RNAPII), associated with different splicing factors (SFs), travels along the gene and transcribes it. When RNAPII reaches an area with high nucleosome occupancy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

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Grants

2012-2015 ISF – Morasha for Neurodegenerative Diseases, Tissue-specific alternative splicing disease

2013-2015 Teva – Neuroscience, Evaluation of therapeutic agents in a mouse model for Familial Dysotonomia

2013-2018 Israel Science Foundation, Identification of novel determinants of splicing regulation

2014-2015 Israel Cancer Research Fund (ICRF) Project Grant



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Genomic Analysis of Hereditary Hearing Loss

Positions

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President, Federation of the Israel Societies for Experimental Biology (ILANIT)
President, Israel Society of Auditory Research
Associate Editor, *European Journal of Human Genetics*

Research

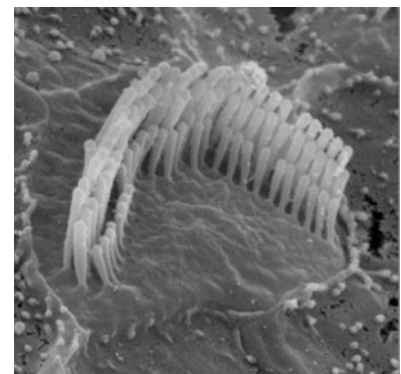
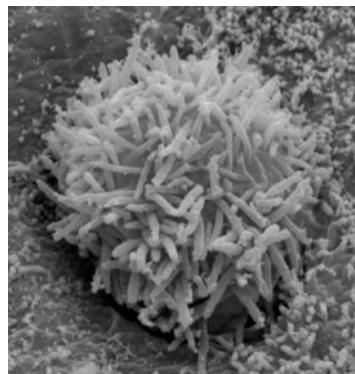
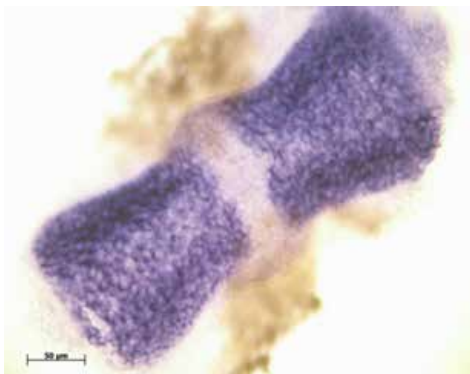
Our primary interest is the genetic basis of hereditary hearing loss or deafness. Our group is working towards the identification, characterization and regulation of genes associated with hereditary hearing loss. For gene discovery, we focus on the Israeli Jewish and Palestinian Arab populations in the Middle East. Our studies have 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.

Publications

Manuscripts

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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).

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Koffler, T., Ushakov, K. and **Avraham, K.B.** (2015) Genetics of hearing loss – syndromic. *Otolaryngol Clin North Am.* doi: 10.1016/j.otc.2015.07.007.

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 Morphodynamics of Mammalian Planar Cell Polarity – a Quantitative Approach, Human Frontier Science Program, Co-PIs: Ping Chen, David Sprinzak, Fumio Matsuzaki

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



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Genomic-scale Bioinformatics Exploration of Gene Regulation

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Publications

Elkon R*, Loayza-Puch F*, Korkmaz G, Lopes R, Breugel PCV, Bleijerveld OB, Altelaar AFM, Wolf E, Lorenzin F, Eilers M, Agami R: Myc coordinates transcription and translation to enhance transformation and suppress invasiveness. *EMBO Rep.* 2015, pii: e201540717. (*Equal contribution).

Elkon R*, Milon B*, Morrison L, Shah M, Vijayakumar S, Racherla M, Leitch CC, Silipino L, Hadi S, Weiss-Gayet M, Barras E, Schmid CD, Ait-Lounis A, Barnes A, Song Y, Eisenman DJ, Elyahu E, Frolenkov GI, Strome SE, Durand B, Zaghoul NA, Jones SM, Reith W, Hertzano R. RFX transcription factors are essential for hearing in mice. *Nat Commun* 2015, 6:8549. (*Equal contribution).

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ML, Shiloh Y. Parallel profiling of the transcriptome, cistrome, and epigenome in the cellular response to ionizing radiation. *Sci Signal.* 2014, 7:rs3. (*Equal contribution).

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Genomic Biomarkers for CNS Drug Response

Positions

Director, National Laboratory for the Genetics of Israeli Populations

Adjunct Professor, University of Florida, Gainesville, FL, USA

Senior Editor, *Pharmacogenomics*

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

Member of the NIH Pharmacogenomics Research Network (PGRN)

Research

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

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

Among genes that we identified as tentative genomic biomarkers for the response to anti-depressant drugs, two genes, CHL1 and ITGB3, have been replicated in clinical cohorts of major depression patients, lending support for our novel research approach.

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

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

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

Publications

Morag A, Kirchheiner J, Rehavi M, **Gurwitz D**. Human lymphoblastoid cell line panels: novel tools for assessing shared drug pathways. *Pharmacogenomics*. 11:327-340 (2010).

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2014 – 2016 SSRI antidepressants as anti-cancer therapy: role for down-regulation of miR-221 and miR-222, Israel Cancer Research Fund (ICRF). Co-PI: Noam Shomron

2014 – 2018 Deciphering beta-amyloid and tau neurotoxicity: Genome-wide expression profiling for sensitivity biomarkers, Israel Science Foundation. Jointly with Illana Gozes

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



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microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position

Senior Lecturer, Sackler Faculty of Medicine

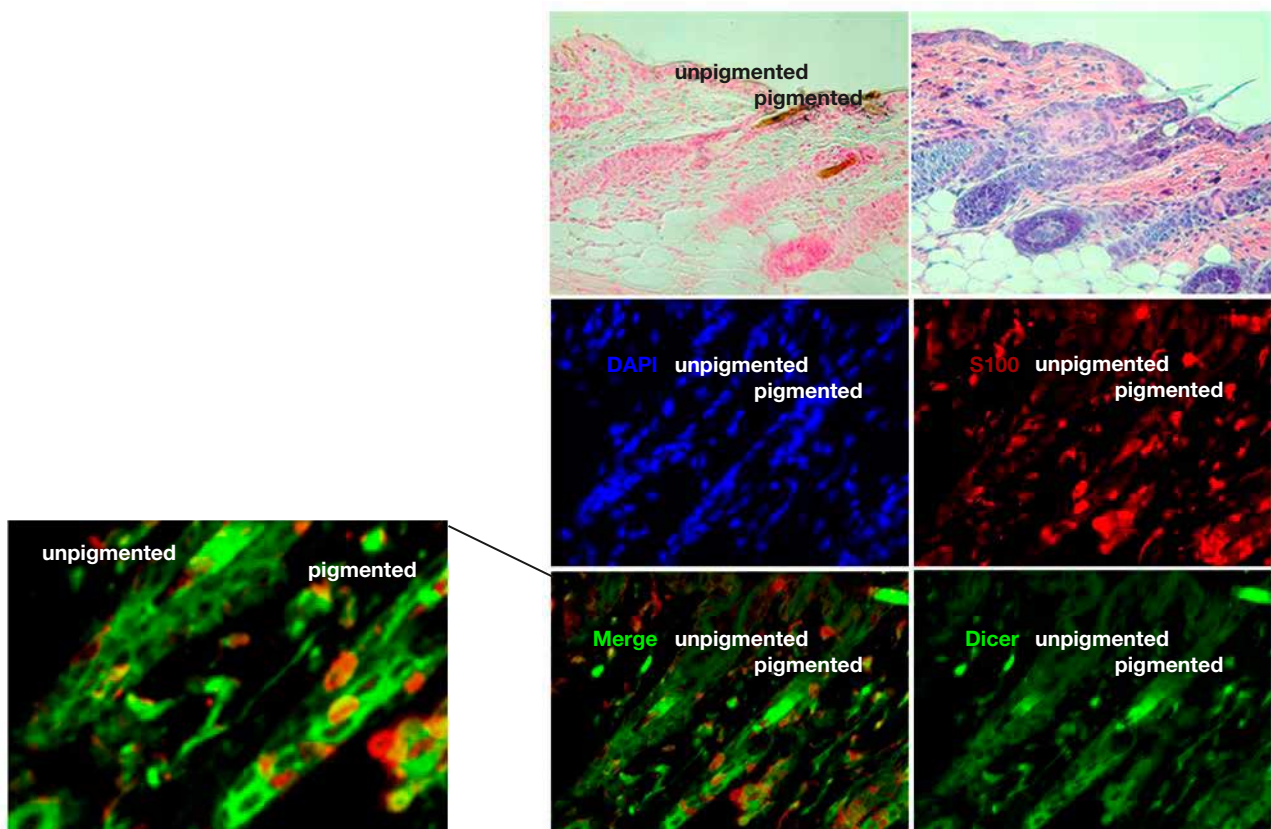
Research

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

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

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Grants

2012-2015 Fritz Thyssen Stiftung

2012-2016 Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease



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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
Pollak Chair of Biological Anthropology
Honorary Research Fellow, King's College Medical School, London, UK

Research

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

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

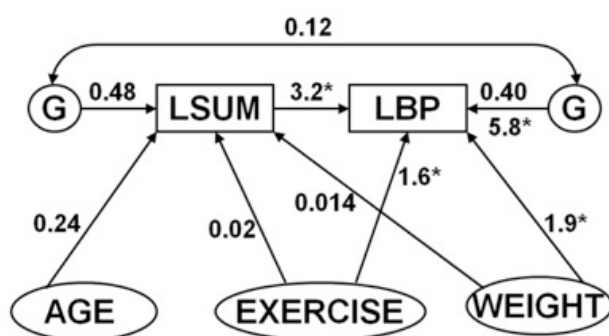
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Path diagram of the main risk factors for low back pain (LBP) in middle-age women. The figure shows contribution of various factors to LBP, including genetic effects (G) and lumbar disc degeneration (LSUM). The results presented as variance components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

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Grants

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



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Genomics and Gene Regulation by Small RNAs

Positions

Senior Lecturer, Sackler Faculty of Medicine

Academic Director, 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

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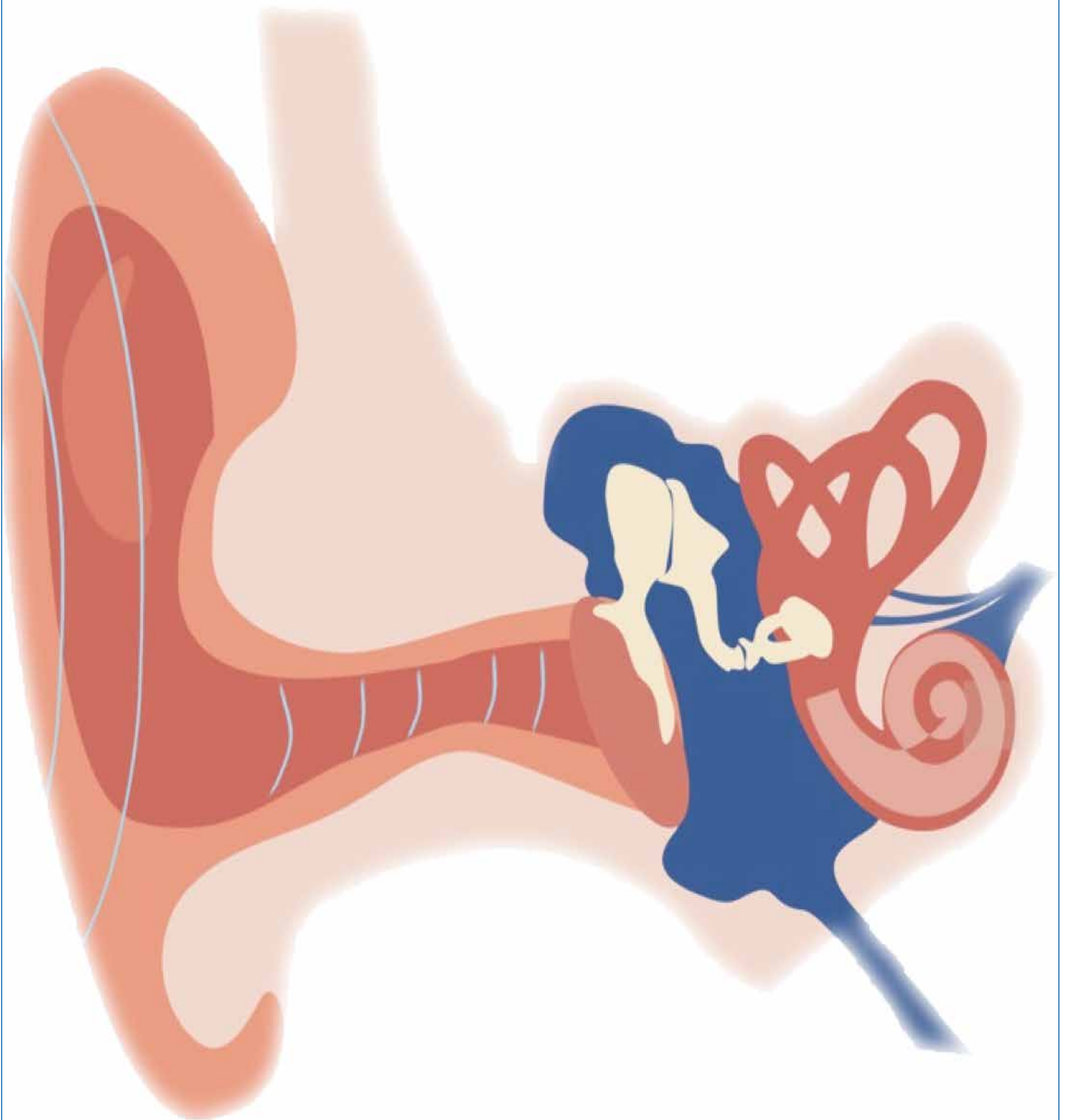
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Grants

2011-2015 I-CORE Program of the Planning and Budgeting Committee, The Israel

	Science Foundation (grant number 41/11)	2014-2016	Israel Cancer Research Fund (ICRF), Acceleration Grant
2013-2016	Israel Cancer Research Fund (ICRF), Research Career Development Award (RCDA)	2014-2016	Binational Science Foundation (BSF)
		2014-2016	Israel Cancer Association
2014-2015	Earlier.org—Friends for an Earlier Breast Cancer Test	2015-2016	Check Point Institute for Information Security
2014-2015	Israeli Ministry of Defence, office of Assistant Minister of Defence for Chemical, Biological, Radiological and Nuclear (CBRN) Defence	2014-2015	Varda and Boaz Dotan Research Center in Hemato-Oncology, Idea Grant
		2015-2018	Interdisciplinary grant of the Israeli Ministry of Science, Technology and Space on the Science, Technology and Innovation for the Third Age
2014-2016	Saban Family Foundation—Melanoma Research Alliance		
2014-2016	Foundation Fighting Blindness		

Hearing, Language & Speech Sciences and Disorders





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Paralinguistic Communication, Phonetics and Psychoacoustics

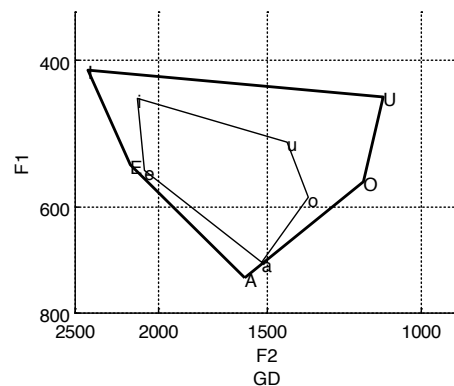
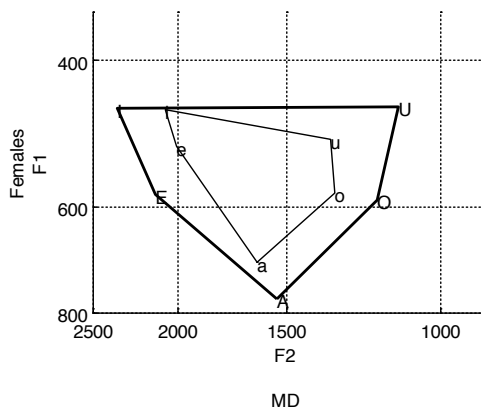
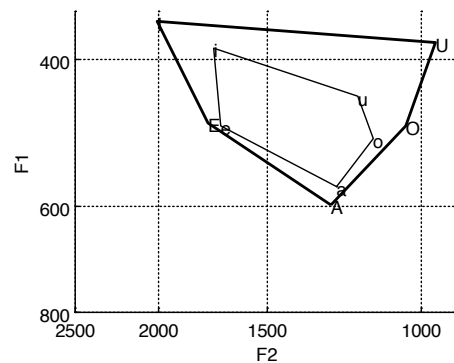
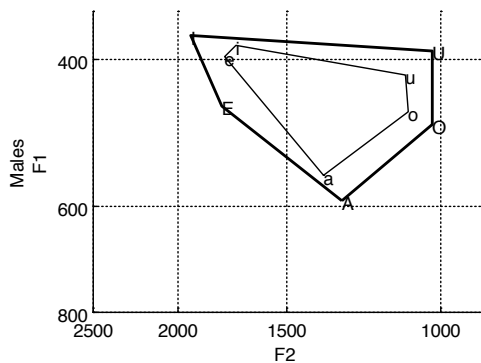
Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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

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

Publications

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Voice, Speaking Rate, Stuttering and Fluency Disorders

Positions

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Research

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

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

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

Publications

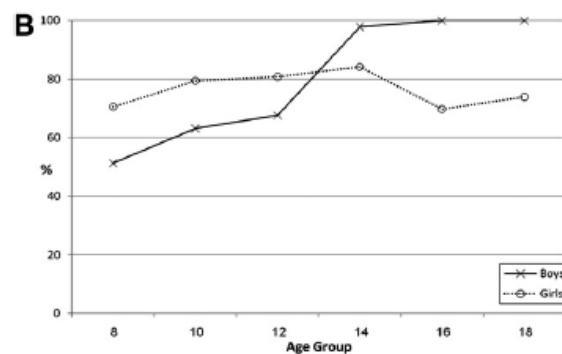
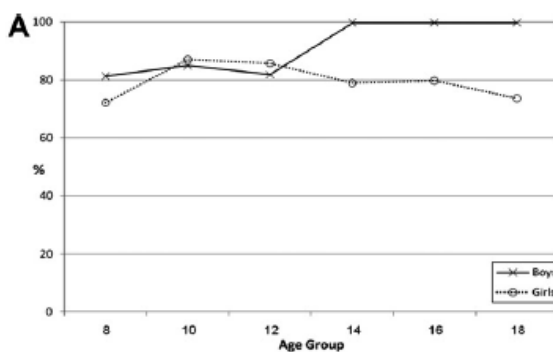
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Correct gender identification rates for boys and girls in the six age groups for (A) sentences and (B) vowels.

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Chapters

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

Positions

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Research

Our research focuses on two main fields:

(a) Learning and plasticity in the auditory system:

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

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

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

Publications

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Auditory Processing in the Normal and Impaired Auditory System

Positions

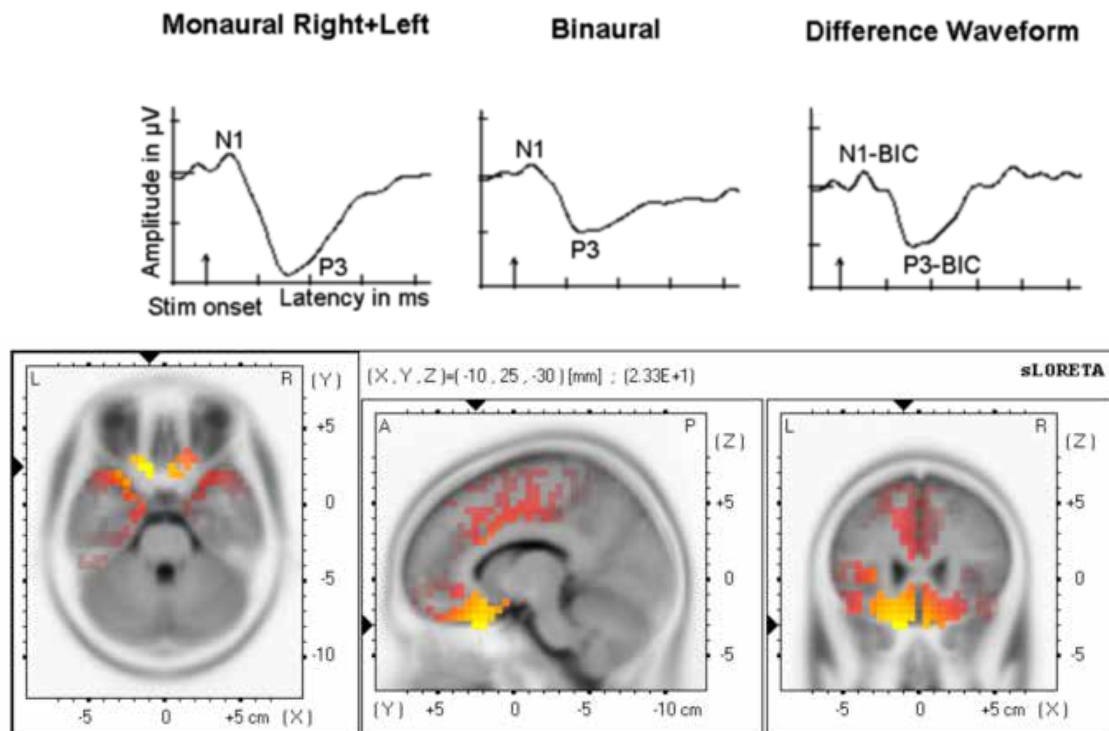
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Research

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

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



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

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

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

Publications

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

Position

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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

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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 functioning in school, in the family and in general
- Educational Audiology
- Auditory rehabilitation of people with hearing loss

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

Our research activities focus on two main areas:

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

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

2. Research of the ramifications of a hearing loss and communication difficulties on the individual's ability to function in various life environments: educational system, home and work environment, as well as the ramifications of the hearing loss

and the communication difficulties on the people in the individual's environment.

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

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

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

Publications

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Hearing Science and Clinical Audiology

Position

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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

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Language Acquisition and Development of Linguistic Literacy

Position

Professor, School of Education and Sackler Faculty of Medicine

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

Member, Academie Europea

Research

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

Publications

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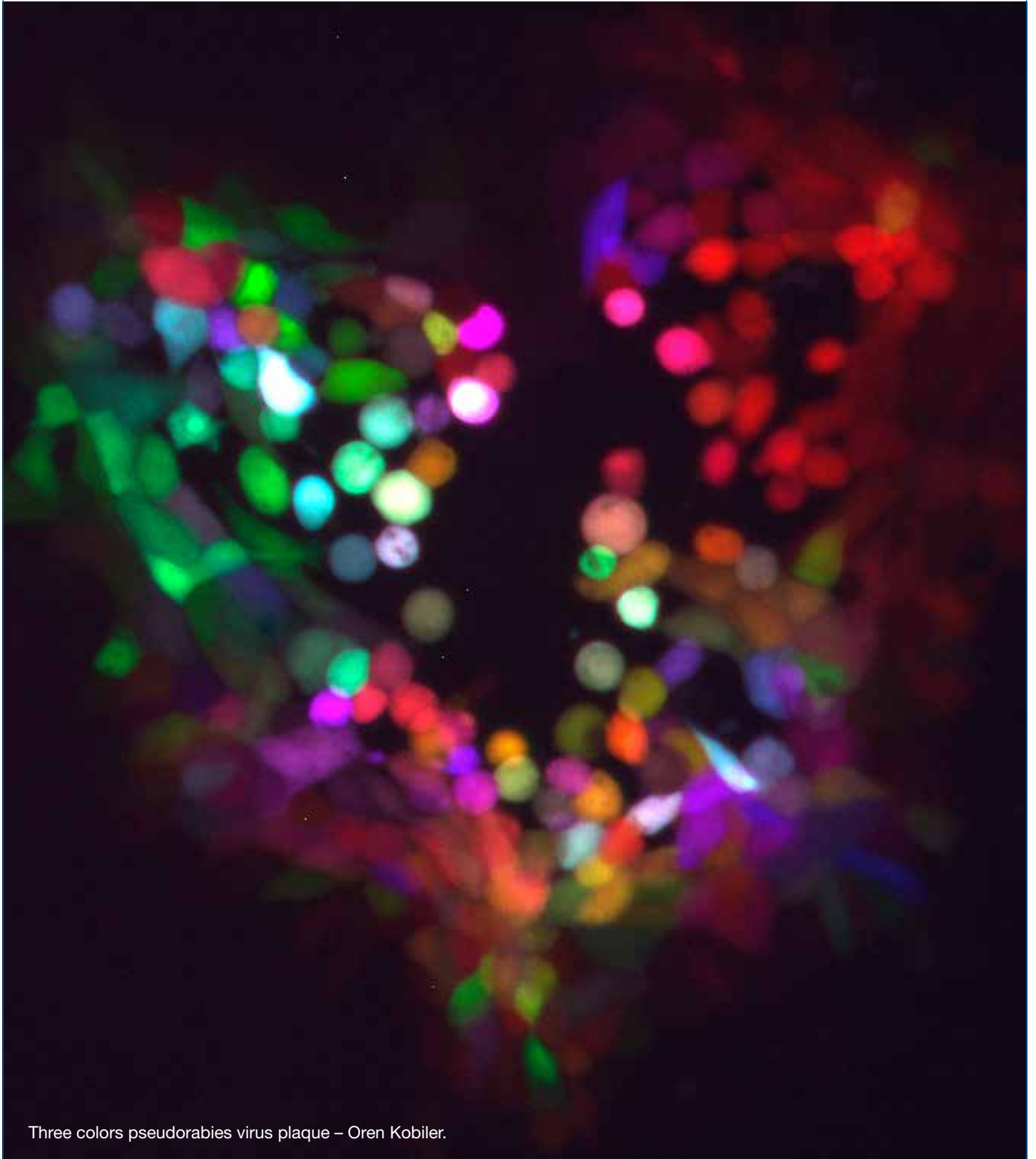
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Grants

2013-2015 Discourse Syntax in Developing Text Production. Chief Scientist, Ministry of Education.

2013-2017 Verb structure and Semantics in Development. Israel Science Foundation.

Infectious Diseases



Three colors pseudorabies virus plaque – Oren Kobilier.



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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

Behnke, J.M., Menge, D., Nagda, S., Noyes, H.A., **Iraqi, F.A.**, Kemp, S.J., Mugambi, J.M., Baker, L.R.,

Wakelin, D. and Gibson, J.P. (2010) Quantitative trait loci for resistance to worm infections and associated immunological and pathological traits in mice: Comparison of loci on chromosomes 5, 8 and 11 in F2 and F6/7 intercross lines of mice. *Parasitol.* 137:311-32.

Nganga, J.K., Soller, M., **Iraqi, F.A.** (2010) Towards high resolution mapping of trypanosomosis resistance loci *Tir2* and *Tir3* by using F₁₂ advanced intercross lines with major locus *Tir1* effect depleted. *Biomed Central Gen.* 11:394.

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Aylor, D.L., Valdar, W., Foulds-Mathes, W., Buus, R.J., Ricardo, A., Verdugo, R.A., Ralph, S., Baric, R.S., Ferris, M.T., Frelinger, F.A., Heise, M., Frieman, M.B., Gralinski, L.E., Bell, T.A., Didion, J.P., Hua, K., Nehrenberg, D.L., Powell, C.L., Steigerwalt, J., Xie, Y., Kelada, S.N.P., Collins, F.S., Yang, I.V.,

Schwartz, D.A., Branstetter, L.A., Chesler, E.J., Miller, D.R., Spence, J., Liu, E.Y., McMillan, L., Sarkar, A., Wang, J., Wang, W., Zhang, Q., Broman, K.W., Korstanje, R., Durrant, C., Mott, R., **Iraqi, F.A.**, Pomp, D., Threadgill, D., Pardo-Manuel de Villena, F. and Churchill, G.A. (2011) Genetic analysis of complex traits in the emerging collaborative cross. *Gen Res* 21:1213-1222.

Durrant, C., Tayem, H., Yalcin, B., Cleak, J., Goodstadt, L., Pardo-Manuel de Villena, F., Mott, R. and **Iraqi, F.A.** (2011) Mapping QTL associated with host susceptibility to *Aspergillus fumigatus* infection in the Collaborative Cross mouse resource population. *Gen Res* 21:1239-1248.

Silva, M.V.B., Sonstegard, T., Hanotte, O., Mugambi, J., Garcia, J.F., Nagda, S., Gibson, J., **Iraqi, F.A.**, McClintock, S., Kemp, S., Boettcher, P., Malek, M., Van Tassell, C.P. and Baker, L.R. (2012) Identification of quantitative trait loci affecting resistance to gastro-intestinal parasites in a double backcross population of Red Maasai and Dorper sheep. *Anim Genet* 43:63-71.

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

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in the Collaborative Cross mouse genetic reference population. *Mamm Genome*. 25:109-19.

Review and editorials

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Hernandez-Valladares M, Rihet P, Iraqi FA (2014) Host susceptibility to malaria in human and mice: compatible approaches to identify potential resistant genes. *Physiol Genomics* 46:1-16.

Grants

2012-2015 European Sequence and Genotyping Institutes (ESGI), Understanding genetic susceptibility to fungal infection using naïve collaborative cross mice (Collaborators: Ron Shamir and Irit Gat-Viks (TAU), Richard Mott (University of Oxford))

2013-2016 EU-FP7-Infrafrontier, European Mouse Mutant and Archiving (EMMA) (co-PI*, collaborators: 23 Members from European countries)

2014-2015 Bela and Zeigmond Altar and Semha Torkeltov Fund for Cancer Research, APC gene in intestinal cancer development in Collaborative Cross mice

2014-2015 Israel Cancer Research Fund (ICRF) Project Grant



Dr. Oren Kobiler, M.D., Ph.D.

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Sackler Faculty of Medicine



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Investigating Viral Genetic Diversity

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Publications

Kobiler O., Lipman Y., Therkelsen K., Daubechies I., and Enquist L.W. (2010). Herpesviruses carrying a Brainbow cassette reveal replication and expression of limited numbers of incoming genomes. *Nat. Commun.* 1:146.

***Kobiler O.**, *Card J.P., McCambridge J., Ebdlahad S., Shan Z., Raizada M.K., Sved A.F., and Enquist

L.W. (2011). Microdissection of neural networks by conditional reporter expression from a Brainbow Herpesvirus. *Proc Natl Acad Sci U S A.* 108:3377-82.

***Kobiler O.**, *Card J.P., Ludmir E.B., Desai V., Sved A.F., Enquist L.W. (2011). A dual infection pseudorabies virus conditional reporter approach to identify projections to collateralized neurons in complex neural circuits. *PLoS One*, 6:e21141.

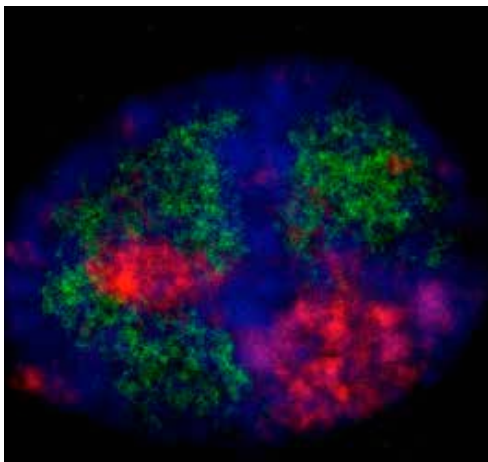
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Taylor MP, **Kobiler O**, Enquist LW. (2012) Alpha herpesvirus axon-to-cell spread involves limited virion transmission. *Proc Natl Acad Sci USA.* 109:17046-51.

Kobiler O, Drayman N, Butin-Israeli V, Oppenheim A. (2012) Virus strategies for passing the nuclear envelope barrier. *Nucleus.* 3:526-39.

Reviews

Szpara M.L., **Kobiler O.**, and Enquist L.W. (2010). A common neuronal response to alphaherpesvirus infection. *J Neuroimmune Pharmacol.* 5:418-27.



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



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Human Mold Infections

Positions

Associate Professor, Sackler Faculty of Medicine
Chair, 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.

Publications

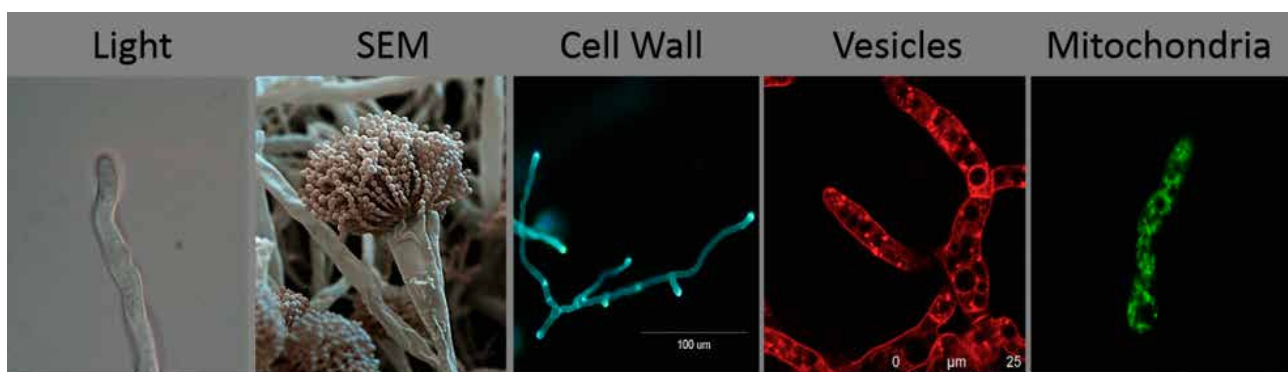
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Hagag S, Kubitschek-Barreira P, Neves GW, Amar D, Nierman W, Shalit I, Shamir R, Lopes-Bezerra L, **Osherov N**. Transcriptional and proteomic analysis of the *Aspergillus fumigatus* Δ *prtT* protease-deficient mutant. *PLoS One.* 2012, 7:e33604.

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Arnusch CJ, Ulm H, Josten M, Shadkchan Y, **Osherov N**, Sahl HG, Shai Y. Ultrashort peptide bioconjugates are exclusively antifungal agents and synergize with



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cyclodextrin and amphotericin B. *Antimicrob Agents Chemother.* 2012, 56:1-9.

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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, 14:3-15

Appel E, Vallon-Eberhard A, Rabinkov A, Brenner O, Shin I, Sasson K, Shadkchan Y, **Osherov N**, Jung S, Mirelman D. Therapy of murine pulmonary aspergillosis with antibody-alliinase conjugates and alliin. *Antimicrob Agents Chemother.* 2010, 54:898-906.

Reviews

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Tavanti A, Naglik JR, **Osherov N**. Host-Fungal Interactions: Pathogenicity versus Immunity. *Int J Microbiol.* 2012, 56:2480.

Grants

2012–2016 Binational Science Foundation

2014–2016 Israel-Italy Cooperation Grant-

2014–2017 Infect-ERA Net Joint European Grant



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Host-Virus Interactions in Bacterial Systems

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

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

Publications

Qimron U, Tabor S, Richardson CC. New details about bacteriophage T7-host interactions. *Microbe*, 5:117-122, 2010.

Edgar R, **Qimron U**. The *Escherichia coli* CRISPR system protects from lysogenization, lysogens, and prophage induction. *J Bacteriol*, 192:6291-6294, 2010.

Yosef I, Goren MG, Kiro R, Edgar R, and **Qimron U**. HtpG is essential for activity of the *Escherichia coli* CRISPR/Cas system. *Proc Natl Acad Sci USA*, 108:20136-41, 2011.

Edgar R, Friedman N, Molshanski-Mor S, and **Qimron U**. Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes. *Appl Environ Microbiol*, 78:744-51, 2012. Highlighted in *Nature Rev Microbiol*, Wall Street Journal, and others.

Goren MG, Yosef I, Edgar R, and Qimron U. The bacterial CRISPR/Cas system as analog of the



mammalian adaptive immune system. *RNA Biology*, 9:549-554, 2012.

Yosef I, Goren MG, and **Qimron U**. Proteins and DNA elements essential for the CRISPR adaptation process in *Escherichia coli*. *Nucl Acid Res*, 40:5569-76, 2012. *Recommended by F1000*

Goren MG, Yosef I, Auster O, and **Qimron U**. Experimental definition of a clustered regularly interspaced short palindromic duplicon in *Escherichia coli*. *J Mol Biol*, 423:14-16, 2012.

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

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

Kiro R, Molshanski-Mor S, Yosef I, Milam SL, Erickson HP, and **Qimron U**. Gene-product 0.4 increases

phage competitiveness by inhibiting host cell division. *Proc Natl Acad Sci USA*, 2013. 110:19549-54; *Recommended by F1000*.

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

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

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

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

Grants

2014-2017 Israeli Ministry of Health Grant

2013-2018 ERC Starting Grant

2014-2019 Israel Science Foundation Grant



Dr. Ella Sklan, Ph.D.

Department of Clinical Microbiology and Immunology
Sackler Faculty of Medicine



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Viral Host Interactions of Positive Strand RNA Viruses

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Current projects in the lab include:

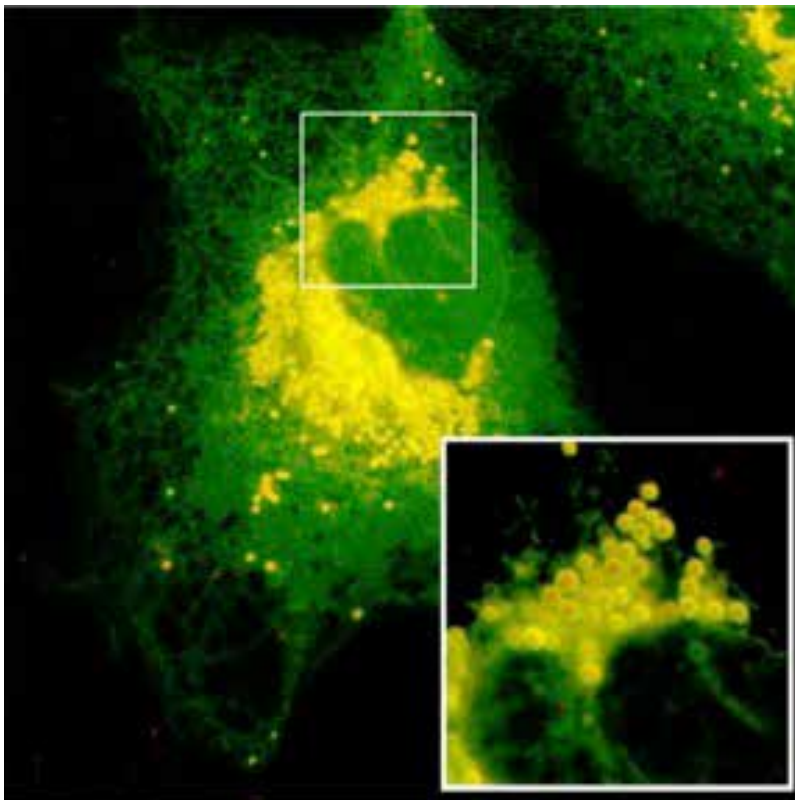
1. Development of systems for the identification and characterization of new interactions between viral and host cell proteins.

2. Using live cell imaging techniques to study HCV assembly.

3. Characterization of the membrane association mechanisms of Dengue virus non-structural proteins.

Publications

Parameswaran P, **Sklan E**, Wilkins C, Burgon T, Samuel M, Lu R, Ansel KM, Heissmeyer V, Einav S, Jackson W, Doukas T, Paranjape S, Polacek C, Barreto dos Santos F, Jalili R, Babrzadeh F, Gharizadeh B, Grimm D, Kay M, Koike S, Sarnow P, Ronaghi M, Ding S, Harris E, Chow M, Diamond MS, Kirkegaard K, Glenn JS, Fire AZ. Six RNA viruses and forty one hosts: viral small RNAs and modulation of



A live hepatoma cell (Huh7) expressing the viral non-structural protein 5A that localizes to the endoplasmic reticulum and lipid droplets.

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Matto M*, **Sklan EH***, David, N, Melamed-Book N, Casanova, JE, Glenn JS, Aroeti B. A Role for ADP-ribosylation factor 1 in the regulation of hepatitis C virus replication. (2011) *J Virol*, 85:946-56. *Equal contribution.

Lee C, Ma H, Hang JQ, Leveque V, **Sklan EH**, Elazar M, Klumpp K, Glenn JS. The hepatitis C virus NS5A inhibitor (BMS-790052) alters the subcellular localization of the NS5A non-structural viral protein. (2011). *Virology*, 414:10-8.

Nachmias D, **Sklan EH**, Ehrlich M, Bacharach E. Human immunodeficiency virus type 1 envelope proteins traffic toward virion assembly sites via a TBC1D20/Rab1-regulated pathway. (2012) *Retrovirology*. 9:7.

Nevo-Yassaf I, Yaffe Y, Asher M, Ravid O, Eizenberg S, Henis YI, Nahmias Y, Hirschberg K, **Sklan EH**. Role for TBC1D20 and Rab1 in hepatitis C virus replication via interaction with lipid droplet-bound nonstructural protein 5A. (2012) *J Virol*. 86:6491-502.

Shlomai A, Rechtman MM, Burdelova EO, Zilberberg A, Hoffman S, Solar I, Fishman S, Halpern Z, **Sklan EH**. The metabolic regulator PGC-1 α links hepatitis C virus infection to hepatic insulin resistance. (2012) *J Hepatol*. 57:867-73.

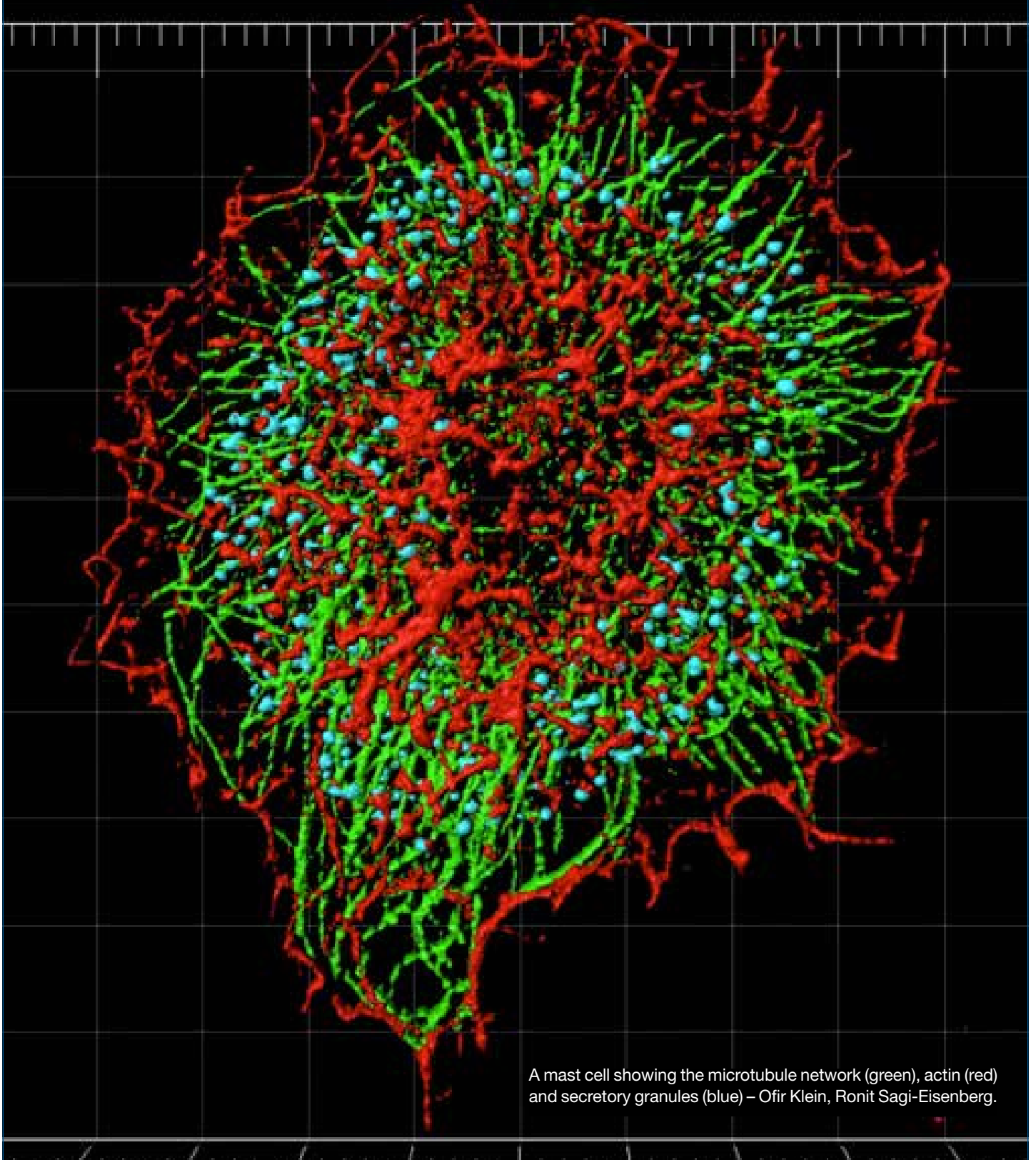
Stern O, Hung YF, Valdau O, Yaffe Y, Harris E, Hoffmann S, Willbold D, **Sklan EH**. An N-terminal amphipathic helix in dengue virus nonstructural protein 4A mediates oligomerization and is essential for replication. (2013) *J Virol*. 87:4080-5.

Hanin G, Shenhar-Tsarfaty S, Yayon N, Hoe YY, Bennett ER, **Sklan EH**, Rao DC, Rankinen T, Bouchard C, Geifman-Shochat S, Shifman S, Greenberg DS, Soreq H. Competing targets of microRNA-608 affect anxiety and hypertension. (2014) *Hum Mol Genet*. 23:4569-80

Grants

2012-2016 Israel Science Foundation (ISF) Grant

Inflammatory and Autoimmune Diseases



A mast cell showing the microtubule network (green), actin (red) and secretory granules (blue) – Ofir Klein, Ronit Sagi-Eisenberg.



Prof. Ariel Munitz, Ph.D.

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Regulatory Mechanisms in Mucosal Inflammation

Position

Senior Lecturer, Sackler Faculty of Medicine

Associate Editor, *Journal of Allergy and Clinical Immunology*

Research

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

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

Publications

Shik D, Moshkovits I, Karo-Atar D, Reichman H, **Munitz A**. IL-33 requires CMRF35-like molecule-1 (CLM-1) expression for induction of myeloid cell activation. *Allergy*. 2014, 69:719-29.

Baruch-Morgenstern NB, Shik D, Moshkovits I, Itan M, Karo-Atar D, Bouffi C, Fulkerson PC, Rashkovan D, Jung S, Rothenberg ME, **Munitz A**. Paired immunoglobulin-like receptor A is an intrinsic, self-limiting suppressor of IL-5-induced eosinophil development. *Nat Immunol*. 2014, 15:36-44.

Moshkovits I, Shik D, Itan M, Karo-Atar D, Bernshtein B, Hershko AY, van Lookeren Campagne M, **Munitz A**. CMRF35-like molecule 1 (CLM-1) regulates eosinophil homeostasis by suppressing cellular chemotaxis. *Mucosal Immunol*, 2013. 7:292-303.

Karo-Atar D, Moshkovits I, Eickelberg O, Königshoff M, **Munitz A**. PIR-B regulates pulmonary fibrosis by suppressing profibrogenic properties of alveolar macrophages. *Am J Res Cell Mol Biol*; 2013: 48;456-464.

Semis R, Shai N, **Munitz, A**, Zaslavsky Z, Polacheck I, Segal E. Pharmacokinetics, tissue distribution and immunomodulatory effect of intralipid formulation of nystatin in mice. *J of Antimicrob Chem*; 2012;67:1716-21.

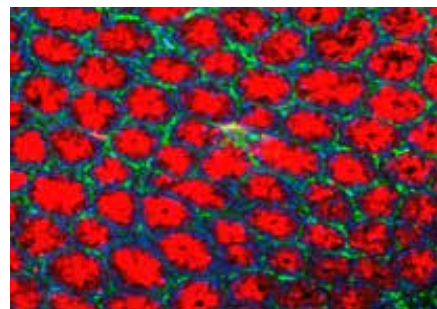
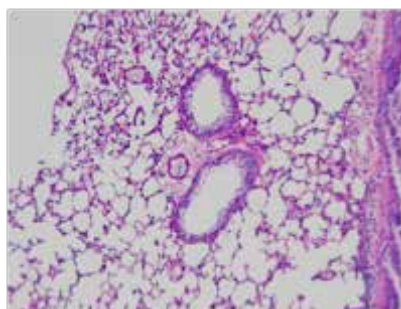
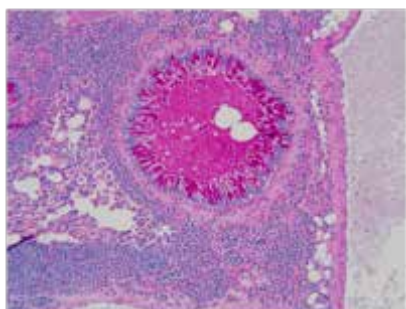


Figure legend: A photomicrograph of a normal lung displaying two large airways and a blood vessel (left). In many inflammatory conditions such as asthma and COPD, the airway is filled with mucus plugs (middle, pink stain). Right – an immunofluorescent stain of resistin-like molecule alpha (red), a proinflammatory,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

Munitz A, Cole ET, Karo-Atar D, Finkelman FD, Rothenberg ME. Resistin-like molecule alpha regulates IL-13-induced chemokine production but not allergen-induced airway responses. *Am J Res Cell Mol Biol*; 2012;46:703-13.

Rothenberg ME, Wen T, Shik D, Cole ET, Mingler M, **Munitz A**. IL-13R α 1 differentially regulates aeroallergen-induced lung responses. *J Immunol*, 2011; 187:4873-4880.

Waddell A, Ahrens R, Steinbrecher K, Donovan B, Rothenberg ME, **Munitz A**, Hogan SP. Colonic eosinophilic inflammation in experimental colitis is mediated by Ly6C(high) CCR2(+) inflammatory monocyte/macrophage-derived CCL11. *J Immunol*. 2011; 186:5993-6003.

Munitz A, Cole ET, Waddell A, Groschwitz K, Ahrens R, Steinbrecher K, Willson T, Han X, Denson L, Rothenberg ME, Hogan SP. Paired immunoglobulin-like receptor B (PIR-B) negatively regulates macrophage activation in experimental colitis. *Gastroenterology*, 2010; 139:530-541.

Reviews and Chapters

Lacy P, **Munitz A**. Mutations in CCR3 render it “missing in action”. *J Allergy Clin Immunology*. 2010;126:158-159.

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

Shik D, **Munitz A**. Inhibitory receptors in activation and suppression of the immune response. *Clin Exper Allergy*. 2010; 40; 700-709.

Munitz A. Inhibitory receptors on myeloid cells: new targets for therapy? *Pharmacol Ther*. 2010; 125; 128-137.

Munitz A. Eosinophil Receptor-Mediated Inhibition. In *Eosinophils in Health and in Disease*. (Elsevier, ed. Lee JJ and Rosenberg HF), 2013; pp. 179-188.

Grants

2013-2016 Fritz Thyssen Stiftung, The role of IL-13R α 1 in pulmonary fibrosis

2012-2016 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”

2014-2017 Israel Ministry of Health

2014-2015 Israeli Cancer Association

2014-2015 ICRF Research Career Development Award



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

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

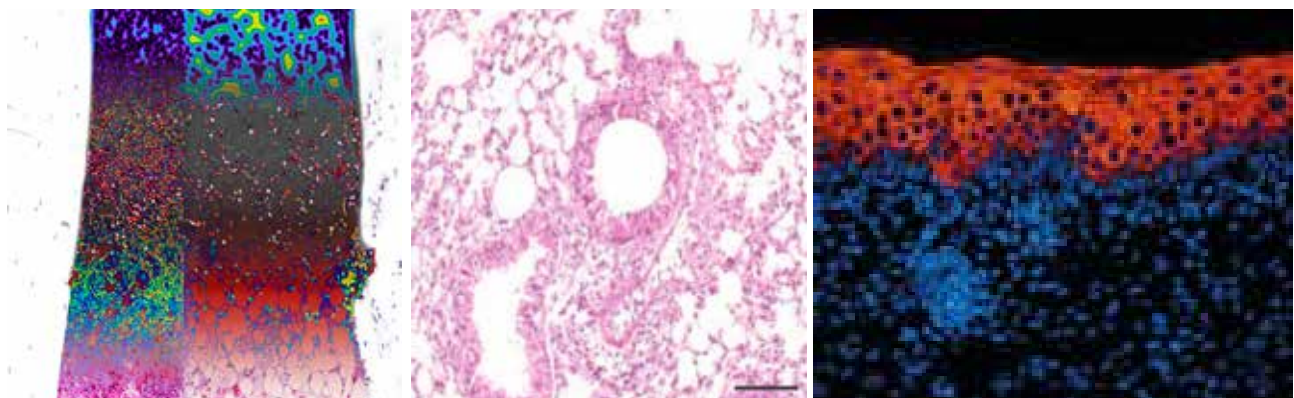
Our research focus is the understanding of the inflammatory response, with particular emphasis on novel NLRs (Nucleotide-binding domain and Leucine-rich repeat containing Receptors), and the non-apoptotic forms of cell death during infection. In particular we are interested in how pathogens (viruses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

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

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

Publications

Lawlor KE, Khan N, Mildenhall A, **Gerlic M**, Croker BA, D'Cruz AA, Hall C, Spall SK, Anderton H, Masters SL, Rashidi M, Wicks IP, Alexander WS, Mitsuuchi Y, Benetatos CA, Condon SM, Wong WWL, Silke J, Vaux DL, Vince JE. RIPK3 promotes cell death,



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

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O'Donnell JA, Kennedy CL, Pellegrini M, Nowell CJ, Cengia L, Masters SL, Hartland EL, Roberts AW, **Gerlic M**, Croker BA. Fas controls neutrophil lifespan during viral and bacterial infection. *J Leukoc Biol*, December 3, 2014, doi: 10.1189/jlb.3AB1113-594RR.

Rickard JA*, O'Donnell JA*, Evans JM*, Lalaoui N, Poh AR, Rogers T, Vince JE, Lawlor KE, Ninnis RL, Anderton H, Hall C, Spall SK, Pheese TJ, Abud HE, Cengia LH, Corbin J, Mifsud S, Di Rago L, Metcalf D, Ernst M, Dewson G, Roberts AW, Alexander WS, Murphy JM, Ekert PG, Masters SL, Vaux DL, Croker BA*, **Gerlic M***, Silke J*#. RIPK1 regulates RIPK3-MLKL-driven systemic inflammation and emergency hematopoiesis. *Cell*, 157, 1175-1188, 2014 *These authors contributed equally to this work. # Corresponding authors.

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Gerlic M, Croker BA, Cengia LH, Moayeri M, Kile BT, Masters SL. NLRP1a expression in Srebp1a deficient mice. *Cell Metabolism*, March 4, 2014.

Gerlic M*, Faustin B*, Postigo A, Yu ECW, Gombosuren N, Krajewska M, Flynn R, Croft M, Way M, Satterthwait A, Liddington RC, Salek-Ardakani S, and Reed JC. Vaccinia Virus F1L protein promotes virulence by inhibiting NLR inflammasome activation. *Proc Natl Acad Sci USA*, 2013; 110:7808-13. *These authors contributed equally to this work..

Proell M, **Gerlic M**, Mace PD, Reed JC, Riedl SJ. The CARD plays a critical role in ASC foci formation:

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Masters SL*, **Gerlic M***, Metcalf M, Preston S, Pellegrini M, O'Donnell JA, McArthur K, Baldwin TM, Chevrier S, Nowell CJ, Cengia LH, Henley KJ, Collinge JE, Kastner DL, Feigenbaum L, Hilton DJ, Alexander WS, Kile BT*, Croker BA*. NLRP1 inflammasome induces pyroptosis of hematopoietic progenitor cells. *Immunity*, 2012;37:1009-1023. *These authors contributed equally to this work.

Haneklaus M, **Gerlic M**, Kurowska-Stolarska M, Rainey AA, Pich D, McInnes IB, Hammerschmidt W, O'Neill LA, Masters SL. Cutting Edge: miR-223 and EBV miR-BART15 Regulate the NLRP3 Inflammasome and IL-1 β Production. *J Immunol*. 2012;189:3795-9.

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Reviews

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Croker BA, Silke J, **Gerlic M**. Fight or flight: regulation of emergency hematopoiesis by pyroptosis and necroptosis. *Curr Opin Hematol*, 22, 293-301, 2015.

Gerlic M, Masters SL. A healthy appetite for *Toxoplasma* at the cellular level. *Immunol Cell Biol*, 92, 813-814, 2014.

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Prof. Ronit Sagi-Eisenberg, Ph.D.

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Biology
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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

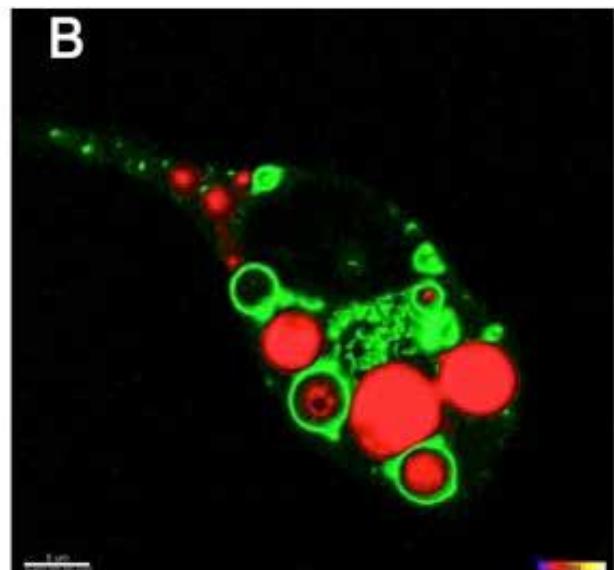
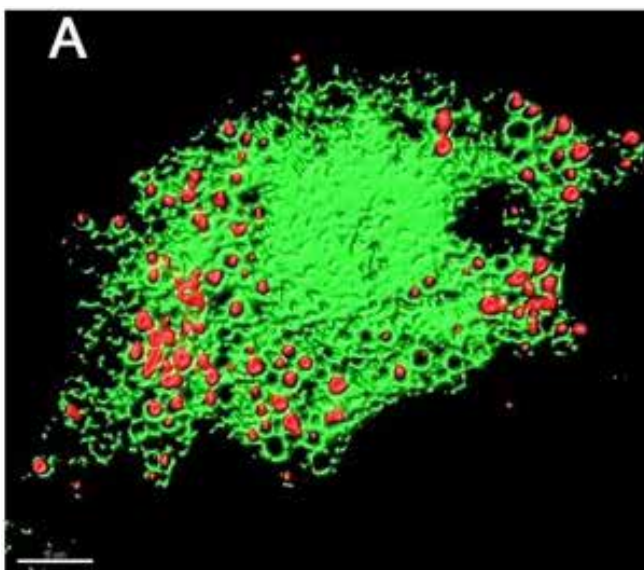
pathophysiologic conditions. Research methods used include confocal microscopy in live and fixed cells; gene cloning; quantitative RT-PCR, pull down-assay; mass spectrometry, and bioinformatics.

Current projects in the lab include:

1. Exploring the genetic connections between the size of the mast cell secretory granules and mastocytosis.
2. Mast cells and cancer – the good, the bad and the ugly.
3. Decoding the Rab networks that control mast cell function.

Publications

Azouz, N.P., Zur, N., Efergan, Ohbayashi, N., Fukuda, M., Amihai, D., Hammel, I., Rothenberg, ME and **Sagi-Eisenberg, R.** Rab5 is a novel regulator of



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

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Bernstein-Molho R., Kollender, Y., Issakov, J., Bickels, J., Dadia S., Flusser, G., Meller, I., **Sagi-Eisenberg. R.** and Merimsky O. Clinical activity of mTOR inhibition in combination with cyclophosphamide in the treatment of recurrent unresectable chondrosarcomas. *Cancer Chemother Pharmacol.* 70, 855-860, (2012).

Azouz NP, Matsui, T., Fukuda, M. and **Sagi-Eisenberg, R.** Decoding the regulation of mast cell exocytosis by networks of Rab GTPases. *J Immunol.* 189, 2169-2180. (2012).

Gorzalczany Y, Gilad Y, Amihai D, Hammel I, **Sagi-Eisenberg R,** and Merimsky O. Combining an EGFR directed tyrosine kinase inhibitor with autophagy-

inducing drugs: a beneficial strategy to combat non-small cell lung cancer. *Cancer Lett.* 310:207-215. (2011).

Baram D, Dekel O, Mekori YA, and **Sagi-Eisenberg R.** Activation of mast cells by trimeric G protein Gi3; coupling to the A3 adenosine receptor directly and upon T cell contact. *J Immunol.* 184:3677-3688. (2010).

Review

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

Grants

2012-2015 The Israel Science Foundation, Dissecting the molecular mechanisms underlying mast cell exocytosis; new insights provided by the small GTPase Rab5

Medical Education and Ethics





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Bioethics, Biolaw and Medical Humanities

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

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

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

Ongoing research projects are:

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

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

Monographs

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

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

Publications

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

Barilain YM, Barnea R. Routine medical care in the military. In: Siegal G, Kasher A. (eds.) Bioethics blue and white. Ha' kibbutz Ha'Me'uhad Press, 2013. [Hebrew] (Forthcoming)

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.

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Barilan YM, Brusa M, Halperin P. Triage in disaster medicine: ethical strategies in various scenarios. In:

Gordijn B, O'mathuna D, Macklin R. (eds.) Ethics in disaster medicine. Dordrecht: Springer, 2012. (Forthcoming)

Shani R, **Barilan YM**. Excellence, deviance and gender: lessons from the XYY episode. *American Journal of Bioethics* 2012; 12:27-30.

Barilan YM. Anatomy. 2nd edition of the Encyclopedia of Applied Ethics. R. Chadwick, ed. San Diego: Academic Press. 2012, pp. 117-126.

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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)

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Shani R, Gross S, **Barilan YM**. Exploring Kuhn's concept of a "scientific paradigm": the case of the "XYY hypothesis". *International Journal of Technology, Knowledge and Society* 2010; 6:47-56.

Barilan YM. The dilemma of good clinical practice in the study of compromised standards of care. *Editorial Critical Care* 2010; 14:176.

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

2012-2015 COST (EU join collaborative grant), Ethics in Disaster Medicine.



Dr. Orit Karnieli-Miller, Ph.D.

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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

Karnieli-Miller, O., Frankel, R.M., & Inui, T.S. (2013). Cloak of compassion or evidence of elitism? an empirical analysis of white coat ceremonies? *Medical Education*, 43, 97-108.

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*equal contributors

Karnieli-Miller, O. Vu, R.T. Frankel, R.M. Holtman, M. Clyman, S. Hui, S.L, & Inui T.S. (2011). Which Experiences in the Hidden Curriculum Teach Students About Professionalism? *Academic Medicine*, 86, 369-377.

Karnieli-Miller, O., Taylor, A.C. Inui, T.S. Ivy, S.S. Frankel, R.M (2011). Understanding values in a large health care organization through work-life narratives of high performing employees. *Rambam Maimonides Medical Journal*, 2, 1-14.

Goldblatt, H. **Karnieli-Miller, O.** Neumann, M. (2011). Sharing qualitative research findings with participants: Study experiences of methodological and ethical dilemmas. *Patient Education and Counseling*, 82, 389-395

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Werner, P., **Karnieli-Miller, O.** Adler, A. & Eidelman, S. (2010). How neurologists tell their patients with alzheimer disease about their diagnosis another side to tarek et al's study. *Alzheimer Disease & Associated Disorders – An International Journal*, 24(2), 115-117.

Karnieli-Miller, O. Taylor, A. Cottingham, A.H. Inui, T.S. Vu R.T. & Frankel R.M. (2010). Exploring the meaning of respect in medical student education: an analysis of student narratives. *Journal of General Internal Medicine*, 25, 1309-1314.

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

Reviews

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diagnostic disclosure of dementia: A systematic review of the first decade of the 21st century. *Alzheimer's & Dementia*, 9, e74–e88.

Grants

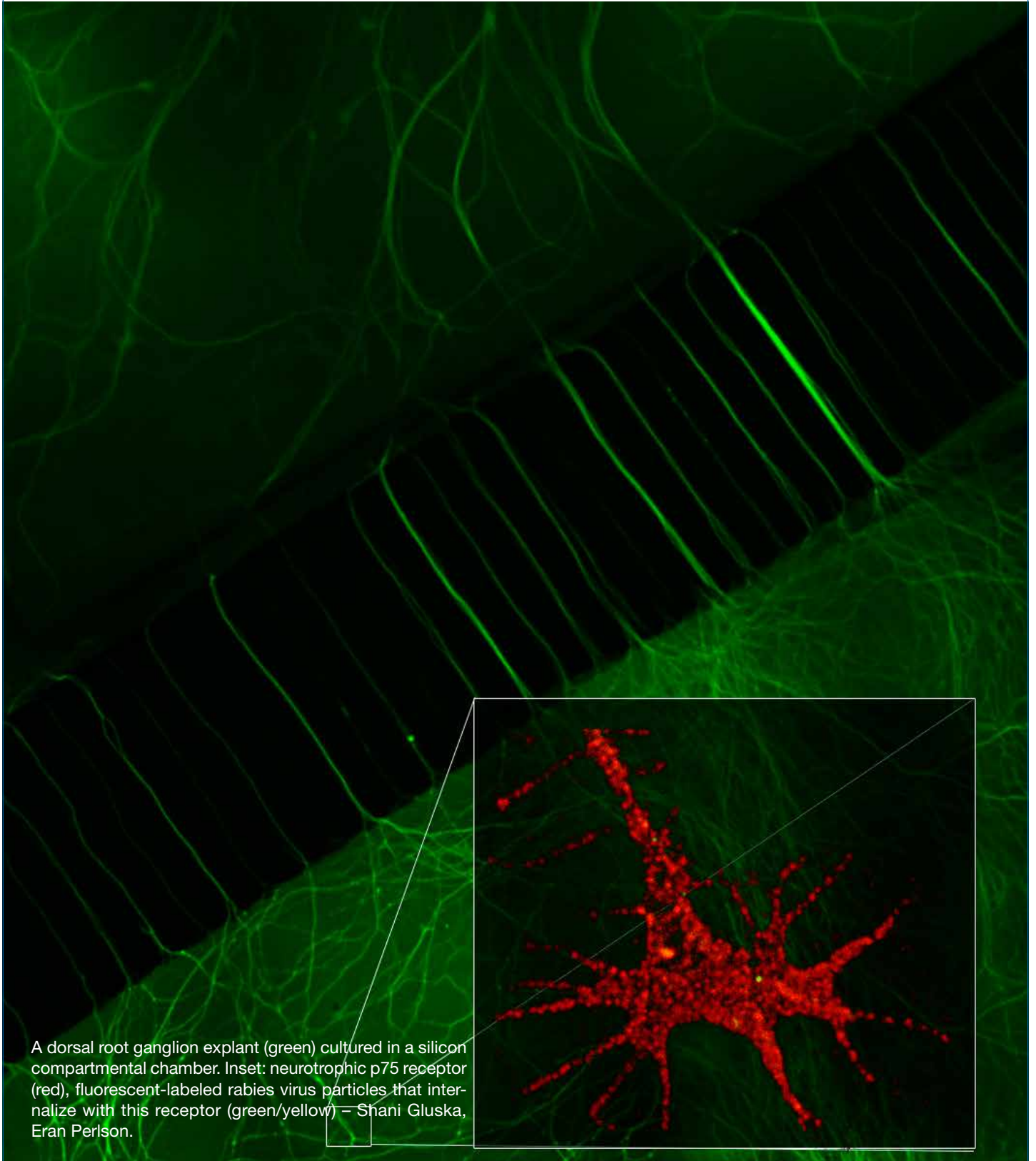
2012-2014 The Magi Foundation, A different beginning: Foundation blocks for combining humor and creativity in constructing doctor-patient relationship, PI

2014-2015 Israel Cancer Association, Using narrative writing on breaking bad news encounters to improve the communication skills of medical professionals in cancer care, PI

2014-2015 The Israel National Institute for Health Policy Research, Organizational and inter-organizational dimensions of health information exchanges in Israel, Co-PI

2014-2016 The Magi Foundation, Identifying best practices for communication challenges of medical clowns with patients parents, adolescent patients and medical teams, PI

Nervous System and Behavioral Disorders



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



Prof. Ruth Ashery-Padan, Ph.D.

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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

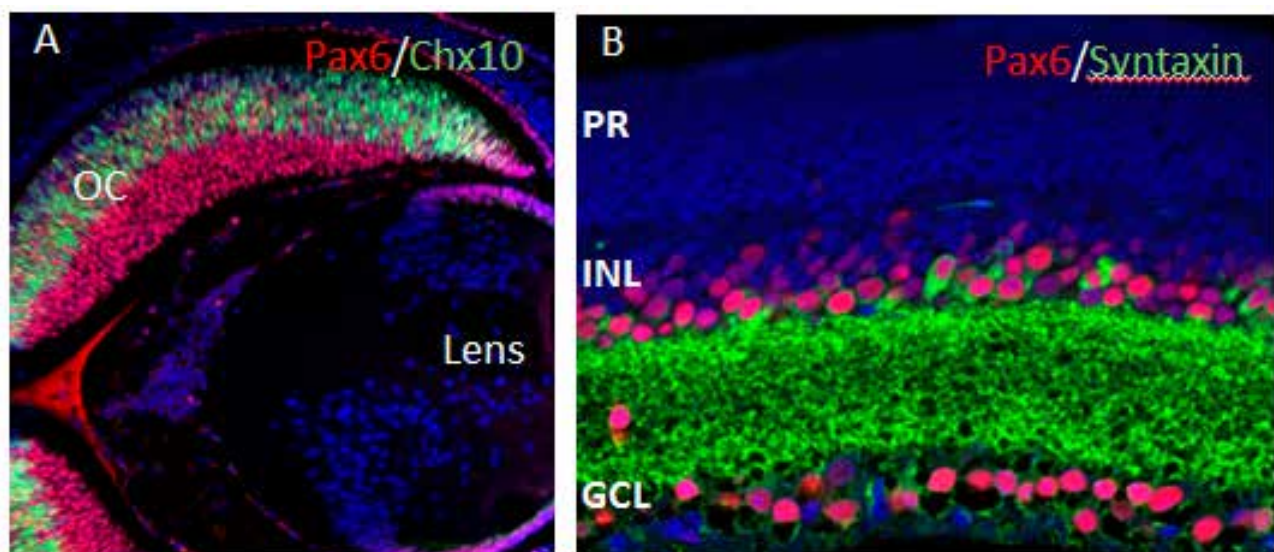
We study the gene networks that transform the embryonic cells into a complex, differentiated organ. We focus on exploring this question by studying the process of eye development as a model for organogenesis. We apply cutting-edge technologies including mouse genetic tools (Cre/loxP), molecular biology, 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

Raviv, S., K. Bharti, S. Rencus-Lazar, Y. Cohen, R. Schyr, N. Evantal, E. Meshorer, A. Zilberberg, M. Idelson, B. Reubinoff, R. Grebe, R. Rosin-Arbesfeld, B.E. Lauderdale, G. Luty, H. Arnheiter, and **R. Ashery-Padan**. PAX6 regulates melanogenesis in the retinal pigmented epithelium through feed-forward regulatory interactions with MITF. *PLoS Genet*, 2014. 10:1004360.

Wolf, L., W. Harrison, J. Huang, Q. Xie, N. Xiao, J. Sun, L. Kong, S.A. Lachke, M.R. Kuracha, V. Govindarajan, P.K. Brindle, **R. Ashery-Padan**, D.C. Beebe, P.A. Overbeek, and A. Cvekl, Histone posttranslational modifications and cell fate determination: lens induction requires the lysine acetyltransferases CBP and p300. *Nucleic Acids Res*, 2013. 41:10199-214



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

Wolf, L., C.S. Gao, K. Gueta, Q. Xie, T. Chevallier, N.R. Poddaturi, J. Sun, I. Conte, P.S. Zelenka, **R. Ashery-Padan**, J. Zavadil, and A. Cvekl. Identification and characterization of fgf2-dependent mRNA:microRNA networks during lens fiber cell differentiation. *G3*, 2013. 3:2239-2255.

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Zembrzycki A, Chou SJ, **Ashery-Padan R**, Stoykova A, O'Leary DD. Sensory cortex limits cortical maps and drives top-down plasticity in thalamocortical circuits. *Nat Neurosci*. 2013, 16:1060-7.

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

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Shaham, O., Y. Menuchin, C. Farhy, and **R. Ashery-Padan**, Pax6: a multi-level regulator of ocular development. *Prog Retin Eye Res*, 2012. 31:351-76.

Magenheim J, Klein AM, Stanger BZ, **Ashery-Padan R**, Sosa-Pineda B, Gu G, Dor Y. Ngn3(+) endocrine progenitor cells control the fate and morphogenesis of pancreatic ductal epithelium. *Dev Biol* 2011, 359:26-36.

Huang J, Rajagopal R, Liu Y, Dattilo LK, Shaham O, **Ashery-Padan R**, Beebe DC. The mechanism of lens placode formation: A case of matrix-mediated morphogenesis. *Dev Biol* 2011, 355:32-42.

Davis N, Mor E, **Ashery-Padan R**. Roles for Dicer1 in the patterning and differentiation of the optic cup neuroepithelium. *Development* 2011, 138:127-138.

Kroeber M, Davis N, Holzmann S, Kritzenberger M, Shelah-Goraly M, Ofri R, **Ashery-Padan R**, Tamm ER. Reduced expression of Pax6 in lens and cornea of mutant mice leads to failure of chamber angle development and juvenile glaucoma. *Hum Mol Genet* 2010, 19:3332-3342.

He S, Purity MK, Wang WL, Wolf L, Chauhan BK, Cveklova K, Tamm ER, **Ashery-Padan R**, Metzger D, Nakai A, Chambon P, Zavadil J, Cvekl A. Chromatin remodeling enzyme Brg1 is required for mouse lens fiber cell terminal differentiation and its denucleation. *Epigenetics Chromatin* 2010, 3:21.

Bandah-Rozenfeld D, Mizrahi-Meissonnier L, Farhy C, Obolensky A, Chowars I, Pe'er J, Merin S, Ben-Yosef T, **Ashery-Padan R**, Banin E, Sharon D. Homozygosity mapping reveals null mutations in FAM161A as a cause of autosomal-recessive retinitis pigmentosa. *Am J Hum Genet* 2010, 87:382-391.

Review

Shaham O, Menuchin Y, Farhy C, **Ashery-Padan R**: Pax6: A multi-level regulator of ocular development. *Prog Retin Eye Res* 2012, 31:351-76.

Grants

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).



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GSK-3 Signaling in Health and Disease

Position

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

Research

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

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

Publications

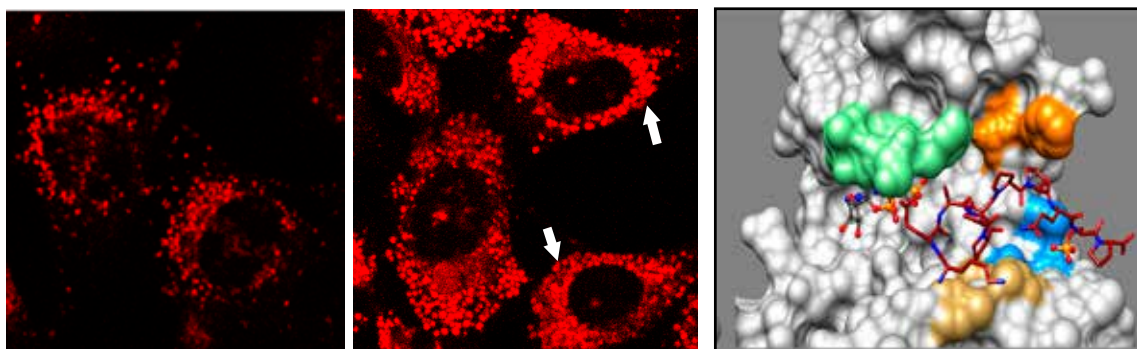
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Treatment with GSK-3 inhibitor restores lysosomal activity, lysosomes shown as red dots (left). Computational model of GSK-3 inhibitor -L803-mts-binding with the substrate binding site (right).

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Reviews

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Neuronal Plasticity and Nerve Cell Protection in Disease

Positions

Professor of Clinical Biochemistry, Sackler Faculty of Medicine

Lily and Avraham Gildor Chair for the Investigation of Growth Factors

Director, Levie-Edershein-Gitter Institute for Functional Brain Imaging

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

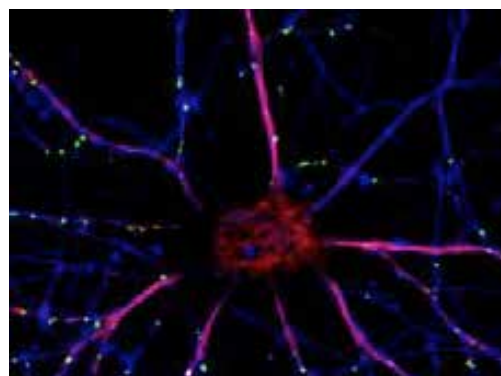
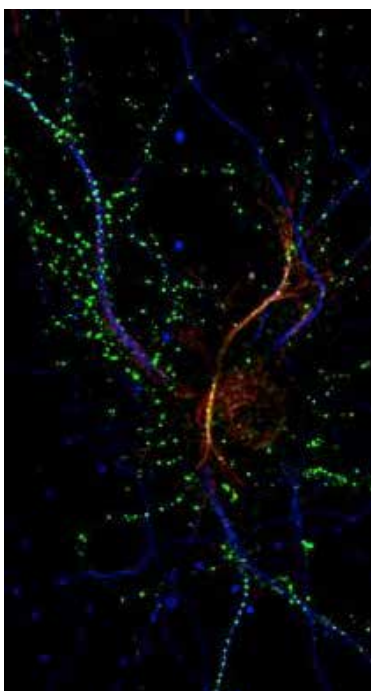
Editor-in-Chief, *Journal of Molecular Neuroscience*

Research

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

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

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



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

Publications

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Reviews

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Grants

2012-2015 Israeli Ministry of Science and Technology – New Models for ALS (with Rivka Ofir)

2014-2018 Israel Science Foundation – Deciphering beta-amyloid and tau

2016-2019

neurotoxicity: Genome-wide RNA sequencing for sensitivity biomarkers- with Dr. David Gurwitz

ERA-NET NEURON – Modelling syndromic autism caused by mutations in the ADNP gene (with Frank Kooy, Pierre-Luc Germain, Christopher E. Pearson)



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

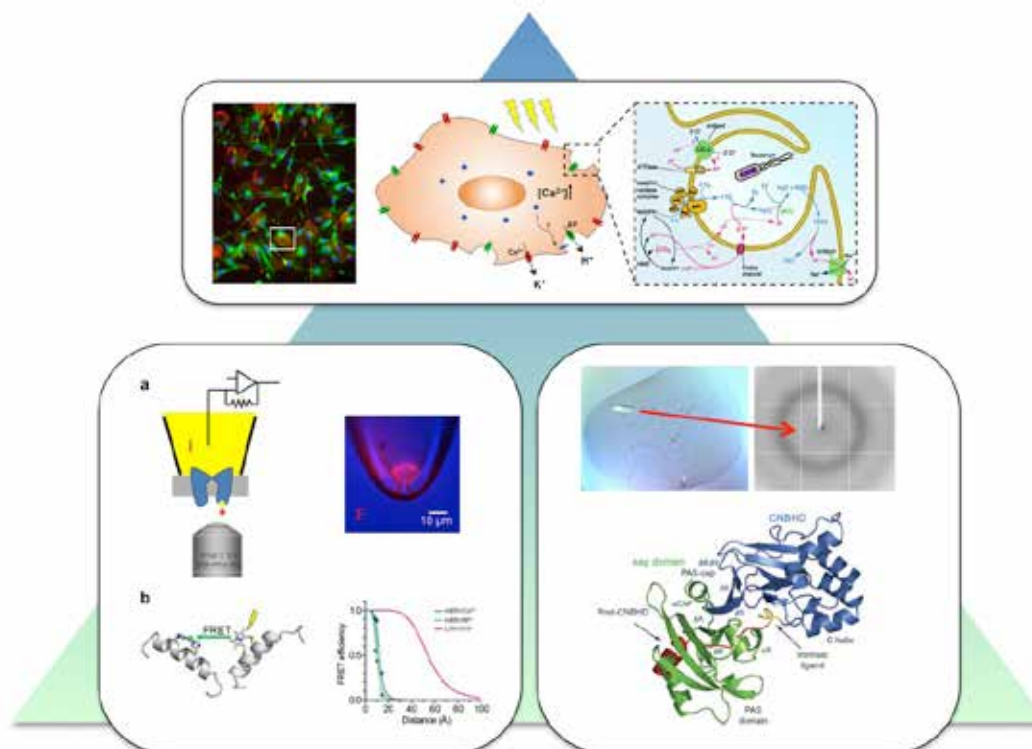
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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

Publications

Manuscripts

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Reviews

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Grants

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



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Brain Mechanisms of Human Emotion Generation & Regulation

Laboratory for Brain and Emotion Experience

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

Positions

Professor, 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

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Sleep and Its Relation to Cognition

Position

Senior Lecturer, Sackler Faculty of Medicine

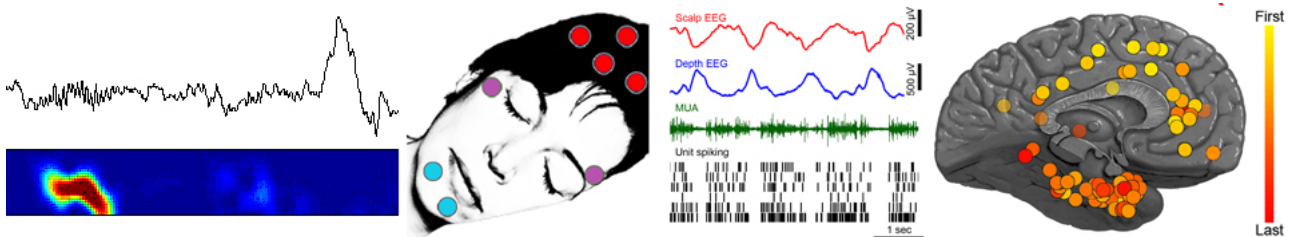
Research

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

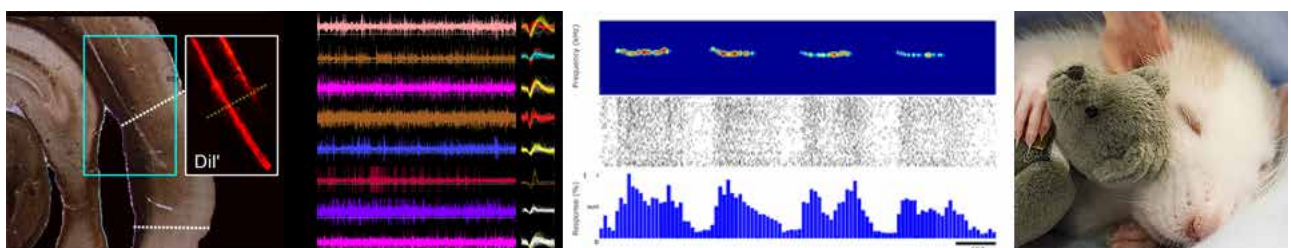
Sleep also involves dramatic changes to our perceptual awareness. Sometimes our consciousness fades altogether while at other times we experience vivid dreams. Although our brain continues to be active,

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

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



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



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

Publications

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Andrillon T*, **Nir Y***, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, Fried I. Sleep spindles in humans: insights from intracranial EEG and unit recordings. *Journal of Neuroscience*. 2011;31:17821-34. (* equal contribution)

Vyazovskiy VV, Olcese U, Hanlon EC, **Nir Y**, Cirelli C, Tononi G. Local sleep in awake rats. *Nature*. 2011;472:443-7.

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Reviews

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Grants

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

2013 – 2018 I-CORE Cognitive Neuroscience



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Sagol School of Neuroscience



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Neural Circuits and Olfactory Perception in *Drosophila*

Position

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

Research

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

Projects in the lab include:

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

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

Publications

Manuscripts

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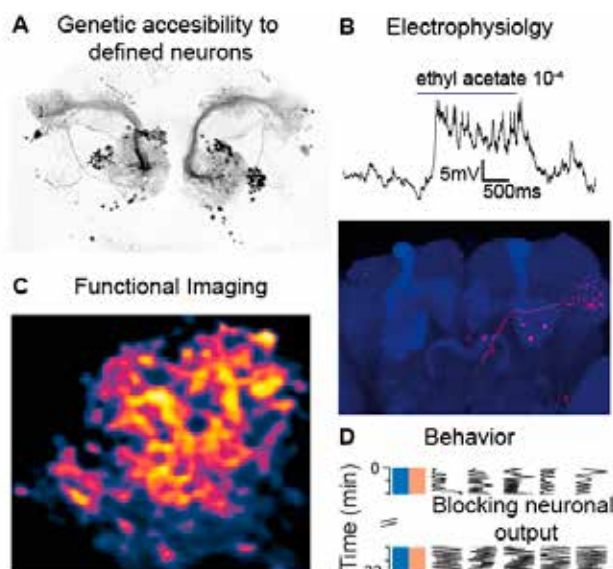
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Review

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Grants

2016-2021 ERC Starting Grant



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



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Molecular Mechanisms of Neurodegeneration

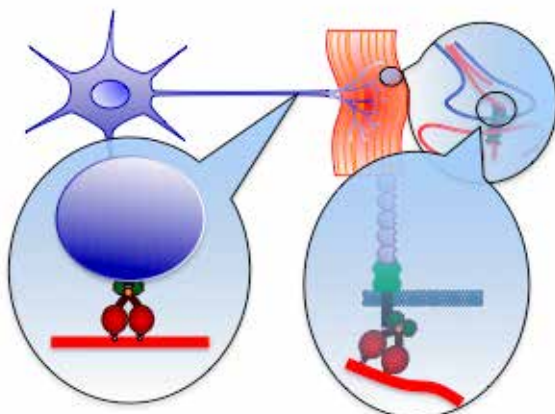
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Neuronal survival and proper function depends on cell-cell communication mediated by ligand-receptor mechanisms. During neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), there is considerable synapse/neuromuscular junction (NMJ) disruption and neuronal cell death. It is non-autonomous processes involve interactions between the neurons to its diverse extracellular microenvironments. The molecular basis for this



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.

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.

Publications

Dadon-Nachum M, Ben-Yaacov K., Ben-Zur T, Barhum Y., Yaffe D, **Perlson E.** and Offen D. (2014). Transplanted modified muscle progenitor cells expressing a mixture of neurotrophic factors delay disease onset and enhance survival of ALS model SOD1 mice. *J Molec Neurosci.* [Epub ahead of print]

Bauer A., Nolden T., Römer-Oberdörfer A., Gluska S., **Perlson E.**, and Finke S (2014). Post-replicative glycoprotein dependent bi-directional rabies virus transport in dorsal root ganglion neurons. *J Virol.* 15;88.



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Gershoni-Emek, N., Zahavi EE., Gluska S., Slobodskoy Y and **Perlson E.** (2014) The Molecular Communication Mechanism of Neuron Survival and Synapse Maintenance. In press.

Grants

2011-2015 ISF (Israel Science Foundation), The Dual Role of Dynein in GDNF Signaling

2011-2015 Marie Curie International Reintegration Grants (IRG), Retrograde Signaling.

2013-2016 Small Molecule Screen for Neuromuscular Junction Maintenance, Rosetrees Trust

2013-2016 E-Rare-2, European Research Projects on Rare Diseases driven by Young Investigators. Project Coordinator. The Molecular Basis of Neurodegeneration and Muscle Atrophy in ALS. (Co-PIs: Roded Sharan, TAU; Edgar Gomes, U of Paris; Marcus Kruger, Max Planck; Del Bene Fillippo, Ins Curie; Alberto Rodendo, 12th Oct Uni Hospital Madrid).

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



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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

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Department of Physiology and Pharmacology
Sackler Faculty of Medicine



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

Publications

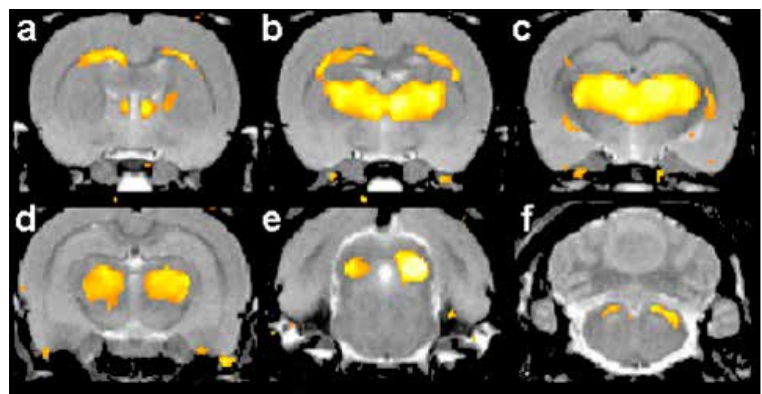
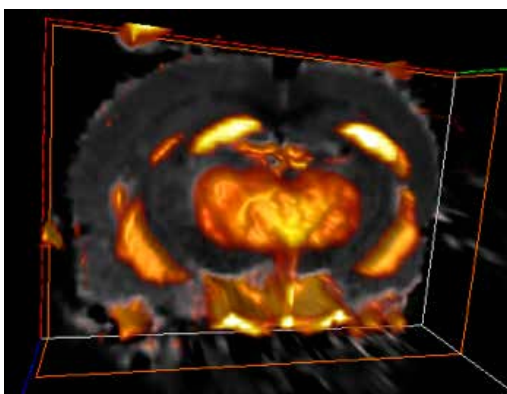
Dror, V., Eliash, S., **Rehavi, M.**, Assaf, Y., Biton I.E., Fattal-Valevsky, A. (2010). Neurodegeneration in thiamine deficient rats – A longitudinal MRI study. *Brain Res.* 1308, 176-184.

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Simchon, Y., Weizman, A., and **Rehavi, M.** (2010). The effect of methylphenidate administration on presynaptic dopaminergic parameters in a rat model for ADHD. *Eur. Neuropsychopharmacol.* 20, 714-720.

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

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Grants

2011-2015 Novel herbal treatment for anxiety disorder, Israel Science Foundation



Prof. Naphtali Savion, Ph.D.

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Sackler Faculty of Medicine



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

The following specific subjects are studied:

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

Publications

R. Ankri, H. Friedman, **N. Savion**, S. Kotev-Emeth, H. Breitbart, R. Lubart. Visible light induces nitric oxide (NO) formation in sperm and endothelial cells. *Lasers in Surg. and Med.*, 42: 348–352, 2010.

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myocardial infarction. *Am. J. Cardiol.* 107: 339–342, 2011.

S. Matetzky, P. Fefer, B. Shenkman, M. Shechter, I. Novikov, **N. Savion**, D. Varon, H. Hod. Statins have an early antiplatelet effect in patients with acute myocardial infarction. *Platelets* 22: 103–110, 2011.

N. Izigov, N. Farzam, **N. Savion**. S-allylmercapto-N-acetylcysteine up-regulates cellular glutathione and protects vascular endothelial cells from oxidative stress. *Free Radic. Biol. Med.* 50: 1131–1139, 2011.

M. Shechter, A. Shechter, H. Hod, P. Fefer, B. Shenkman, N. Koren-Morag, M.S. Feinberg, D. Harats, B.A. Sela, **N. Savion**, D. Varon, S. Matetzky. Brachial artery endothelial function predicts platelet function in control subjects and in patients with acute myocardial infarction. *Platelets*, 23:202–210, 2012.

S. Mendelboum Raviv, K. Szekeres-Csiki, A. Jenei, J. Nagy, B. Shenkman, **N. Savion**, J. Harsfalvi. Coating conditions matter to collagen matrix formation regarding von Willebrand factor and platelet binding. *Thromb. Res.* 129: e29–e35, 2012.

G. Spectre, L. Zhu, M. Ersoy, P. Hjendahl, **N. Savion**, D. Varon, N. Li. Platelets selectively enhance lymphocyte adhesion on subendothelial matrix under arterial flow conditions. *Thromb. Haemost.* 108: 328–337, 2012.

J. Schneiderman, K. Schaefer, F.D. Kolodgie, **N. Savion**, S. Kotev-Emeth, R. Dardik, A.J. Simon, M. Halak, C. Pariente, I. Engelberg, S. Konstantinides, R. Virmani. Leptin locally synthesized in carotid atherosclerotic plaques may be associated with lesion instability and cerebral emboli. *J. Am. Heart Assoc.* 2012; 1: e001727.

M. Tao, P. Yu, B.T. Nguyen, B. Mizrahi, **N. Savion**, G. Sukhova, F.D. Kolodgie, R. Virmani, C.K. Ozaki, J. Schneiderman. Locally applied leptin induces regional aortic wall degeneration in apoe deficient

mice preceding aneurysm formation. *Arterioscler. Thromb. Vasc. Biol.* 33:311-20, 2013.

I. Ben Aharon, H. Bar Joseph, M. Tzabari, B. Shenkman, N. Farzam, M. Levi, R. Shalgi, S.M. Stemmer, **N. Savion**. Doxorubicin-induced vascular toxicity – Targeting potential pathways may reduce procoagulant activity. *PLoS ONE*, 8: e75157, 2013.

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

P. Fefer, R. Beigel, N. Rozenberg, M. Shechter, S. Gannot, D. Varon, **N. Savion**, S. Matetzky. Evaluation of Platelet Response to Different Clopidogrel Dosing Regimens in Patients with Acute Coronary Syndrome in Clinical Practice. *Platelets*, Mar 11, 2014 [Epub ahead of print].

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

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

Grants

2013 – 2014 Baharv Fund for Glaucoma Research, Sackler Faculty of Medicine.



Dr. Inna Slutsky, Ph.D.

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Sackler Faculty of Medicine



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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

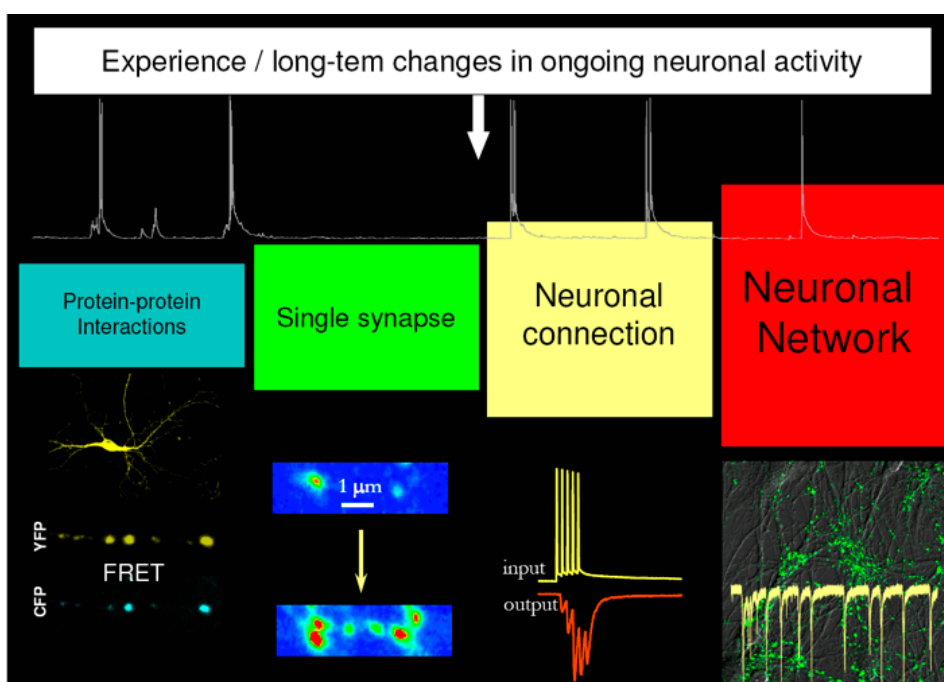
Research

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

Fogel H, Frere S, Segev O, Bharill S, Shapira I, Gazit N, O'Malley T, Slomowitz E, Berdichevsky Y, Walsh Dominic M, Isacoff EHUD Y, Hirsch Joel A, **Slutsky I** (2014) APP homodimers transduce an amyloid- β -mediated increase in release probability at excitatory synapses. *Cell Reports*, <http://dx.doi.org/10.1016/j.celrep.2014.04.024>.



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Laviv T, Vertkin I, Berdichevsky Y, Fogel H, Riven I, Bettler B, Slesinger PA, **Slutsky I.** (2011) Compartmentalization of the GABAB receptor signaling complex is required for presynaptic inhibition at hippocampal synapses. *J Neurosci.* 31:12523-12532.

Laviv, T., Riven, I., Dolev, I., Vertkin, I., Balana, B., Slesinger, P. A., and **Slutsky, I.** (2010). Basal GABA

Regulates GABA(B)R Conformation and Release Probability at Single Hippocampal Synapses. *Neuron* 67, 253-267.

Slutsky, I., Abumaria, N., Wu, L. J., Huang, C., Zhang, L., Li, B., Zhao, X., Govindarajan, A., Zhao, M. G., Zhuo, M., Tonegawa, S., Liu, G. (2010). Enhancement of Learning and Memory by Elevating Brain Magnesium. *Neuron* 65, 165-177.

Grants

2011 – 2016, Evolution of Alzheimer's Disease: From Dynamics of Single Synapses to Memory Loss, European Research Council Starting Grant.



Prof. Arie S. Solomon, M.D., Ph.D.

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Basic and Applicative Research of Eye Physiology, Diseases and Function

Positions

Associate Professor, Sackler Faculty of Medicine

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

International Committee Member, ARVO

Research

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

The following specific subjects are studied:

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

Publications

Rosenzweig S, Raz-Prag D, Nitzan A, Galron R, Paz M, Jeserich G, Neufeld G, Barzilai A **Solomon AS**. *Graefes Arch Clin Exp Ophthalmol* 2010;248:1423-35.

Cohen Y, Belkin M, Yehezkel O, Solomon AS, Polat U. Dependency between light intensity and refractive

development under light-dark cycles. *Exp Eye Res* 2011;92:40-6.

Skaat A, **Solomon AS**, Moroz I, Hai OV, Rechtman E, Vishnevskaya Dai V, Rotenstreich Increased electroretinogram a-wave amplitude after intravitreal bevacizumab injection for neovascular age-related macular degeneration. *Acta Ophthalmol* 2011;89:269-73.

Raz-Prag D, Galron R, Segev-Amzaleg N, **Solomon AS**, Shilo Y, Barzilai A, Frenkel D. A role for vascular deficiency in retinal pathology in a mouse model of ataxia-telangiectasia. *Am J Pathol* 2011;179:1533-41.

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Cohen Y, Peleg E, Belkin M, Polat U, **Solomon AS** (2012) Ambient Illuminance, retinal dopamine release and refractive development in chicks. *Exp. Eye Res.* 103:33-40.

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

Grants

2012 – 2015 European Union FP7



Dr. Eran Stark, M.D., Ph.D.

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Sagol School of Neuroscience



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Spiking Network Mechanisms Underlying Cognition

Position

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

Research

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

Publications

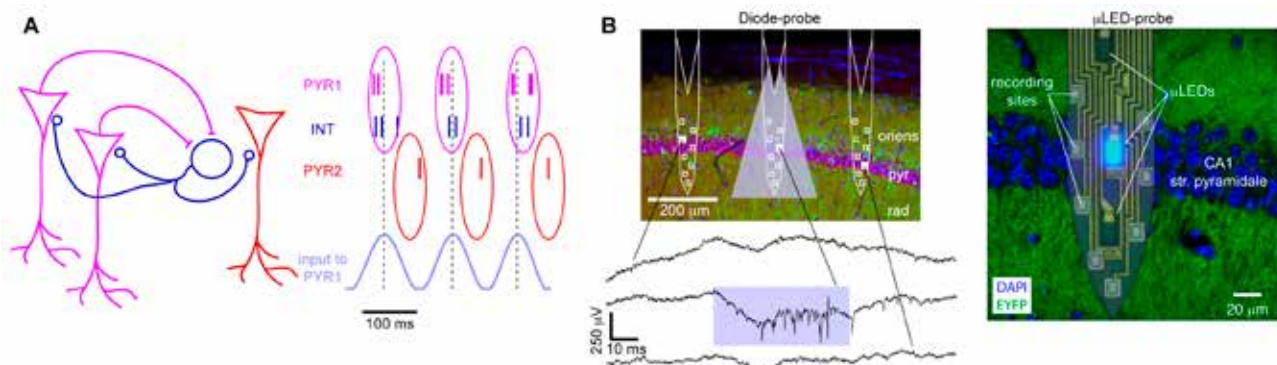
Wu F*, **Stark E***, Ku P, Wise K, Buzsáki G, Yoon E (2015) Monolithically integrated μ LEDs on silicon neural probes for high-resolution optogenetic studies in behaving animals. *Neuron*, in press.

Stark E, Roux L, Eichler R, Buzsáki G (2015) Local generation of multi-neuronal spike sequences in the hippocampal CA1 region. *Proc. Natl. Acad. Sci. USA* 112:10521-6.

English D, Peyrache A, **Stark E**, Roux L, Vallentin D, Long M, and Buzsáki G (2014) Excitation and inhibition compete to control spiking during hippocampal ripples: intracellular study in behaving mice. *J. Neurosci.* 34:16509-16517.

Stark E*, Roux L*, Eichler R*, Senzai Y, Royer S, Buzsáki G (2014) Pyramidal cell-interneuron interactions underlie hippocampal ripple oscillations. *Neuron* 83:467-80.

Berenyi A, Somogyvari Z, Nagy A, Roux L, Long J, Fujisawa S, **Stark E**, Leonardo A, Harris T, Buzsáki G (2014) Large-scale, high-density (up to 512 channels)



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

recording of local circuits in behaving animals. *J. Neurophysiol.* 111:1132-49.

Stark E, Eichler R, Roux L, Fujisawa S, Rotstein H, Buzsáki G (2013) Inhibition-induced theta resonance in cortical circuits. *Neuron* 80:1263-76.

Wu F, **Stark E**, Im M, Cho IJ, Yoon ES, Buzsáki G, Wise KD, Yoon E (2013) An implantable neural probe with monolithically integrated dielectric waveguide and recording electrodes for optogenetic applications. *J. Neural Eng.* 10:056012.

Stark E, Koos T, Buzsáki G (2012) Diode-probes for spatiotemporal optical control of multiple neurons in freely-moving animals. *J. Neurophysiol.* 108:349-63.

Vandecasteele M, M S, Royer S, Belluscio M, Berényi A, Diba K, Fujisawa S, Grosmark A, Mao D, Mizuseki K, Patel J, **Stark E**, Sullivan D, Watson B, Buzsáki G (2012) Large-scale recording of neurons by movable silicon probes in behaving rodents. *J. Vis. Exp.* 61:e3568.

English D, Ibanz-Sandoval O, **Stark E**, Tecuapetla F, Buzsáki G, Deisseroth K, Tepper JM, Koos T (2011) GABAergic mechanisms mediate the reinforcement-related signals of striatal cholinergic interneurons. *Nat. Neurosci.* 15:123-30.

Reviews

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

Roux L, **Stark E**, Sjulson L, Buzsáki G (2014) In vivo optogenetic identification and manipulation of GABAergic interneuron subtypes. *Curr. Opin. Neurobiol.* 26C:88-95.

Grants

2016-2021 ERC Starting Grant



Dr. Tami Bar-Shalita, Ph.D., O.T.

Department of Occupational Therapy
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Sackler Faculty of Medicine



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Investigating Sensory Modulation Disorder (SMD) Over Life Span

Positions

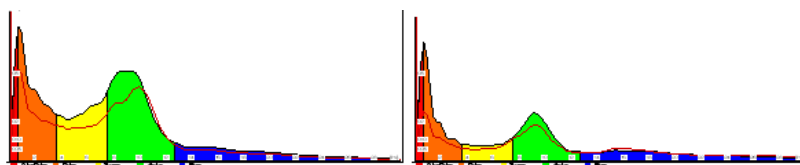
Lecturer, Sackler Faculty of Medicine

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.

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.



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

Publications

Manuscripts

Bar-Shalita, T., Vatine, J.J., Yanitsky, D., Parush, S., Weissman-Fogel, I. (2014) Atypical central pain processing in sensory modulation disorder: absence of temporal summation and higher after-sensation. *Exp Brain Res* 232, 587-595.

Bar-Shalita, T., Parush, S. Pain and sensory modulation disorder (abstracts from the Gerry Schwartz and Heather Reisman 3rd International Conference). *Int J Child Health Hum Dev* 2013;6:385

Bar-Shalita, T., Boni, O., Gevir, D., & Doryon, Y. (2013). The Israeli Occupational Therapy Code of Ethics. The Israeli Occupational Therapy National higher professional committee, Israel's Occupational Therapy Association.

Bar-Shalita, T., Vatine, J.J., Parush, S., Deutsch, L., Seltzer, Z. Psychophysical correlates in adults with sensory modulation disorder. *Disabil Rehabil.* 2012, 34:943-50.

Bar-Shalita, T., Vatine, J.J., & Parush, S. Hebrew translation to the Faces Pain Scale-Revised (FPS-R) in languages other than English. In: *Pediatric Sourcebook*, 7th ed. 2010, www.painsourcebook.ca

Bar-Shalita, T., Yochman, A., Shapiro-Rihtman, T., Vatine, J.J., Parush, S. The Participation in Childhood Occupations Questionnaire (PICO-Q): A Pilot Study. *Physical & Occupational Therapy In Pediatrics.* 2009, 29: 295-310.

Bar-Shalita, T., Vatine, J.J., Seltzer, Z., Parush, S. Psychophysical correlates in children with sensory modulation disorder (SMD). *Physiol Behav.* 2009, 98:631-639.



Prof. Sivia Barnoy, R.N., Ph.D.

Department of Nursing
Stanley Steyer School of Health Professions
Sackler Faculty of Medicine



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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 caregiver’s point of view. We wish to turn the spotlight onto the patient’s point of view, and on how they feel after bringing Internet information to an appointment with their doctor or nurse.

Publications

Barnoy, S., Levy, O. and Bar-Tal Y. (2010). Nurse or Physician: whose recommendation influences more the decision to take genetic tests? *Journal of Advanced Nursing*, 66, 806-813.

Elkind, S, Rottem, S., Rechnitzer, H., Vaisid, T., **Barnoy, S.** & Kosower, N.S. (2010). Calpastatin is elevated in *Mycoplasma hyorhinis*-infected SH-SY5Y neuroblastoma cells. *FEMS Microbiology letters*, 304, 62-68,

Kushnir, T., Bachner, Y. and **Barnoy, S.** (2010). Exploration of the link between speaking English as a foreign language and Internet use among nurses in Israel. *Online Journal of Nursing Informatics*, 14(3).

Elkind, E., Vaisid, T., Kornspan, J. D., **Barnoy, S.**, Rottem, S. & Kosower, N. S. (2011). Neuroprotective effects of *Mycoplasma hyorhinis* against amyloid- β -peptide toxicity in SH-SY5Y human neuroblastoma cells are mediated by calpastatin upregulation in the mycoplasma-infected cells. *Neurochemistry International*, 58, 497-503.

Barnoy, S., Levy, O. & Bar-Tal, Y. (2011). What makes patients perceive their health care worker as an epistemic authority? *Nursing Inquiry*, 19, 128-133.

Barnoy, S., Pruss, D., Ehrenfeld, M. and Kushnir, T. (2011). Epistemic authority and nurses’ reactions to medical information retrieved from internet sites

of different sites of different credibility. *Nursing and Health Sciences*, 13, 366-370.

Itzhaki, M., Bar-Tal, Y. & **Barnoy, S.** (2013). Staff and lay people's reactions to family presence during resuscitation: The effect of blood, resuscitation outcome and gender – a quasi-experimental study. *Journal of Advanced Nursing*, In press.

Itzhaki, M., Bluvstein, I., Raz, S. and **Barnoy, S.** (2013). Factors affecting the actions and emotional reactions of nursing teachers following encounters with students who present them with Internet Information. *Nursing Education Today*, 33, 8842–8846.

Elkind, E Vaisid, T., Kornspan, J. D., **Barnoy, S.**, Rottem, S. & Kosower, N.S. (2012). Calpastatin upregulation in *Mycoplasma hyorhinitis*-infected cells is promoted by the mycoplasma lipoproteins via the NF-κB pathway. *Cellular Microbiology*, 14:840-851.

Gilbar, R. & **Barnoy, S.** Disclosure of genetic information to relatives in Israel: between privacy and solidarity. (2012). *New Genetics and Society*, 31:391-407.

Skirton, H., **Barnoy, S.** Erdem, Y., Ingvaldstad, C., Pestoff, R., Teksen, F. & Williams, J. (2012). Suggested components of the curriculum for nurses and midwives to enable them to develop essential

knowledge and skills in genetics. *Journal of Genetic Counseling*, 3:323-9.

Prows, C. A., Hopkin, R. J., **Barnoy, S.** & Van Riper, M. (2013). An update of childhood genetic disorders. *Journal of Nursing Scholarship*, 45, 34-42.

Tabak, N., Itzhaki, M., Sharon, D. and **Barnoy, S.** (2013). Intentions of nurses and nursing students to tell the whole truth to patient and family members. *Journal of Clinical Nursing*, 22, 1434-1441. DOI: 10.1111/j.1365-2702.2012.04316.x

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

Kagan, I. and **Barnoy, S.** (2013). Organizational culture safety and medical error reporting by Israeli nurses. *Journal of Nursing Scholarship*, 45, 273-280.

Gilbar R, Shalev S, Spiegel R, Pras E, Berkenstadt M, Sagi M, Ben-Yehuda A, Mor P, Perry S, Zaccai TF, Borochowitz Z, **Barnoy S.** Patients' attitudes towards disclosure of genetic test results to family members: the impact of patients' sociodemographic background and counseling experience. *J Genet Couns.* 2015 Sep 14



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

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L. Rosenberg, T. Jarus, **O. Bart**, N. Z. Ratzon. Can personal and environmental factors explain dimensions of participation of children without developmental disabilities? *Child: Care, Health & Development*, 37, 266-275, 2011

O. Bart, T. Jarus, Y. Erez, L. Rosenberg. How do young children with DCD participate and enjoy daily activities? *Research in Developmental Disabilities*, 32, 1317-1322, 2011

T. Jarus, **O. Bart**, G. Rabinovich, A. Sadeh, L. Bloch, T. Dolfin, I. Litmanovitz. Effects of prone and supine positions on sleep state and stress responses in preterm infants. *Infant Behavior and Development*, 34, 257-263, 2011

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B. Soref, N.Z. Ratzon, L. Rosenberg, Y. Leitner, T. Jarus, **O. Bart**. Personal and Environmental Pathways to Young Children's Participation. *Child: Care, Health & Development*, 38, 561-571, 2012.

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Prof. Ruth Defrin, Ph.D.

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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

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G. Zeilig, S. Enosh, D. Rubin-Asher, B. Lehr, **R. Defrin**. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. *Brain* 2012;135:418-30.

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E. Peles, S. Schreiber, T.Hetzroni, M. Adelson, **R. Defrin**. The Differential Effect of Methadone Dose and of Chronic Pain on Pain Perception of Former Heroin Addicts Receiving Methadone Maintenance Treatment. *Journal of Pain* 2011;12:41-50.

R. Defrin, H. Gruener, S. Schreiber, CG. Pick. Quantitative somatosensory testing of subjects with chronic post-traumatic headache: Implications on its mechanisms. *European Journal of Pain* 2010;14:924-931.

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Chapter

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Models and Rehabilitation of Grasping

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

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.

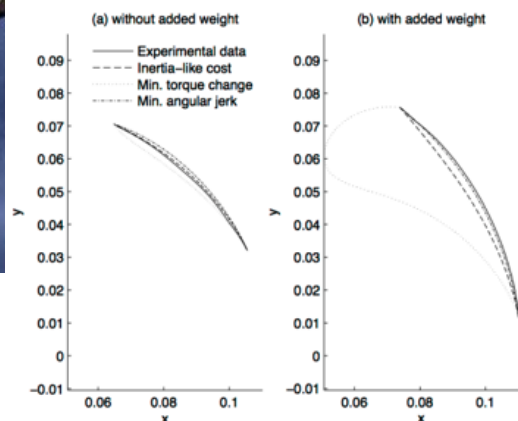
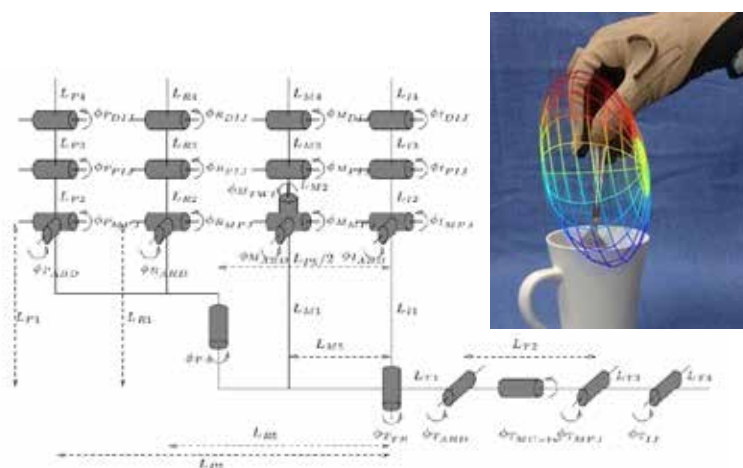
Publications

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Park, J., Pažin, N. **Friedman, J.**, Zatsiorsky, V.M. and Latash, M.L. (2014) Mechanical properties of the human hand digits: Age-related differences. *Clinical Biomechanics*, 29: 129-137.

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

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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 brain-stem function in neonates. We postulate that central auditory processing disorders (CAPD) manifested later in life can already be detected at this early stage of life using this method. We plan to continue to investigate the development of the efferent system and its importance for hearing throughout the life span, from childhood to old age, under difficult listening conditions and in subjects with communication disorders.

Publications

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for atypical auditory brainstem response in young children with suspected autism spectrum disorders. *Developmental Medicine & Child Neurology*, 54:23-29.

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Emotional Management, Cultural Competence and Decision-Making

Positions

Head, Genetic BA Nursing Program

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

Koren A, Mintz A & **Itzhaki M**. Is this a mistake? Perception of nursing students' errors by clinical perceptors. *Body of Knowledge – The Israel Journal for Nursing Research* 2014, 11, 2-14. (Hebrew)

Melnikov S*, **Itzhaki M***, Kagan I. Israeli nurses' intention to report for work in an emergency or disaster. *Journal of Nursing Scholarship* 2013, 46, 134-42 (*Equally contributing authors)

Itzhaki M & Koton S. Knowledge, perceptions and thoughts of stroke among Arab-Muslim Israelis.

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Coffey A, McCarthy G, Weathers E, Friedman M, Gallo K, Ehrenfeld M, **Itzhaki M**, Chan S, Li W, Poletti P, Zanotti R, Molloy D, McGlade C & Fitzpatrick J. Nurses' preferred end-of-life treatment choices in five countries. *International Nursing Review* 2013, 33, 842-846.

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Itzhaki M, Bar-Tal Y, Barnoy S. Reactions of staff members and lay people to family presence during resuscitation: the effect of visible bleeding, resuscitation outcome and gender. *Journal of Advanced Nursing* 2012, 68:1967-77.

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Harpaz I, Mozes V, Mintz L, Zilberman N, **Itzhaki M**. Self fulfillment as a motive to change. From Hi

Tech to nursing. *Nurse in Israel*, 2011, 186, 40-44. (Hebrew).

Ea E, **Itzhaki M**, Ehrenfeld M, Fitzpatrick J. Acculturation among immigrant nurses in Israel and the US. *International Nursing Review*, 2010, 57, 443-448.

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Chapter

Nelson J, **Itzhaki M**, Ehrenfeld M, Tinker A, Hozak S, Johnson S. Nurses' caring for self: A four – country descriptive study (England, Israel, New Zealand and the USA). In J. Nelson & J. Watson (Eds.), *Measuring caring. International Research on Caritas as Healing* (pp. 357-370). 2011, New York, NY: Springer Publishing Company



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Quality of Care and Patient Safety

Positions

Lecturer, Sackler Faculty of Medicine

Head, Nursing Continuous Education Unit

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

Research

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

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

Publications

Toren, O., Kerzman, H., **Kagan, I.** (2011). The difference between professional image and job satisfaction of nurses who studied in a post-basic education program and nurses with generic

education: a questionnaire survey. *Journal of Professional Nursing*, 27, 28-34

Hendel, T. & **Kagan, I.** (2011). Professional image and intention to emigrate among Israeli nurses and nursing students. *Nurse Education Today*, 31, 259-262.

Baum, A., Pinchuk., M., **Kagan, I.** (2012). Job satisfaction and intention to leave the workplace among psychiatric nurses working in mental health hospital”, *The Nurse in Israel*, 190, 42-46 [Hebrew]

Melnikov, S., Kigli-Shemesh, R., Shor, R., Gon-Osishkin, M. **Kagan, I.** (2012). Closing an open psychiatric ward: organizational change and its effect on staff uncertainty, self-efficacy, and professional functioning. *Perspectives in Psychiatric Care*, 49, 103-9

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Kagan, I., Cohen, R., Fish, M., Peri, H. (2014). Developing and implementing a computerized nursing quality control system in general medical center. *Journal of Nursing Care Quality (JNCQ)*, 29, 83-90.

Frishman, S., Theilla, M., Singer, P., Avraham, Z., Libman, C., **Kagan, I.** (2014). JCI Accreditation and Its multiprofessional Impact on nutrition care at Rabin Medical Center, Israel. Invited (peer-reviewed) paper, published on official site of Joint Commission International (JCI): <http://www.>

jointcommissioninternational.org/new-study-jci-accreditation-and-nutrition-care-at-rabin-medical-center/ and also in JCInsight, official newsletter of JCI, <http://www.jointcommissioninternational.org/assets/3/7/jcinsightapril2014.pdf>

Kagan, I., Fish, M., Farkash-Fink, N., Barnoy, S. (2014) Computerization and its contribution to care quality and improvement: the nurses' perspective. *Int J Med Inform.* 83, 881-8

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



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

Positions

Lecturer, Sackler Faculty of Medicine

Research

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

Publications

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Lipskaya-Velikovsky, L., Jarus, T., & Kotler, M. Factors predicting employment status following in-patient evaluation among persons with schizophrenia. *Work (in press)*



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Physical activity, gait and posture in people with neurological diseases

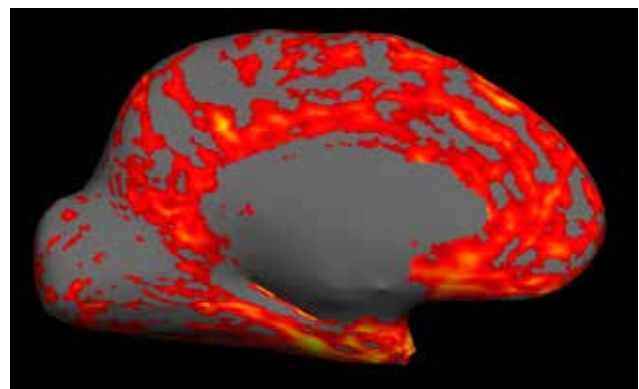
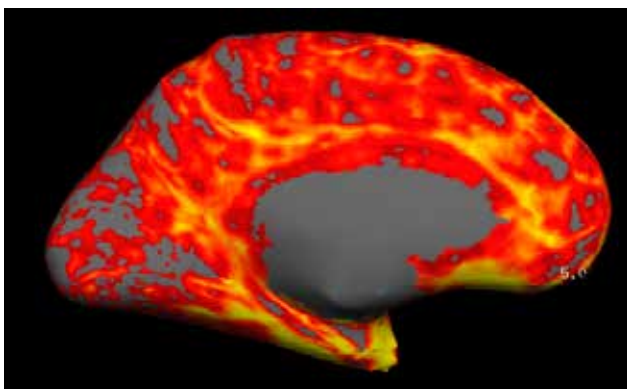
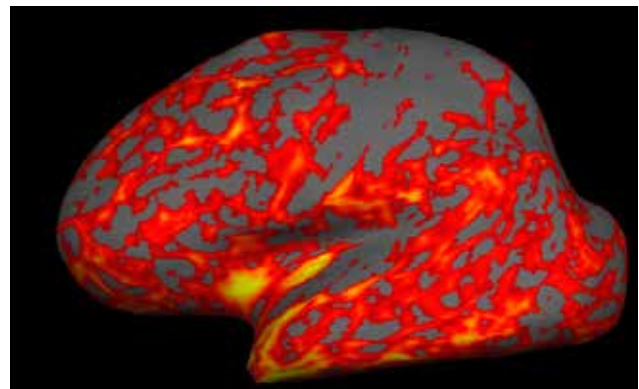
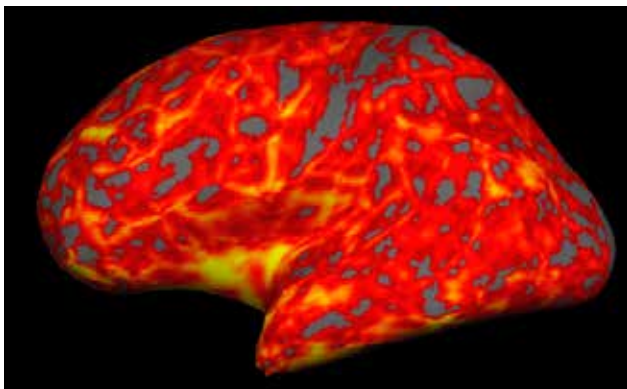
Position

Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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Grants

2014 – National Multiple Sclerosis Society Pilot Grant.



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Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

Position

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Physical Therapy

Associate Editor, Rehabilitation, Journal of Electromyography & Kinesiology

Research

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

and understanding laws of motor control and sensorimotor integration.

Publications

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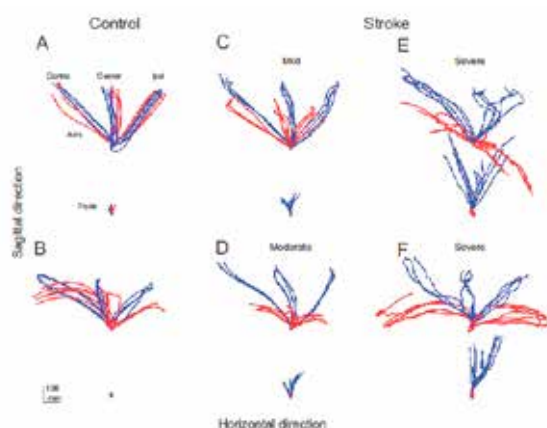


Fig. 2



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

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Spinal Form and Function

Position

Senior Lecturer, Sackler Faculty of Medicine

Member, Associate Board, Spine Journal

Research

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

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

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

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

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

Publications

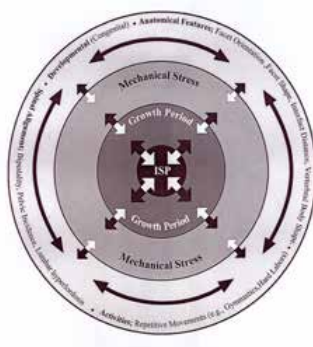
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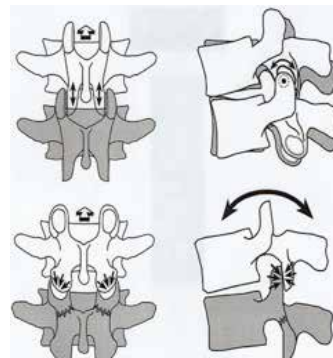
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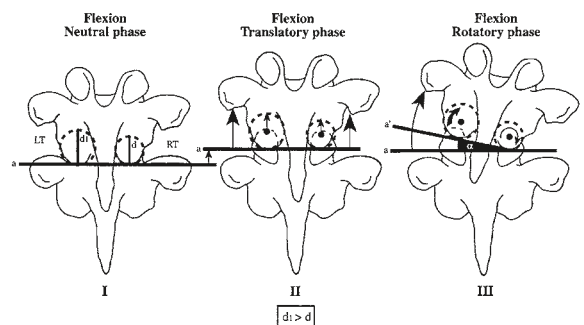
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A



B



C

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Attitudes Toward Organ/Tissues Donation and Transplantation

Position

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

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Functioning. *Perspectives in Psychiatric Care*. 2013, 49, 103-109.

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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:

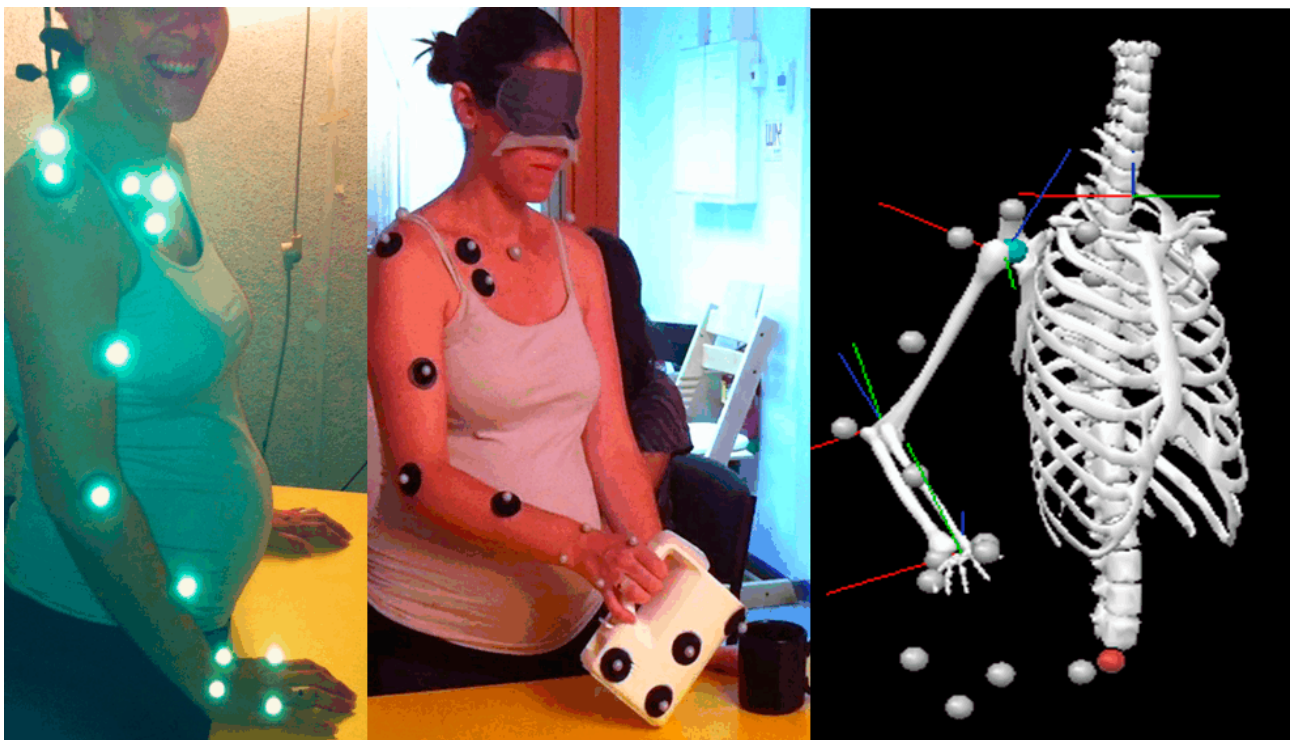
1. Design of new evaluation and treatment tools for clinicians, based on state-of-the-art technologies.
2. Quantification, evaluation and feedback, provided to the motor-impaired patient by utilizing real-time data of the kinematics, kinetics and muscular activity patterns.
3. Development of innovative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

Publications

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Chapter

Portnoy S, Gefen A. Patient-specific modeling of subjects with a lower limb amputation, *Patient-Specific Modeling in Tomorrow's Medicine, Studies in Mechanobiology, Tissue Engineering and Biomaterials* Volume 09, 2012, pp 441-459.



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Gaming as a Means of Rehabilitation of Neurological and Geriatric Populations

Position

Senior Lecturer, Sackler Faculty of Medicine

Head of M.Sc. Program, Department of Occupational Therapy

Research

Our research focuses on achieving a better understanding of the factors hindering and facilitating recovery posts-stroke. 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, Givon N, Weingarden H, Nota, A., & Zeilig, G. Eliciting upper extremity purposeful movements using video games a comparison with traditional therapy for stroke rehabilitation. *Neurorehabil Neural Repair*, 2014, Feb 10. [Epub ahead of print]

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Grants

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Investigating the Ergonomics of Occupational Tasks and Driving Rehabilitation

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

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

Publications

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Grants

- | | |
|-----------|--------------------------------------|
| 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 Role of Glutamate Excitotoxicity in Neurodegenerative and Malignant Diseases

Position

Lecturer, Sackler Faculty of Medicine

Research

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

Publications

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implanted glioma. *Invest New Drugs*. 30; 2226-35, 2012.

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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

Theilla M, Schwartz B, Zimra Y, Shapiro H, Anbar R, Rabizadeh E, Cohen J, Singer P. Enteral n-3 fatty acids and micronutrients enhance percentage of positive neutrophil and lymphocyte adhesion molecules: a potential mediator of pressure ulcer healing in critically ill patients. *British Journal Nutrition*. 1: 1-6, 2011

Theilla M, Schwartz B, Cohen J, Shapiro H, Anbar R, Singer P. Impact of a nutrition formula enriched in fish oil and micronutrients on pressure ulcer in ICU patients. *American Journal of Critical Care*. 21: 2-7, 2012.

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Chapter

Singer P, **Theilla M**, Cohen J. Intravenous lipids: what do the guidelines say. Institute for Nutrition Research and Critical Care Department. *In press*.



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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

Muhsen K, W. Na'amnah, Y. Lesser, I. Volovik, **D. Cohen**, T. Shohat. Determinates of underutilization of amniocentesis among Israeli Arab women. *Prenat Diagn.* 2010, 30:138-43.

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N. Al Shuaibi, R. Bassal, R. Yishai, M.S. Green, A. Leventhal. 2009. A Middle East sub-regional laboratory-based surveillance network on foodborne diseases established by Jordan, Israel, and the Palestinian Authority. *Epidemiol Infect.* 2010, 138:1443-8.

Rendi-Wagner, P., J. Tobias, L. Moerman, S. Goren, R. Bassal, M.S. Green, **D. Cohen**. The seroepidemiology of *Bordetella pertussis* in Israel – Estimate of incidence of infection. *Vaccine* 2010, 28:3285-90.

Muhsen Kh, L. Shulman, E. Kasem, U. Rubinstein, J. Shachter, A. Kremer, S. Goren, I. Zilberstein, G. Chodick, M. Ephros, **D. Cohen** for the TAU-HCLV Rota Study Group. Effectiveness of rotavirus vaccines for prevention of rotavirus gastroenteritis-associated hospitalizations in Israel: a case-control study. *Hum Vaccin.* 2010, 6:450-4.

Wiser, I., N. Orr, B. Kaufman, S. Segev, Z. Smetana, A. Bialik, N. Epstein, E. Mendelson, R. Catane, **D. Cohen**. Immunosuppressive treatments reduce long term immunity to smallpox among breast cancer patients. *J Infect. Dis.* 2010, 201:1527-34.

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Muhsen K, Barak M, Henig C, Alpert G, Ornoy A, **Cohen D**. Is the association between *Helicobacter pylori* infection and anemia age dependent? *Helicobacter*. 2010, 15:467-72.

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Reviews

Bassal R, REISFELD A, ANDORN N, YISHAI R, NISSAN I, AGMON V, PELED N, BLOCK C, KELLER N, KENES Y, TARAN D, SCHEMBERG B, KEN-DROR S, ROUACH T, CITRON B, BERMAN E, GREEN M.S, SHOCHAT T, **Cohen D**. Recent trends in the epidemiology of non-typhoidal *Salmonella* in Israel (1999-2009). *Epidemiol Infect* 2012, 140:1446-53.

Muhsen K, **Cohen D**, Spungin-Bialik A, Shohat T. Sero-prevalence, correlates and trends of *Helicobacter pylori* infection in the Israeli population. *Epidemiol Infect* 2012, 140:1207-14.

Cohen D, Muhsen K. Association between *Helicobacter pylori* colonization and glycosylated hemoglobin levels: Is this another reason to eradicate *Helicobacter pylori* in adulthood? *J Inf Dis*; 2012;205:1183-5 (editorial)

Grants

2011-2015 European Union, Development of vaccines against *Shigella* and enterotoxigenic *E. coli* enteric diseases. Leader of 2 WPs.

2013-2016 Israel National Institute for Health Policy and Health Services Research "Evaluation of the impact of the introduction of universal immunization with the rotavirus vaccine on the burden of severe childhood diarrhea associated with rotavirus in Israel"



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Aging and End of Life

Positions

Professor, Department of Health Promotion, Sackler Faculty of Medicine

Director, Minerva Center for the Interdisciplinary Study of End of Life

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

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Cohen-Mansfield, J., Thein, K., Dakheel-Ali, M., Regier, N.G., & Marx, M.S. (2010) The value of social attributes of stimuli for promoting engagement in

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Chapters

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Cardiovascular Disease Epidemiology

Positions

Associate Professor, Sackler Faculty of Medicine

Adjunct Associate Professor of Epidemiology, College
of Medicine, Mayo Clinic, Minnesota

Research

Our research covers a wide array of topics related to the epidemiology of cardiovascular diseases. These include risk factor and biomarker evaluation, secular trend analysis, and outcomes research. We have a particular interest in assessing long-term prognosis after acute myocardial infarction. This type of investigation usually combines data from multiple sources, including interviews and questionnaires, laboratory measurements involving blood specimens, and clinical details obtained through medical records and examinations. We are also interested in methodological aspects involved in conducting and interpreting observational studies.

Publications

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term survival after myocardial infarction. *Circulation* 2010; 121:375-83.

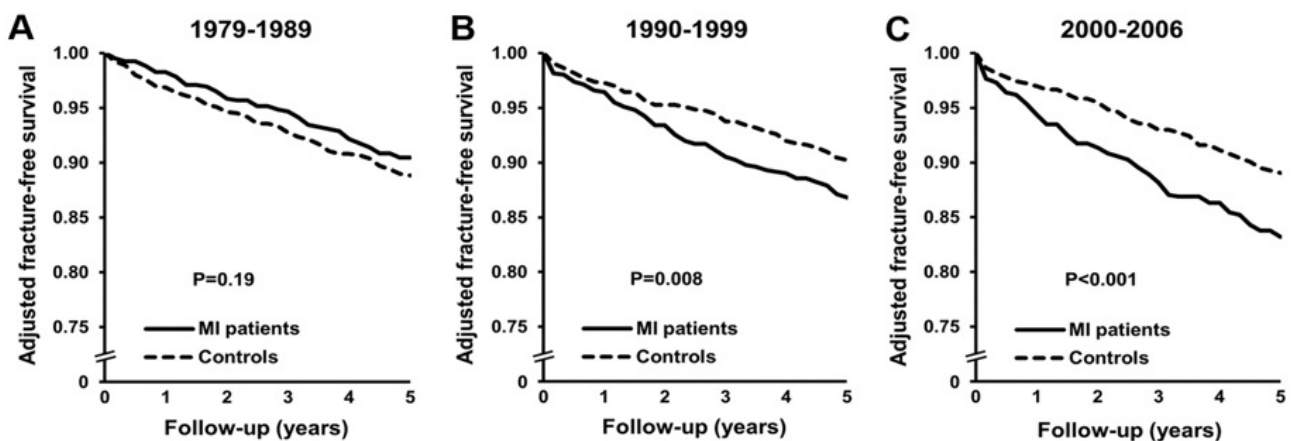
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Gerber Y, Jaffe AS, Weston SA, Jiang R, Roger VL. Prognostic value of cardiac troponin T post-myocardial infarction: A contemporary community experience. *Mayo Clin Proc* 2012;87:247-54.

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

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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

Publications

Muhsen K, Athamna A, Spungin-Bialik A, Alpert G, Cohen D. Presence of *H. pylori* in a sibling is associated with a long term increased risk of *H. pylori* infection in Israeli Arab children. *Helicobacter*. 2010; 15; 108-113

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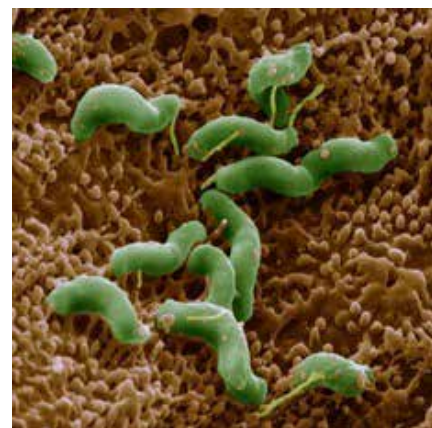
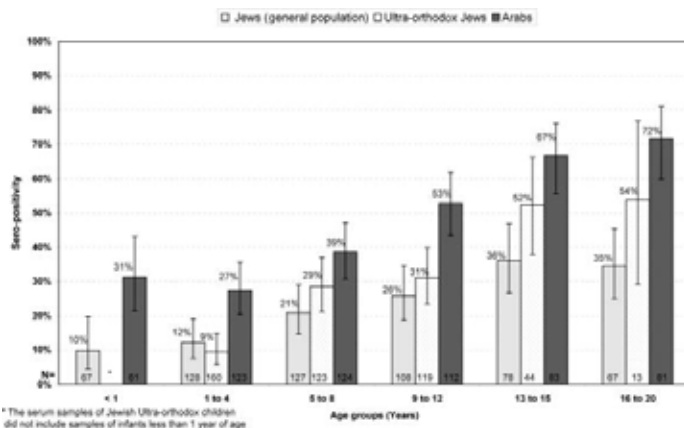
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Muhsen K, Ornoy A, Akawi A, Alpert G, Cohen D. *Helicobacter pylori* infection is associated with diminished cognitive function in children at early school age. *BMC Pediatrics*. 2011; 11:43.

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pylori infection among Israeli Arab infants. J Trop Pediatrics. 2012; 58:208-213.

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Farag TH, Nasrin D, Wu Y, **Muhsen K**, Blackwelder W, Sommerfelt H, Panchalingam S, Nataro JP, Kotloff KL, Levine MM. Some epidemiological, clinical, microbiological and organizational assumptions that influenced the design and performance of GEMS-1. Clin Infect Dis. 2012; 55 Suppl 4:S225-31.

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Muhsen K, Pasetti MF, Reymann MK, Graham DY, Levine MM. *Helicobacter pylori* infection affects immune responses following vaccination of typhoid-naïve U.S. adults with attenuated *Salmonella* Typhi oral vaccine CVD 908-*htrA*. J Infect Dis. 2014, 209:1452-8

Human OMSC co-expressing neural crest markers – p75 (red) and pluripotency associated markers – Oct4 (green) are located in specific niches within the lamina propria of the adult human oral mucosa.

Boyd MA, Tennant SM, Saague VA, Simon R, **Muhsen K**, Ramachandran G, Cross AS, Galen JE, Pasetti MF, Levine MM. Serum bactericidal assays to evaluate typhoidal and nontyphoidal salmonella vaccines. Clin Vaccine Immunol. 2014;21:712-21.

Chapter

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Grants

- | | |
|-----------|--|
| 2013-2016 | MAOF award, Higher Council for Education- Israel |
| 2013-2016 | Israel National Institute for Health Policy and Health Services Research (Co-PI with Prof. D. Cohen) |
| 2014-2015 | Bill and Melinda Gates Foundation, Multicenter study with University of MD |
| 2014-2015 | Israel Cancer Association |
| 2014-2016 | Israel National Health Policy Research Institute |



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Epidemiology of Parkinson's Disease and Environmental Epidemiology

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, School of Public Health Seminars

Research

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

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

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

Publications

Huber-Mahlin V, Giladi N, Herman T, **Peretz C**, Hausdorff JM. Progressive nature of a higher level gait disorder: a 3-year prospective study. *J Neurol*. 2010; 257:1279-86

Zaidenstein R, **Peretz C**, Nissan I, Reisfeld A, Yaron S, Agmon V, Weinberger M. The epidemiology of extraintestinal non-typhoid Salmonella isolates in Israel: the effects of patient's age and sex. *Eur J Clin Microbiol Infect Dis*. 2010; 29:1103-9

Weinberger M, Yaron S, Agmon V, Yishi R, Andorn N, **Peretz C**. Curtailed short-term and long-term survival following infection with non-typhoid Salmonella in Israel. *Clin Microbiol Infect*. 2011; 17:278-84

Peretz C, Korczyn AD, Aharonson V, Birnboim S, Shatil E, Giladi N. Individualized computer-based cognitive training improves cognitive performance in elderly subjects: a randomized, prospective, double blind study with an active comparator *Neuroepidemiol*. 2011; 36:91-9.

Chillag-Talmor O, Giladi N, Linn S, Gurevich T, El-Ad B, Silverman B, Friedman N, **Peretz C**. Use of a refined drug tracer algorithm to estimate prevalence and incidence of Parkinson's Disease in a large Israeli population. *J Parkinson's Dis*. 2011; 1: 35-47.

K. Agay-Shay, M. Friger, S. Linn, A. Peled, Y. Amitai, **C. Peretz**. Periodicity and time trends in the incidence of congenital malformations conceptions among Jews and Muslims in Israel, 1999-2006. *Birth Defects Res A*. 2012; 94: 438-48.

Chillag-Talmor O, Giladi N, Linn S, Gurevich T, El-Ad B, Silverman B, Friedman N, **Peretz C**. Estimation of Parkinson's disease survival in Israeli men and women, using health maintenance organization pharmacy data in a unique approach. *J Neurol*. 2012; 260:62-70.

Weinberger M, Agmon V, Yaron S, Nissan I, **Peretz C**. Geographical variations in Salmonella incidence in Israel 1997-2006: the effect of rural residency. *Epidemiol Infect*. 2012; 12:1-10.

Agay-Shay K, Amitai Y, **Peretz C**, Linn S, Friger M, Peled A. Exploratory spatial data analysis of congenital malformations in Israel, 2000-2006. *ISPRS Int J Geo-Inf*. 2013; 2:237-255

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

Leone M, D'Ippoliti D, De Sario M, Analitis A, Menne B, Katsouyanni K, De' donato FK, Basagana X, Salah AB, Casimiro E, Dörtbudak Z, Iñiguez C, **Peretz C**, Wolf T, Michelozzi P. A time series study on the effects of heat on mortality and evaluation of heterogeneity into European and Eastern-Southern Mediterranean

cities: results of EU CIRCE project. *Environ Health*. 2013; 12:55.

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Improving Public Health, and Control Tobacco Use and Exposure

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

Affiliated Faculty, Harvard Global Center for Tobacco Control

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

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

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

Ginsberg G, Rosenberg E, **Rosen L**. Issues in estimating smoking-attributable mortality in Israel. *European Journal of Public Health* 2010; 20: 113-119.

Rosen L, Zucker D, Rosen B, Connolly G. Secondhand smoke levels in Israeli bars, pubs, and cafes before and after implementation of smoke-free legislation. *Eur J of Public Health* 2011;21:15-20.

Rosen L, Ben Noach M. Systematic reviews on tobacco control from Cochrane and the Community Guide: Different methods, similar findings. *Journal of Clinical Epidemiology* 2010 63:596-606.

Rosen L, Brody D, Zucker D, Manor O, Meier M, Rosen B, Lev E, Engelhard D. Spreading the handwashing message: An alternative to traditional media campaigns. *Am J of Infec Control* 2010;38:562-4.

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.

Rosen L, Rosenberg E, McKee M, Gan-Noy S, Levin D, Mayshar E, Shacham G, Borowski J, Bin Nun G, Lev B. A framework for developing an evidence-based, comprehensive tobacco control program. *Health Research Policy and Systems* 2010, 8:17.

Rosen L, Zucker D, Brody D, Engelhard D, Meir M, Manor O. Enabling hygienic behavior among preschoolers: Improving environmental conditions through a multi-faceted intervention. *Am J of Health Promotion* 2011, 25:248-256 .

Rosen LJ, Guttman N, Hovell M, Ben Noach M, Winickoff J, Tchernokovski S, Rosenblum J, Rubenstein U, Seidmann V, Vardavas CI, Klepeis NE, Zucker D. Development, design, and conceptual

issues of Project Zero Exposure: A program to protect young children from tobacco smoke exposure. *BMC Public Health* 2011, 11:508.

Rosen L, Ben Noach M, Winickoff J, Hovel M. Parental Smoking Cessation to Protect Young Children: A Systematic Review and Meta-analysis. *Pediatrics* 2012, 129:141-152.

Rosen L. Tobacco smoke exposure and children. *Environment and Health*. Fall, 2011. (Hebrew)

Ben Noach M, Steinberg D, Goldsmith R, Shimony T, Rosen L. Ethnic differences in patterns of secondhand smoke exposure among adolescents in Israel. *Nicotine and Tobacco Research*. 2012, 14:648-56.

Knishkowsky B, Verbov G, Amitai Y, Stein-Zamir C, Rosen L. Reaching Jewish ultra-orthodox adolescents: results from a targeted smoking prevention trial. *International Journal of Adolescent Medicine and Health*. 2012, 24:173-9.

Rosen L, Rier D, Schwartz R, Oren A, Kopel A, Gevman A, Zeller M, Connolly G. Public support for smoke-free areas in Israel: A case for action. *Health Policy*. 2012, 106:161-8.

Rosen L, Rier D, Connolly G, Oren A, Landau C, Schwartz R. Do health policy advisors know what the public wants? An empirical comparison of how health

policy advisors assess public preferences regarding smoke-free air, and what the public actually prefers. *Israel Journal of Health Policy Research* 2013, 2:20.

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

Rosen L, Myers V, Hovell M, Zucker D, Ben Noach M. Meta-analysis of Parental Protection of Children From Tobacco Smoke Exposure. *Pediatrics* 2014;133:698-714.

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

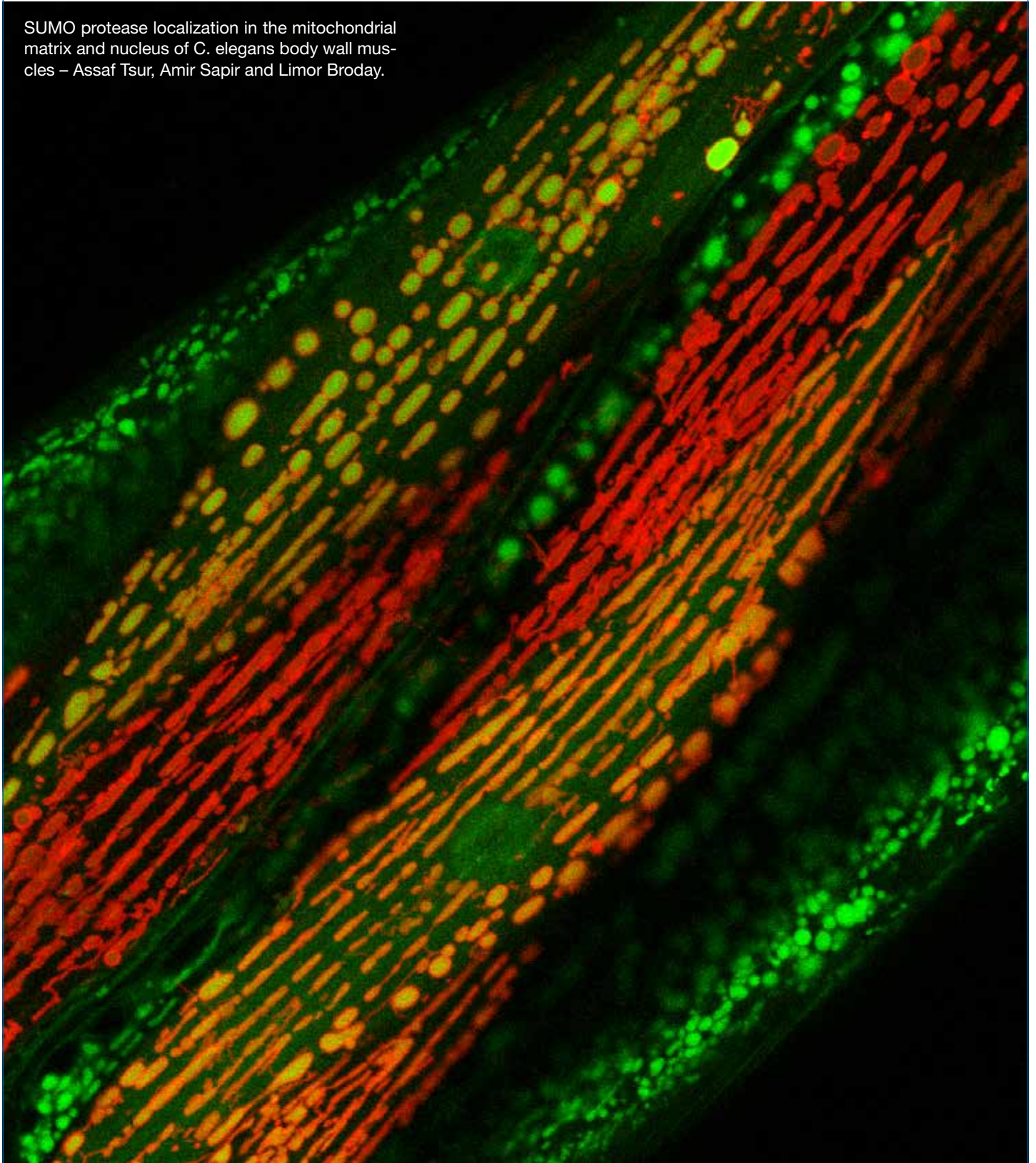
Rosen L, Rozhavski V, Levine H, Sela T, Bar-Ze'ev Y, Molina-Hazan V, Zarka S. Smoking initiation among Israeli adolescents: A 24-year time-to-event analysis. *Prev Med (In Press)*

Grants

2008-2015 Intervention to prevent young child exposure to tobacco smoke. Flight Attendant Medical Research Institute.

Reproduction, Development and Evolution

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





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

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Current lab projects:

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

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

Publications

Darom, A., Bening-Abu-Shach, U., **Broday L.** 2010. RNF-121 is an ER-membrane E3 ubiquitin ligase required for ER homeostasis and regulation of PAT-3/ β -integrin levels. *Mol Biol Cell* 21:1788-1798.

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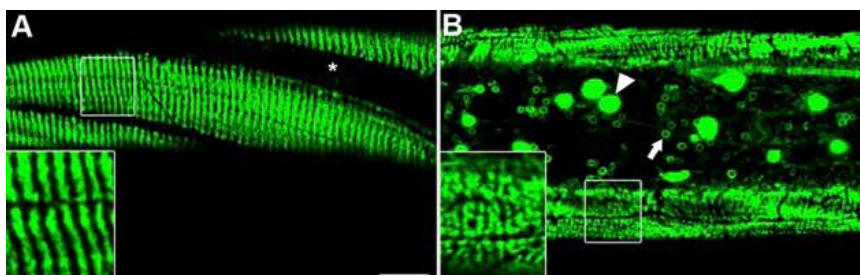
Sapir, A., Tsur, A., Koorman, T., Ching, K., Mishra, P., Bardenheier, A., Podolsky, L., Bening-Abu-Shach, U., Boxem, M., Chou, TF., **Broday, L.**, Sternberg, P.W. 2014. Controlled sumoylation of the mevalonate pathway enzyme HMGS-1 regulates metabolism during aging. *Proc Natl Acad Sci USA* 111:E3880-E3889.

Grants

2011–2015 The role of SUMO in the assembly of cytoskeletal intermediate filaments, The Israel Science Foundation (ISF).

2014–2015 Israel Cancer Research Fund (ICRF) Project Grant (co-PI Chen Luxenburg)

2014–2016 ICRF Project Grant



(A) Organization of the *C. elegans* epidermal intermediate filament protein IFB-1 in circumferential bands in wild-type animal.
(B) Abnormal filaments and formation of inclusions in *smo-1* deleted worms.



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Genetic and Hormonal Regulation of Bone Metabolism

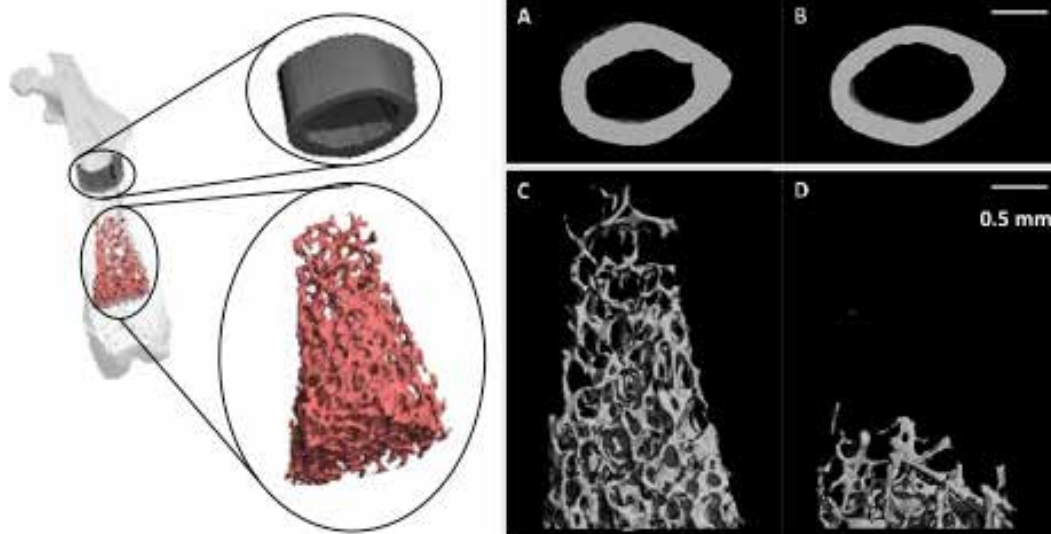
Position

Senior Lecturer, Sackler Faculty of Medicine

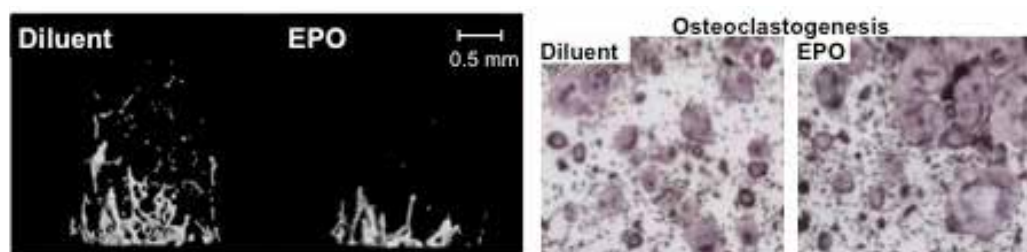
Research

Our laboratory focuses on the genetic and hormonal regulation of bone remodeling, microarchitecture and strength. These traits have a high degree of heritability, and one aspect of our research is to characterize new genetic determinants of bone remodeling as well as elucidate the mechanism of action of selected genes.

Hormones also play critical roles in the regulation of bone mass and structure. We investigate the actions of sex hormones with emphasize on the skeletal dimorphism between males and females, and their interaction with other genes and transcription factors. We also study the effect of erythropoietin, the main hormone that regulate blood cells production in the bone tissue in general and on the bone cells in particular. Lastly, we examine the impact of titanium particles on the secretion of inflammatory cytokines and on bone resorption.



Genetic regulation of bone microarchitecture: μ CT images from diaphyseal cortical (A,B) and metaphyseal trabecular bone (C,D). Note the structural differences due solely to genetic diversity between the animals.



Erythropoietin (EPO)-induced bone loss: μ CT images from EPO-treated mice versus controls (left) showing dramatic bone loss due to increased osteoclastogenesis (right).

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Chapter

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Grants

2012-2017	Israel Science Foundation (ISF) Grant
2013-2015	Rothstein Foundation
2015-2016	American Society for Bone and Mineral Research GAP Award



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Evolutionary Medicine, Paleopathology and Bio-history

Position

Professor, Sackler Faculty of Medicine

Head, Dan David Laboratory for the Search and Study of Modern Humans

Director, Tassia and Joseph Meychan Chair for the History and Philosophy of Medicine

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.

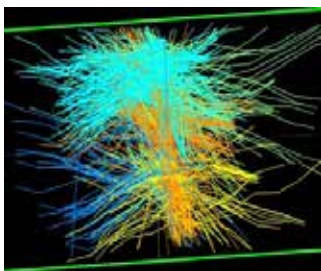
Publications

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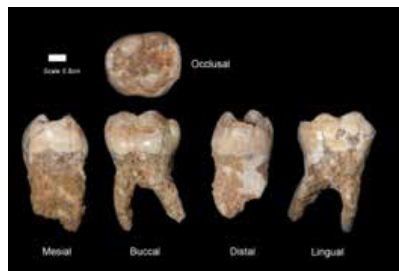
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3D reconstruction of the annulus fibrosus, MRI study. Disc herniation project.



Teeth from Qesem cave 300,000 years. Modern human origin project.



Hyperostosis frontalis interna (HFI) identified via CT and direct observation (skeletal).

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Reviews

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Theoretical Biophysics of Membranes and Cytoskeleton

Position

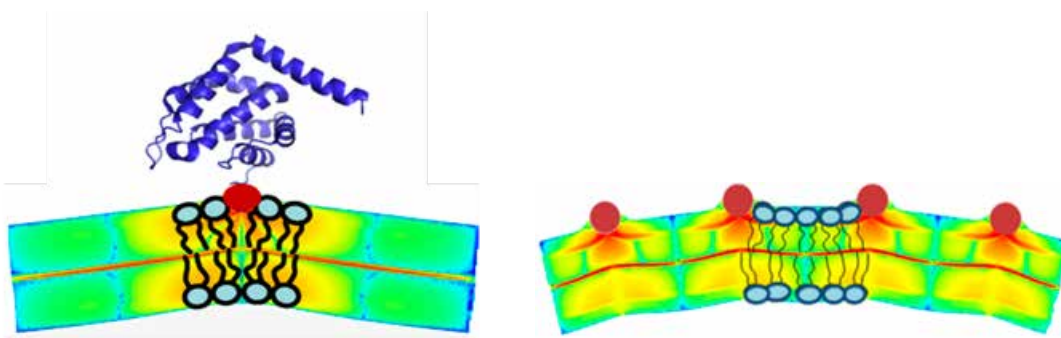
Professor, Sackler Faculty of Medicine
Joseph Klafner Chair in Biophysics

Research

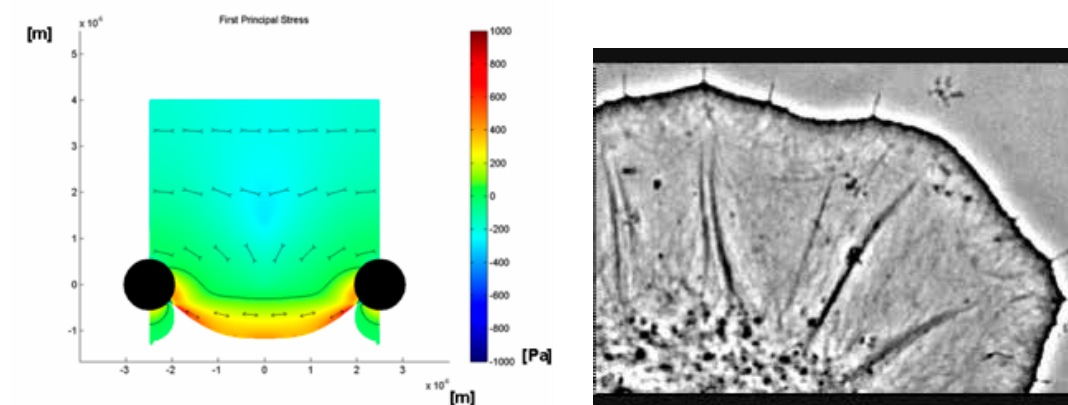
We model the mechanisms of shaping and remodeling of intracellular membranes by specialized proteins that includes generation of large membrane curvatures, membrane fission and fusion. Our goal is to reveal the common mechanistic themes in the function of membrane shaping proteins acting in different intracellular systems. In this way, we hope to be able to understand whether every stage of membrane

shaping needs a special protein or the same protein machinery can enable both membrane curvature generation and fission and/or fusion. Specifically, we model the action of BAR domain proteins, Epsins and Dynamins in endocytosis, Reticulons and their partners in shaping the Endoplasmic Reticulum, and ESCRT-III complexes in fission of cytokinetic tubes.

We model the mechanisms underlying the dynamic organization of the actin cytoskeleton and the system of cell adhesion in polarizing and moving cells. Our major goal is to understand the mechanosensitivity of the cytoskeletal systems and its role in the system temporal rearrangements and steady-state structures.



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



Computational modeling of lamellipodium boundary formation resulting from actin-focal adhesion interaction (left), the phenomenon observed in moving fibroblasts (right, courtesy of A. Verkhovsky).

Publications

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Reviews

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F. Campelo, C. Arnarez, S.J. Marrink, **M.M. Kozlov**. Helfrich model of membrane bending: From Gibbs theory of liquid interfaces to membranes as thick anisotropic elastic layers. *Adv Colloid Interface Sci*. 208: 25-33, 2014

Grants

2011-2015 The Israel Science Foundation (ISF), Membrane Shaping by Proteins



Dr. Hila May, Ph.D.

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Laboratory for Bio-History and Evolutionary Medicine

Position

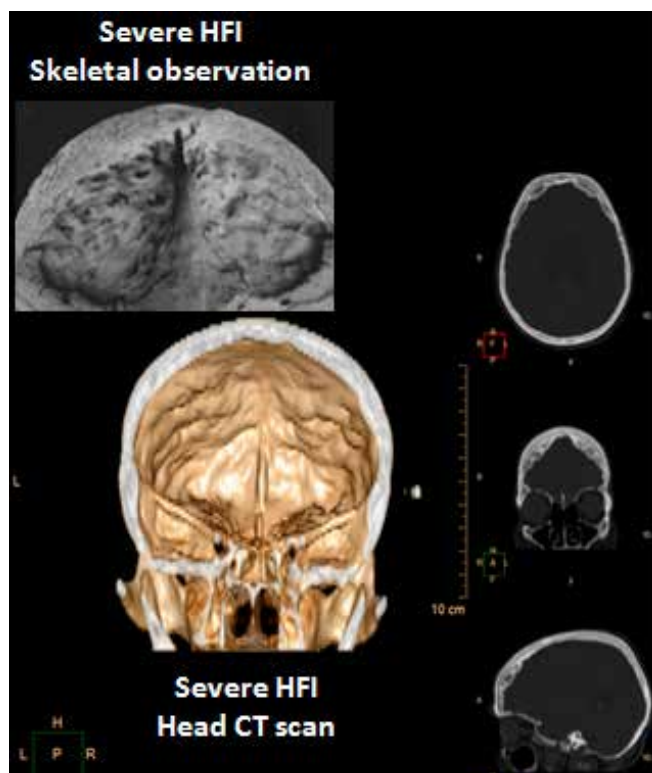
Lecturer

Research

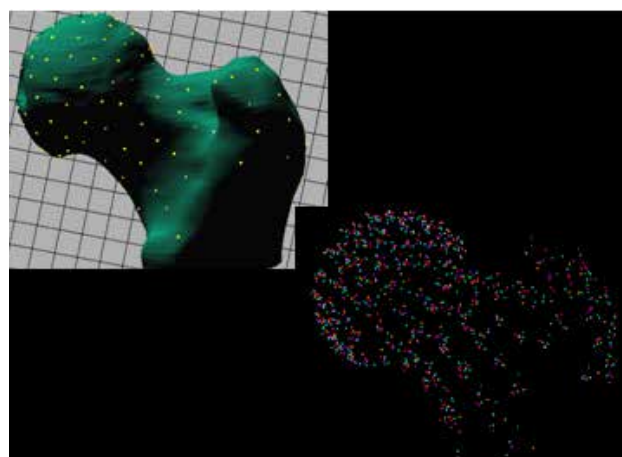
Inter-disciplinary laboratory focusing on two major topics: evolutionary history of anatomical systems and their impact on current population health, and reconstruction of ancient populations' daily life, based on their skeletal remains, with emphasis on the interaction between genetic and socio-cultural factors.

The bio-history study of ancient populations is based on both morphological and molecular (aDNA) methods.

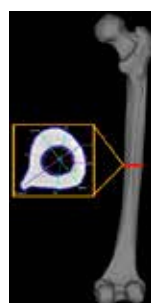
Reconstructing past population daily life: revealing daily activities of prehistoric and historic populations is a challenging task considering the evidence at hand (bones). Nevertheless, bones may furnish us with information otherwise not available, e.g., division of labor, social stratification, intensity of physical activities, health and nutrition, demography (sex ratio, mortality, family size, etc.). Beside traditional methods, the studies are being carried out utilizing advanced 3D analysis methods based on CT, micro-CT and 3D surface scans. The accompanied genetic studies, in addition to supporting and confirming observed pathologies in the bones, i.e., identifying pathogens suspected to cause diseases such as TB, leprosy, etc., also contribute to questions related to populations' migration from and to the Southern



Hyperostosis frontalis interna (HFI) identified via CT and direct observation (skeletal).



Geometric-morphometrics analysis of the proximal femur.



Femoral mid-shaft cross-sectional analysis of hunter-gatherer (Natufian), dated to ~15,000 years ago.

Levant, and questions related to population structure (e.g., extended family) and biological relationships between the local populations.

The evolutionary medicine studies focus on the quest for evolutionary explanations for common diseases found in modern human populations. We estimate the benefits and costs behind anatomical changes through evolution in order to better understand how compromised designs are being developed, and their outcomes (i.e., diseases).

Publications

G Dar, Y Masharawi, S Peleg, N Steinberg, **H May**, B Medlej, N Peled, I Hershkovitz. Schmorl's nodes distribution in the human spine and its possible etiology. *Eur Spine J*, 19, 670-675, 2010.

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Sackler Faculty of Medicine



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searcher.asp?id=abfd-
fkcg



Reproduction in Animal Models and in Humans

Positions

Professor, Sackler Faculty of Medicine

Gabriel Pinkas Chair for the Prevention and Diagnosis
of Congenital Anomalies

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.

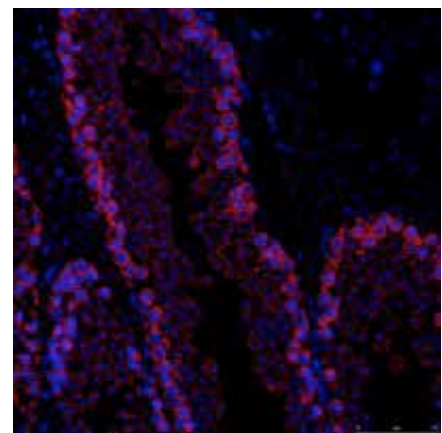
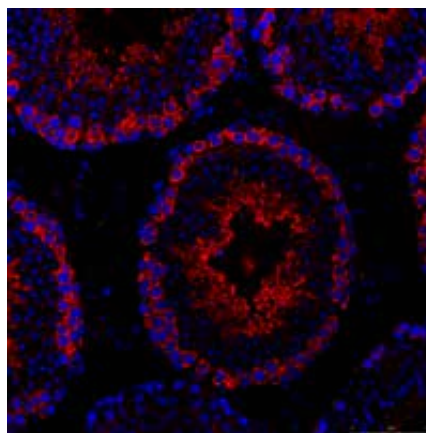
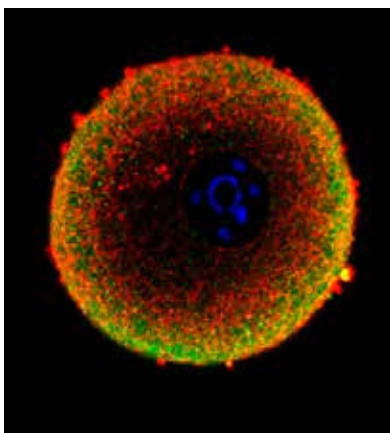
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Left panel- Human oocyte stained for DNA (blue); cytoskeleton (tubulin; red); protein (Fyn kinase; green). Arrow – Germinal vesicle (genetic material); C- Cytoplasm. Confocal microscopy. Right panels -Section of sperm producing tubules in mouse testis before (left) and after treatment with chemotherapy (right). The drug led to loss of sperm (S) production. DNA (blue); protein (DAZL; red). Immunofluorescent microscopy.

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Eliyahu, E., Shtraizent, N., **Shalgi, R.** and Schuchman, E. H. Construction of conditional acid ceramidase knockout mice and *in vivo* effects on oocyte development and fertility. *Cell Physiol Biochem.* 30:735-748, 2012.

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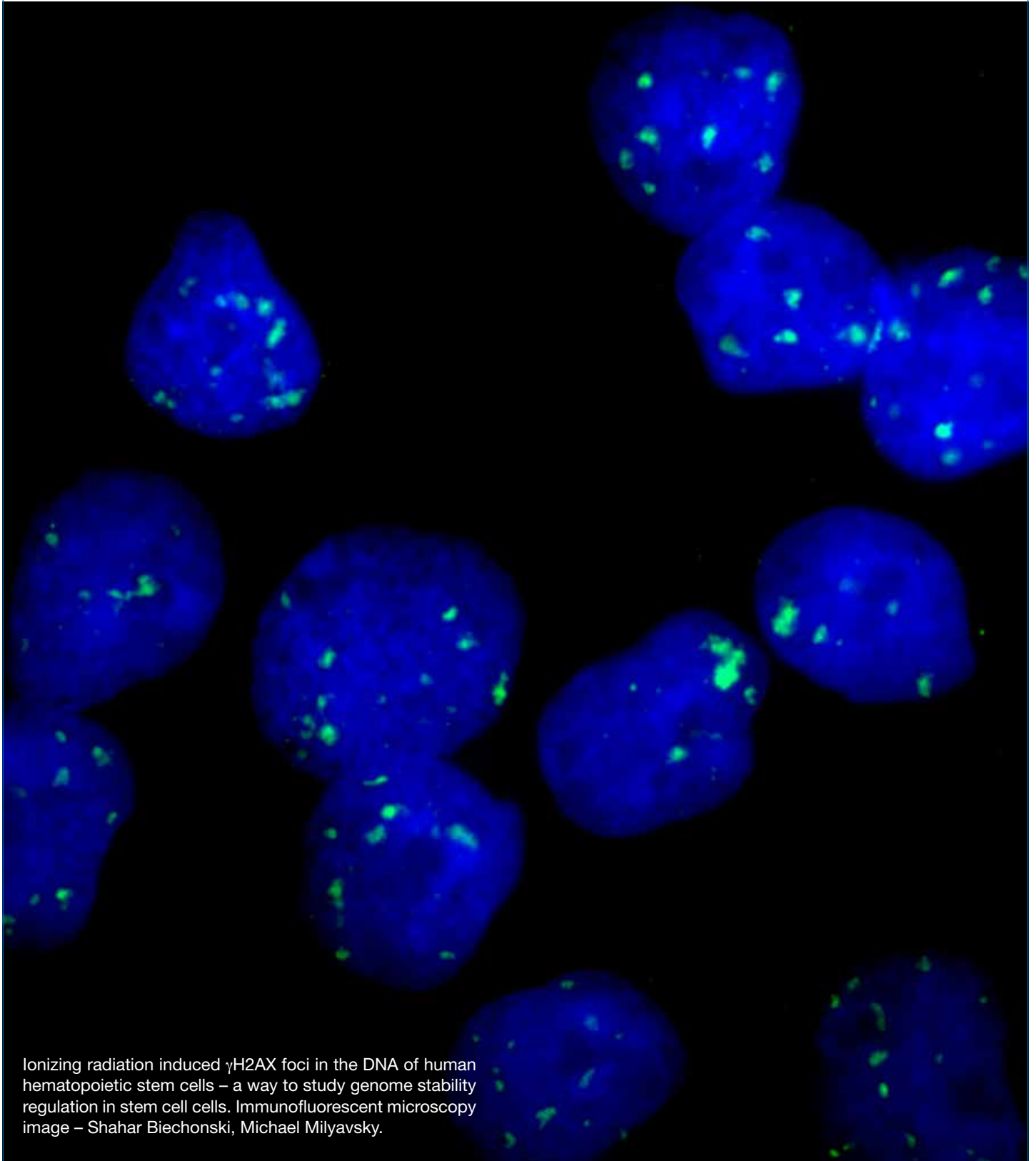
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Grants

2014-2018 Israel Science Foundation (ISF) – Post transcription regulation of Fyn kinase by miR-125a-3p in the ovary – potential relevance to ovarian function

2015-2016 Lau Mintz Foundation, Sackler School of Medicine, TAU – The role of miR-125a-3p and Fyn in oocytes’ meiosis

Stem Cells and Regenerative Medicine



Ionizing radiation induced γ H2AX foci in the DNA of human hematopoietic stem cells – a way to study genome stability regulation in stem cell cells. Immunofluorescent microscopy image – Shahar Biechonski, Michael Milyavsky.



Prof. Dafna Benayahu, Ph.D.

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Biology
Sackler Faculty of Medicine



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Musculoskeletal – Stem cells and Nanotechnology

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Cell and Developmental Biology

Research

Our interest is to follow the differentiation of skeletal stem cells and their lineage fate. The balance between skeletal stem cells and the adipose lineage is studied at the cellular and molecular biology levels. In silico characterization using bioinformatics of genes profiling and identification of biomarkers networks to identify markers for stem cells. Recent projects we gave shown that biomechanics play a role in the stem cells activation and function under normal physiology and along aging. The ultimate goal of the research is to study how to improve the stem cells functionality. Such knowledge will provide novel approaches to combat skeletal changes due to aging or metabolic disease. The use of stem cell is also developed towards tissue regeneration along with development of novel collagen-based-scaffold.

Research methods used include bioinformatics, gene cloning, qRT-PCR, cell biology analysis including immunofluorescence, scanning electron microscopy and biochemistry. Nanotechnology combines the cell fate differentiation with multidisciplinary approaches for the development new plat formed for cell analysis.

Publications

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adenocarcinoma cells. *Journal of Steroid Biochemistry and Molecular Biology* 130:36-44.

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Marcus Y, Shefer G, Sasson K, Kohen F, Limor R, Pappo O, Nevo N, Biton I, Bach M, Berkutzki T, Fridkin M, **Benayahu D**, Shechter Y, Stern N. 2013. Angiotensin 1-7 as a novel means to prevent the metabolic syndrome: lessons from the fructose-fed rat model. *Diabetic* 62(4):1121-1130

Shefer G, Rauner G, Stuelsatz P, **Benayahu D**, Yablonka-Reuveni Z. 2013 Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. *FEBS J.* 280(17): 4063-4073

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Grants

2012 -2016 Israel Science Foundation Jointly with A. Gefen



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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

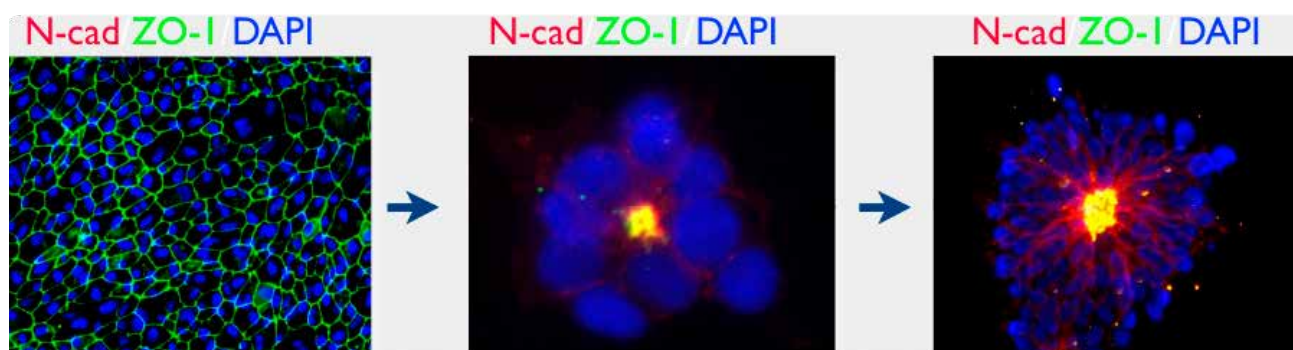
studying nervous system development and disease, making cells for therapy and discovering novel drugs.

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.

Publications

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

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Edri R*, Yaffe Y*, Ziller MJ, Mutukula N, Volkman R, David E, Jacob-Hirsch J, Malcov H, Levy C, Rechavi G, Gat-Viks I, Meissner A, Elkabetz Y. Analyzing human neural stem cell ontogeny by consecutive isolation of Notch active neural progenitors. *Nat Commun.* 2015 (In press). *Equal contribution

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epigenetic footprinting. *Nature* 518, 355-9 (2014). **Equal corresponding author

Grants

- 2010-2015 ISF, Self-renewal of ES cell-derived neural stem cells
- 2012-2015 IRG, Modeling neural diseases with neural rosettes
- 2013-2015 BrightFocus, Roles for RPE-specific microRNAs in retinal diseases
- 2013-2016 Morasha, Modeling pathogenesis of cerebral disorders



Dr. Michael Milyavsky, Ph.D.

Department of Pathology
Sackler Faculty of Medicine



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DNA Damage Response in Normal and Leukemia Hematopoietic Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

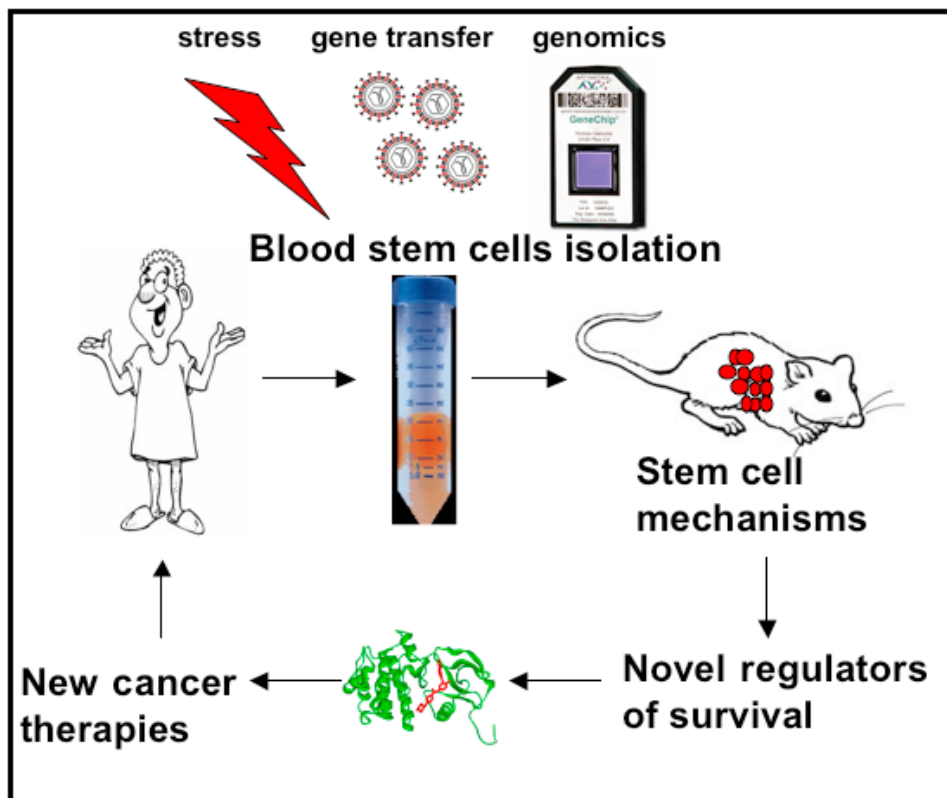
Research

Accumulation of unrepaired DNA damage in hematopoietic stem cells (HSC) is associated with bone marrow failure and accelerated leukemogenesis. Our laboratory aims to understand how HSC cope with DNA damage to preserve normal blood regeneration and to limit the risk of leukemogenesis. In addition, we strive to discover how leukemia stem cells escape therapy and try to devise strategies to prevent this from happening. To address these questions we study DNA damage signaling and its outcomes in highly purified human normal and leukemia cell subsets. We employ flow cytometry,

immunofluorescent and biochemical analyses, lentiviral gene transfer-mediated functional screens, expression/microRNA profiling, clonal *in vitro* assays and, most importantly, *in vivo* repopulation mouse assays of human normal HSC and leukemia-initiating cells.

Publications

Buganim, Y., I. Goldstein, D. Lipson, **M. Milyavsky**, S. Polak-Charcon, C. Mardoukh, H. Solomon, E. Kalo, S. Madar, R. Brosh, M. Perelman, R. Navon, N. Goldfinger, I. Barshack, Z. Yakhini, and V. Rotter. 2010. A novel translocation breakpoint within the BPTF gene is associated with a pre-malignant phenotype. *PLoS ONE*: 5: e9657.



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Review

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Grants

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2014-2015 ICRF Research Career Development Award

2014-2019 Israel Science Foundation (ISF) Grant: Elucidation of DNA damage response mechanisms in human normal and malignant hematopoietic stem cells.

2014-2016 Varda and Boaz Dotan Center for Hematological Malignancies: Chromatin Structures Governing Therapy Resistance In Myeloid Leukemia