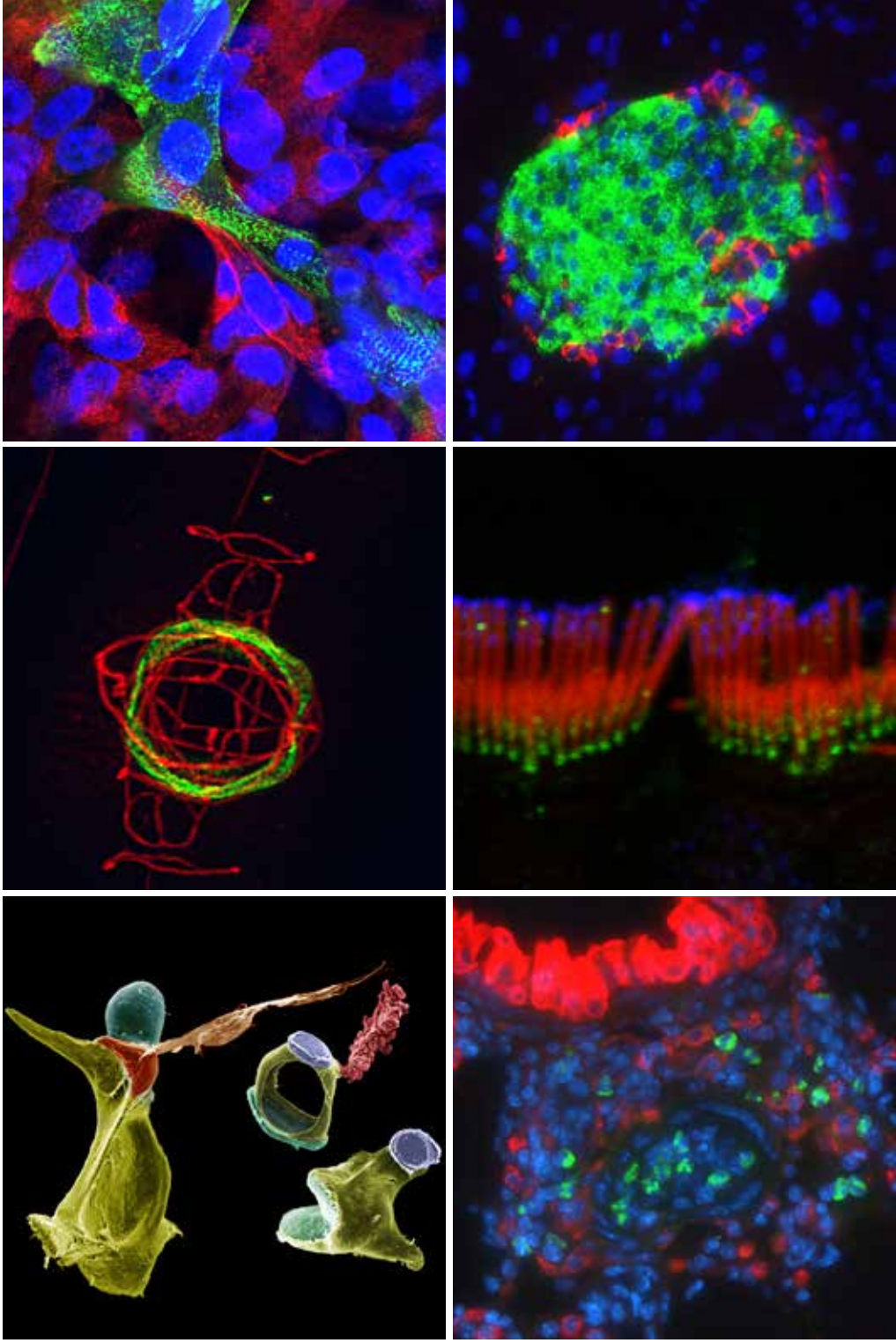

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine

Preclinical Research 2020

TEL AVIV UNIVERSITY

Sections

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 Shivatski, 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.

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

The Sackler Faculty of Medicine

The Sackler Faculty of Medicine is Israel's largest medical research and training complex. The Sackler Faculty of Medicine of Tel Aviv University (TAU) was founded in 1964 following the generous contributions of renowned U.S. doctors and philanthropists Raymond, and the late Mortimer and Arthur Sackler. Research at the Sackler Faculty of Medicine is multidisciplinary, as scientists and clinicians combine efforts in basic and translational research. Research is conducted in the laboratories on the TAU campus, and in the clinical facilities affiliated to the Faculty. The Faculty of Medicine includes the Sackler School of Medicine, the School of Health Professions, the School of Public Health, and the School of Dental Medicine. Education takes place in all these schools and in the Graduate School of Medicine, School of Continuing Medical Education, the New York State American Program and the B.Sc. Program in Medical Life Sciences. This network of preclinical and clinical teams helps realize the ultimate goals of the research: the basic understanding of human pathophysiology and the prevention, diagnosis and treatment of disease. The research of 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 imited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians in 181 Sacker affiliated departments and institutes in 17 hospitals hold academic appointments at TAU. The Gitter-Smolarz Life Sciences and Medicine Library serves students and staff and is the center of a consortium of 15 hospital libraries.

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

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

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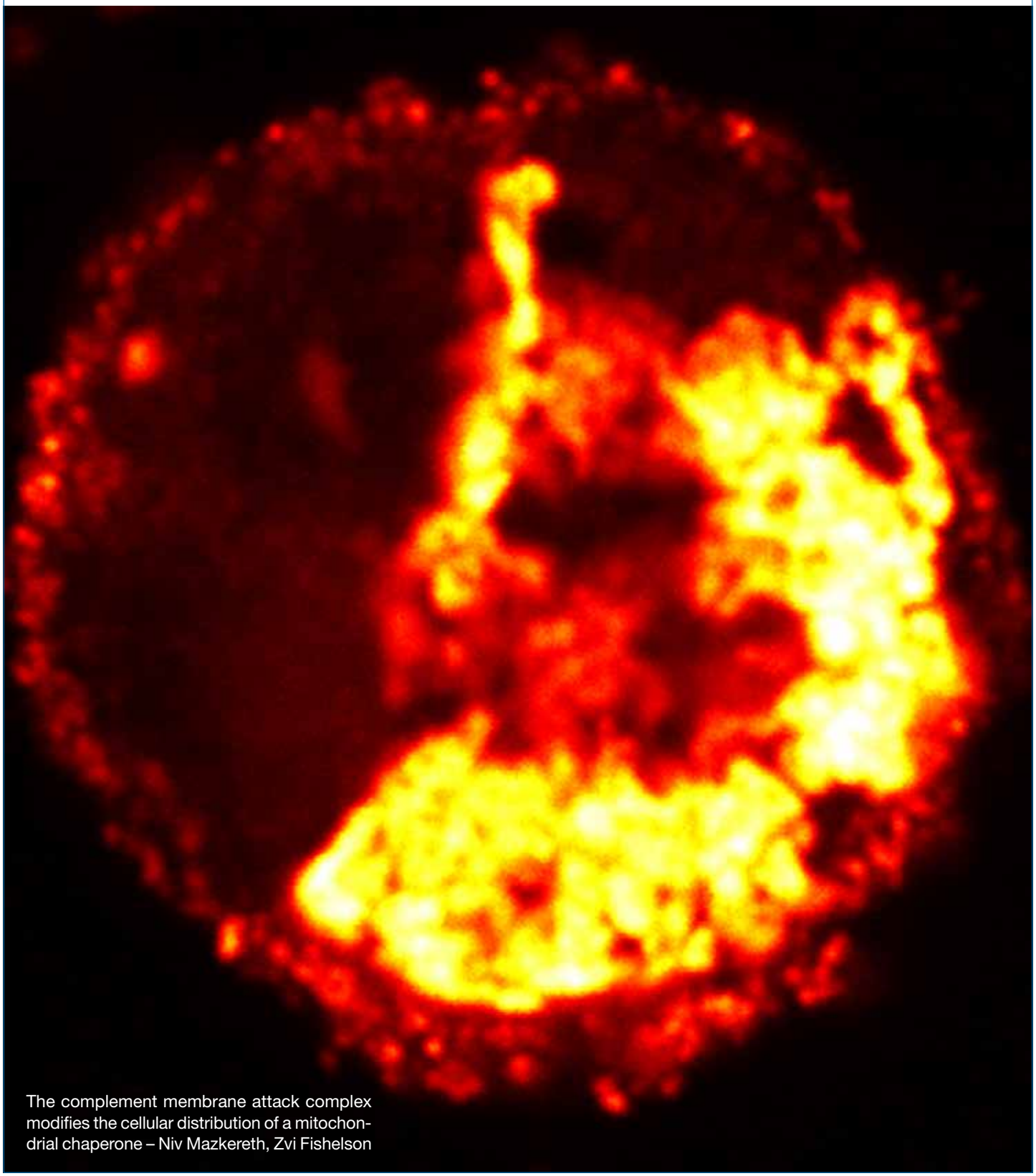
Cancer and Molecular Therapies



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

Dr. Uri Ben-David

Department of Human Molecular Genetics and Biochemistry
Sackler School of Medicine
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

Cancer Genetics

Position

Senior Lecturer, Sackler Faculty of Medicine

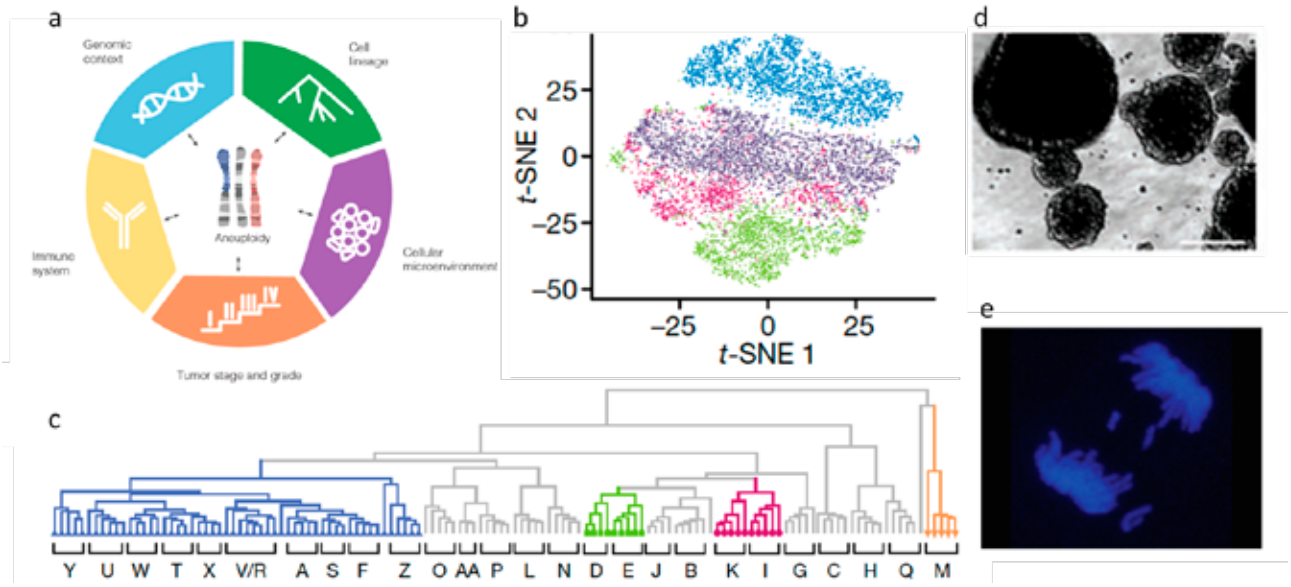
Research

Our lab studies cancer genetics, with three main research interests:

1) The main focus of the lab is on an under-studied trait of cancer, called aneuploidy – the presence of an abnormal number of chromosomes in cancer cells — and the potential of using this trait to target cancer cells and eliminate tumors. We combine experimental and computational approaches to uncover the basic biology underlying this hallmark of cancer, to track its origins and to uncover its cellular consequences. By doing so, we strive to expand our understanding of the genetic basis of cancer, and to make aneuploidy a therapeutic target for cancer treatment. While aneuploidy is common across most cancer types, research in the lab is mostly focused on epithelial solid tumors, and especially on breast cancer and colon cancer.

2) The study of the complex genetics of human cancer depends on cancer model systems. These models reflect the biology of actual human tumors only to a certain extent, and evolve in ways that pose both risks and opportunities for cancer research. The lab studies the genomic stability and evolution of cancer model systems, in order to optimize their application in biomedical research, with an emphasis on aneuploidy research.

3) Human stem cells share fundamental characteristics with human cancer cells, and thus make for a unique model system to study cancer genetics. The lab uses human stem cells as a tool for aneuploidy research and for the identification of cancer vulnerabilities.



(a) Aneuploidy patterns are determined by the cellular context, and can affect multiple facets of cancer biology. (b) Gene expression analyses can identify driver genes that underlie the recurrence of common aneuploidies. (c) Studying isogenic model systems can help uncover the cellular consequences of aneuploidy. (d) *In vitro* transformation assays are used to study the phenotypic effects of aneuploidy. (e) microscopy analyses of mitoses can reveal how aneuploidy arises.

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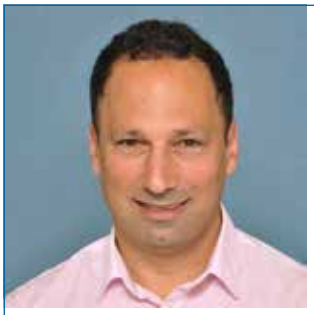
2020 Israel Cancer Association (ICA), "Identifying cellular vulnerabilities induced by the most common chromosomal change in breast cancer"

2020 Cancer Biology Research Center (CBRC), "Identifying clinically-actionable vulnerabilities of del17p breast cancer cells"

2019-2020 Eimert Research Fund on Solid Tumors, Tel Aviv University, "Studying PI3K pathway dependency in breast cancer cells with a deletion of chromosome arm 17p"

2019-2022 Azrieli Foundation, "Identifying and characterizing an aneuploidy-induced vulnerability to inhibition of KIF18A"



Dr. Yaron Carmi, Ph.D.

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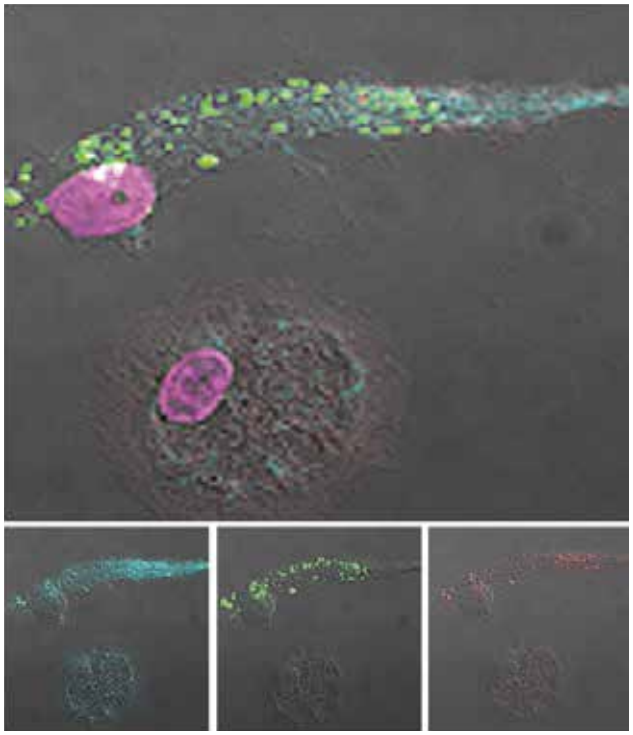
Cellular and Molecular Mechanisms of Antigen-Restricted Tumor Immunity

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

The goal of our work is to provide a detailed understanding of the mechanisms, signals and molecular pathways that regulate discriminating self from non-self and give rise to tumor-specific cytotoxic T cell immunity. Our specific aims are to address the following: 1) What are the cellular and molecular elements that enable the immune system to recognize subtle antigenic variations from self to initiate a cytotoxic immune response? 2) How is the specificity of the induced immune response determined? In other words, what is the process by which the presentation of diverse antigens by DC is reduced to activation of specific effector T cells? Understanding the means by which DC and T cells communicate to initiate antigen-restricted tumor immunity and how these processes are regulated will provide a roadmap for designing novel, more potent cancer immunotherapies.



Confocal microscopy showing the take up of tumor cells (in green) coated with IgG (red) by dendritic cells and their loading on MHCII molecules (cyan). Carmi Y. et al. 2015. *Nature* 521:99-104.

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Engleman EG, Spitzer M. and Carmi Y. Methods and Compositions for Treating Individuals That Have Cander and for Identifying Individuals Responsive to Immunotherapy. 62/447,959

Grants

2017-2019	Alon Award for Outstanding Young Scientists
2017-2020	Swiss Bridge Award: *Elucidating the Mechanisms by Which Tumor-Binding Antibodies Enable T Cells Infiltration into the Tumor Microenvironment*
2018-2022	Israel Science Foundation

Dr. Merav Cohen, Ph.D.

Department of Clinical Microbiology and Immunology
Sackler Faculty of Medicine

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URL: mcohenlab.com

Molecular Insight into Cellular Crosstalk During Tissue Development and Disease

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our lab focuses on exploring cellular communication between immune cells and tissue resident cells, by using state-of the art single-cell RNA sequencing technologies. We are eager to reveal the consequences of immune-controlled cellular interactions on the molecular properties of tissue-immune niche, tissue physiological development and tissue–specific pathologies, specifically cancer. We combine experimental mouse models, advanced genomic technologies and computational analysis, together with study of clinical samples, in order to expand our understanding on developmental pathologies and mechanisms of cancer induction, progression, and immune suppression in the tumor microenvironment and metastatic sites. By assessment of similarities and discrepancies in interactome molecular signature, between tissue development and pathological conditions, we strive to reveal novel immunotherapy targets.

Publications

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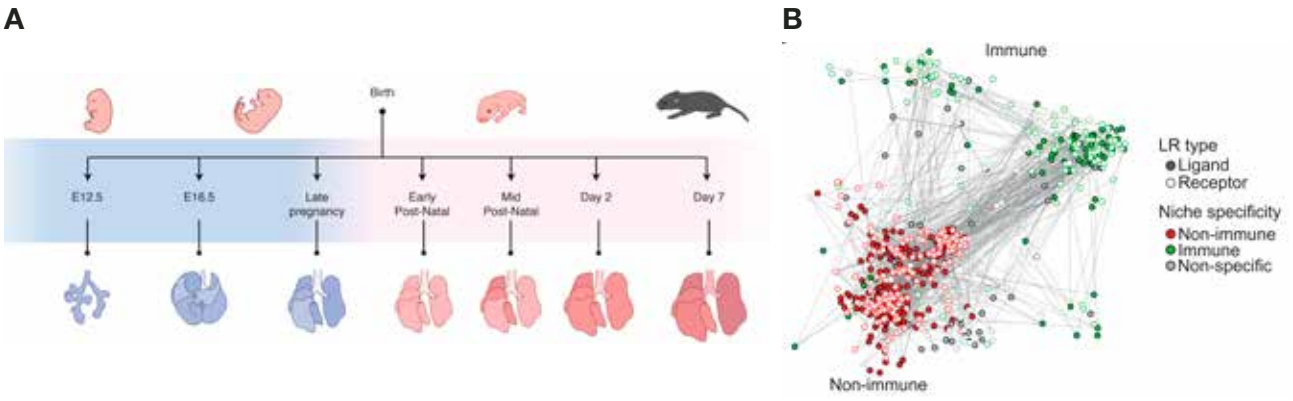

Immune-resident cell molecular crosstalk during mouse lung development. **A**. We isolated immune and non-immune cells along crucial time points of lung development, starting from early stages of embryogenesis to the neonatal period, and performed single-cell RNA-sequencing. **B**. Based on the single-cell RNA-sequencfing data, we analysed ligands and receptors expressed by different cell states and mapped the molecular signaling of intercellular communiation between immune niche and the lung resident cells.

map reveals basophil role in macrophage imprinting. *Cell*. 1;175:1031-1044.e18.

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Review

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Prof. Neta Erez, Ph.D.

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Cancer Related Inflammation in Tumor Progression and Metastasis

Position

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Pathology

Research

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

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

The major cause of cancer mortality is metastasis to distant organs. Currently, metastatic cancers are incurable and available therapies can only prolong life to a limited extent. Therefore, uncovering the mechanisms that facilitate metastasis is an urgent and unmet clinical need. Nevertheless, changes in the metastatic microenvironment that enable the growth of disseminated tumor cells are poorly characterized, and are the major focus of our research.

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

Publications

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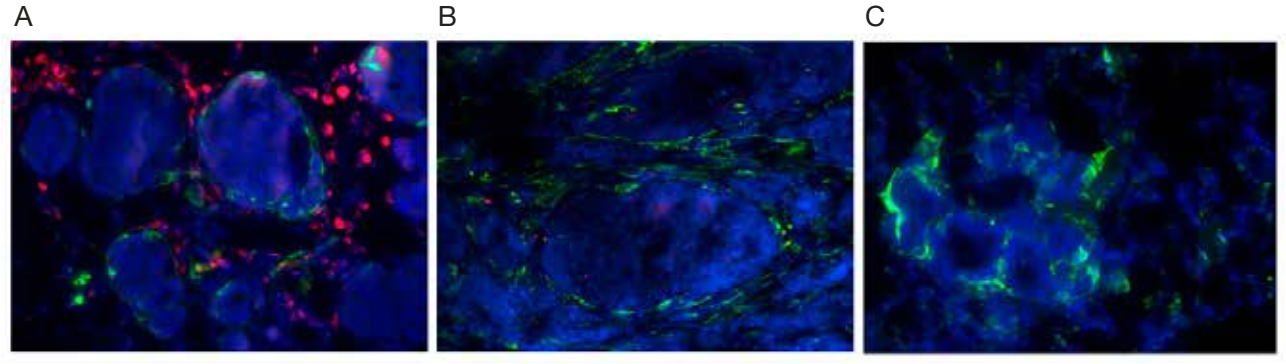

A, B: Cancer Associated Fibroblast (CAFs) accumulate around mammary tumors in tissue Sections from the MMTV-PyMT transgenic mouse model. Green-aSMA, Blue-DAPI, Red-FSP-1. **C**: Immunofluorescent staining showing activated fibroblasts in lung metastases in MMTV-PyMT mice. Blue- DAPI. Green –aSMA.

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Grants

2015–2019	European Research Council (ERC) Starting Grant. Uncovering the Role of Cancer Associated Fibroblasts in Facilitating Breast Cancer Metastasis
2017-2020	German Research Foundation (DFG). Characterizing the functional role of astrogliosis and neuroinflammation in melanoma brain metastasis.
2017-2019	Israel Cancer Research Foundation (ICRF). Project Grant, Uncovering the role of fibroblasts in facilitating breast cancer metastasis and therapy resistance via NLRP3 inflammasome signaling.
2018-2019	Israel Cancer Association (ICA), Uncovering the role of fibroblasts in facilitating breast cancer chemoresistance and metastasis via pro-inflammatory signaling.
2018-2022	Israel Science Foundation (ISF), Uncovering the role of the NLRP3 inflammasome in cancer-associated fibroblasts in facilitating breast cancer progression and metastasis.
2019-2023	Medical Research Council (MRC), UK, Mechanisms underlying inhibition of melanoma brain metastases upon immune checkpoint targeting

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Molecular Analysis of Cancer Immunoresistance

Positions

The Roberts-Guthman Chair in Immunopharmacology

Professor Emeritus, Sackler Faculty of Medicine

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

Hillman Y., Mazkereth N., Farberov L., Shomron N. and **Fishelson Z.**, Regulation of complement-dependent cytotoxicity by microRNAs miR-200b, miR-200c and miR-217, *J. Immuno*l. 196: 5156-5165, 2016.

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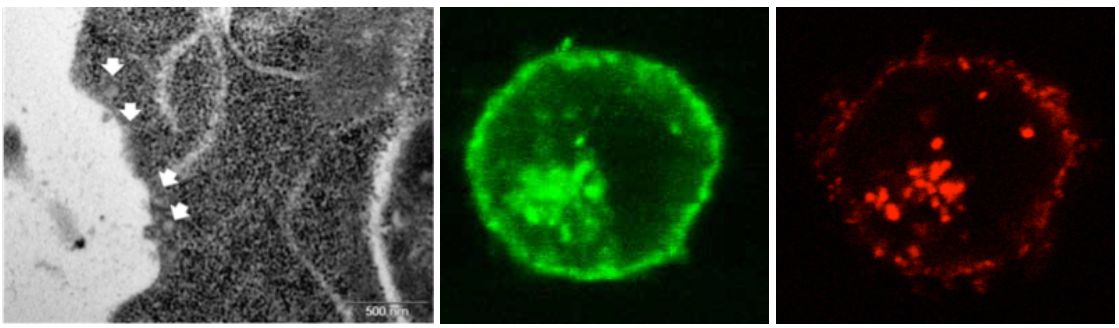

EM analysis demonstrates elevated formation of endosomes in K562 cells responding to an ongoing immune attack (left). Caveolin-1 (green) and complement C9 (red) co-localize in early and late endocytic vesicles of K562 cancer cells following complement attack on the cells (right 2 panels).

Reviews

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Grants

2015-2020 Complement-dependent cytotoxicity of cancer cells: toxic and evasion mechanisms (ISF)

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Cancer Proteomics

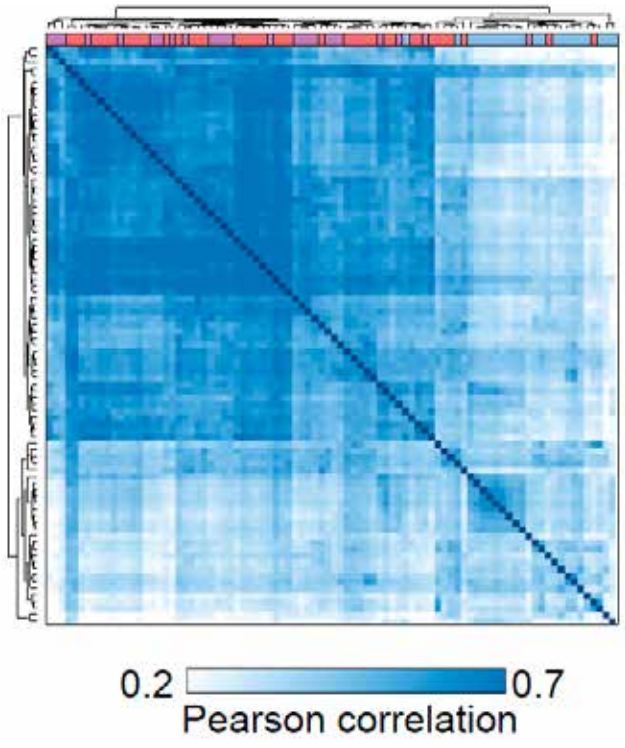
Position

Associate Professor, Sackler Faculty of Medicine

Director, Interdepartmental Core Facility (Zabam)

Research

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



Correlation matrix of proteomes of breast cancer and healthy tissue

Publications

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Reviews

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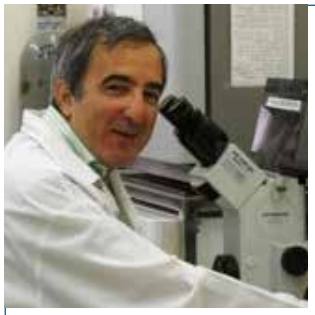
Shenoy, A. & **Geiger, T***. Super-SILAC: Current trends and future perspectives. *Expert Reviews of Proteomics* 12, 13-19 (2015). *Corresponding author.

Grants

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

2016-2019 ISF (Israel Science Foundation): Proteogenomic analysis of tumor heterogeneity in breast cancer

2018-2019 Israel Innovation Authority (Nofar program): Discovery of biomarkers for early detection of ovarian cancer



Prof. Shai Izraeli, M.D

Division of Pediatric Hematology and Oncology,
Schneider Children's Medical Center;
Department of Human Molecular Genetics &
Biochemistry, Sackler Faculty of Medicine

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Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions

Professor, Sackler Faculty of Medicine

Chair, Varda and Boaz Dotan Research Center for Hematological Malignancies

Dora and Gregorio Shapiro Chair of Hematological Malignancies

Head, Division of Pediatric Hematology and Oncology, Schneider Children's Medical Center

Research

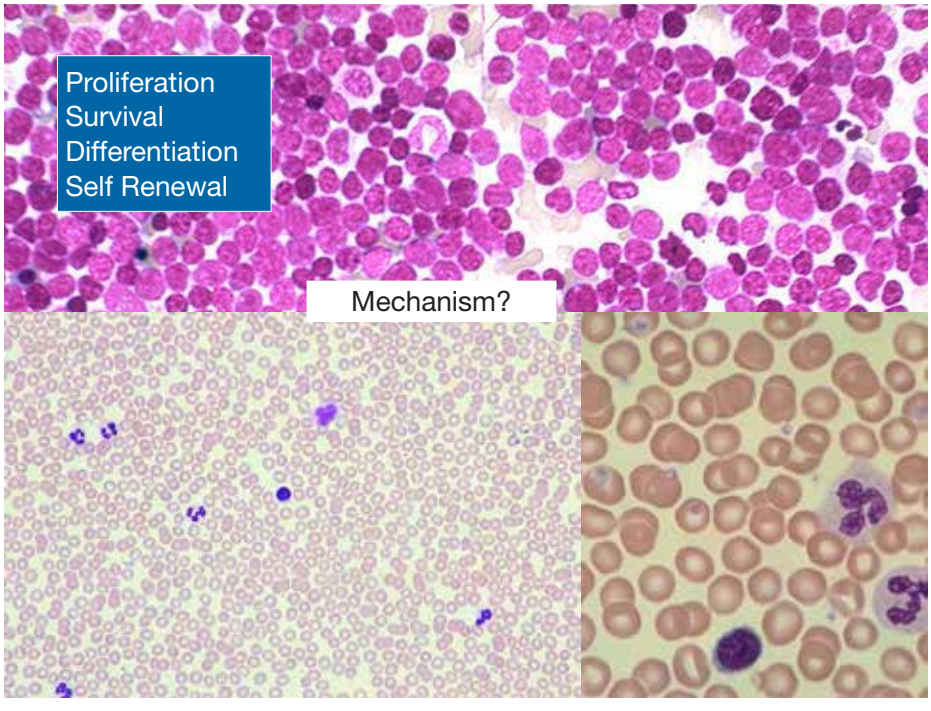
We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

Our research is divided into two major topics:

1. Basic, translational and clinical research of leukemia.

2. The role of cancer predisposing genes in the development of childhood 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



We study the mechanism of transformation of normal hematopoiesis (bottom) to leukemia (upper panel).

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 consistingof 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.

Publications

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Grants

2016-2019	German Israel Foundation
2018-2021	ISF-NSFC mechanisms and targeting of high risk ALL in children and young

Prof. Yona Keisari, Ph.D.

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URL: http://med.tau.ac.il/Professor_Yona_Keisari

Development of Cancer Treatments Integrating Radiotherapy or Electrochemical Ablation and Immunotherapy

Positions

Professor Emeritus, Sackler Faculty of Medicine

President, Israeli Society for Cancer Research

Associate Editor, *Mediators of Inflammation*

Research

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

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

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

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

Publications

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Prof. Rafi Korenstein, Ph.D.

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Interaction of Nanomaterials and Electromagnetic Fields with Cells

Positions

Professor Emeritus, Sackler Faculty of Medicine

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

Editorial Board, *Bioelectromagnetics*

Research

The research activity addresses the following lines of research:

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

Publications

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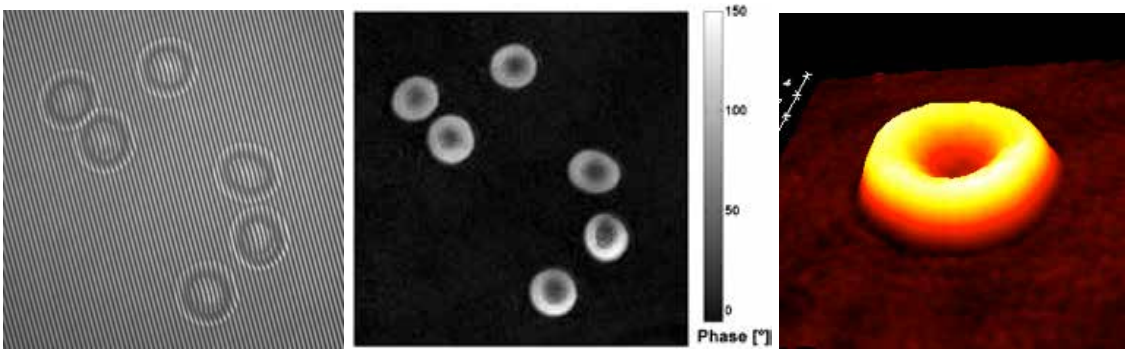

Hologram image of red blood cells (left), reconstructed phase image (middle) and 3D reconstruction of a single red blood cell (right)

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Grants

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

2019-2023 European Commission – Horizon 2020 EC funded consortium on: "Development and Implementation of a Sustainable Modelling Platform for NanoInformatics" (achronym – "NanoInformaTIX").

2019-2022 EuroNanoMed III on "Cationic gold particles mediated mRNA targeted delivery" (achronym – "CONCORD").

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The Wnt Signaling Pathway and Colorectal Cancer

Position

Associate Professor, Sackler Faculty of Medicine

Chair, Search Committee

Research

The lab focuses on the molecular and biochemical aspects of the Wnt signal transduction pathway. This important pathway plays a major role in various cellular processes including homeostasis, proliferation and differentiation. Thus, aberrant activation of the cascade can be extremely harmful and is implicated in many cancer syndromes and especially colorectal cancer. Our aim is to understand the molecular events underlying Wnt signaling, 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. We utilize different screening approaches to identify novel components of the Wnt cascade. Aldolase, EDD, CPE, HTRA1 and 14-3-3 are some of the new Wnt signaling regulators that were isolated and characterized in our lab.

2. *Ribosomal Read-Through therapy*. Certain compounds mediate ribosomal read-through of premature stop codons. We are working on identifying new and potent read-through agents and treating different diseases by restoring expression of full-length proteins.

3. *Developing new anti-colorectal cancer treatment strategies*. Based on our read-through preliminary results, a clinical trial was designed in collaboration with Dr. Revital Kariv from the Sourasky Medical Center. APC restoration is tested in inherited colorectal cancer caused by an APC germline nonsense mutation. Further analysis is conducted in colonic organoids – three-dimensional structures that mimic the gut and serve as an efficient tool in the investigation of cancer development.

4. *The effect of Wnts on blood cells*. Studying the Wnt pathways in blood cells is a completely new line of research, where we show that Wnts extend the life span of erythrocytes and improve their quality during storage and after transfusion.

Publications

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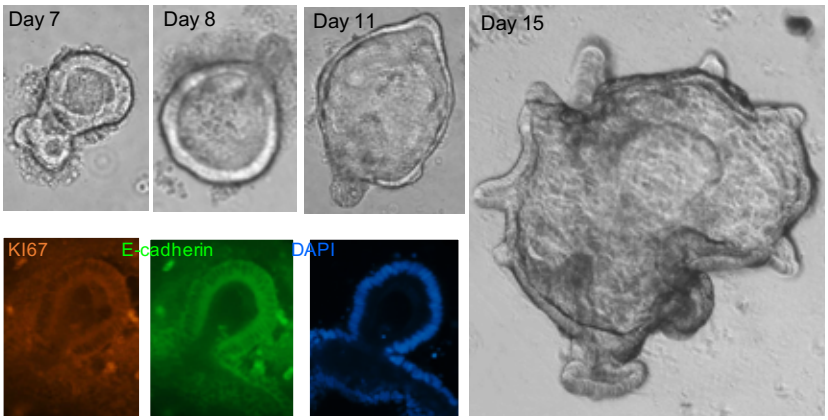
Colonic organoids



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Kariv R, Caspi M, Fliss-Isakov N, Shorer Y, Shor Y, Rosner G, Brazowski E, Beer G, Cohen S, **Rosin-Arbesfeld R**. (2020) Resorting the function of the colorectal cancer (CRC) gate keeper adenomatous Polyposis Coli (APC). *Int J Can* 146:1064-1074.

Grants

2016-2019	DOTAN RESEARCH CENTER in HEMATO-ONCOLOGY – Wnt5a – a novel treatment for hematological malignancy associated anemia
2018-2021	GIF – Systematic understanding of APC stop codon mutation read-through
2018-2022	BSF – The Role of STRIPAK in Cell-Cell Junctions
2018-2020	SPARK – Preventing Cancer by Treating Predisposing Mutations
2018-2020	Fondation Jérôme Lejeune – Macrolide induced correction of mutations causing Rett syndrome (RTT)
2020-2022	Israel Cancer Association Grant, Promoting personalized therapeutic intervention for FAP patients harboring APC nonsense mutations

Prof. Ronit Satchi-Fainaro, Ph.D.

Department of Physiology and Pharmacology
Sackler Faculty of Medicine

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URL: http://medicine.mytau.org/satchi-fainaro/

Angiogenic Switch Using Rationally-Designed Theranostic Nanomedicines

Positions

Professor, Sackler Faculty of Medicine

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

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

Faculty Coordinator, Postgraduate Program in Nanotechnology

Associate Editor, *Advanced Drug Delivery Reviews*

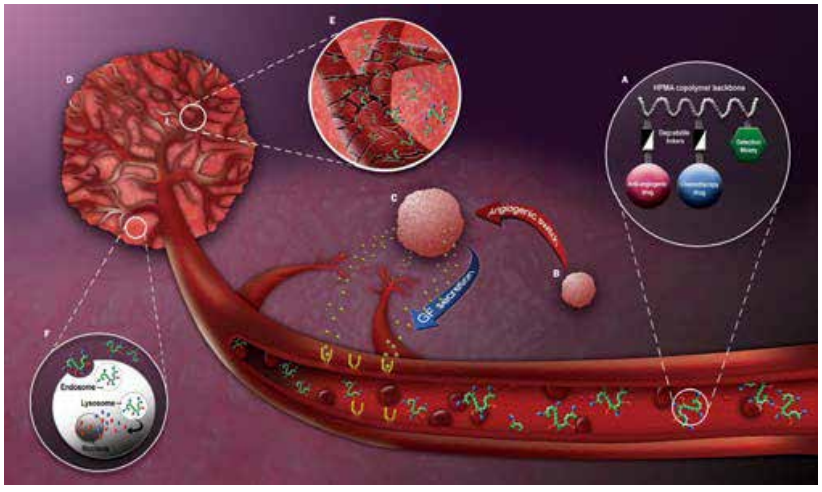
Associate Editor, *Nanomedicine: Nanotechnology, Biology and Medicine*

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

Research

Our research interests include investigations relating to tumor biology, tumor dormancy, mechanism of action of angiogenesis inhibitors, self-assembly of polymeric architectures and novel approaches to target cancer. Throughout, we have maintained an interest in understanding the biological rationale for the design of polymer therapeutics suitable for transfer into clinical testing. Our primary interests are the molecular basis of tumor angiogenesis and the rational design of polymer therapeutics. Our research includes identification and characterization of genes and microRNAs associated with the switch from a dormant avascular tumor phenotype to a fast-growing angiogenic tumor in human cancers and their corresponding mouse models.

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



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

in mice, syngeneic and transgenic mice models), pharmacokinetics and pharmacodynamics and 3D printing.

Publications

Redy-Keisar O, Ferber S, **Satchi-Fainaro R*** and Shabat D*, NIR Fluorogenic Dye as a Modular Platform for Prodrug Assembly: Real-Time in vivo Monitoring of Drug Release, *ChemMedChem,* 10(6): 999-1007 (2015). *Corresponding authors.

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Shatsberg Z, Zhang X, Ofek P, Malhotra S, Krivitsky A, Scomparin A, Tiram G, Calderón M, Haag R, **Satchi-Fainaro R.** Functionalized nanogels carrying an anticancer microRNA for glioblastoma therapy, Journal of Controlled Release, 239:159-68 (2016).

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Gibori H, Eliyahu S, Krivitsky A, Ben-Shushan D, Epshtein Y, Tiram G, Blau R, Ofek P, Sang Lee J, Ruppin E, Landsman L, Barshack I, Golan T, Merquiol E, Blum G and **Satchi-Fainaro R**, Amphiphilic nanocarrier-induced modulation of PLK1 and miR-34a leads to improved therapeutic response in pancreatic cancer, *Nature Communications*, 9(1):16 (2018).

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Eilon-Shaffer T*, Roth-Konforti M*, Eldar-Boock A, **Satchi-Fainaro R**, Shabat D, ortho-Chlorination of phenoxy 1,2-dioxetane yields superior chemiluminescent probes for in vitro and in vivo imaging. *Organic & Biomolecular Chemistry*, 16(10):1708-1712 (2018). *Equal contribution

Vossen LI*, Markovsky E*, Eldar-Boock A, Tschiche HR, Wedepohl S, Pisarevsky E, **Satchi-Fainaro R***, Calderon M*, Pegylated Dendritic Polyglycerol Conjugate Targeting Ncam-Expressing Neuroblastoma: Limitations and Challenges. *Nanomedicine*, 14(4):1169-1179 (2018). *Corresponding authors

Blau R, Epshtein Y, Tiram G, Pisarevsky E, Israeli S, Yeini E, Krivitsky A, Eldar-Boock A, Ben-Shushan D, Green O, Ben-Nun Y, Merquiol E, Schwartz H, Blum G, Erez N, Grossman R, Ram Z, Shabat D, **Satchi-Fainaro R**, Image-Guided Surgery Using Near-Infrared Turn-ON Fluorescent Nanoprobes for Precise Detection of Tumor Margins, *Theranostics*, 24;8(13):3437-3460 (2018).

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Grants

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"

2016-2020 Merck Global Healthcare (co-PI, Shabat), Tagging of heteroaryl chemotherapeutic drug molecules with a ketone functional group and employing it for Antibody-drug conjugates application.

2016-2021 Morris Kahn Foundation, 3D-printed cancer modeling.

2017-2020 European Innovative Research & Technological Development Projects in Nanomedicine, framework of the ERA-NET EuroNanoMed-II: MultiNano@MBM (Co-PIs: Florindo, Jung, Recio)

2018-2021 MSCA-ITN-2017: Innovative Training Networks, Bio-orthogonal catalysis for cancer therapy (THERACAT).

2018-2023 Israel Science Foundation (ISF) grant, Elucidating tumor-host interactions to design precision nanomedicines for the prevention and treatment of melanoma.

2018-2025 Israel Cancer Research Foundation (ICRF) Professorship, P-selectin–targeted nanomedicines and immunotherapy for brain metastases prevention.

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The ATM-Mediated DNA Damage Response

Positions

Professor Emeritus, Sackler Faculty of Medicine

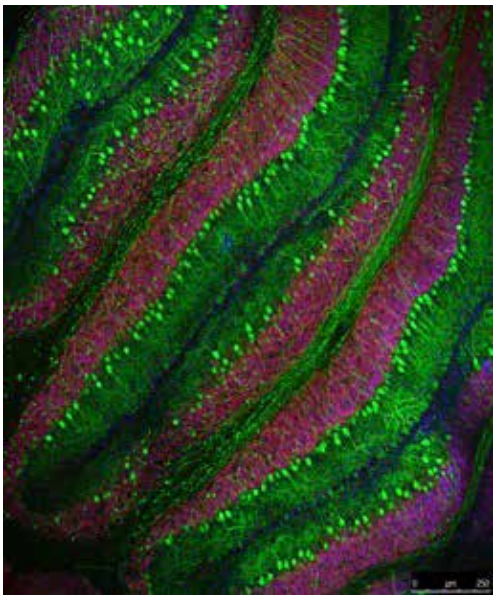
David and Inez Myers Chair in Cancer Genetics

ICRF Research Professorship

Research

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

Genetic defects in the DNA damage response lead to genomic instability syndromes, which usually include tissue degeneration, cancer predisposition, and sensitivity to specific DNA damaging agents. A prototype genomic instability syndrome is A-T. The disease is characterized by neuronal degeneration, immunodeficiency, chromosomal instability, sensitivity to ionizing radiation, and cancer predisposition. Our lab has been investigating A-T since its establishment in 1985. In 1995, after 8 years of intensive work, we identified the gene that is defective (mutated) in A-T patients and called it *ATM* (A-T, Mutated). We went on to study the activity of its product, the ATM protein, which turned out to be an enzyme with an activity alled “protein kinase”.



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.

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.

Publications

Meir, M., Galanty, Y., Kashani, L., Blank, M., Khosravi, R., Fernández-Ávila, M.J., Cruz-Garcia, A., Star, A., Shochat, L., Thomas, Y., Garrett, L.J., Chamovitz, D.A., Bodine, D.M., Kurz, T., Huertas, P., Ziv, Y., and **Shiloh, Y.** (2015) The COP9 signalosome is vital for timely repair of DNA double-strand breaks. *Nucleic Acids Res.* 43: 4517-4530.

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Grants

2014 – 2021 Israel Cancer Research Fund (ICRF Professorship)

2015 – 2020 The A-T Children's Project

2016- 2020 US-Israel Binational Science Foundation

Prof. Ilan Tsarfaty, Ph.D.

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

Position

Associate Professor, Sackler Faculty of Medicine

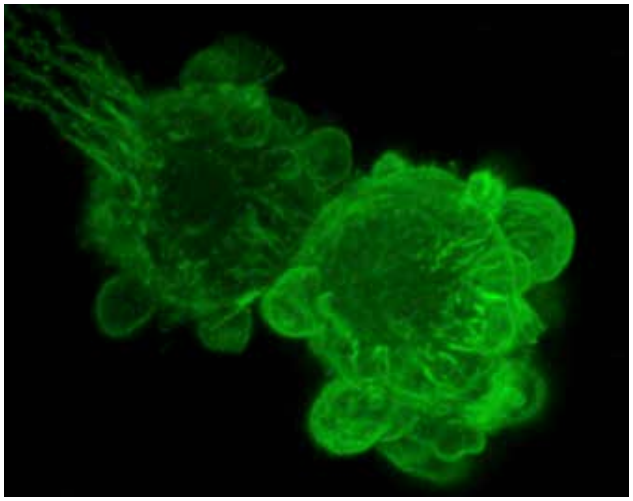
Israeli Representative, Euro Bioimaging

Research

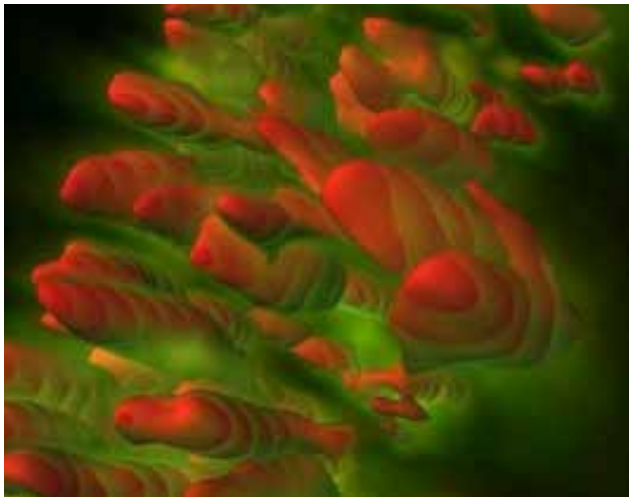
Breast cancer is the most common malignant disease in western women. In the majority of cases, the cause of death in cancer patients is not the primary tumors, but complications derived from metastases. Cancer cell motility, invasion, and metabolism are fundamental steps in metastasis. MET, a tyrosine kinase receptor and its ligand, Hepatocyte Growth Factor/Scatter Factor (HGF/SF), induce specific signal transduction and metabolic pathways in tumor cells, leading to cell motility and invasion. MET FDA approved, and novel inhibitors are ideal for the treatment of patients with aberrant MET expression.

We are studying the effect of MET induced different motility patterns in ER-HER2 positive and TNBC cell lines. We developed classical image analysis and machine learning (ML) infrastructure to evaluate single-cell motility based on kinetic and morphological parameters. The single-cell machine learning uncovered a unique sub-population in the TNBC cell line that is abolished upon MET inhibition and chemotherapy. We are modeling this unique motility and studying the molecular mechanisms of this process. We are also developing single-cell infrastructure to screen for anti-MET and other driver gene product inhibitors. We are also evaluating the possibility to use this infrastructure for personalizing treatment for cancer patients

We hypothesize that MET constitutive activation initiates tumorigenicity in association with inherited driver modifier genes (IDMGs). We have created a novel mice model based on 20 CC lines baring different genetic backgrounds that overexpress the mutated MET receptor (Metmut-CC). We show that MET and specific IDMGs induce non - compaction cardiomyopathy of the heart muscle, which leads to embryo lethality. We also identified 30 MET-IDMGs candidates that promote oncogenic signaling that dictates the development of MET induced carcinomas, lymphomas or sarcomas. The expression levels of those genes, in combination



Met localization in blebbing cells



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

with MET, increase the prognostic capability by two orders of magnitude.

New evidence demonstrates that the crosstalk between p53/BRCA1 and MET signaling plays a significant role in tumor development and in response to therapy. Li-Fraumeni syndrome (LFS) is a rare cancer predisposition inherited in an autosomal dominant fashion that involves a germline mutation of tumor protein 53 (TP53). We are developing a deleted p53, BRCA1-CC animal in stand-alone, or in combination with Metmu models. Using the deleted p53 model, we isolated p53 specific IDMGs that dictate the development of sarcoma, lymphoma, and germ cell tumor. We are using the crisper analysis to study the role of these newly identified IDMGs in tumorigenesis and metastasis

The potential benefits of applying machine learning methods to omics data are becoming increasingly apparent, especially in clinical settings. We are utilizing molecular, cellular patho radiomics ML approaches to study the molecular mechanism of MET/p53/BRCA in tumorogenesis, isolating novel targets and developing new modalities for personalized, targeted therapy

QTL analysis defines a region in the genome that contains many genes. Only a few of those genes are the IDMGs that we are trying to isolate. We are using classical bioinformatics and ML to develop a knowledge-based candidate gene selection method. Based on this approach, we isolated several candidate IDMGs. We hypothesize that digital pathology and CT-derived radiomic features of MET/p53/BRCA-induced tumors can characterize tumor development, have prognostic value, and are in association with modifier genes. We are developing ML to study the digital pathology and radiomic features to distinguish differences in tumor types and correlate with gene association using QTL analysis. We are performing Kaplan-Meier and Cox regression based on features to build a prognostic model for overall survival.

Our previous research had an essential contribution to the use of MET inhibitor as a novel target for therapy. We hope that our current basic research will further contribute to the identification of novel MET/p53/BRCA targets and biomarkers that will facilitate targeted personalized therapy.

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 orthotropicly into mice mammary glands. Contrast media ultrasound-based Met functional molecular imaging (FMI) demonstrated that HGF/SF-induced increased hemodynamics is dependent on Met concentration and can be dramatically reduce upon inhibition of the receptor and it's signaling pathway; Whole animal spectral imaging enabled detection of sub-millimeter metastases demonstrating fast developing micrometastatic spread of the tumor; Macro to Micro and two photon confocal imaging demonstrated HGF/SF-induced changes in blood flow at single vessel resolution, localization of metalloprotease and catapsine activity at the tumor edge and increase in single cell motility.

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

Publications

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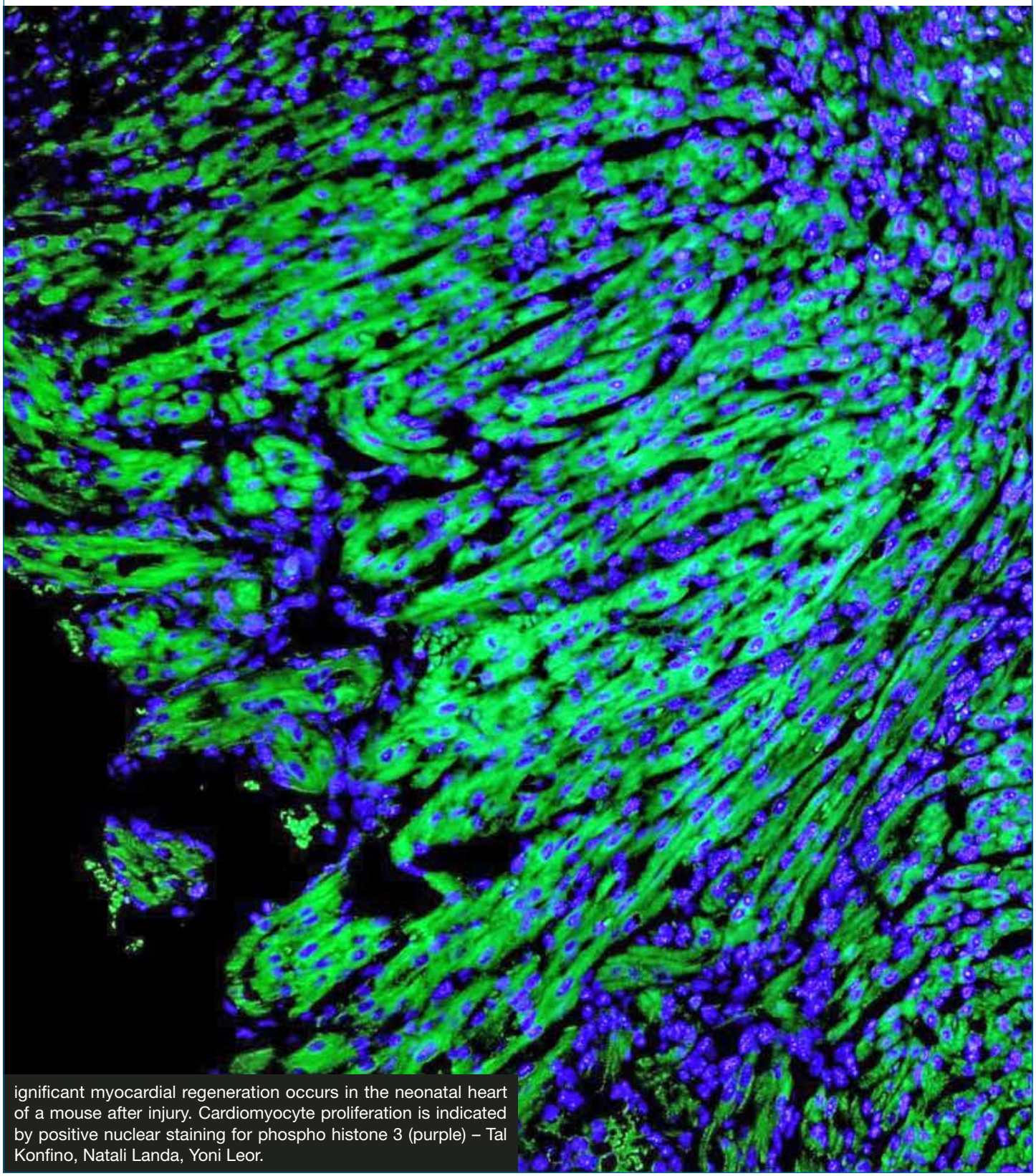
Kidron D, Bar-Lev Y, **Tsarfaty I**, Many A, Tauman R. The effect of maternal obstructive sleep apnea on the placenta. *Sleep*. 2019;42(6).

Grants

2017-2019	Israel Science Foundation
2004-2020	Breast Cancer Research Foundation
2017-2021	Israel Science Foundation
2020-2021	Leon Recanati Heritage Center

Cardiovascular Research and Diseases



ignificant 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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Normal and Diseased Potassium Channels in Human Brain and Heart

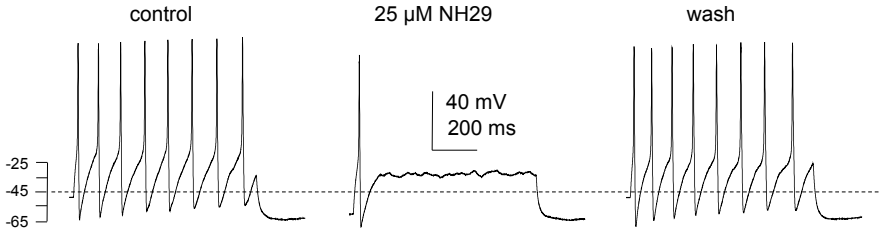
Position

Professor, Sackler Faculty of Medicine

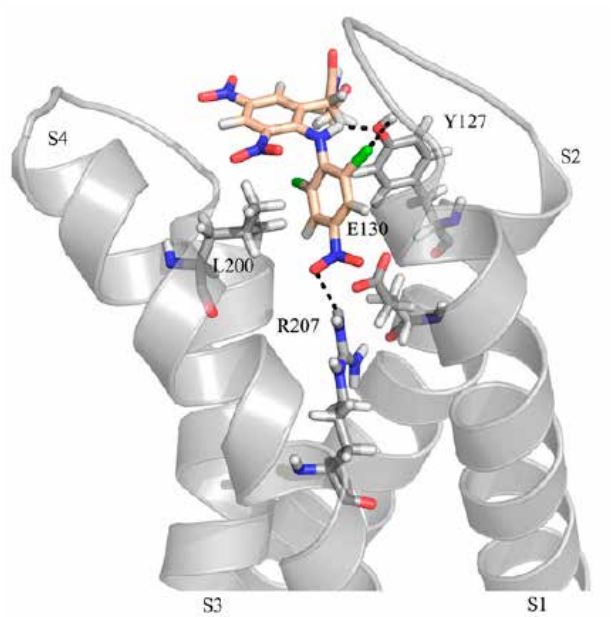
Andy Libach Professorial Chair in Clinical Pharmacology and Toxicology

Research

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



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



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

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

Publications

Manuscripts

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Grants

2018-2021	Israel Science Foundation, Calmodulin and PIP2 interactions in Kv7 potassium channels
2020-2022	Kamin, SK4 K+ channel blockers: a new treatment for atrial fibrillation

Prof. Nathan Dascal, Ph.D.

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

Position

Professor of Physiology, Sackler Faculty of Medicine

Morris and Helen Mauerberger Chair for Neuropharmacology

Research

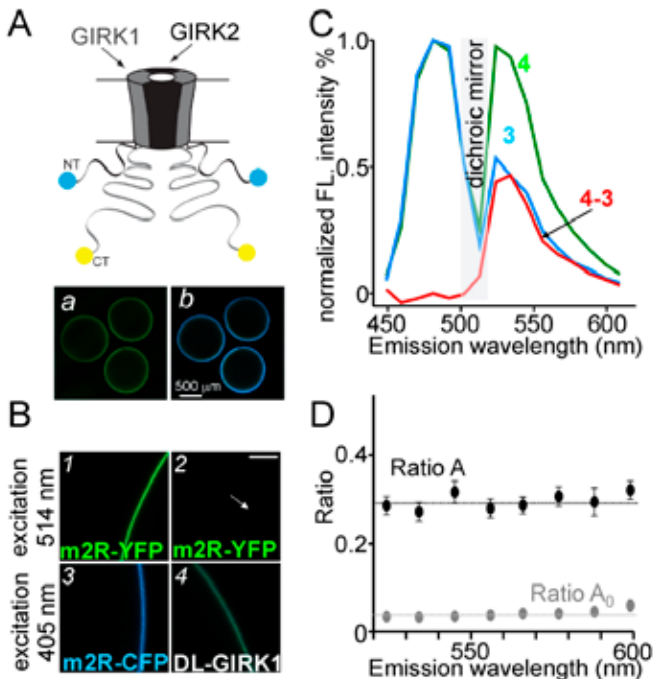
Electrical activity of excitable cells is their most important feature, which allows the performance of fundamental functions of brain, heart and muscle. We are addressing a key issue in modern cardiology and neurobiology: how neurotransmitters regulate cardiac cells and neurons by acting on ion channels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

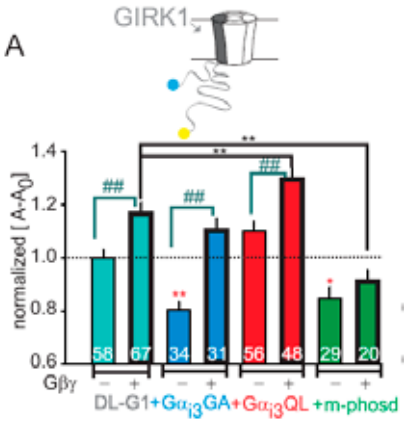
Function and regulation of receptors, G proteins, Ca^{2+} and K^{+} channels in health and disease; Ion channel-related hereditary cardiac and neurological disorders (channelopathies); Mechanisms of coupling of G protein-coupled receptors with effectors; Molecular mechanisms of bipolar disorder.

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

Publications

Benmocha Guggenheimer A, Almagor L, Tsemakhovich V, Tripathy DR, Hirsch JA,**Dascal N**. Interactions between N and C termini of α1C subunit regulate inactivation of CaV1.2 L-type Ca(2+). *Channels* (Austin). 2016;10:55-68.





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,** Gα and Gβγ synergistically alter the conformation of GIRK1 subunit.

Yakubovich D, Berlin S, Kahanovitch U, Rubinstein M, Farhy-Tselnicker I, Styr B, Keren-Raifman T, Dessauer CW, **Dascal N**. A quantitative model of the GIRK1/2 channel reveals that its basal and evoked activities are controlled by unequal stoichiometry of Gα and Gβγ. *PLoS Comput Biol*. 2015;11

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Kahanovitch U, Berlin S & Dascal N. (2017) Collision coupling in the GABAB receptor – G protein – GIRK signaling cascade. *FEBS Lett* 591, 2816-2825

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Raifman TK, Kumar P, Haase H, Klussmann E, Dascal N & Weiss S. (2017) Protein kinase C enhances plasma membrane expression of cardiac L-type calcium channel, CaV1.2. *Channels (Austin)*, 1-12.

Tabak G, Keren-Raifman T, Kahanovitch U, **Dascal N**. Mutual action by Gγ and Gβ for optimal activation of GIRK channels in a channel subunit-specific manner. *Sci Rep*. 2019;9(1):508.

Reviews

Dascal N, Kahanovitch U. The roles of Gβγ and Gα in gating and regulation of GIRK channels. *Int Rev Neurobiol*. 2015;123:27-85.

Weiss S, **Dascal N**. Molecular aspects of modulation of L-type calcium channels by protein kinase C. *Curr Mol Pharmacol*. 2015;8:43-53.

Grants

2018-2022 Israel Science Foundation (ISF). Mechanisms of subunit-dependent gating of GIRK channels by G proteins: quantitative physiology and modeling.

2019-2021 German-Israel Foundation (GIF). Novel mechanisms of regulation of cardiac L-type Ca channels by protein kinase A, with Enno Klussmann, MBC Berlin.

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Investigating the Cardiac Autonomic System Among Brain Damaged Patients

Position

Senior Lecturer

Research

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

Publications

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Amichai T, Eylon S, Dor-Haim H, Berger I, **Katz-Leurer** M. Cardiac autonomic system response to submaximal test in children with cerebral palsy. Pediatr Phys Ther. 2017 29:125-128.

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Cohen-Holzer M, Sorek G, Kerem J, **Katz-Leurer** M. The impact of combined constraint-induced and bimanual arm training program on the perceived

hand-use experience of children with unilateral cerebral palsy. Dev Neurorehabil. 2017;20:355-360.

Steinhart S, Kornitzer E, Baron AB, Wever C, Shoshan L, **Katz-Leurer M**. Independence in self-care activities in children with myelomeningocele: exploring factors based on the International Classification of Function model. Disabil Rehabil. 2016;10:1-7.

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Raphaely Beer N, Bornstein NM, Soroker N, **Katz-Leurer M**. Autonomic cardiac response to static and dynamic muscle contractions in post-stroke and healthy subjects. Eur Neurol. 2016;75:207-12

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Amichai T, Eylon S, Dor-Haim H, Berger I, **Katz-Leurer M**. Cardiac autonomic system response to submaximal test in children with cerebral palsy. Pediatr Phys Ther. 201729:125-128.

Cohen-Holzer M, **Katz-Leurer M**, Meyer S, Green D, Parush S. The effect of bimanual training with or without constraint on hand functions in children with unilateral cerebral palsy: a non-randomized clinical trial. Phys Occup Ther Pediatr. 2017;37:516-527.

Cohen-Holzer M, Sorek G, Kerem J, **Katz-Leurer M.** The impact of combined constraint-induced and bimanual arm training program on the perceived hand-use experience of children with unilateral cerebral palsy. Dev Neurorehabil. 2017;20:355-360.

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Katz-Leurer M, Rotem H, Shofer M, Meyer S.Pediatric cardio-autonomic response to variable effort after severe traumatic brain injury. Brain Inj. 2016,15:1-4.

Raphaely Beer N, Bornstein NM, Soroker N, **Katz-Leurer M.** Autonomic cardiac response to static and dynamic muscle contractions in post-stroke and healthy subjects. Eur Neurol. 2016;75:207-12.

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Shapira-Vadler O, Treger I, **Katz-Leurer M.** Muscle strength, function and heart autonomic regulation system recovery at the sub-acute stage post stroke. Eur Neurol. 2015;74:154-7

Mori T, Lustman A, **Katz-Leurer M.**Self-measurement of upper extremity volume in women post-breast cancer: reliability and validity study. Physiother Theory Pract. 2015;31:283-7.

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Grants

2018-2020 European Research Projects on External Insults to the Nervous System

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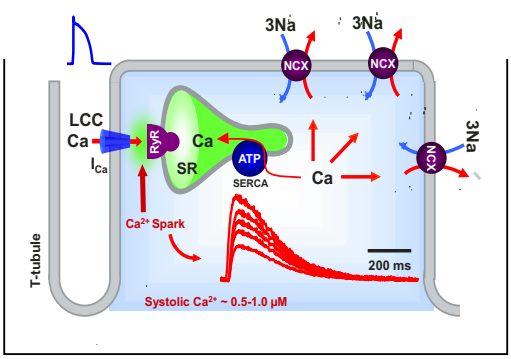
Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

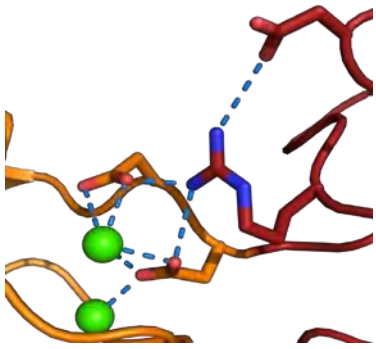
Positions

Professor, Sackler Faculty of Medicine

Research

Calcium (Ca^{2+}) is a major regulator in the living cell. In many cell-types the Na^{+}/Ca^{2+} exchanger proteins (NCX) represent a major Ca^{2+} extruding system and thus, play a key role in regulating the Ca^{2+}-dependent events in the cell. Three NCX genes form numerous splice variants, which are expressed in a tissue-specific manner to regulate excitation–contraction coupling in heart, long-term potentiation and learning in brain, blood pressure, immune responses, neurotransmitter and hormone secretion, kidney Ca^{2+} reabsorption, mitochondrial 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-threating arrhythmias and contractile malfunction. Selective pharmacological targeting of NCX variants is expected to recover Ca^{2+} homeostasis in predefined cell types and thus, may improve desired activity of altered tissues/organs. Since this breakthrough remains challenging our research efforts are focused on two principle issues: a) To resolve structure-activity relationships underlying the function and regulation of diverse NCX variants; b) To develop new experimental approaches for selective pharmacological targeting of tissue-specific NCX variants with a goal of providing new opportunities for preventing and effective treatment of harmful diseases. In this respect we investigate structure-activity relationships in the wild-type and mutated proteins by exploring a wide spectrum of techniques (stopped-flow and ion-flux assays, FRET, SAXS, ITC, X-ray crystallography, confocal microscopy, patch-clamp, etc). In searching the regulatory mechanisms of CBD1 and CBD2 domains we found that the tissue-specific splice segment, located on CBD2, shapes the regulatory specificity of the primary Ca^{2+} sensor located on CBD1. These findings may allow the identification of drug candidates targeting the disease-related NCX variants.





Publications

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Grants

2018-2023 Israeli Science Foundation

Prof. Jonathan Leor, M.D.

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

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Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions

Professor of Cardiology, Sackler Faculty of Medicine

Chair, MD-PhD Program

Director, Neufeld Cardiac Research Institute, Tel Aviv University

Director, Tamman Cardiovascular Research Institute, Sheba Medical Center

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

David Halpern Chair of Cellular and Molecular Cardiology

Research

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

Publications

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

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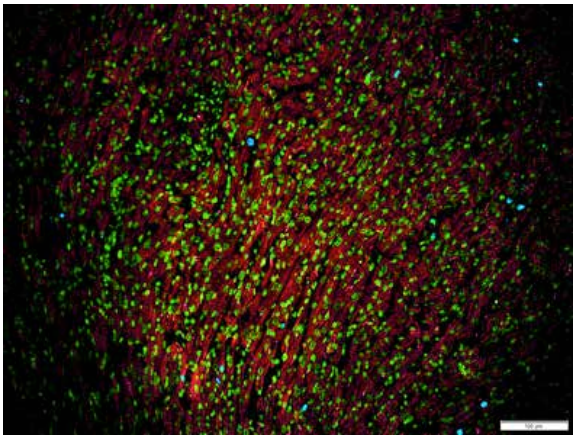

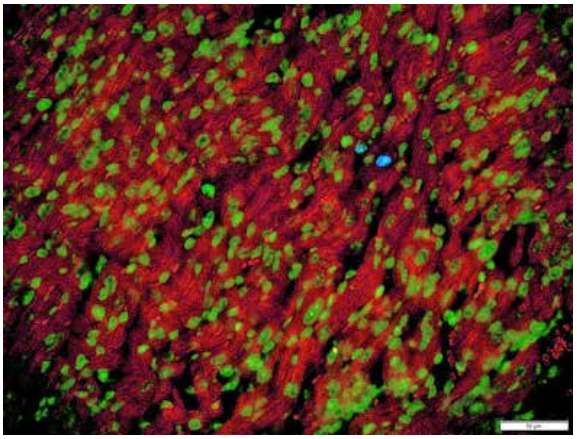

Myocardial regeneration in a neonatal heart of a mouse, 3 days after apical resection. We used the heart of a newborn mouse to study the mechanism of myocardial regeneration and repair. The regenerating myocardium is characterized by cardiomyocyte (cardiac actin, red) dedifferentiation, and proliferation.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

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Grants

2014-2019	Israel Science Foundation, Role of macrophages in myocardial regeneration
2020-2021	Israeli Innovation Authority COVID-19 Grant

Dental Health and Medicine

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Laboratory of Bioinspired Materials and Nanotechnology

Positions

Senior Lecturer, Sackler Faculty of Medicine

TAU Center for Nanoscience and Nanotechnology

The Center for the Physics and Chemistry of Living Systems

Research

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

Publications

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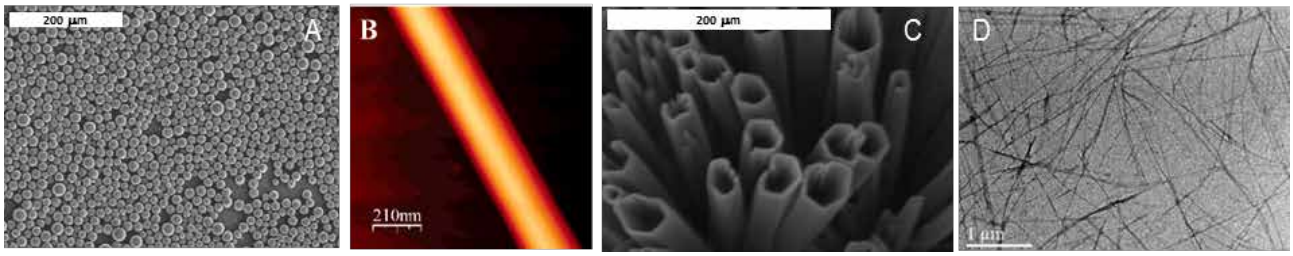

Self-Assembled Nano-Structures: (A) Scanning electron microscopy micrograph of peptide nanospheres. **(B)** Atomic force microscopy image of a peptide nanotube. **(C)** Array of ordered vertically aligned peptide nanotubes. **(D)** Transmittance electron microscopy micrograph of 3D hydrogel demonstrating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

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Zafrani, Y., Kaizerman, D., Hadar, M., Bigan, N., Granot, E., Ghosh, M., **Adler-Abramovich, L.**, Patolsky, F. and Cohen, Y. Pillararene-based two-component thixotropic supramolecular organogels: complementarity and multivalency as prominent motifs. *Chem. Eur. J.*, 2018. 24, 1.

Arnon, Z.A., Pinotsi, D., Schmidt, M., Gilead, S., Guterman, T., Sadhanala, A., Ahmad, S., Levin, A., Walther, P., Kaminski, C.F., Fandrich, M., Kaminski Schierle G.S., **Adler-Abramovich, L.**, Shimon, L.J.W. and Gazit E. Opal-like multicolor appearance of self-assembled photonic array. *ACS Appl. Mater. Interfaces*, 2018, 10, 20783.

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Tao, K., Levin, A., **Adler-Abramovich, L.**, Gazit, E. Fmoc-modified amino acids and short peptides: simple bio-inspired building blocks for the fabrication of functional materials. *Chem. Soc. Rev.*; 2016: 45, 3935-3953.

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Ghosh, M., Halperin-Sternfeld, M., **Adler-Abramovich, L.** Bio mimicking of extracellular matrix. *biological and bio-inspired nanomaterials: Assembly, Mechanisms and Properties*, Springer Nature Singapore 2018; in press

Grants

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

Prof. Tamar Brosh, Ph.D.

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Biochemical Aspects of Dental Restorations and Orthodontic Tooth Movement

Positions

Professor, Sackler Faculty of Medicine

Head, Department of Oral Biology

Research

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

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

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

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

Publications

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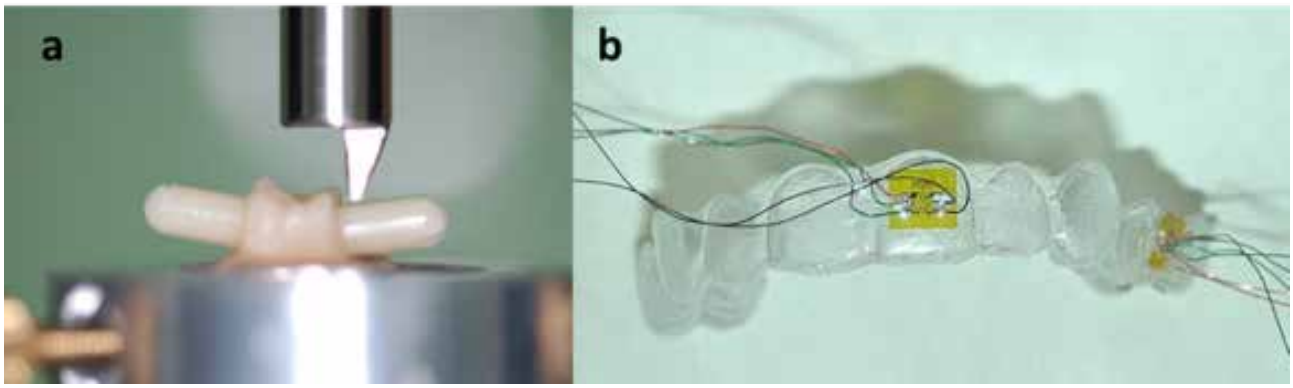
Cohen H, Kugel C, May H, Medlej B, Stein D, Slon V, Hershkovitz I, **Brosh T**.The impact velocity and bone fracture pattern: Forensic erspective. *Forensic Sci Int*. 2016, 7;266:54-62.

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

Pilo R, **Brosh T**, Geron V, Levartovsky S, Eliades G . Effect of silane reaction time on the repair of a nanofilled composite using tribochemical treatment. *J Adhes Dent*. 2016;18:125-34.

Maman E, Yehuda C, Pritsch T, Morag G, **Brosh T**, Sharfman Z, Dolkart O. Detrimental effect of repeated and single subacromial corticosteroid injections on the intact and injured rotator cuff: a biomechanical



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

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Gigi R, Dolkart O, Sharfman ZT, Goldstein Y, **Brosh T**, Rath E, Maman E, Chechik O. Biomechanical evaluation of two arthroscopic techniques for biceps tenodesis: triple loop suture versus simple suture. *J Shoulder Elbow Surg* 2017; 26:165-169.

Chakraborty P, Guterman T, Adadi N, Yadid M, **Brosh T**, Adler-Abramovich L, Dvir T, Gazit E. A self-healing, all-organic, conducting, composite peptide hydrogel as pressure sensor and electrogenic cell soft substrate. *ACS Nano*. 2018, doi: 10.1021/acsnano.8b05067.

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Prof. Ilana Eli, D.M.D.

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Behavioral Sciences in Dentistry

Positions

Professor Emeritus, Sackler Faculty of Medicine

Research

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

Research topics:

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

Publications

G. Bronner, N. Kitrey, N. Uziel, **I. Eli**, G. Raviv, J. Ramon, E. Elran. Correlation between premature ejaculation and female vaginal penetration difficulties. *Int J Impot Res,* 7:152-156, 2015.

I. Eli. Hypnosis as a treatment modality for chronic pain management: Level of evidence. *J Oral Facial Pain Headache*, 30, 85-86, 2016.

A. Emodi-Perlman, I**. Eli**, P. Friedman-Rubin, T. Greenberg, S. Heiliczer, E. Winocur. Occupation as potential factor for temporomandibular disorders, bruxism and cervical pain- a controlled comparative study. *Eur J Oral Sci*, 2016 (in press).

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Uziel N, Meyerson J, Birenzweig Y, **Eli** I. Professional burnout and work stress among Israeli dental assistants. *Psychol Health Med*. 2019, 24:59-67.

Chapters

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

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

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

Senior 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 constrains 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.

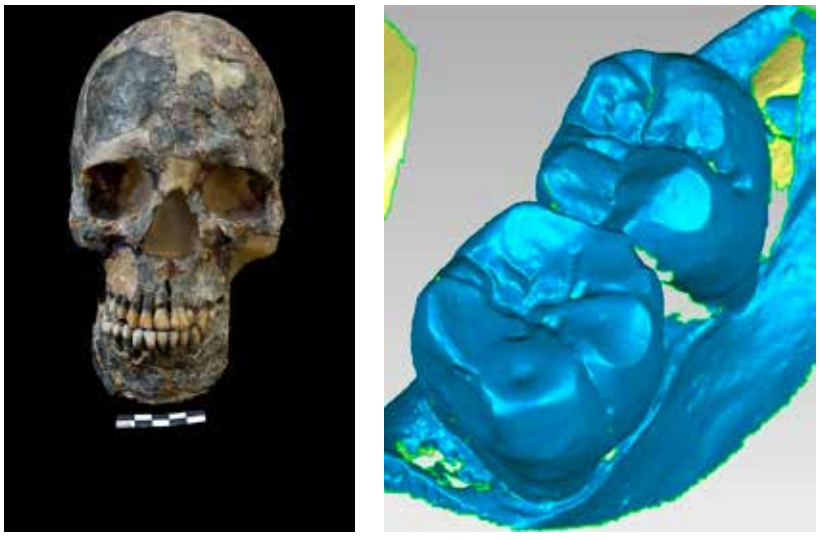
Publications

Sarig, R., Hershkovitz I., Nir, S., May H., Vardimon, A.D. Rate and pattern of Inter-Proximal Dental Attrition. European Journal of Oral Sciences 123, 276-281. 2015.

Hardy K., Radini A., Buckley., **Sarig R.,** Copeland L., Gopher A., Barkai R. Dental calculus reveals potential respiratory irritants and ingestion of essential plant-based nutrients at Lower Palaeolithic Qesem Cave Israel. Quaternary International, 398, 129-135. 2015.

Hershkovitz, I., Weber, G.W., Fornai, C., Gopher, A., Barkai, R., Slon, V., Quam, R., Gabet, Y., **Sarig R.** New Middle Pleistocene dental remains from Qesem Cave (Israel) Quaternary International, 398, 148-158. 2016.

Sarig, R., Gopher, A., Barkai, R., Rosell, J., Blasco, R., Weber, G.W., Fornai, C., Sella-Tunis, T., Hershkovitz,



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).

I. How did the qesem cave people use their teeth? Analysis of dental wear patterns. Quaternary International, 398, 136-14. 2016.

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Fornai, C., Benazzi, S., Gopher, A., Barkai, R., **Sarig, R.,** Bookstein, F. L., Hershkovitz, I., Weber, G. W. The Qesem Cave hominin material (part 2): A morphometric analysis of dm 2-QC2 deciduous lower second molar. Quaternary International, 398, 175-189.2016 .

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May, H., Sella-Tunis, T., Pokhojaev, A., Peled, N., **Sarig, R.** Changes in mandible characteristics during the terminal Pleistocene to Holocene Levant and their association with dietary habits. *Journal of Archaeological Science: Reports*, 2018

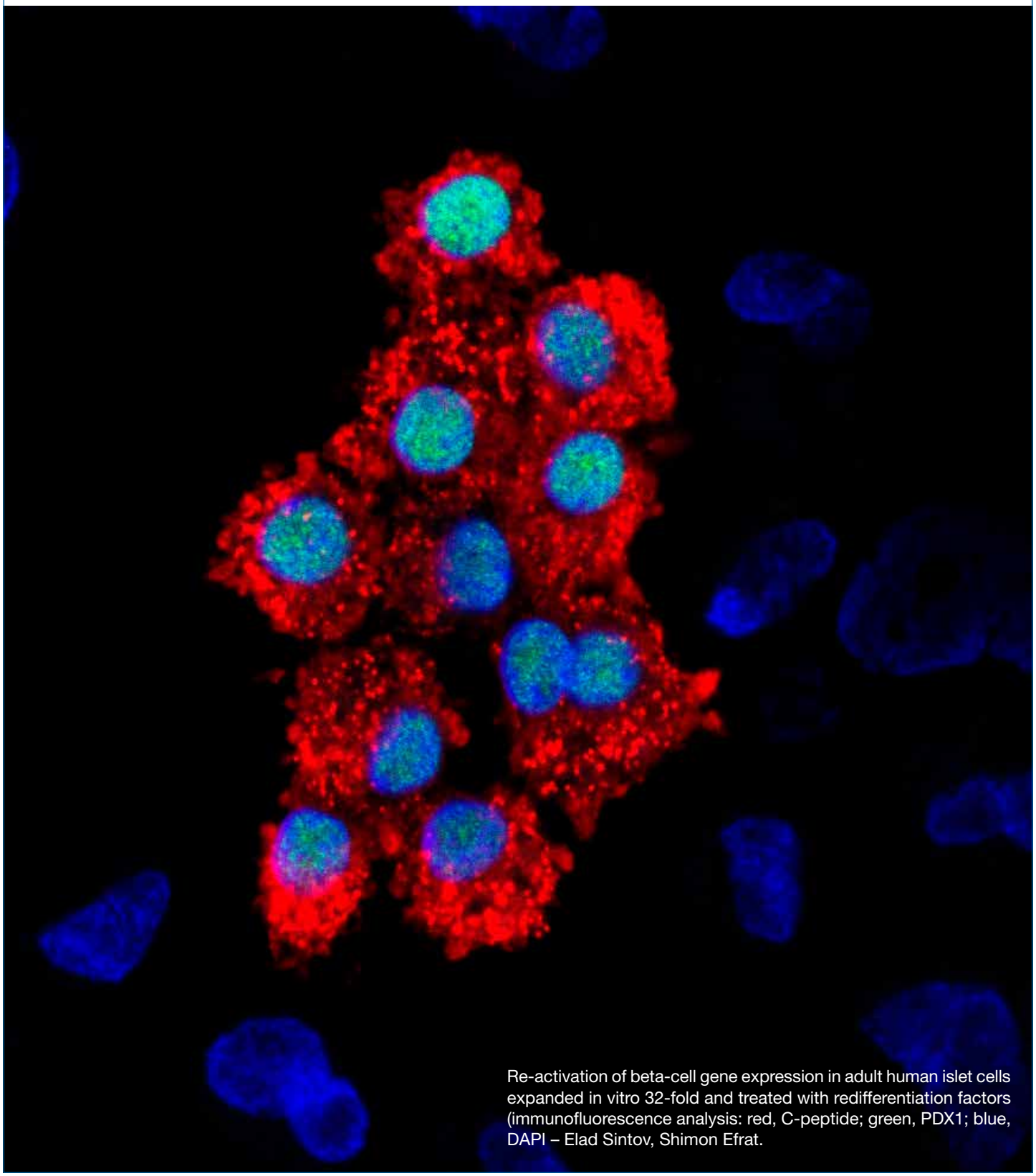
Pokhojaev, A., Habashi, W., May, H., Schulz-Kornas, E., Shvalb, N., **Sarig, R.** Examination of the interproximal wear mechanism: facet morphology and surface texture analysis. *Journal of Dental Research*, 0022034518785140, 2018.

Harney, E., May, H., Shalem, D., Rohland, N., Mallick, S., Lazaridis, I., **Sarig, R.**, Stewardson, K., Nordenfelt, S., Patterson, N., Hershkovitz, I., Reich, D. Ancient DNA from Chalcolithic Israel reveals the role of migration in cultural transformation. *Nature Communications*, 9, 3336, 2018.

Grants

2016-2019	Israel Science Foundation
2018-2019	Irene Levi-Sala CARE Archaeological Foundation
2018-2020	Recanati Medical Research Foundation, Sackler Faculty of Medicine
2018-2021	National Geographic Society
2019-2021	Australian Research Council

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.

Prof. Shimon Efrat, Ph.D.

Department of Human Molecular Genetics and Biochemistry
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Cell Replacement Therapy for Diabetes

Position

Professor, Sackler Faculty of Medicine

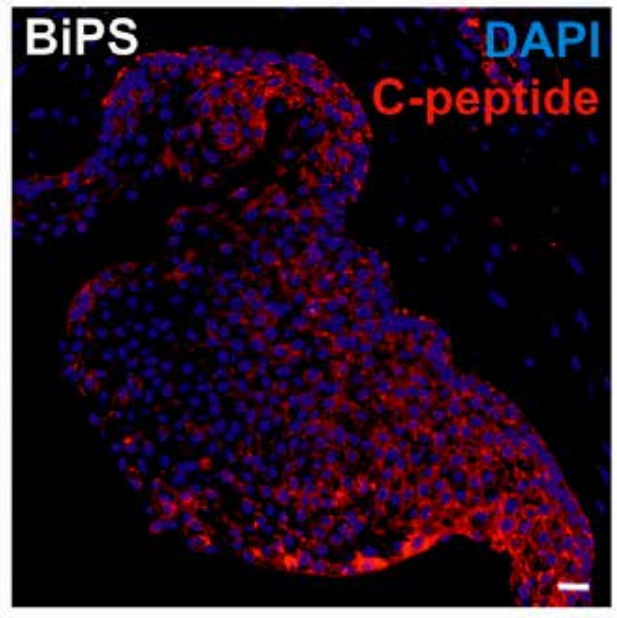
Chair, Department of Human Molecular Genetics and Biochemistry

Nancy Gluck Regan Chair in Juvenile Diabetes

Research

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

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



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

Nathan G, Kredo-Russo S, Geiger T, Lenz A, Kaspi H, Hornstein E, **Efrat S** (2015) miR-375 promotes redifferentiation of adult human β cells expanded in vitro. *PLoS One* 10: e0122108.

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

Toren-Haritan G, **Efrat S** (2015) TGFβ pathway inhibition redifferentiates human pancreatic islet β cells expanded in vitro. *PLoS One* 10: e0139168.

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

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

Reviews

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

Prof. Koret Hirschberg, Ph.D.

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dl.dropbox.com/u/236135/Site/Home.html

Intracellular Membrane Trafficking

Position

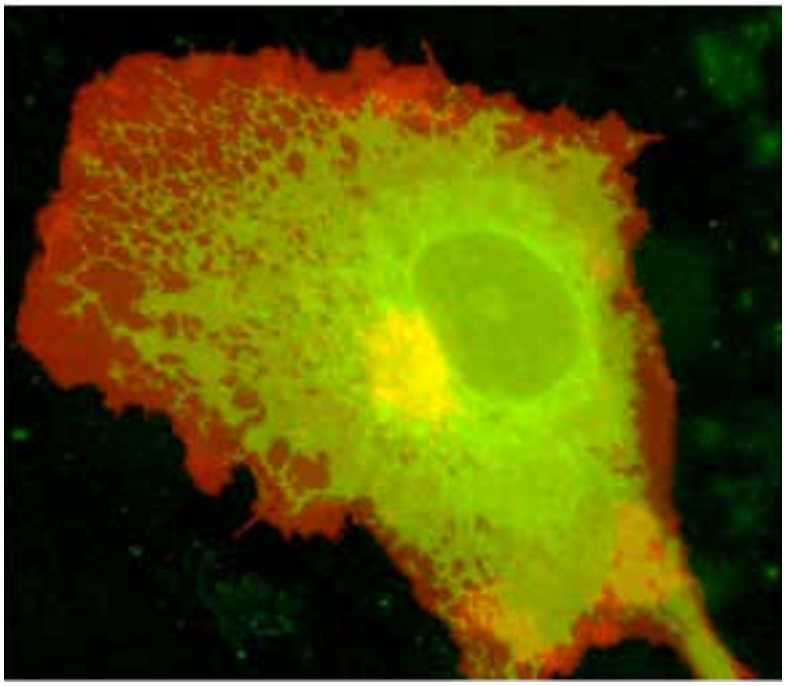
Professor, Sackler Faculty of Medicine

Research

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

To understand these processes in detail, one must recognize that protein–protein as well as protein-lipid interactions are involved. Studying the 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



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

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

Publications

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

Klein O, Roded A, **Hirschberg K**, Fukuda M, Galli SJ, Sagi-Eisenberg R. Imaging FITC-dextran as a reporter for regulated exocytosis. J Vis Exp. 136, 2018.

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

Grants

2016-2019 Israel Science Foundation (ISF)

Dr. Limor Landsman, Ph.D.

Department of Cell and Developmental Biology
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limorl@tauex.tau.ac.il
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Beta-Cell Function and Dysfunction: the Role of Microenvironmental Cues

Position

Senior Lecturer, Sackler Faculty of Medicine

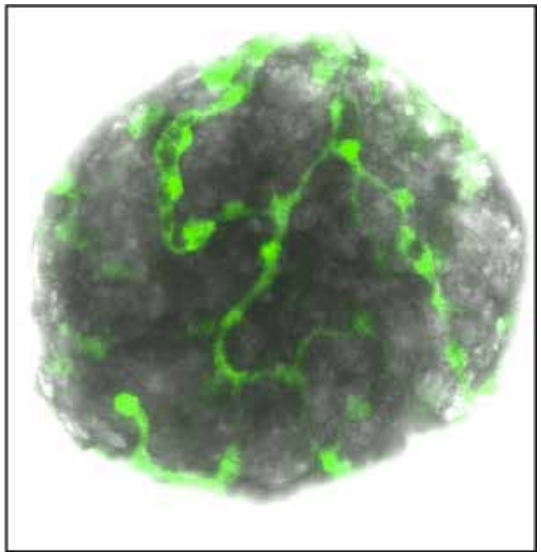
Director, Biomed@TAU Research Hub, Developmental Biology

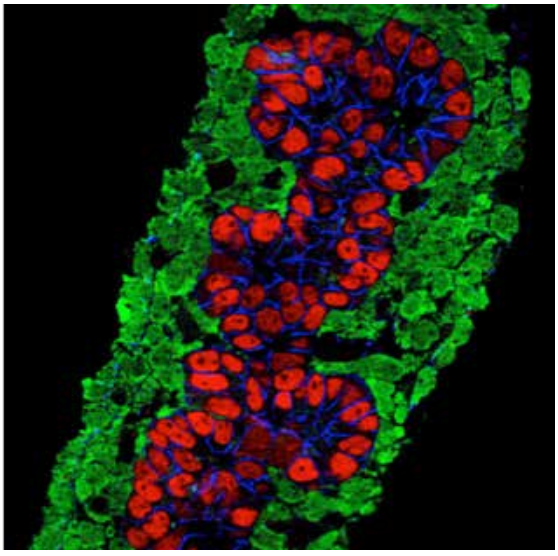
Research

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

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

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





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

cell types in both healthy and diseased mouse models.

Publications

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Reviews

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Almaça J, Caicedo A, and **Landsman L**. Beta-cell dysfunction in diabetes: the islet microenvironment as an unusual suspect. *Diabetologia*. (2020)

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Grants

2018–2021	Future and Emerging Technologies (FET) Open, European Commission
2017–2019	European Foundation for the Study of Diabetes (EFSD) / Novo Nordisk Programme for Diabetes Research in Europe
2018-2023	Israel Science Foundation (ISF) Individual Research Grant

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

Positions

Professor, Sackler Faculty of Medicine

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

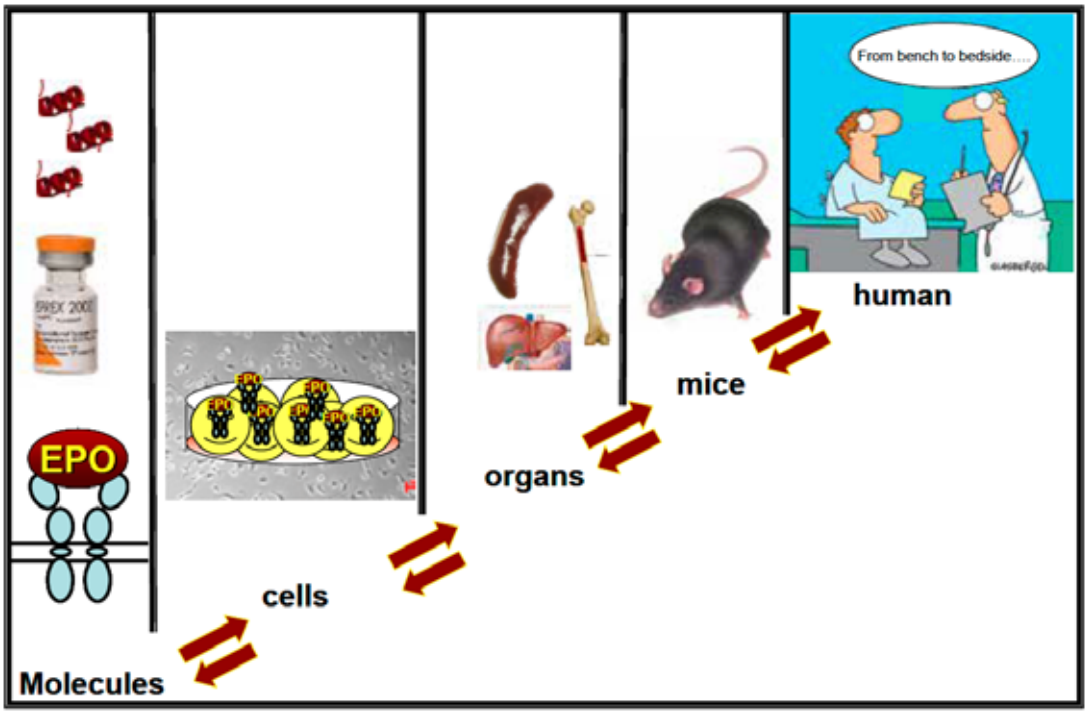
The Lily and Avraham Gildor Chair for the Investigation of Growth Factors

Research

Our research is focused on erythropoietin (EPO), the major hormone that regulates erythropoiesis, operating via activation of its cell surface receptor (EPO-R) on erythroid progenitor cells. Our choice to work on this EPO/EPO-R system was initiated to employ it as a model for understanding basic mechanisms of hormone/receptor function and regulation. Through this research, in a longstanding collaboration with Prof. Mittelman from the Sourasky Medical Center, we made a novel, original discovery, suggesting that EPO may actually act as a pleiotropic hormone with anti-neoplastic, immunomodulatory activities. Our research is thus focused on both the basic mechanisms of hormone/receptor interaction, as well as the function of this hormone as an immunomodulator, and as we have most recently shown, a regulator of bone metabolism (in collaboration with Dr. Yankel Gabet from the Department of Anatomy and Anthropology, Sackler Faculty of Medicine). The studies are based on a variety of in-vitro and murine experimental models, and also include an avenue of elucidating the relevance and possible clinical application of the results.

Publications

Maxwell P., F. Melendez-Rodríguez, K. B Matchet, J. Aragones, N. Ben-Califa, H. Jaekel, L. Hengst, H. Lindner, A. Bernardini, U. Brockmeier, J. Fandrey, F. Grunert, H. Oster, M. Mittelman, M. El-Tanani, M.



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

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Gavish R, Watad S, Ben-Califa N, Goldberg OJ, Haskin O, Davidovits M, Koren G, Falush Y, **Neumann D**, Krause I. Response to erythropoietin in pediatric patients with chronic kidney disease: insights from an in vitro bioassay. *Pediatr Nephrol*. 2018;33(11):2123-2129.

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Grants

2017-2021	Israel Science Foundation – A Role for Erythropoietin in Regulation of Bone Metabolism by Monocytes and B cells
2018-2020	German Israeli Foundation (Together with Y. Gabet, TAU and B. Wielockx and M. Rauner, Dresden) – Pathophysiological impact of erythropoietin on bone density and strength
2020	Dotan Seed Grant (Together with Y Gabet, M Mittelman, H Oster) Cell Competition as a Driver of Clonal Expansion and Dominance in Myelodysplastic Syndromes
2020-2021	Dotan Hemato Oncology Fund, Cancer Biology Research Center, Tel Aviv University (Together with Y Gabet, M Mittelman, H Oster) Implementation of a non-erythropoietic derivative of erythropoietin for improving skeletal outcome in multiple myeloma and myelodysplastic syndromes
2020-2021	Israel Cancer Association (Together with Y Gabet) Cannabinoid agonist raises hemoglobin levels: Implications for treating anemia in cancer
2020	Gassner Fund (Together with Y Gabet, V Shalev).

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Molecular Biology of the Insulin-Like Growth Factor System

Positions

Professor, Sackler Faculty of Medicine

Head, Yoran Institute for Human Genome Research

Lady Davis Chair in Biochemistry

Research

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

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

Publications

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Laron, Z. and **Werner, H.** (2020) Insulin: a growth hormone and potential oncogene. Ped. Endocrinol. Rev. 17 (Suppl 1):191-197.

Grants

2014-2019 "Investigation of metabolic genes associated with cancer protection pathways in a rare congenital IGF1 deficiency". Israel Science Foundation.

2018-2019 Identification of TXNIP as a novel IGF1-dependent longevity gene. Recanati Fund for Medical Research, Tel Aviv University

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Role of the Insulin Receptor in Skin and Implications to Diabetes

Position

Senior Lecturer, Sackler Faculty of Medicine

Co-editor Diabetes/Metabolism Research and Reviews

D-Cure scientific committee

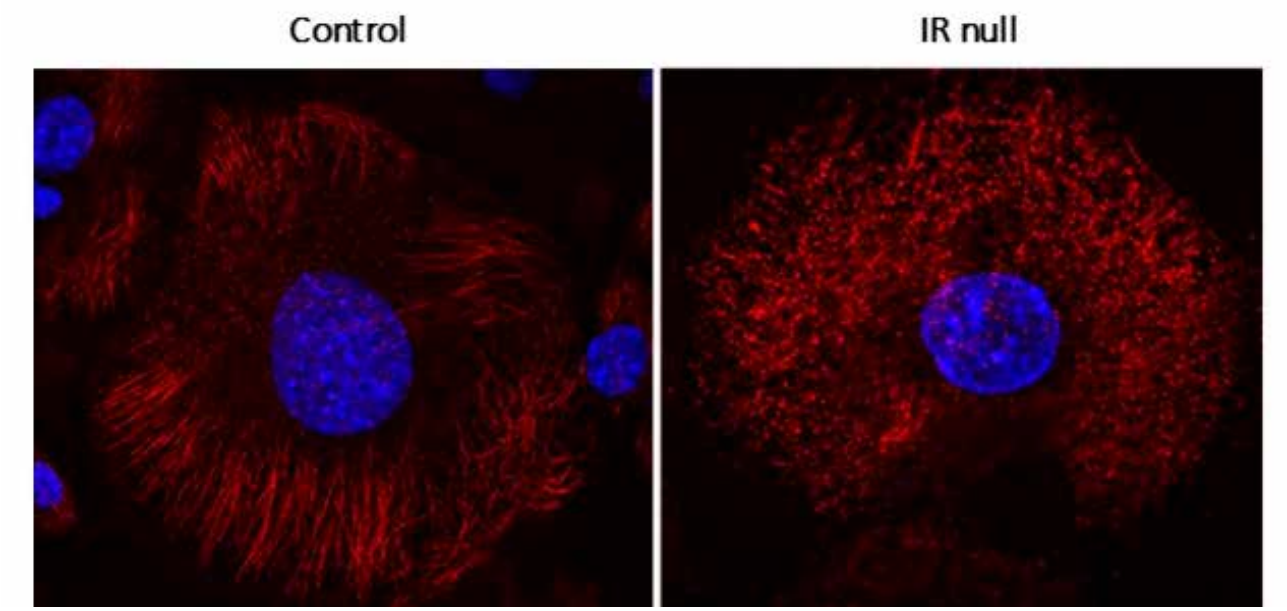
Research

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

Our research interests center on the role of insulin and the IR in skin. The importance of insulin and the IR in skin is evident when insulin action is impaired in insulin resistance and diabetes: One of the major known insulin resistance- and diabetes-associated skin complications is the impaired wound healing leading to amputations, increased illness and high mortality rates. Another skin complication associated with insulin resistance and diabetes is the marked increase in the risk, aggression, and recurrence of non-melanoma skin cancer.

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

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



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

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

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

Publications

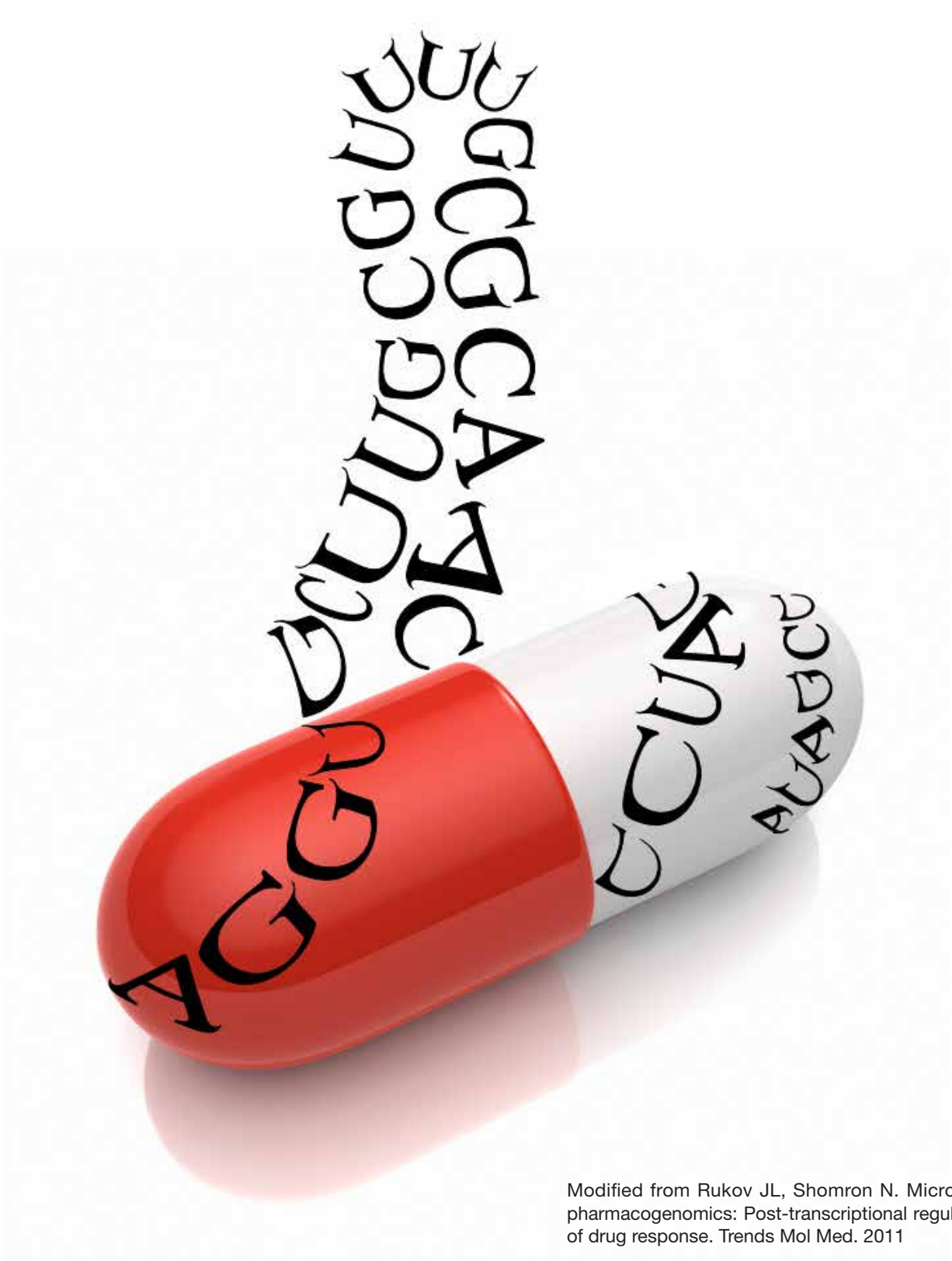
Weingarten G., Ben Yaakov A., Dror E., Russ J., Magin TM, Kahn CR, and **Wertheimer E**: Insulin receptor plays a central role in skin carcinogenesis by regulating cytoskeleton assembly. FASEB J. 2019, in press.

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

Patent

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

Genomics & Personalized Medicine



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Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders & Cancer

Positions

Professor, Sackler Faculty of Medicine

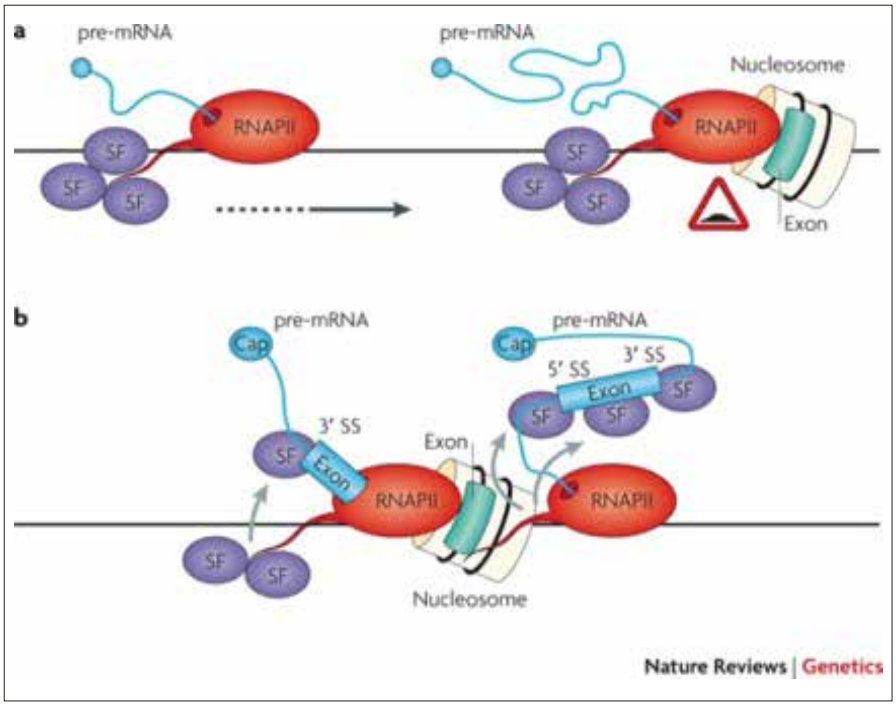
Boris Quentin Chair in Pathological Chemistry

Research

By utilizing the unique strengths of our research group in bioinformatic analyses as well as in genomic and advanced molecular biology methodologies, we are able to make groundbreaking discoveries in the field of alternative splicing. We study how alternative splicing generates higher level of organism complexity, especially in human. However, this comes with a price, and alternative splicing also inflicts many genetic disorders and cancer. Our research involves these two facets of alternative splicing. On one hand, we found how new functions evolved via the generation of new exons (mostly in human). We have also showed how different layers of gene expression affect each other, and found that chromatin organization and epigenetic markers (DNA methylation) mark the exon-intron structure. We also found that during the evolution of warm-blooded organisms two exon-intron gene architectures developed, and these also reflect the different effects of mutations on splicing in cancer and other genetic disorders. On the other hand, we study the impact of splicing abnormalities on colon and lung cancer, and we have recently discovered a new therapy for Familial Dysautonomia, a neurodegenerative disease caused by a splicing defect in the nervous system.

Publications

Danial-Farran N, Brownstein Z, Gulsuner S, Tammer L, Khayat M, Aleme O, Chervinsky E, Aboleile Zoubi O, Walsh T, **Ast G**, King M-C, Avraham KB,* Shalev SA.* (2018) Genetics of hearing loss in the Arab



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

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Reviews

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Grants

2016-2019	DKFZ-MOST, Network-based analysis of alternative splicing regulation
2018-2020	German-Israel Research Foundation Grant
2020-2024	Israel Precision Medicine Partnership Program (IPMP), with the Israel Science Foundation (with Talma Hendler)

Prof. Karen B. Avraham, Ph.D.

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Genomic Analysis of Hereditary Hearing Loss

Positions

Professor, Sackler Faculty of Medicine

Vice Dean, Sackler Faculty of Medicine

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

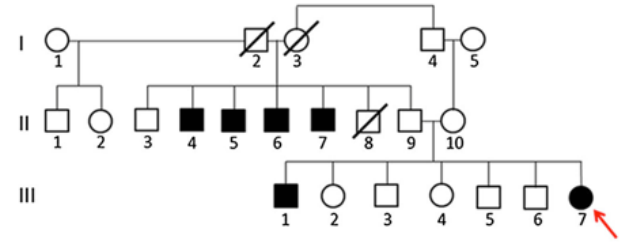
Associate Editor, *European Journal of Human Genetics, Human Genomics*

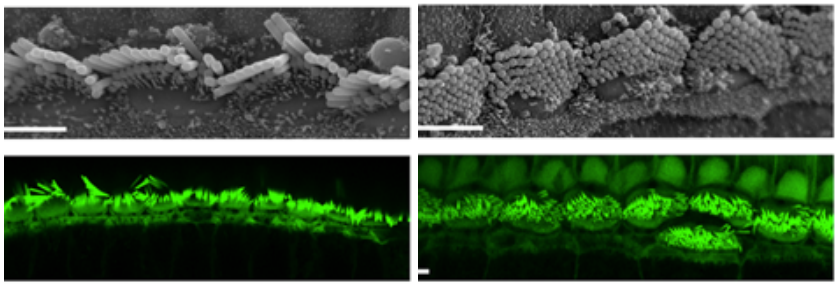
Director, Biomed@TAU Research Hubs

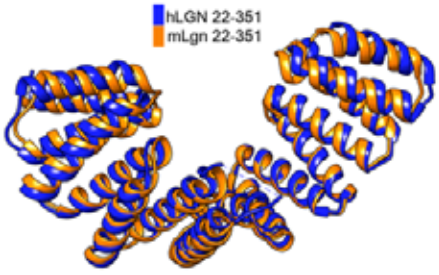
Director, Single Cell Genomics Core

Research

Our primary interest is the genetic basis of hereditary hearing loss or deafness. Our group is working towards the identification, characterization and regulation of genes associated with hereditary hearing loss. For gene discovery, we focus on the Israeli Jewish and Palestinian Arab populations in the Middle East. Our studies have led to the identification of mutations in over 30 genes, since this is a genetically heterogeneous disease. We are employing deep sequencing, also known as massively parallel sequencing, to identify mutations using the latest genomic technology. Our work has provided the link between gene discovery and clinical diagnosis in genetic clinics in medical centers throughout Israel. In addition, we have studied the auditory and vestibular systems of a dozen mouse mutants, focusing on mutation identification, morphological and functional analysis of the organ of Corti and its cells, and behavioral analysis of hearing and balance disorders. This has allowed us to define the pathways leading to deafness in mouse models for human deafness. We have demonstrated that microRNAs are essential for development and function of inner ear hair cells in vertebrates through microRNA expression, mouse mutants and target identification. We have recently isolated long non-coding RNAs (lncRNAs) by RNA-seq from the cochlear and vestibular sensory epithelium. Reconstruction and filtering of the transcriptome of the inner ear led to 3,239 lncRNA genes, yielding 721 novel lncRNAs. We are now working on understanding their mechanisms in the auditory and vestibular systems. Finally, we are building epigenomic maps of DNA methylation, chromatin structure, and histone







Variants in GPSM2 lead to lead to hearing loss in humans and mice. a) Palestinian Arab family with profound hearing loss. b) Structural alignment of the human and mouse GPSM2 N-terminus region, indicating high structural similarity. c) The Gpsm2 truncation in mice causes defective morphogenesis of hair bundles of inner and outer hair cells. From Bhonker et al. 2016.

modifications of the auditory system and integrating them with transcriptomics to establish pathway-specific transcriptional regulatory networks (TRNs).

Publications

Manuscripts

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Grants

2016 – 2019	Identification of a Network of Short and Long Noncoding RNAs Controlling Mammalian Inner Ear Development. Israel Science Foundation.
2018-2020	Function of microRNAs in the peripheral and central auditory system. German-Israeli Foundation for Scientific Research and Development (GIF). Co-PI: Hans Gerd Nothwang
2018-2023	National Institutes of Health/NIDCD R01
2019-2020	Tel Aviv University Breakthrough Innovative Research Grant, Circumventing Irreversible Ototoxic Effects of Aminoglycoside Antibiotics Required for the Treatment of Infectious Diseases, with Co-PI: Micha Fridman, School of Chemistry, TAU
2019-2023	Ernest and Bonnie Beutler Research Program of Excellence in Genomic Medicine Award
2019-2023	Big Data to Therapy: Personalized Medicine for the Deaf in the Diverse Jewish Population, Israel Precision Medicine Partnership Program (IPMP)

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Genomic-scale Bioinfomatics 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 bioinofrmatics 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

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Grants

2018 – 2022 The epitranscriptome in regulation of RNA fate (DIP)

2018 – 2022 Genomic delineation of transcriptional networks that determine auditory hair cells fate (BSF)

2019 – 2020 Multi-layer analysis of the dynamic interplay between 3D genome organization and gene regulation during early stem cell differentiation (KBT)

2019 – 2022 Genomic analysis of alternative polyadenylation in health and disease (ISF)

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Genomic Biomarkers for CNS Drug Response

Positions

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

Senior Editor, *Pharmacogenomics*

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

Member of the NIH Pharmacogenomics Research Network (PGRN)

Research

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

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

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

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

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

Publications

Chouchana L, Fernández-Ramos AA, Dumont F, Marchetti C, Ceballos-Picot I, Beaune P, **Gurwitz D**, Loriot MA. Molecular insight into thiopurine resistance: transcriptomic signature in lymphoblastoid cell lines. *Genome Me*d. 7:37 (2015).

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M, Crisafulli C, Calabrò M, Holsboer F, Stingl J. CHL1, ITGB3 and SLC6A4 gene expression and antidepressant drug response: results from the Munich Antidepressant Response Signature (MARS) study. *Pharmacogenomics*. 16:689-701 (2015).

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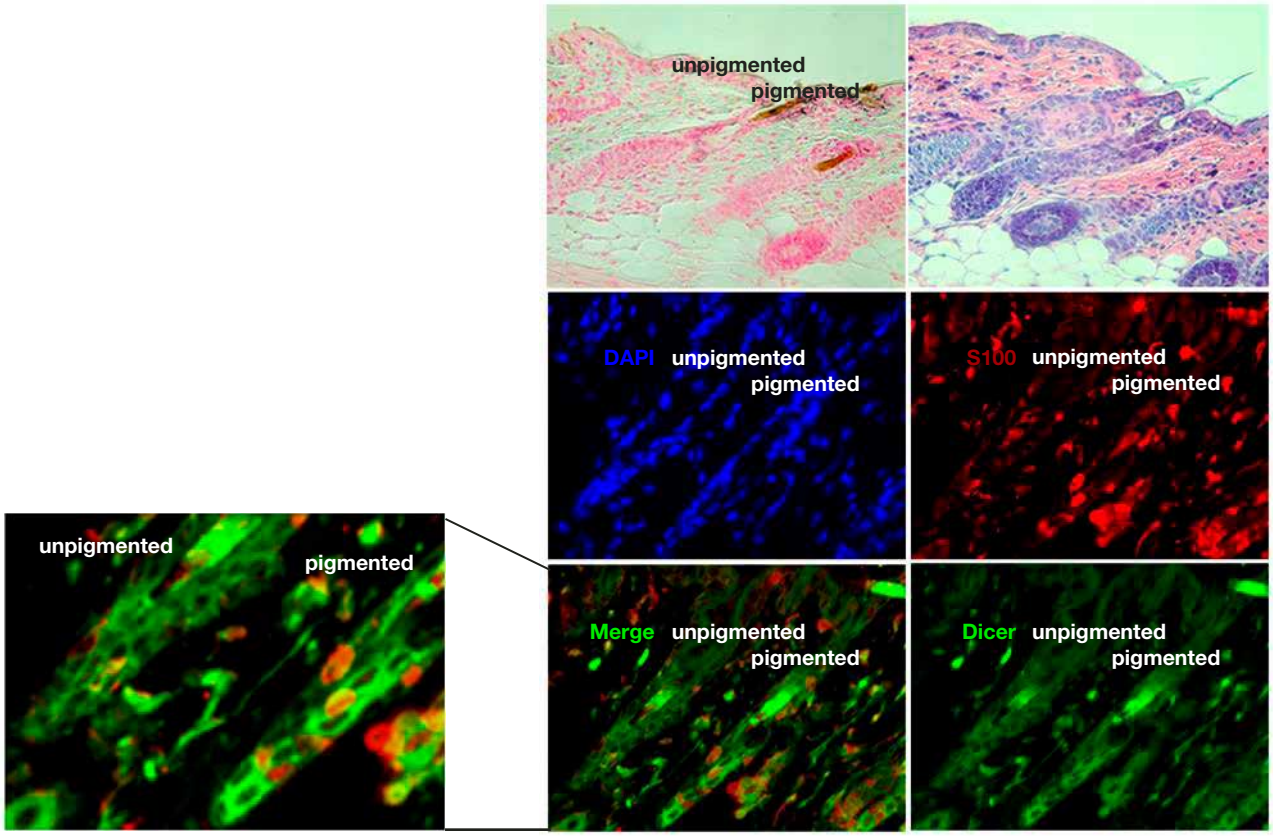
microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our scientific interests involve the role of microRNAs in development, differentiation and malignant transformation. Focusing our studies on melanocytes will provide the foundation for developing novel approaches in the prevention, diagnosis, and treatment of skin cancer in general and melanoma in particular. In addition, we are intrigued by the possibility of using these systems as a model for exploring basic microRNA biogenesis beyond the cell specific context.



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

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Grants

2016-2019	Melanoma Research Alliance (MRA)
2016-2021	European Research Council (ERC)

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Genetic and Metabolic Research of Age-Dependent Chronic Degenerative Disease

Positions

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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 n 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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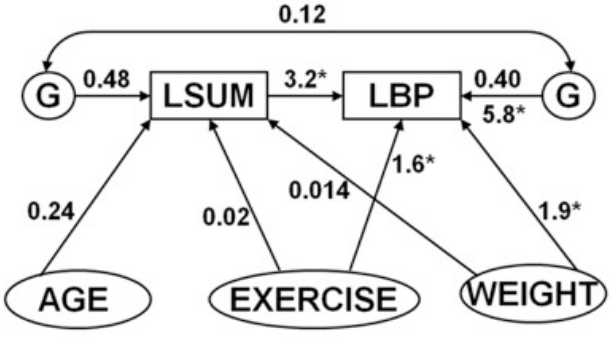

Path diagram of the main risk factors for low back pain (LBP) in middle-age women. The figure shows contribution of various factors to LBP, including genetic effects (G) and lumbar disc degeneration (LSUM). The results presented as variance components (portions) and odds ratios (marked by *). According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

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Genomics, Gene Regulation, and Human Diseases

Positions

Associate Professor, Sackler Faculty of Medicine, Sackler Faculty of Medicine

Academic Director, ScienceAbroad

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Sagol School of Neuroscience

Research

The Shomron research team focuses on the analysis of genomics aimed at understanding human diseases. Combining high-throughput methods and bioinformatics (such as Artificial Intelligence and Deep Learning), our team's research explores DNA changes and gene regulators. Our goal is to reach a global perspective on the roles DNA and RNA play during disease development.

Among our projects: Identification of microRNAs that are in the intersection of several oncogenes; Revealing the effect of coding and non-coding RNAs on pharmacogenomics and personalized medicine; Profiling pathogens in human tissues based on deep sequencing of DNA and RNA molecules; Running advanced rapid DNA and RNA sequencing together with Deep Learning analysis for real-time feedback during medical scenarios.

Overall we aim to deepen our understanding of disease development in order to generate a significant impact through translating ideas into clinical reality.

Publications

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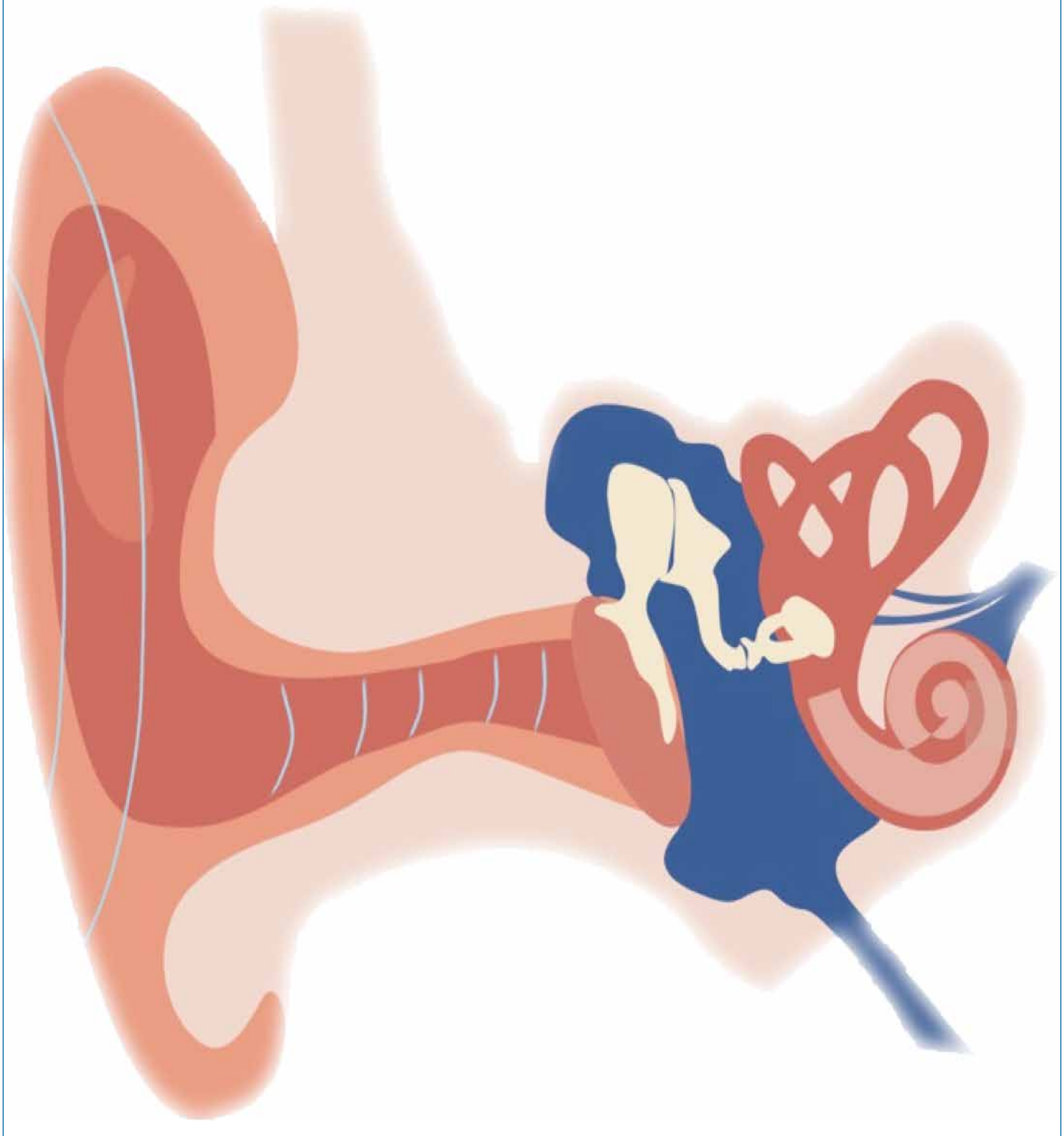
Grants

2018-2019	Breakthrough Award
2018-2020	Zimin Deep Learning and Engineering Grant
2018-2020	Israeli Ministry of Defense
2018-2021	Adelis Foundation
2017-2020	Foundation Fighting Blindness and Israeli Ministry of Health
2016-2021	Israel Science Foundation
2020-2021	IMOD Mafat
2020-2024	Israel Precision Medicine Partnership Program (IPMP), with the Israel Science Foundation

Hearing, Language & Speech Sciences and Disorders



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Paralinguistic Communication, Phonetics and Psychoacoustics

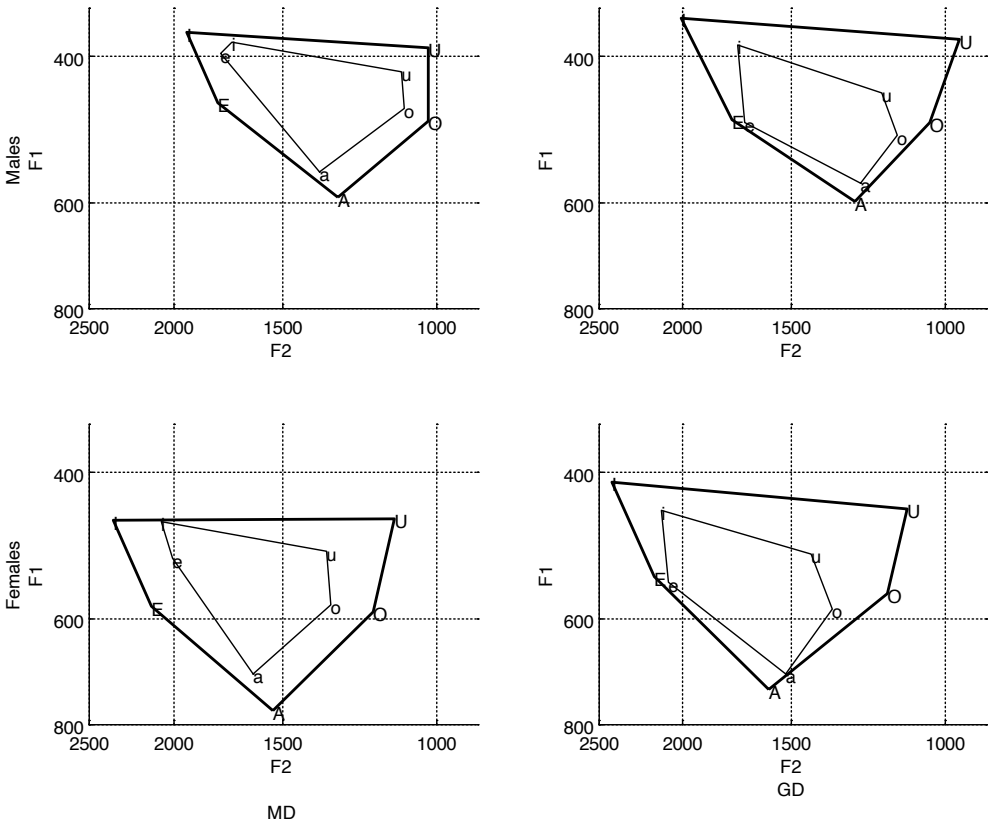
Positions

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 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 of emotion and music.

Publications

Globerson E, **Amir N**, Kishon-Rabin L, Golan O. Prosody recognition in adults with high-functioning autism spectrum disorders: from psychoacoustics to cognition. *Autism Res*. 8:153-63 (2015).

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Voice, Speaking Rate, Stuttering and Fluency Disorders

Positions

Associate Professor, Sackler Faculty of Medicine

Research

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

In the area of voice, we are highly interested in characterizing vocal properties related to different physical, physiological and emotional conditions, and on the professional voice. This line of research involves exploring and identifying acoustic, aerodynamic, percpetual and acoustic measures that differentiate, for example, between people with and without laryngeal pathologies, people who experience various emotional or social conditions, and women at different hormonal conditions and phases (e.g., using birth-control pills, pregnancy, menstrual cycle, etc.).

Publications

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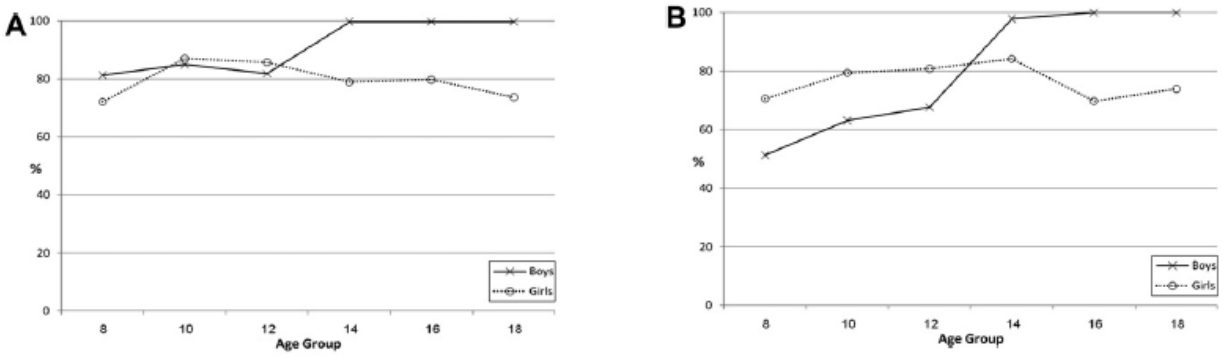

Correct gender identification rates for boys and girls in the six age groups for (A) sentences and (B) vowels.

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Grants

2017-2021 Israel Science Foundation, Cerebral and cerebellar white matter pathways controlling Speech Rate

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

Positions

Senior Lecturer, Sackler Faculty of Medicine

Head, Department of Communication Disorders, Steyer School of Health Professions

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 limplications:

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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Language Processing in Healthy and Brain Damaged Bilingual Speakers

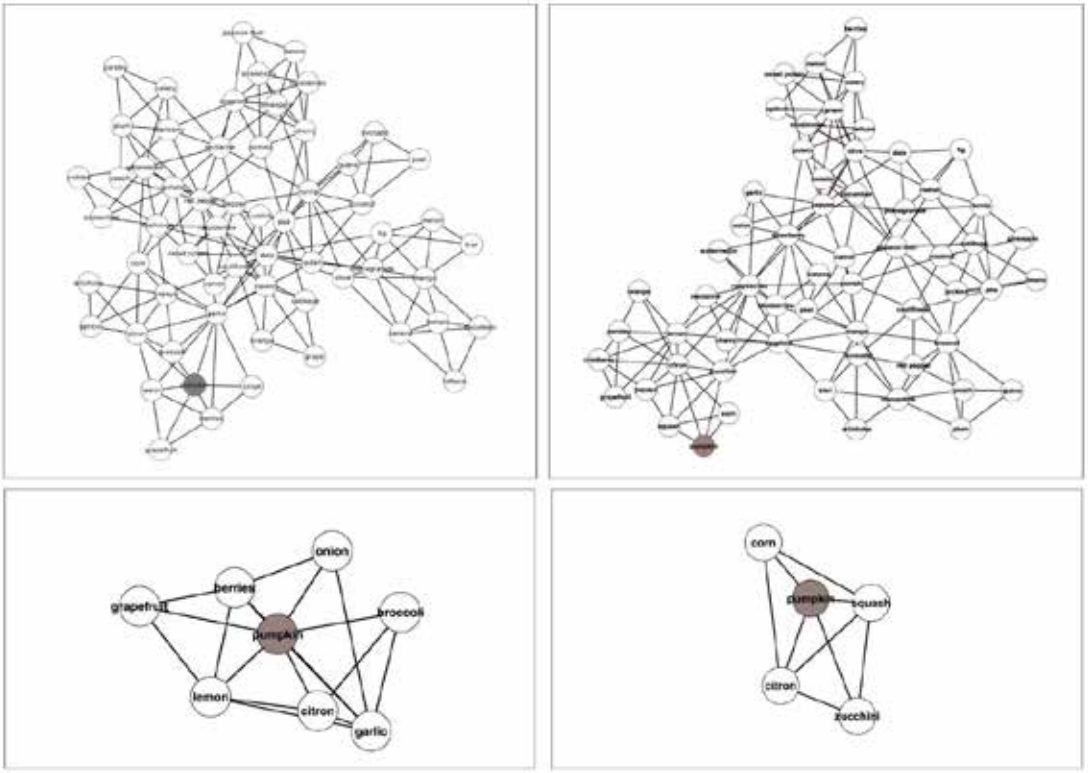
Position

Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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

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

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

Publications

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Auditory Neuroscience and Hearing Rehabilitation

Positions

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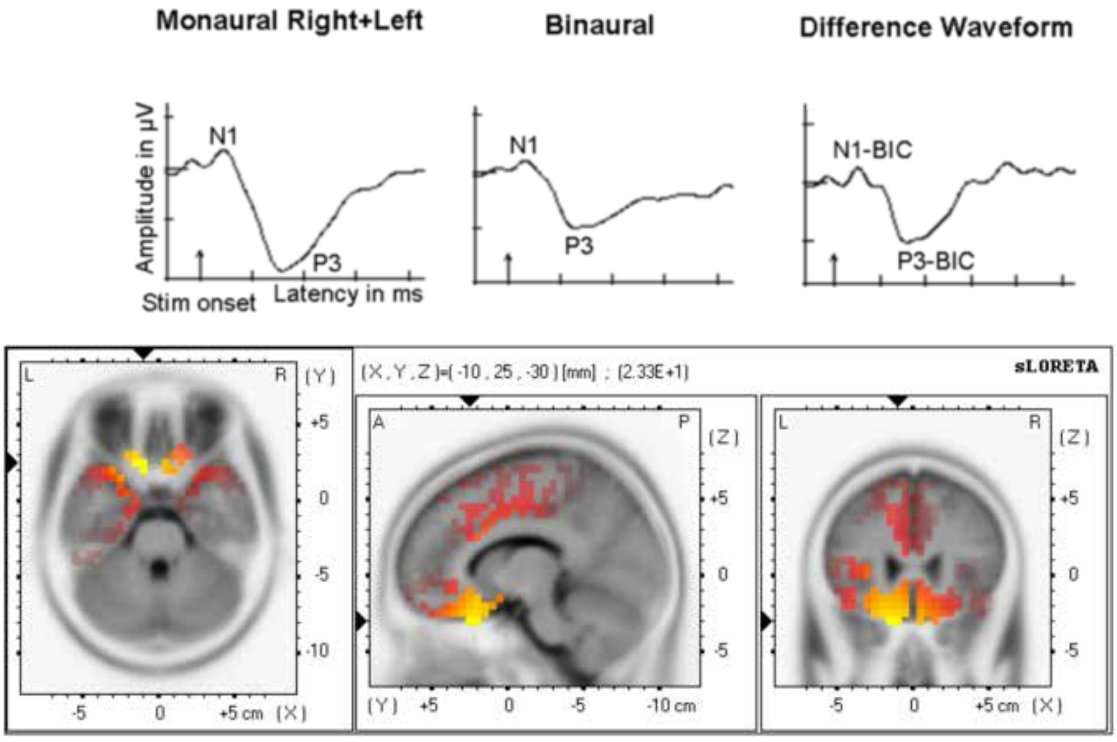
Head, Hearing, Speech, and Language Center, Sheba Medical Center, Tel Hashomer

Co-Director- Cochlear Implant Program. Sheba Medical Center, Tel Hashomer

Research

Within the fields of auditory neuroscience, audiology, and hearing rehabilitation research focuses on cortical biomarkers of auditory processing in the normal and impaired auditory system. Of special interest are the effects of bilateral and unilateral auditory deprivation habilitated by cochlear implants (CI) and hearing aids (HA) on brain electrical activity during auditory processing. Over the years we developed complex linguistic tasks that exposed atypical auditory processing strategies as a result of hearing loss, auditory processing disorders, and increasing age. We provided evidence for cortical binaural processing markers, reflecting integration of linguistic information provided to the two ears in normal hearing listeners. Currently, the effect of increasing age on binaural processing is under study, showing that already in middle aged listeners



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 –binarual 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.

binaural processing is less efficient. Altered binaural markers were found in children with CI, HA, and a combination of a CI in one ear and a HA in the other, shedding light on the neural mechanisms that underlie impaired sound localization and speech understanding in noise in these children. Another line of research focuses on the effect of increasing age and cochlear implantation on auditory-cognitive processing.

Continuous clinical experience in audiology and hearing rehabilitation have set the ground for clinical research on the use of objective measures for diagnosing auditory processing deficits in children with autism, selective mutism, (central) auditory processing disorders, and for evaluating hearing outcomes in patients with CI and HA. A main interest is to transform research findings into rehabilitative approaches and technologies for auditory disorders.

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

Van de Heyning P, Távora-Vieira D, Mertens G, Van Rompaey V, Rajan GP, Müller J, Hempel JM, Leander D, Polterauer D, Marx M, Usami SI, Kitoh R, Miyagawa M, Moteki H, Smilsky K, Baumgartner WD, Keintzel TG, Sprinzl GM, Wolf-Magele A, Arndt S, Wesarg T, Zirn S, Baumann U, Weissgerber T, Rader T, Hagen R, Kurz A, Rak K, Stokroos R, George E, Polo R, Medina MDM, **Henkin Y**, Hilly O, Ulanovski D, Rajeswaran R, Kameswaran M, Di Gregorio MF, Zernotti ME. Towards a unified testing framework for single-sided deafness studies: A consensus paper. Audiol Neurootol. 2017;21(6):391-398.

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Grants

2019-2022 DFG: Markers of auditory-cognitive aging: Evidence from normal hearing listeners and cochlear implant recipients

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Hearing Science and Clinical Audiology

Position

Professor Emeritus, Sackler Faculty of Medicine

Research

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

Our research has been conducted in two areas:

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

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

B. Research on auditory plasticity in human subjects

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

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

Publications

L. Kishon-Rabin, J. Kuint, **M. Hildesheimer**, D. Ari-Even Roth. Delay in auditory behaviour and preverbal vocalization in infants with unilateral hearing loss. Developmental Medicine and Child Neurology, 57, 1129-36, 2015.

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

Position

Professor, Sackler Faculty of Medicine

Head, Steyer School of Health Professions

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 analogoues to language learing in infants and in older children. We utilze primarily behavioral measures that are occasionally supplemented with electriphysiological 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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/pa/ in Hebrew-learning and Arabic-learning infants. *Infant Behavior and Development*.42, 86-99, 2016.

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Review

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Chapters in Books

Kishon-Rabin L. & Boothroyd A. The Role of Hearing for Speech and Language Acquisition and Processing. In D. Ravid and A. Baron, (eds): *Handbook of Communication Disorders: Theoretical, Empirical, and Applied Linguistic Perspectives*. Mouton de Gruyter, Inc. 2018

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Kishon-Rabin L (2018). Implicit learning of auditory rules and statistical sequences with verbal and non-verbal stimuli in children with cochlear implants compared to normal-hearing peers. Ministry of Health, Chief Scientist.

Grants

2018-2019 Ministry of Health: Implicit auditory learning in children with cochlear implants compared to normal hearing

2019-2022 Israel Science Foundation (ISF): The effect of hearing loss on dyadic and triadic interaction and word learning of hearing (with Osnat Segal)

2020 Sima Lior Research Award: Audio-visual synchrony perception in prelingual hearing impaired with cochlear implants compared to normal hearing: A combined behavioral and fNIRS study

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Speech and Hearing Sciences and Rehabilitative Audiology

Position

Professor, Sackler Faculty of Medicine and School of Education

Dean of Students, Tel Aviv University

Research

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

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

Our research activities focus on two main areas:

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

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

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

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

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

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

Publications

Michael, R., **Most, T.**, & Cinamon, R. G. (2015). Career-related parental support of adolescents with hearing loss: Relationships with parents' expectations and occupational status. *American Annals of the Deaf*, *160*, 60-72.

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Brand D, Zaidman-Zait A, **Most T**. Parent couples' coping resources and involvement in their children's intervention program. *J Deaf Stud Deaf Educ*. 2018;23(3):189-199.

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Books

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Chapters

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Hearing Science and Clinical Audiology

Position

Professor Emeritus, Sackler Faculty of Medicine

Chair, Department of Communication Disorders, Tel Aviv University

Senior Audiologist, Speech and Hearing Center, Sheba Medical Center

Research

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

a. Improving the signal to noise ratio in sensory aids (hearing aids and cochlear implants). Recently we demonstrated a significant beneficial effect of a single channel Cochlear-based Noise Reduction Algorithm (CNRA) in hearing aids users and cochlear implants recipients. Further investigation is required for improving CNRA performance at lower SNRs and in different noise spectra.

b. Investigating the influence of aging on the recognition of speech in background noise: Aging is known to induce physio-pathological changes in the entire auditory pathways. While there is a comprehensive documentation of this difficulty amongst elderly people aged 65 years and above, limited information is available on middle-aged listeners.

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

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

Publications

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

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

Prof. Dorit Ravid, Ph.D.

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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

Ravid D, Vered L. Hebrew verbal passives in Later Language Development: the interface of register and verb morphology. J Child Lang. 2017;44(6):1309-1336.

Grants

2017-2021 Research grant, Israel Science Foundation

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Auditory Training to Improve Speech-In-Noise Perception

Positions

Lecturer, Sackler Faculty of Medicine

Board Member, Israel Society for Auditory Research (ISAR)

Research

We study the possibility to improve the cognitive and psychoacoustic skills that underlie speech-in-noise perception via behavioral auditory training. We focus on examining the characteristics of auditory perceptual learning, including generalization of the learning gains to untrained conditions and tasks, susceptibility of the learning process to interferences, reactivation and retention of the training-induced improvements over time in children and in adults. Along with our collegues, we developed a theoretical model that explains the constraints of auditory skill learning in childhood and suggests that obtaining optimal outcomes from auditory training in children is not age dependent per se, but rather depends on the maturity of the task-specific sensory processing and task-related high-order cognitive abilities, which can be recognized following a short training. This model proposes that training may best be tailored for each child individually, depending on his or her maturation of these underlying mechanisms. As our research goal is to design effective training protocols for improving speech-in-noise perception in different pathological populations, we also examine the specific difficulties in noise for hearing impaired listeners who use cochlear implant (CI) devices. We suggest that late CI implantation in individuals with pre-lingual deafness may limit high level reorganization of the spectral representation of sound. Thus, late-implanted CI users may straggle to understand speech in noisy environments due to poor utilization of the formant frequencies information necessary for talker discrimination and speech perception. These findings raise the possibility that auditory training that will focus on perceiving and translating the formant frequencies of a specific talker of interest may be most beneficial for speech-in-noise perception.

Publications

Zaltz Y, Ari-Even Roth D, Kishon-Rabin L. Is the role of external feedback in auditory skill learning age-dependent? *Journal of Speech Language and Hearing Research.* 60 (12): 3656-3666. 2017.

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Zaltz Y, Goldsworthy RL, Eisenberg LS, Kishon-Rabin L. Children with normal hearing are efficient users of fundamental frequency and vocal tract length cues for voice discrimination. *Ear and Hearing.* 41(1):182–193. 2020.

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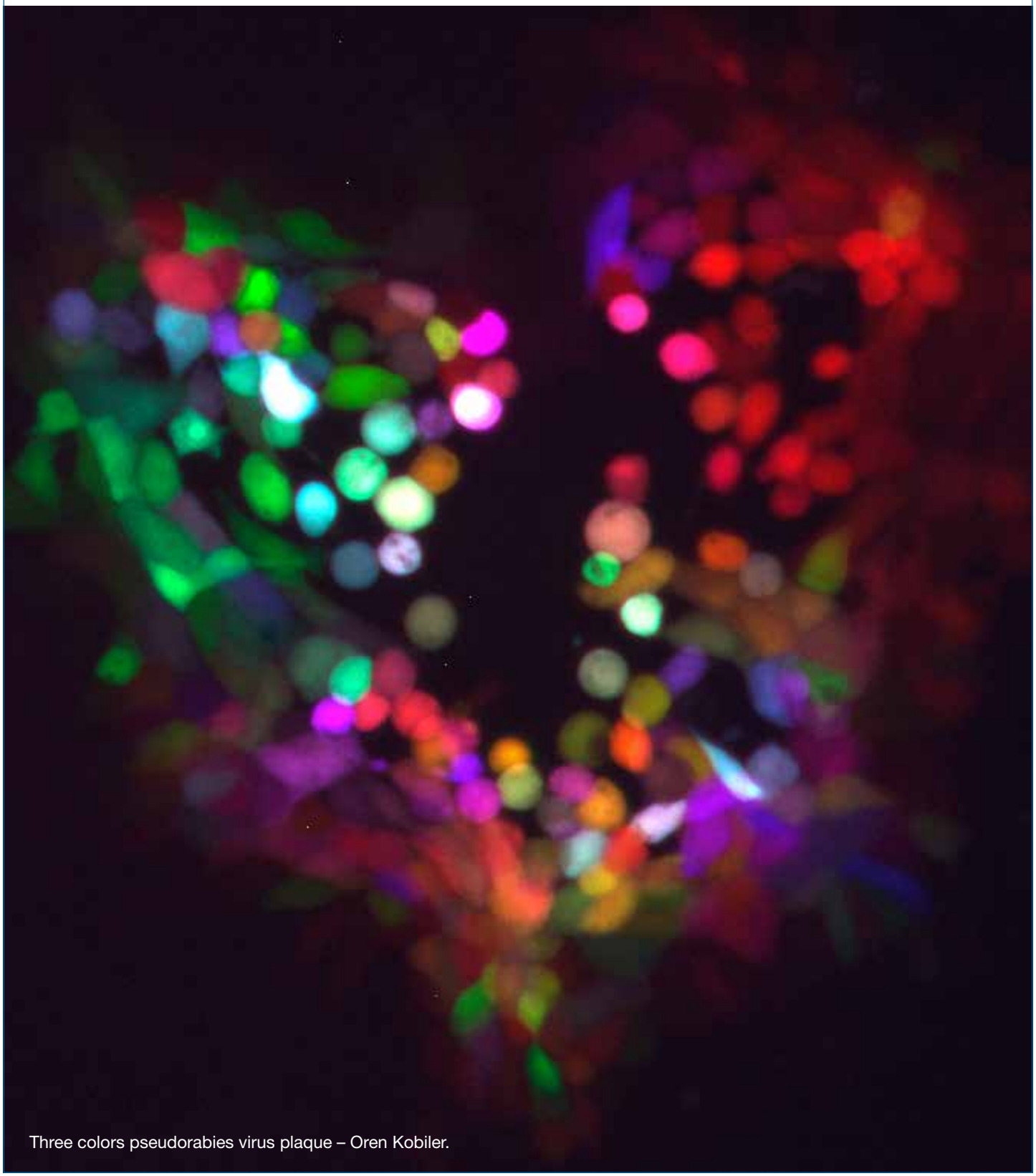
Zaltz Y, Bugannim, Y, Doreen Zechoval, Kishon-Rabin, L, Ronen Perez. Listening in noise remains a significant challenge for cochlear implant users: Evidence from early deafened and those with progressive hearing loss compared to peers with normal hearing. *Journal of Clinical Medicine*. 9(5): E1381. 2020.

Infectious Diseases



Three colors pseudorabies virus plaque – Oren Kobiler.

Prof. Elhanan Borenstein, Ph.D.

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Computational Study of the Human Microbiome

Positions

Associate Professor, Sackler Faculty of Medicine

Associate Professor, Blavatnik School of Computer Science

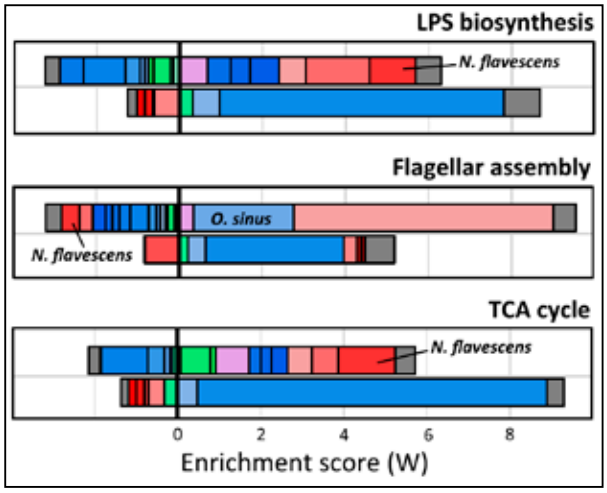
External Professor, Santa Fe Institute

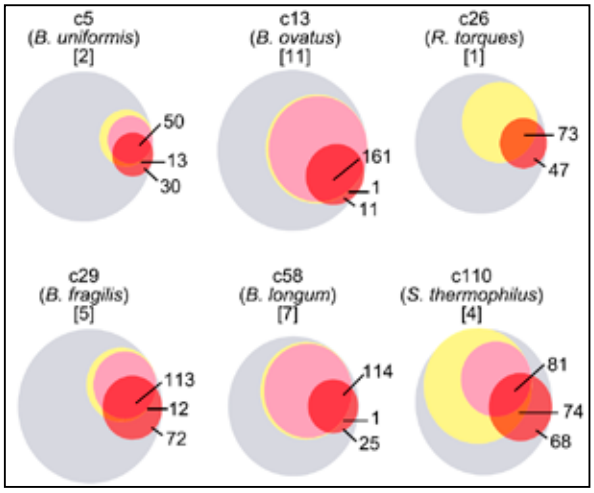
Associate Editor, *PLOS Computational Biology*

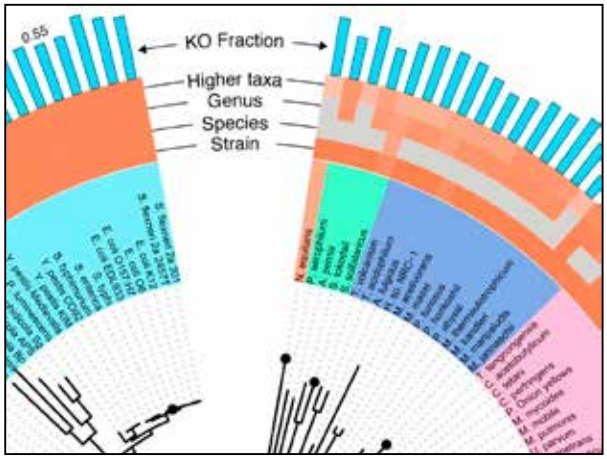
Editorial Board, *Microbiome*

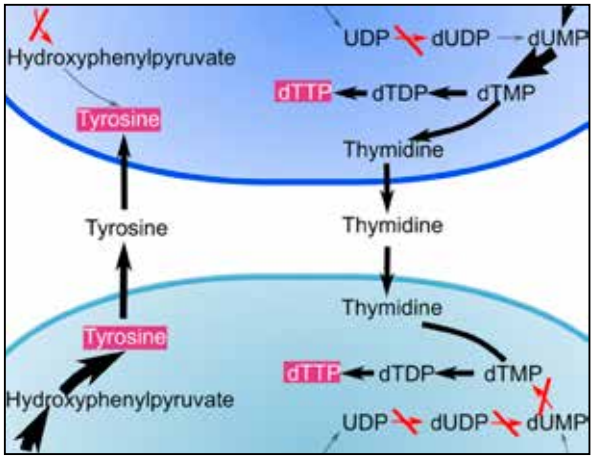
Research

The human microbiome – the complex ensemble of microorganisms that populate the human body – has a tremendous impact on our health. World-wide research initiatives and recent advances in high-throughput technologies have provided exciting insights into the previously uncharted composition of the microbiome and revealed marked compositional changes associated with a wide range of diseases.









Computational systems biology of the human microbiome: Systematic characterization and analysis of the taxonomic drivers of functional shifts in the human microbiome (top left). Identification of strain-level copy-number variation across human gut microbiome species (top right). Comparative analysis of short-read functional metagenomic annotation (bottom left). Metabolic model-based analysis of the emergence of bacterial cross-feeding (bottom right)

To date, however, a system-level understanding of the human microbiome and of its impact on the host is still lacking.

To address this challenge, we develop a variety of novel computational methods for studying the human microbiome, analyzing multi-omic microbiome data, and informing microbiome-based therapy. Our research combines multiple computational approaches, including systems biology, metabolic and genomic modeling, metagenomic analysis, machine learning, data science, and complex networks theory. We specifically aim to go beyond simple comparative microbiome analyses and to study the microbiome as a complex ecosystem. This systems-level approach is crucial to resolving fundamental questions concerning the human microbiome and its role in human health, with numerous biomedical applications.

Research in the lab is multidisciplinary in nature and spans several levels of abstraction, ranging from state-of-the-art computational methods for analyzing microbiome metagenomic data to theoretical studies of mathematical and computational models.

Specific research topics include:

- Metagenomic systems biology and computational modeling of the human microbiome.
- Computational methods for multi-omic analysis of microbiome-derived data.
- Computational design of microbiome maniplulation and microbiome-based therapy.
- Application of machine learning and data science to microbiome research.
- Model-based study of the relationship between the gut microbiome and the host diet.
- Species interaction, community structure, and assembly rules of microbial communities.
- Computational metagenomics and analysis of taxonomic and functional variation across health and disease.

Publications

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Greenblum S, Carr R, **Borenstein E**. Extensive strain-level copy-number variation across human gut microbiome species. *Cell*. 2015; 160(4):583-594.

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McNally CP, **Borenstein E**. Metabolic model-based analysis of the emergence of bacterial cross-feeding via extensive gene loss. *BMC systems biology*. 2018; 12(1):69.

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Nelson MT, Pope CE, Marsh RL, Wolter DJ, Weiss EJ, Hager KR, Vo AT, Brittnacher MJ, Radey MC, Hayden HS, Eng A, Miller SI, **Borenstein E**, Hoffman LR. Human and extracellular DNA depletion for metagenomic analysis of complex clinical infection samples yields optimized viable microbiome profiles. *Cell Reports* 26 (8), 2019.

Eng A, **Borenstein E**. Microbial community design: methods, applications, and opportunities, *Current Opinion in Biotechnology*, 2019.

Reviews

Noecker C, **Borenstein E**. Getting personal about nutrition. *Trends in Molecular Medicine*. 2016; 22(2):83-85.

Grants

2013-2019	NIAID/NIH: Impact of the vaginal microbiome on Chlamydia trachomatis acquisition (with Balkus)
2017-2021	NIH/NIGMS: Metabolic model-based integrative study of the relationship between the gut microbiome, metabolome, and diet
2018-2023	NIH/NIA: The Dog Aging Project: Genetic and Environmental Determinants of Healthy Aging in Companion Dogs (with D Promislow, M Kaeberlein, UW)
2016-2021	NIH/NIOSH: The Healthy Diary Worker Study (with RA Fenske, UW)
2015-2019	NIH/NIDDK: The relationship of fecal microbiomes and nutritional status in CF (with L Hoffman, UW)

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Human Antibody Responses in Health and Disease

Position

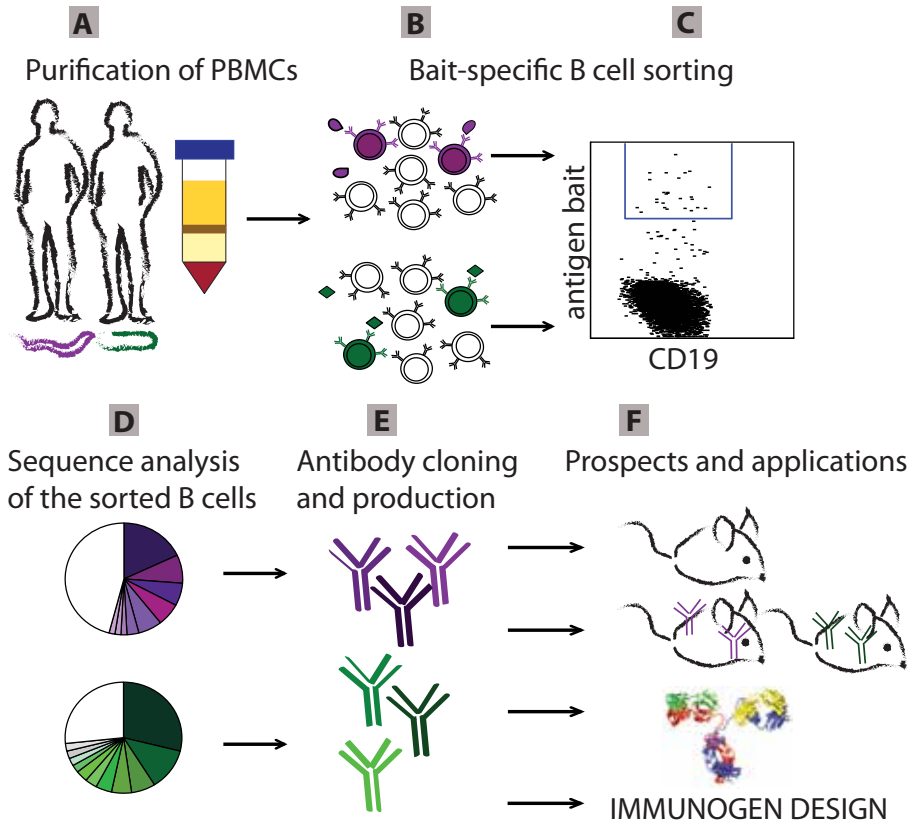
Senior Lecturer, Sackler Faculty of Medicine

Research

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

Each one of us possesses a diverse repertoire of naïve B cells, expressing one type of membrane antibody on each cell. This diversity allows us to respond to a variety of different invaders. When a naïve B cell encounters an antigen, it migrates to the secondary lymph organs, where it interacts with other cells of the immune system. There, B cells undergo affinity maturation, which is one of the most remarkable phenomena in nature. During affinity maturation, somatic mutations are introduced in antibody genes, and subsequently both antibody strength and affinity are improved, while weak and autoimmune antibodies are deleted. B cells then differentiate into antibody-secreting plasma cells and long-lived memory B cells.

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



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

Publications

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Medina-Ramírez M, Garces F, Escolano A, Skog P, de Taeye SW, Del Moral-Sanchez I, McGuire AT, Yasmeen A, Behrens AJ, Ozorowski G, van den Kerkhof TLGM, **Freund NT**, et al, Sanders RW. Design and crystal structure of a native-like HIV-1 envelope trimer that engages multiple broadly neutralizing antibody precursors in vivo. *J Exp Med.* 2017;214:2573-2590.

Wang H, Gristick HB, Scharf L, West Jr. AP, Galimidi RP, Seaman MS, **Freund NT**, Nussenzweig MC, Bjorkman PJ Asymmetric recognition of HIV-1 Env trimer by V1V2 loop-targeting antibodies. *Elife* 2017, 26;6.

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Escolano A, Steichen J, Dosenovic P, Kulp D, Golijanin J, Sok D, **Freund NT**, Araki T, Lowe S, Chen S, Heinemann J, Oliveira T, Gitlin A, Hui-Yao K, Georgeson E, Karen L, Francisco S, Gazumyan A, Burton D, Schief W.R, Nussenzweig M.C Sequential Immunization Elicits broadly neutralizing anti-HIV- 1 antibodies in Ig knock in mice. *Cell.* 2016, 8;166:1445

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Freund NT, Roitburd-Berman A, Sui J, Marasco WA, Gershoni JM. Reconstitution of the receptor-binding motif of the SARS coronavirus *Protein Eng. Des. Sel*. 2015, 28:567-75.

Freund NT, Scheid JF, Mouquet H, Nussenzweig MC. Amplification of highly mutated human Ig lambda light chains from an HIV-1 infected patient. *J Immunol Methods.* 2015, 418:61-5.

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Grants

2020-2021 Campbell Foundation

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Genetic Bases of Host Response to Infections and Chronic Diseases

Position

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

Dorman A, Daria Baer, Tomlinson I, Mott R and **Iraqi FA** (2015) Intestinal polyp development in Collaborative Cross mice carrying the ApcMin/+ mutation. *Am Int J Cont Sci Res* 396: 1.

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

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Dorman A, Daria Baer, Tomlinson I, Mott R and **Iraqi FA** (2016) Genetic analysis of intestinal polyp development in Collaborative Cross mice carrying the *ApcMin*/+ mutation. *BMC Genetics* 17:46.

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Abu Toamih Atamni H, Nashef A, **Iraqi FA**. The Collaborative Cross mouse model for dissecting genetic susceptibility to infectious diseases. *Mamm Genome*. 2018;29:471-487.

Review and editorials

Meehan T, Blake A, Bottomley J, Castro A, Fessele S, Fray M, Kenyon J, Koscielny G, Mallon AM, Massimi M, Matteoni R, Relac M, Steinkamp R, Wilkinson P, Hrabe de Angelis M, Brown S, Tocchini-Valentini G, Herault Y, Ramirez-Solis R, Kollias G, Ulfhake B, Demengeot J, Fremond C, Bosch F, Montoliu L, Flicek RSP, Schughart K, Brakebusch C, Sedlacek R, Radislav T, McKerlie C, Malissen B, **Iraqi FA**, Jonkers J, Holger R, Huylebroeck D, Parkinson H, Raess M, Hagn M. (2015) INFRAFRONTIER- Providing mutant mouse resources as research tools for the international scientific community. *Nucleic Acid Res* 43: 1171-1175.

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

Kafkafi N, Agassi J, Chesler EJ, Crabbe JC, Crusio WE, Eilam D, Gerlai R, Golani I, Gomez-Marin A, Heller R, **Iraqi F**, Jaljuli I, Karp NA, Morgan H, Nicholson G, Pfaff DW, Richter SH, Stark PB, Stiedl O, Stodden V, Tarantino LM, Tucci V, Valdar W, Williams RW, Würbel H, Benjamini Y. Reproducibility and replicability of rodent phenotyping in preclinical studies. *Neurosci Biobehav Rev*. 2018;87:218-232.

Grants

2016-2020 United States-Israel Binational Science Foundation (BSF)

2018-2020 German-Israel Foundation Grant (GIF)

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

Department of Clinical Microbiology and Immunology
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

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

Cohen E. and **Kobiler O**. (2016). Herpes simplex virus-1 gene expression correlates with the number of viral genomes initiating infection in single cells. *PLoS Pathogens* 12 (12), e1006082

Shapira L., Ralph M., Tomer E., Cohen S. and **Kobiler O**. (2016). Histone Deacetylase inhibitors reduce the number of herpes simplex virus-1 genomes initiating expression in individual cells. *Front. Microbiol.* 7:1970.

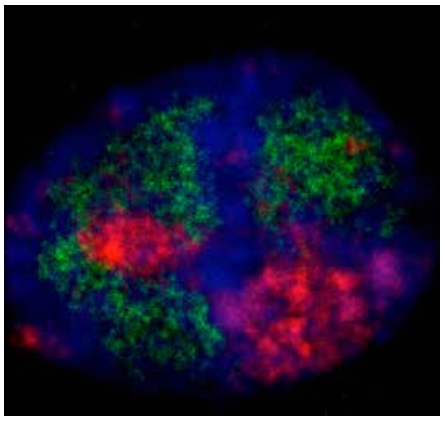
Drayman N, Karin O, Mayo A, Danon T, Shapira L, Rafael D, Zimmer A, Bren A, **Kobiler O** and Alon U (2017). Dynamic proteomics of herpes simplex virus infection. *mBio* 8:e01612-17.

Grants

2014-2019 Grant, Israel Science Foundation (ISF)

2014-2019 Equipment Grant, Israel Science Foundation (ISF)

2016-2020 BSF, co-PI Dr. Weitzman Matthew



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

Prof. Nir Osherov, Ph.D.

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Human Mold Infections

Positions

Associate Professor, Sackler Faculty of Medicine

Chair, M.Sc. Committee, Sackler School of Medicine

Director, Ella Kodesz Institute of Host Defense against Infectious Diseases

Research

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

The goals of my lab are:

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

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

Publications

Dietl AM, Binder U, Shadkchan Y, **Osherov N**, Haas H. Siroheme is essential for assimilation of nitrate and sulfate as well as detoxification of nitric oxide but dispensable for murine virulence of *Aspergillus fumigatus*. *Front Microbiol*. 2018;9:2615.

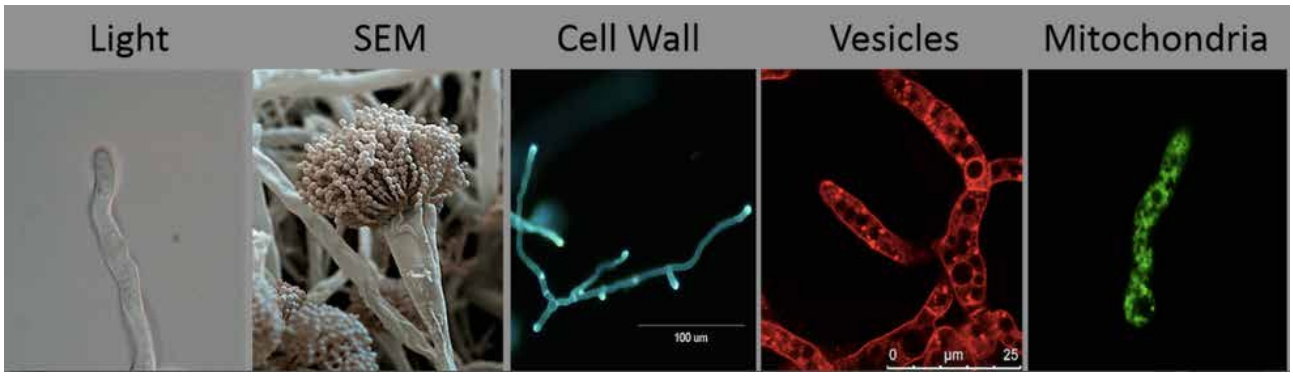
Dietl AM, Meir Z, Shadkchan Y, **Osherov N**, Haas H. Riboflavin and pantothenic acid biosynthesis are crucial for iron homeostasis and virulence in the pathogenic mold Aspergillus fumigatus. *Virulence*. 2018;9:1036-1049.

Yang K, Shadkchan Y, Tannous J, Landero Figueroa JA, Wiemann P, **Osherov N**, Wang S, Keller NP. Contribution of ATPase copper transporters in animal but not plant virulence of the crossover pathogen Aspergillus flavus. *Virulence*. 2018;9:1273-1286.

Meir Z, **Osherov N**. Vitamin biosynthesis as an antifungal target. *J Fungi* (Basel). 2018;4(2).

Bertuzzi M, Hayes GE, Icheoku UJ, van Rhijn N, Denning DW, **Osherov N**, Bignell EM. Anti-aspergillus activities of the respiratory epithelium in health and disease. *J Fungi* (Basel). 2018;4(1).

Wiemann P, Perevitsky A, Lim FY, Shadkchan Y, Knox BP, Landero Figueora JA, Choera T, Niu M, Steinberger AJ, Wüthrich M, Idol RA, Klein BS, Dinauer MC, Huttenlocher A, **Osherov N**, Keller NP.



The pathogenic mold *Aspergillus fumigatus*

Aspergillus fumigatus copper export machinery and reactive oxygen intermediate defense counter host copper-mediated oxidative antimicrobial offense. *Cell Rep*. 2017;19:2174-2176.

Ben Yaakov D, Shadkchan Y, Albert N, Kontoyiannis DP, **Osherov N**. The quinoline bromoquinol exhibits broad-spectrum antifungal activity and induces oxidative stress and apoptosis in *Aspergillus fumigatus. J Antimicrob Chemother*. 2017;72:2263-2272.

Kaltdorf M, Srivastava M, Gupta SK, Liang C, Binder J, Dietl AM, Meir Z, Haas H,**Osherov N**, Krappmann S, Dandekar T. Systematic identification of anti-fungal drug targets by a metabolic network approach. *Front Mol Biosci*. 2016;3:22.

Osherov N, Ben-Ami R. Modulation of host angiogenesis as a microbial survival strategy and therapeutic target. *PLoS Pathog*. 2016;12:e1005479.

Vaknin Y, Hillmann F, Iannitti R, Ben Baruch N, Sandovsky-Losica H, Shadkchan Y, Romani L, Brakhage A, Kniemeyer O, **Osherov N**. Identification and characterization of a novel aspergillus fumigatus rhomboid family putative protease, RbdA, Involved in hypoxia sensing and virulence. Infect Immun. 2016;84:1866-78.

Hover T, Maya T, Ron S, Sandovsky H, Shadkchan Y, Kijner N, Mitiagin Y, Fichtman B, Harel A, Shanks RM, Bruna RE, García-Véscovi E, **Osherov N**. Mechanisms of bacterial (*Serratia marcescens*) attachment to, migration along, and killing of fungal hyphae. *Appl Environ Microbiol*. 2016;82:2585-94.

Halperin A, Shadkchan Y, Pisarevsky E, Szpilman AM, Sandovsky H, **Osherov N**, Benhar I. Novel water-soluble amphotericin B-PEG conjugates with low toxicity and potent in vivo efficacy. *J Med Chem*. 2016;59:1197-206.

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

Mircus G, Albert N, Ben-Yaakov D, Chikvashvili D, Shadkchan Y, Kontoyiannis DP, **Osherov N**. Identification and characterization of a novel family of selective antifungal compounds (CANBEFs) that interfere with fungal protein synthesis. *Antimicrob Agents Chemother*. 2015;59:5631-40.

Grants

2018-2022 Israel Science Foundation Network 'Moked'

2018-2020 China-Israel Grant

Prof. Udi Qimron, Ph.D.

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Host-Virus Interactions in Bacterial Systems

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Clinical Microbiology and Immunology

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

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.

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Yosef I, Edgar R, Levy A, Amitai G, Sorek R, Munitz A, and **Qimron U.** Natural selection underlies apparent stress-induced mutagenesis in a bacteriophage

infection model. *Nature Microbiol*, 1, article #16047, 2016.

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

Yosef I, Goren MG, Globus R, Molshanski-Mor S, and **Qimron U.** Extending the host range of bacteriophage particles for DNA transduction. Molecular Cell, 66(5):721-728, 2017. Cover page – Molecular Cell June 1, 2017.

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

Reviews

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

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

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

Sternberg S, Richter H, Charpentier E, and **Qimron U**. Adaptation in CRISPR-Cas systems. *Molec Cell*, 61(6):797-808, 2016.

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

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

Globus R, and **Qimron U**. A Technological and Regulatory Outlook on CRISPR Crop Editing. *J Cell Biochem*, 119:1291-1298, 2018.

Reichman H, Itan M, Rozenberg P, Yarmolovski T, Brazowski E, Varol C, Gluck N, Shapira S, Arber N, **Qimron U**, Karo-Atar D, Lee JJ, Munitz A. Activated eosinophils exert antitumorigenic activities in colorectal cancer. *Cancer Immunol Re*s. 2019.

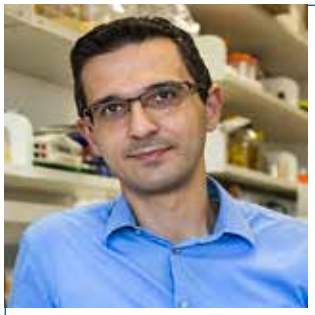
Auster O, Globus R, Yosef I, **Qimron U**. Optimizing DNA transduction by selection of mutations that evade bacterial defense systems. *RNA Biol*. 2018:1-5.

Tabib-Salazar A, Liu B, Barker D, Burchell L, **Qimron U**, Matthews SJ, Wigneshweraraj S. T7 phage factor required for managing RpoS in *Escherichia coli*. *Proc Natl Acad Sci USA*. 2018;115:E5353-E5362.

Grants

2014-2019 Israel Science Foundation Grant

2019-2022 European Research Council Consolidator Grant



Dr. Dor Salomon, Ph.D.

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Bacterial Protein Secretion Systems and Toxins

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

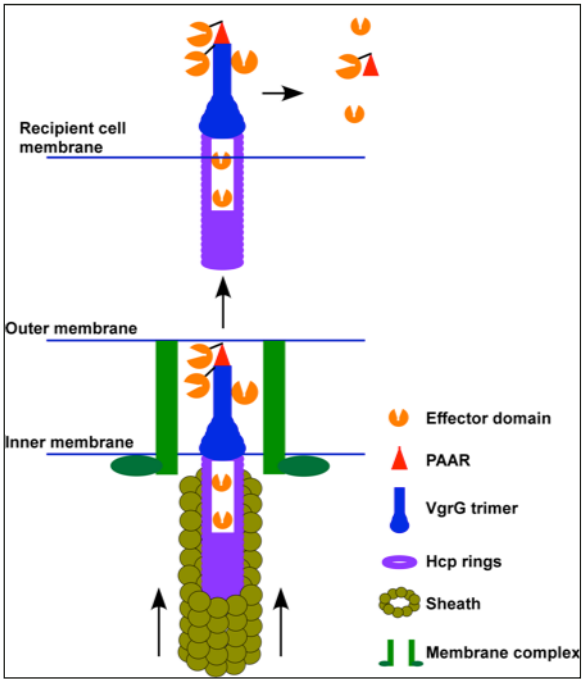
The T6SS is a contact-dependent protein delivery system that is found in many Gram-negative bacteria. It uses a contractile apparatus to propel an inner-tube, which is decorated with toxic effector proteins, outside of the bacterial cell and into an adjacent recepient cell, where effectors are deployed.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

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

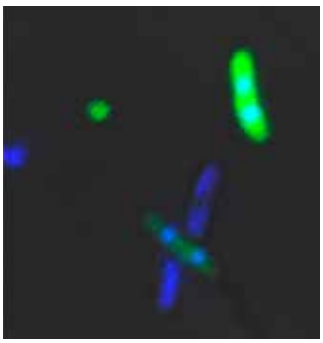
Publications

Fridman, CM., Keppel, K., Gerlic, M., Bosis, E.#, & **Salomon, D.**# (2020). A comparative genomics methodology reveals a widespread family of membrane-disrupting T6SS effectors. *Nature*

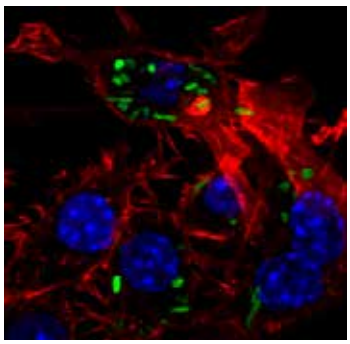
A



B



C



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

Communications, accepted for publication. # Co-corresponding authors

Cohen, H., Baram, N., Edry-Botzer, L., **Salomon, D.**#, & Gerlic, M.# (2020). Vibrio pore-forming leukocidin activates pyroptotic cell death via the NLRP3 inflammasome. *Emerging Microbes & Infections*. 9(1):278-290 # Co-corresponding authors

Jana, B., Fridman, CM., Bosis, E.#, & **Salomon, D.**# (2019). A modular effector with a DNase domain and a marker for T6SS substrates. *Nature Communications*, 10:3595 # Co-corresponding authors

Ben-Yaakov, R. & **Salomon, D.** (2019). The regulatory network of Vibrio parahaemolyticus type VI secretion system 1. *Environmental Microbiology*, 21(7):2248-2260.

Dar Y, **Salomon D**, Bosis E. The antibacterial and anti-eukaryotic Type VI secretion system MIX-effector repertoire in *Vibrionaceae*. *Mar Drugs*. 2018;16(11).

Ray A, Schwartz N, de Souza Santos M, Zhang J, Orth K, **Salomon D**. Type VI secretion system MIX-effectors carry both anti-bacterial and anti-eukaryotic activities. *EMBO Reports*. 2017, 18(11):1978-1990.

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

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

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

Salomon D, Klimko JA, Trudgian DC, Kinch LN, Grishin NV, Mirzaei H, Orth K. Type VI secretion system toxins horizontally shared between marine bacteria. *PLoS Pathog*. 2015, 25;11:e1005128.

Grants

2016-2019	Alon Fellowship
2017-2022	European Research Council (ERC) Starting Grant
2017-2021	Israeli Science Foundation (ISF) Grant
2020-2022	Recanati Foundation Grant

Prof. Esther Segal, Ph.D.

Department of Clinical Microbiology and Immunology

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

Positions

Professor (Emeritus), Sackler Faculty of Medicine

President, Israel Society of Medical Mycology (ISMM)

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

FECMM, Fellow of ECMM

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

Research

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

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

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

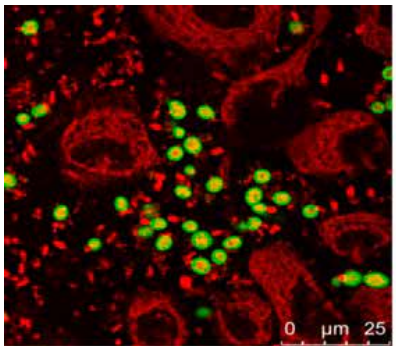
Publications

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

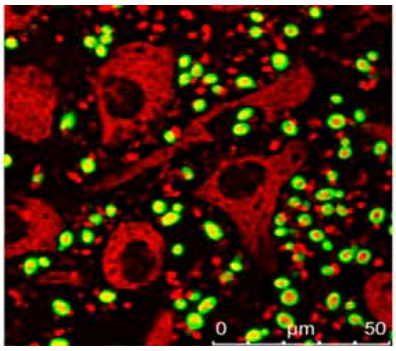
Semis R, Nahmias M, Lev S, Frenkel M, **Segal E**. Evaluation of antifungal combinations of nystatin-intralipid against Aspergillus terreus using checkerboard and disk diffusion methods. *J Mycol Med*. 2015;25:63-70

Segal R, Shemer A, Hochberg M, Keness Y, Shvarzman R, Mandelblat M, Frenkel M, **Segal E**. Onychomycosis in Israel: epidemiological aspects. *Mycoses*. 2015; 58: 133-9

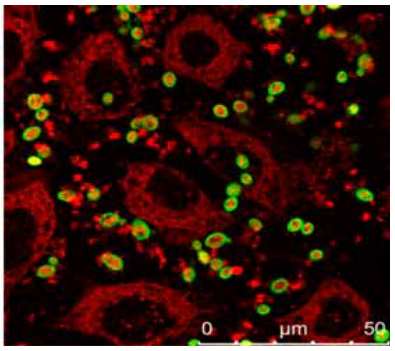
Frenkel M, Mandelblat M, Alastruey-Izquierdo A, Mendlovic S, Semis R, **Segal E**. Pathogenicity of *Candida albicans* isolates from bloodstream and mucosal candidiasis assessed in mice and Galleria mellonella. *J Mycol Med*. 2016; 261-8



CBS strain



S strain



M strain

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

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

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

Grants

2018-2019 Maratier Fund

Dr. Ella Sklan, Ph.D.

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Viral Host Interactions of RNA Viruses

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Current projects in the lab include:

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

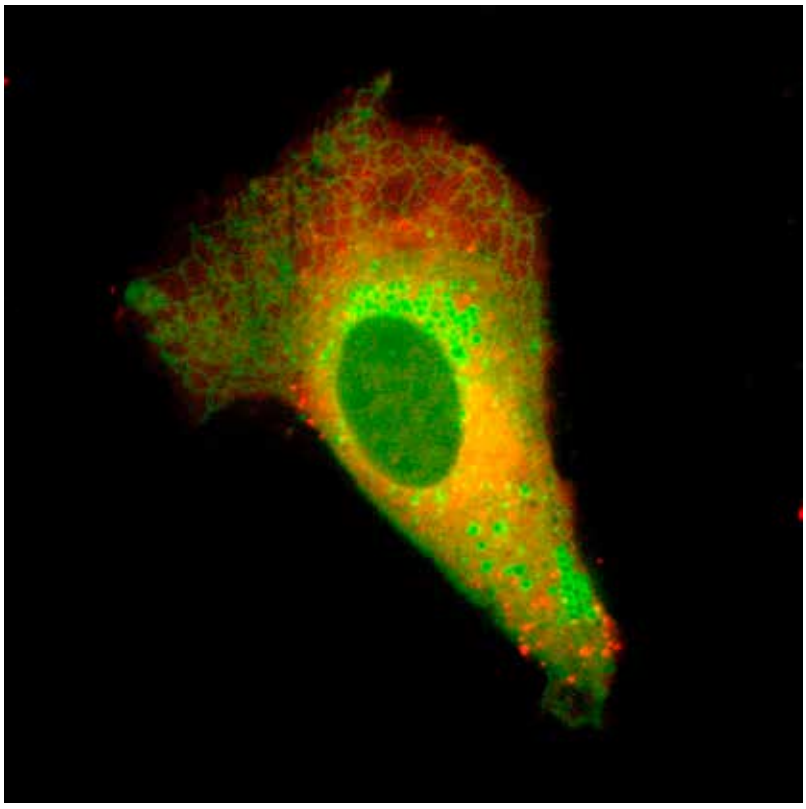
2. Using live cell imaging techniques to study viral-host interactions.

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

4. Drug resistance to viral hepatitis-induced Hepatocelluar carcinoma

Publications

David, N, Yaffe Y, Hagoel L, Elazar M, Glenn JS, Hirschberg K, **Sklan EH.** (2015) The interaction between the Hepatitis C proteins NS4B and NS5A is involved in viral replication. *Virology*, 475C:139-149.



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

Cho NJ, Lee C, Pang P, Pham EM, Fram B, Nguyen K, Xiong A, **Sklan EH**, Elazar M, Koytak ES, Kersten C, Kanazawa KK, Frank CW, Glenn JS. (2015) Phosphatidylinositol 4,5-bisphosphate is an HCV NS5A ligand and mediates replication of the viral genome. *Gastroenterology*, 148:616-25.

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

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

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

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

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

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

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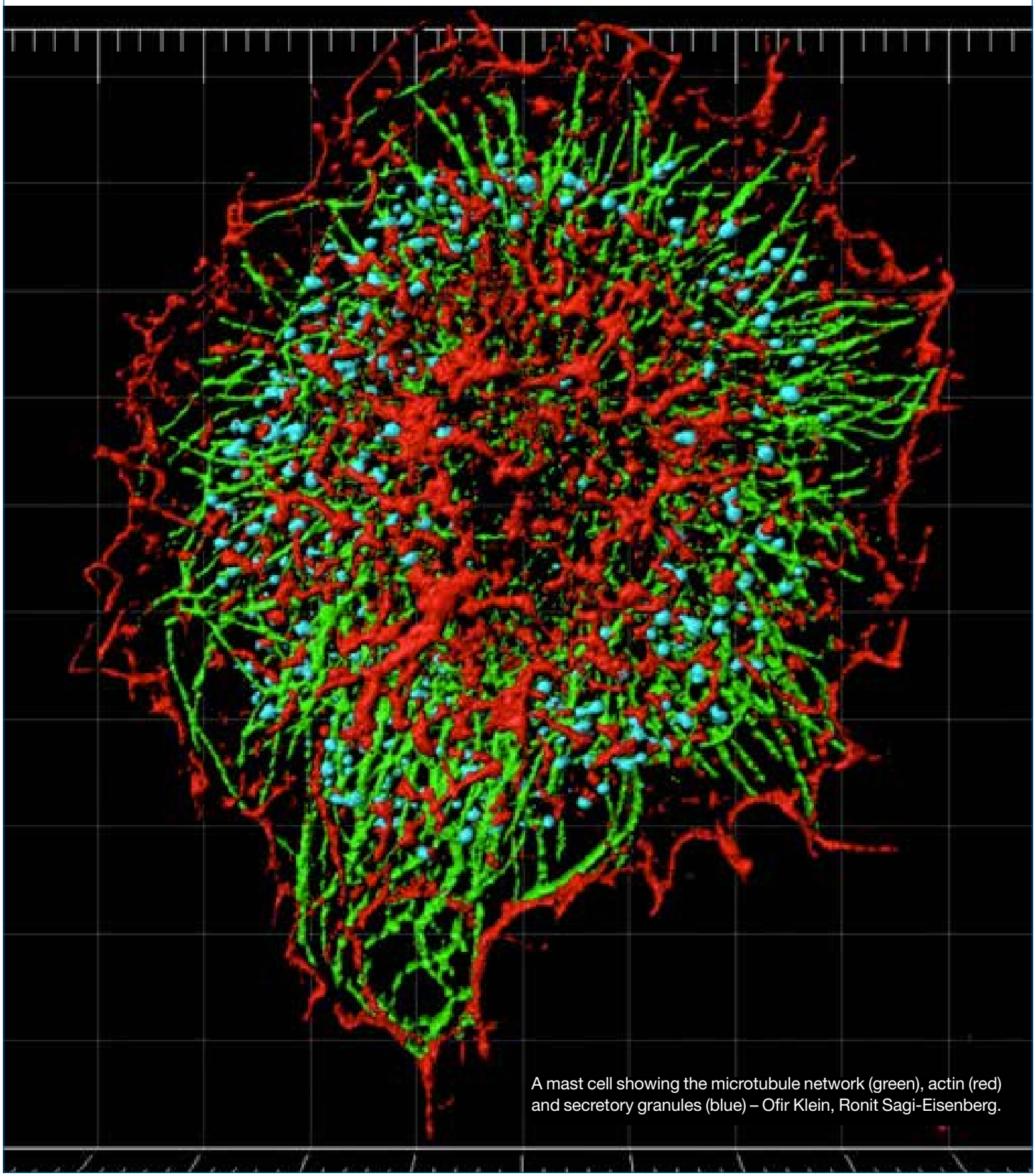
Inflammatory and Autoimmune Diseases



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

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Protein interaction studies and disocvery of new therapeutics for specific immune modulation

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our laboratory is focused on the discovery and development of novel protein modulators as the basis for new therapeutics. Of main interest are the challenging targets belonging to the biological space of protein-protein interactions (PPIs). To study and discover new modulators, we are integrating cutting-edge computational, biophysical and cellular biology tools. We are specifically interested in the interaction of calcineurin-NFAT proteins known as **T-cell activation switch** and in immune checkpoint receptors that function as the **T-cell inhibition switch**. In addition, we are developing new optimized proteins as biomarkers and theraeputics for various cancer types.

Publications

Sun Y, Harpazi B, Wijerathna-Yapa A, Merilo E, de Vries J, Michaeli D, **Gal M**, Cuming AC, Kollist H, Mosquna A. A ligand-independent origin of abscisic acid perception. Proc Natl Acad Sci USA. 2019

Sterlin Y, Pri-Tal O, Zimran G, Park SY, Ben-Ari J, Kourelis J, Verstraeten I, **Gal M**, Cutler SR, Mosquna A. Optimized small-molecule pull-downs define MLBP1 as an acyl-lipid-binding protein. Plant J. 2019

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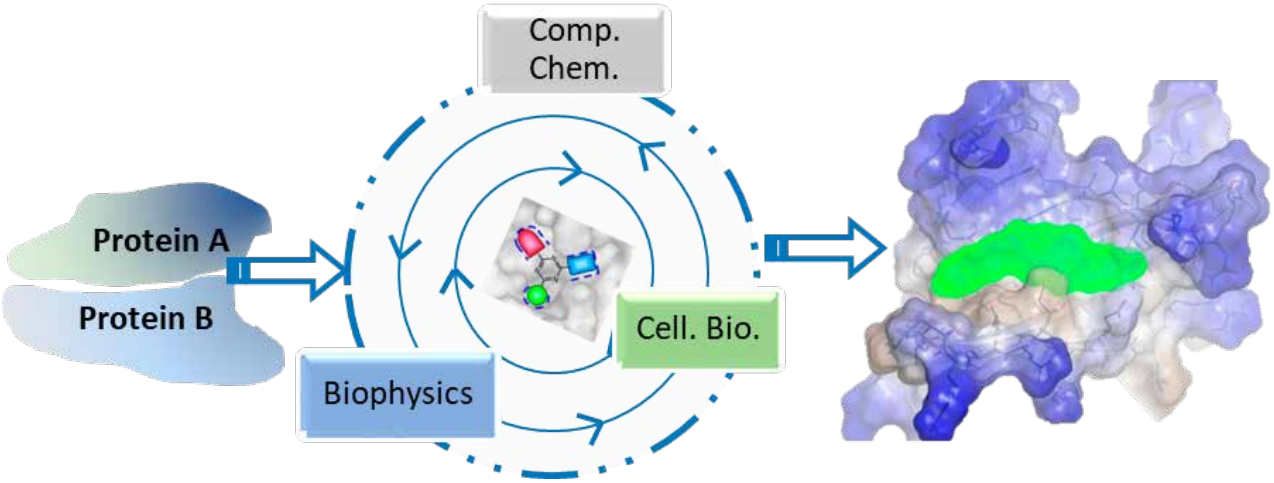

Development of discovery “engine” – an efficient and innovative technological platform to study molecular recognition for the study and discovery of new bio-active molecules.

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Patent

New Methaionine Metabolic Pathway Inhibitors. I. Bloch, E. Cohen, R. Amir and **M. Gal** (2019) PCT/IL2019/050070

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Systems Immunology

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

The main interst of the lab is to study gene circuits of immune cells involving differentiation, activation and regulation following stimulation, immunotherapies or cell-cell interactions. We focus on exploring these cells and circuits mainly in the context of the tumor microenvironment. We apply cutting-edge technologies including mouse tumor models, molecular biology, single cell RNA-seq and other high-troughput genetic and genomic methods, combined with advanced computational approaches to identify and functionally characterize genes that play an important role in immune cell circuits and their effect on tumor growth. Using this approach will enable deep studies of immune cell signaling in the context of interaction with tumor-resident cell types and tumor microenvironment. Moreover, this approach could be readily adapted to study the effect of these genetic circutes in other settings, such as immune cells in organ-specific autoimmunity. These unique signaling signatures could become new 'biomarkers' and facilitate our understanding of both disease pathogenesis, diagnosis and treatment.

Induction and transcriptional regulation of a "co-inhibitory" gene module in T cells by IL-27. The IL-27-induced gene program overlaps with multiple signatures of T cell dysfunction and tolerance. a, Panels I–VI, t-SNE plots of the 588 CD8+ single-cell tumor infiltrating lymphocites (dots) harvested from wild-type mice bearing B16F10 melanoma. b, Graphical representation of the overlap of 57 IL-27-induced cell-surface receptors or cytokine genes with genes expressed in different states of T cell non-responsiveness. This work identified a critical molecular circuit that underlies the co-expression of co-inhibitory receptors in T cells and allowed the identification of novel regulators of T cell function that can be targeted to regulate autoimmunity and anti-tumor immunity.

Publications

Rubino SJ, Mayo L, Wimmer I, Siedler V, Brunner F, Hametner S, **Madi A**, Lanser A, Cox L, Rezende RM, Butovsky O, Lassmann H, Weiner HL: Acute microglia repopulation induces type 1 interferon-driven neurodegeneration in the somatosensory system. *Nature Comm*. (accepted).

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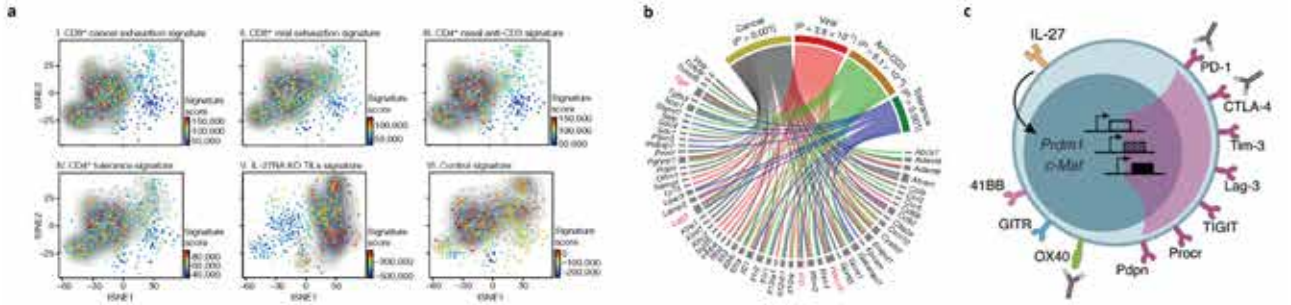

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Gabriely G, Pires da Cunha A, Rezende RM, Kenyon B, **Madi A**, Vandeventer T, Rubino S, Garo L, Kolypetri P, Lanser A, Moreira T, Caetano Faria AM, Lassmann H, Kuchroo V, Murugaiyan G and Weiner HL: Targeting latency-associated peptide promotes anti-tumor immunity. *Science Immunol.* 2017, 2(11): eaaj1738.

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Regulatory Mechanisms in Mucosal Inflammation

Position

Professor, Sackler Faculty of Medicine

Associate Editor, *Journal of Allergy and Clinical Immunology*

Research

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

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

Publications

Reichman H, Itan M, Rozenberg P, Yarmolovski T, Brazowski E, Varol C, Gluck N, Shapira S, Arber N, Qimron U, Karo-Atar D, Lee JJ, **Munitz A**. Activated eosinophils exert antitumorigenic activities in colorectal cancer. *Cancer Immunol Res.* 2019.

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Lee EH, Itan M, Jang J, Gu HJ, Rozenberg P, Mingler MK, Wen T, Yoon J, Park SY, Roh JY, Choi CS, Park WJ, **Munitz A**, Jung Y. Eosinophils support adipocyte maturation and promote glucose tolerance in obesity. *Sci Rep.* 2018;8:9894.

Grace JO, Malik A, Reichman H, **Munitz A**, Barski A, Fulkerson PC. Reuse of public, genome-wide, murine eosinophil expression data for hypotheses development. *J Leukoc Biol.* 2018;104:185-193.

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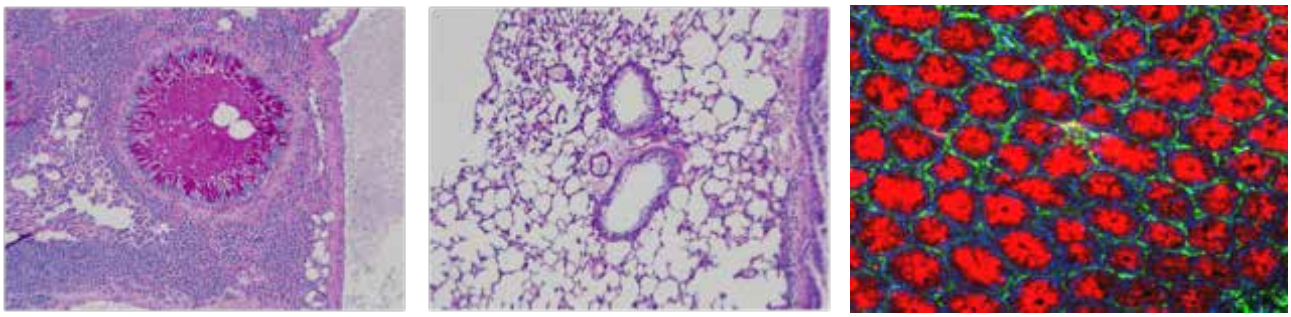

Figure legend: A photomicrograph of a normal lung displaying two large airways and a blood vessel (left). In many inflammatory conditions such as asthma and COPD, the airway is filled with mucus plugs (middle, pink stain). Right – an immunofluorescent stain of resistin-like molecule alpha (red), a proinflammatory,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

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Moshkovits I, Karo-Atar D, Shik D, Reichman H, Itan M, Ejarque-Ortiz A, Hershko AY, Tian L, Coligan JE, Sayos J, **Munitz A**. CD300f associates with IL-4 receptor a and is required for IL-4-induced cellular responses. *Proc Natl Acad Sci USA*; 2015:112;8708-13.

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Grants

2015-2020 The Israel Science Foundation Individual Research grant #95/11; Title: Regulation of GI eosinophils by CLM-1

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

Position

Associate Professor, Sackler Faculty of Medicine

Research

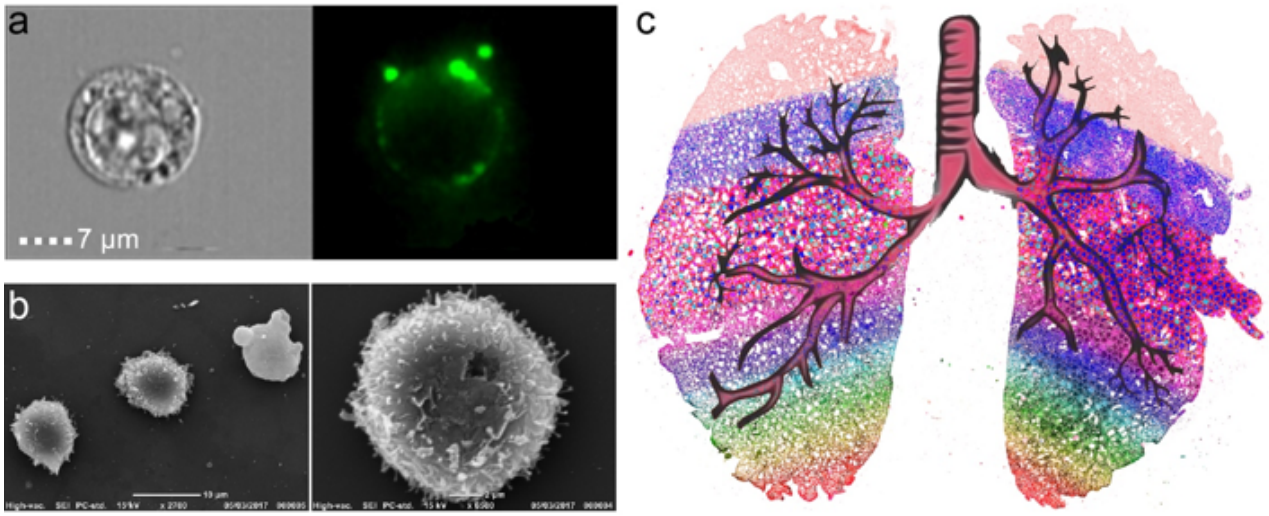
Cell death, an essential cellular process, facilitates the removal of damaged or infected cells, and is necessary for the resolution of immune responses. Recently, two new forms of cell death were identified: 1) pyroptosis - a caspase-1 dependent cell death, and; 2) necroptosis, a RIPK3/MLKL-dependent caspase independent cell death. The latter was suggested to eliminate infected cells when apoptosis is suppressed. Although world-renowned scientists have studied these two non-apoptotic cell deaths for the last 15 years, numerous fundamental questions regarding their components and activity have yet to be answered. Thus, our lab focuses on learning the mechanisms of necroptosis and pyroptosis to ultimately harness this knowledge to fight cancer and improve the health of infectious and inflammatory diseases patients.

Today our laboratory focuses mainly on four projects:
1. Investigate the mechanisms of the non-apoptotic cell death, necroptosis and pyroptosis.
2. Study the immunological consequences of necroptosis and pyroptosis during allergic and inflammatory disease in the skin, lung, liver and intestinal.
3. Study the role of necroptosis and pyroptosis during infectious diseases.
4. Develop cancer immunotherapy based on non-apoptotic cell death.

Publications

Erlich, Z, Shlomovitz, I, Edry-Botzer, L, Cohen, H, Frank, D Wang, H, Lew, AM, Lawlor, KE, Zhan, Y, Vince, J Gerlic M. Macrophages, rather than DCs, are responsible for inflammasome activity in the GM-CSF BMDC model. Nat. Immunol. (2019). doi:10.1038/s41590-019-0313-5

Shlomovitz I, Erlich Z, Speir M, Zargarian S, Baram N, Edry-Botzer L, Munitz A, Croker BA, Gerlic M. Necroptosis directly induces full-length bioactive IL-33 release, FEBS J. February 2019.



a. Extracellular vesicle release during necroptosis as seen using Imagestream. **b.** Morphology changes and outer-membrane breaks during necroptosis as seen under Electron Microscopy. **c.** Inhibiting necroptosis in IL-33-dependent allergic airway inflammation – anti-necroptosis treated (left) vs untreated (right) lung.

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Zargarian S, Shlomovitz I, Erlich Z, Hourizadeh A, Ofir-Birin Y, Croker BA, Regev-Rudzki N, Edry-Botzer L, **Gerlic M**. Phosphatidylserine externalization, "necroptotic bodies" release, and phagocytosis during necroptosis. *PLoS Biol*, June 2017.

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Reviews

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Molecular Basis of Allergic Diseases: Genomic and Functional Analyses

Positions

Professor, Sackler Faculty of Medicine

Chair, Department of Cell and Developmental Biology

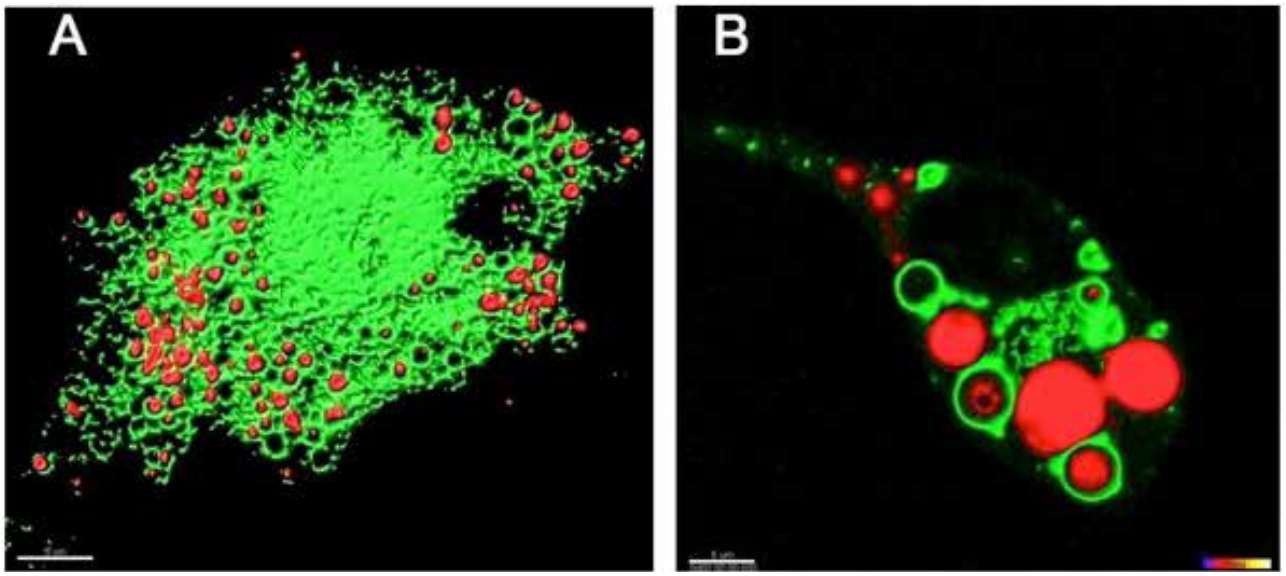
Director, Biomed@TAU Research Hub, Membrane Communication & Remodeling

Research

Our primary interest is the molecular basis of allergic and allergy related diseases, including skin allergy and asthma. Specifically, we explore the mechanisms underlying release of allergic (i.e. histamine) and inflammatory (i.e. cytokines) mediators from activated mast cells. Our research focuses on deciphering the signaling networks that link mast cell activation with mediator release and characterization of genes that could serve as cellular targets for the future development of anti allergic and asthma drugs. To this end, we combine functional genomics and phenotype driven screens of mast cells, activated by multiple stimuli, in order to recapitulate human pathophysiologic conditions. Research methods used include confocal microscopy in live and fixed cells; gene cloning; quantitative RT-PCR, pull down-assay; mass spectrometry, and bioinformatics.

Current projects in the lab include:

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



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

Publications

Klein O, Roded, A, Hirschberg K, Fukuda M, Galli SJ, and **Sagi-Eisenberg, R.** Imaging FITC-dextran as a Reporter for Regulated Exocytosis. *J Vis Exp* 2018; 136, e57936.

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

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

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

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

Azouz NP, Fukuda M, Rothenberg ME, **Sagi-Eisenberg R**. Investigating mast cell secretory granules; from biosynthesis to exocytosis. J Vis Exp. 2015;95:52505.

Rudich N, Dekel O, **Sagi-Eisenberg R**. Down-regulation of the A3 adenosine receptor in human mast cells upregulates mediators of angiogenesis and remodeling. Mol Immunol. 2015;65:25-33.

Reviews

Falcone FH, Wan D, Barwary N and **Sagi-Eisenberg R**. RBL cells as models for in vitro studies of mast cells and basophils. *Immunol Rev.* 2018; 282, 47-57.

Siebenhaar F, Falcone FH, Tiligada E, Hammel I, Maurer M, **Sagi-Eisenberg R**, Levi-Schaffer F. The search for Mast Cell and Basophil models – Are we getting closer to pathophysiological relevance? *Allergy* 2015;70:1-5.

Grants

2015-2019	The Israel Science Foundation
	The role of the small GTPase Rab12 in mast cell degranulation and trafficking of the secretory granules
2018-2022	Binational Science Foundation
	Elucidating the roles of the small GTPase Rab5 in regulating mast cell secretory granule biogenesis and compound exocytosis

Medical Education and Ethics

Dr. Oren Asman, LL.D., Adv.

Department of Nursing
Sackler Faculty of Medicine

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Bioethics, Health Law and Medical Humanities

Positions

Senior Lecturer, Sackler Faculty of Medicine

Executive Vice President, World Association for Medical Law – WAML

Research

Our research focuses on ethical and legal aspects of biomedicine and health professions. Some studies are based on a normative-polemical analysis, while others use quantitative research methods or mixed methods. A large portion of this work is done in collaboration with professionals and researchers from different disciplines.

Our multicultural society and the interprofessional nature of current clinical practice, along with the developments in biomedical research, treatment methods and technology are all a setting for our bioethical deliberation and research. We are particularily interested in the ethical and legal implications of psychiatric and neurological conditions that influence one's thoughts, feelings and behabiours. The legal concept of competence which we focus on in our research brings to the fore some of the shortcomings of current medicine in realms where spirituality, philosophy and epistemology meet; the extent of respect for patients' autonomy during periods of lesser cognitive function is the main ethical focal point in this regard.

The empirical bioethics branch of our research focuses on thoughts, intentions and/or actual behaviors of health care professionals regarding activities of bioethical relevance, such as clinical research or interaction of professionals with the media. While some view normative bioethics to be the main or the only real bioethics research; we believe that combining both approaches provides a better basis for decision making and policy adaptation, as the empirical informs and influences the normative discussion.

Our primary research and teaching topics:

- Clinical research ethics
- Ethical and legal aspects of mental health and brain science
- Ethical and legal aspects of nursing and nursing education
- Public discourse on health issues, ethics and law
- Islamic law and bioethics

Publications

Bergman-Levy T, **Asman O**, Dahan E, Greenberg B, Hirshmann S & Strous R. Specific ethical codes for mental health care professionals –Do we need to annotate. Israeli Medical Association Journal. 2016,18(8), 454-460.

Asman O. Religion, Bioethics and Health Law in Israel. in *Health Law – A book in honor of Prof. Guilherme de Oliveira*, Vol I (Centro Direito Biomedico, Portugal, 2016) 107-130.

Asman O & Barilan YM. The songs of the sirens and the wax in the ears – An autonomy-based tool for DBS device users. American Journal of Bioethics – Neuroscience. 2017, 8(2), 120-122.

Asman O, Barnoy S, Menlinkov S, Tabak N. Research misconduct in Nursing – an Israeli survey. Nursing Ethics. 2017 DOI: 10.1177/0969733017727152.

Barilan YM & **Asman O**. Research Ethics, Military Medical Ethics and the Challenges of International Law. American Journal of Bioethics. 2017. 17(10) 54-56.

Asman O, Tabak N, Professional Standards Expected of Nurses from an Israeli Legal Perspective. Medicine and Law. 2017. 36(4) 53-72.

Asman O, Bergman-Levy T, Greenberg B & Strauss R. Psychiatrists' Media Involvement: A survey of attitudes. Israeli Journal of Psychiatry and Related Sciences. 2018.

Grants

2017-2019 The Israel National Institute for Health Policy Research

Prof. Yechiel Michael Barilan, M.D., M.A.

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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 excrusion to qualitative research.

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

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

Ongoing research projects are:

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

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

Monographs

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

Publications

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

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

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

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

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

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

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

Barilan YM and Asman O. Research ethics, military medical ethics and the challenges of International humanitarian law. American Journal of Bioethics. 2107; 17:53-55.

Chapters

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

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

Dr. Ilana Dubovi, Ph.D.

Department of Nursing, Stanley Steyer School of Health Professions at the Faculty of Medicine.

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Educational Technology to Leverage Patients and Health-Care Practitioners Education

Positions

Lecturer, Sackler Faculty of Medicine

Research

The research area is a synergy of learning sciences, educational technology, and health-related sciences. In particular, we are interested in exploring how patients' education, as well as health-care providers ongoing training, can be leveraged via novel and powerful educational technology.

Our primary research topics:

- We develop novel multi-media-based interactive computerized tools that support patients' learning about and management of their own diseases and related medical treatments to improve health outcomes. We show that following learning with our computerized tools, patients with type 1 diabetes were able to improve their own blood glucose regulation. Now, we are seeking to design tools that support cancer patients and patients with chronic illnesses.
- Using intelligent multi-modal analytics technology, we are able to support health-care practionaires' learning and training processes. We study how fine-tuned to leraners needs educational technology impoves health-care quality of care and patient safety.

Publications

Dubovi I, Levy ST, & Dagan E. (2017). Now I know how! The learning process of medication administration among1. nursing students with non-immersive desktop virtual reality simulation. *Computers and Education*, 113, 16-27.

Dubovi I, Dagan E, Sader-Mazbar O, Nasar L, & Levy ST. (2018). Nursing students learning the pharmacology of diabetes mellitus with complexity-based computerized models: A quasi-experimental study. *Nurse Education Today, 61*, 175-181.

Levy S.T, Peleg R, Ofeck E, Tabor N, **Dubovi I**, Bluestein S, & Ben-Zur H. (2018). Designing for discovery learning of complexity principles of congestion by driving together in the traffic Jams simulation. *Instructional Science, 46,* 105-132.

Dubovi I. (2018). Designing for online computer-based clinical simulations: evaluation of instructional approaches. *Nurse Education Today, 69*, 67-73.

Dubovi I, Levy, S.T. & Dagan, E. (2018). Situated simulation based learning environment to improve proportional reasoning in nursing students.

a

b

c

Educational Technology. (a) Young patient with type 1 diabetes is learning with interactive educational models that simulate biochemical processes related to diabetes and its medical treatment/ (b) Study in progress, young patient with cancer learns to control side effects of chemotherapeutic treatments via learning with educational technology. (c) Nursing students practicing safety behaviours via immersive Virtual Reality simulation.

International Journal of Science and Mathematics Education, 1-19.

Dagan, E., **Dubovi, I**., Levy, M., Zuckerman-Levin, N., & Levy, S. T. (2019). Adherence to diabetes care: knowledge of biochemical processes has a high impact on glycemic control among adolescents with type-1 diabetes. *Journal of advanced nursing, 75*, 2701-2709.

Dubovi, I. (2019). Online computer-based clinical simulations: The role of visualizations. *Clinical Simulation in Nursing, 33*, 35-41.

Dubovi, I., & Lee, V. R. (2019). Instructional support for learning with agent-based simulations: A tale of vicarious and guided exploration learning approaches. Computers & Education, 142, 103644.

Lee, V. R., & **Dubovi, I**. (2019). At home with data: Family engagements with data involved in type 1 diabetes management. *Journal of the Learning Sciences, 29*, 11-31.

Dubovi, I., Levy, S. T., Levy, M., Zuckerman Levin, N., & Dagan, E. (2020). Glycemic control in adolescents with type 1 diabetes: Are computerized simulations effective learning tools? *Pediatric Diabetes*. *21*, 328-338.

Grants

2015 – 2018	Ministry of Health, Chief Scientist
2019 - 2021	National Leage of Nursing Research Grant
2020 – 2021	Faculty of Medicine Collaborative Grant (with Dr Orit Karnieli-Miller, School of Medicine)
2020 - 2021	Joy Neuro-Welness Research Grant

Prof. Orit Karnieli-Miller, Ph.D.

Department of Medical Education
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Studying Doctor-Patient Relationships, Communication and Medical Professionalism

Positions

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Medical Education

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

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

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

Research

Our primary research and teaching interests are focused on:

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

Publications

Michael, K., Solenko L, Yakhnich, L, **Karnieli-Miller O.** (2018). Significant life events as a journey of meaning making and change among at-risk youths. *Journal of Youth Studies*, 2018; 21, 4, 441-460.

Zisman-Ilani Y, Roe D, Elwyn G, Kupermintz H, Patya N, Peleg I, **Karnieli-Miller O.** (2018). Shared decision making for psychiatric rehabilitation services before discharge from psychiatric hospitals. *Health Commun.* 2018 [Epub ahead of print].

Karnieli-Miller, O, Michael, K., Eidelman, S., and Meitar, D. (2018). What you 'see' is how you communicate: medical students' meaning making of a patient's vignette. *Patient Education and Counseling*, 101, 1645–1653.

Karnieli-Miller, O, Neufeld Kroszynski, G. (2018). The potential of argumentation theory in enhancing patient-centered care in breaking bad news encounters. *Journal of Argumentation in Context,* 7, 120–137.

Karnieli-Miller O, Michael K, Segal O, Steinberger A. (2017). Assessing an intervention focused on enhancing interpersonal communication skills and humor: a multi-method quasi-experiential study among medical students. *Health Commun*. 2017:1-13.

Bril-Barniv, S., Moran, G. S., Naaman, A., Roe, D., **Karnieli-Miller, O.** (2017). A qualitative study examining experiences and dilemmas in concealment and disclosure of people living with serious mental illness. *Qualitative Health Research*, 27(4) 573–583.

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

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

Karnieli-Miller, O., Miron-Shatz, T., Siegal, G., & Zisman-Ilani, Y. (2017). On the verge of implementing

shared decision making in Israel: An overview and future directions. Z. Evid. Fortbild. Qual. Gesundh. Wesen (ZEFQ), http://dx.doi.org/10.1016/j.zefq.2017.05.007

Hart, Y., Czerniak, E., **Karnieli Miller, O**., Mayo, A., Ziv, A., Biegon, A., Citron, A., & Alon, U. (2016). Automated video analysis of non-verbal communication in a medical setting. *Frontiers in Psychology*. 7, 130

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

Czerniak, E., Biegon, A., Ziv, A., **Karnieli-Miller, O.**, Weiser, M., Alon, U., & Citron, A. (2016). Manipulating the placebo response in experimental pain by altering doctor's performance style. *Frontiers in Psychology* 7, 874

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

Zisman-Ilani, Y., Roe, D., **Karnieli-Miller, O.** (2015) Involving patients in decision making: understanding the past and planning the future. Quality in Medicine, 3, 10-12. 2015 (Hebrew)

Michael K., Solenko L., **Karnieli-Miller, O.** (2015). Perspectives of significant life events among at-risk youth. *Society and Welfare*, 35, 537-562 (*Hebrew*).

Karnieli-Miller, O. Nissim, G., Goldberg, M. (2015). "It's In the Cards:" The contribution of illustrated metaphor cards to exploring values within narratives. *Qualitative Health Research,* 1-14.

Reviews

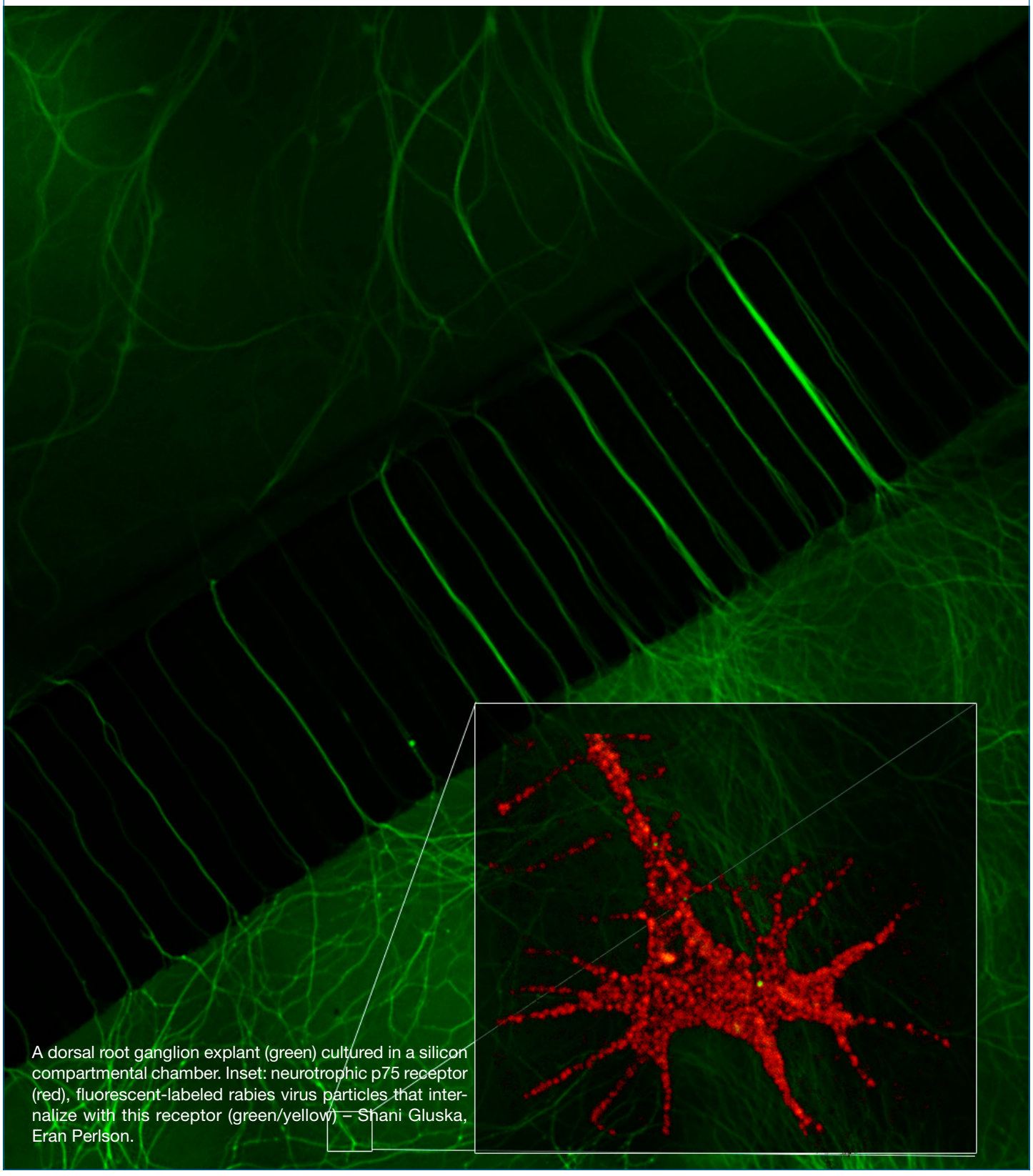
Yamin, A., Roe, D., **Karnieli-Miller, O**. (2017). Reviewing from the inside and out – the processes of parents of people coping with a mental illness enrolled in a group intervention to reduce self-stigma. In A. Shalev and N. Lidor-Hadass (Eds.,) *From Invisibility to Partnership: Paths to Recovery and Coping with Mental Illness in the Family* (Hebrew). Kiryat Ono: Ono Academic College, pp 117-130 (vol 2).

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

Grants and Chapters

2016–2020	Preventing burnout and enhancing professionalism in the surgical unit care and medical teams
2017–2019	*Israel National Institute for Health Policy Research*, Enhancing Patient Centered Care through Understanding Barriers and Promotors to Implementing Shared Decision Process in Diabetes (with Eddy Karnieli & Yaara Zisman-Ilani)
2017–2020	*The Israel National Institute for Health Policy Research*, Improving Patients' Quality of Care through Enhancing Physicians' Professionalism and Preventing Burnout in a Surgical Division (with Guy Lahat, Nathaniel Laor, Keren Michael, Daniel Hamiel)
2020–2021	Faculty of Medicine Collaborative Grant (with Dr Ilana Dubovi, School of Health Professions)

Nervous System and Brain Disorders



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

Prof. Ruth Ashery-Padan, Ph.D.

Department of Human Molecular Genetics and Biochemistry
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Investigating the Molecular Basis of Visual System Development

Positions

Professor, Sackler Faculty of Medicine

Committee Member, Israel Society of Developmental Biology

Research

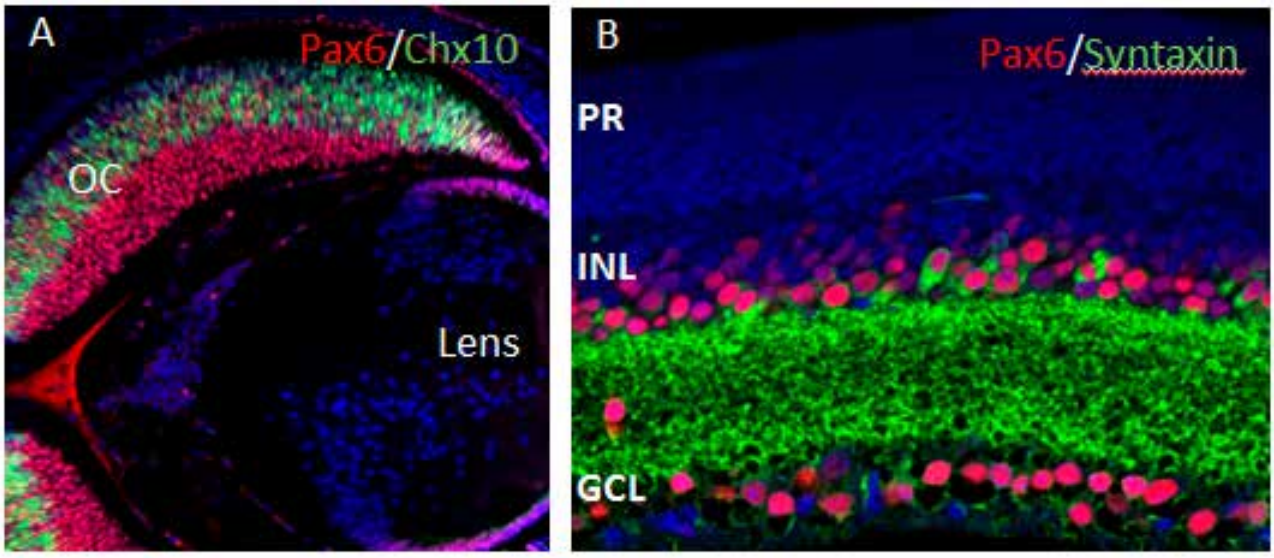
We study the gene networks that transform the embryonic cells into a complex, differentiated organ. We focus on exploring this question by studying the process of eye development as a model for organogenesis. We apply cutting-edge technologies including mouse genetic tools (Cre/loxP), molecular biology,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

Publications

Lam PT, Padula SL, Hoang TV, Poth JE, Liu L, Liang C, LeFever AS, Wallace LM, **Ashery-Padan R**, Riggs PK, Shields JE, Shaham O, Rowan S, Brown NL, Glaser T, Robinson ML. Considerations for the use of Cre recombinase for conditional gene deletion in the mouse lens. *Hum Genomics*. 2019;13:10.

Cohen-Tayar Y, Cohen H, Mitiagin Y, Abravanel Z, Levy C, Idelson M, Reubinoff B, Itzkovitz S, Raviv S, Kaestner KH, Blinder P, Elkon R, **Ashery-Padan R**. Pax6 regulation of Sox9 in the mouse retinal pigmented epithelium controls its timely differentiation and choroid vasculature development. *Development*. 2018;145(15).

Swisa A, Avrahami D, Eden N, Zhang J, Feleke E, Dahan T, Cohen-Tayar Y, Stolovich-Rain M,



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.

Kaestner KH, Glaser B, **Ashery-Padan R**, Dor, Y. PAX6 maintains beta cell identity by repressing genes of alternative islet cell types. *J Clin Invest* 2017;127, 230-243.

Remez LA, Onishi A, Menuchin-Lasowski Y, Biran A, Blackshaw S, Wahlin KJ, Zack DJ, **Ashery-Padan R**. Pax6 is essential for the generation of late-born retinal neurons and for inhibition of photoreceptor-fate during late stages of retinogenesis. *Dev Biol*, 2016; doi:10.1016/j.ydbio.2017.09.030.

Menuchin-Lasowski Y, Oren-Giladi P, Xie Q, Ezra-Elia R, Ofri R, Peled-Hajaj S, Farhy C, Higashi Y, Van de Putte T, Kondoh H, Huylebroeck D, Cvekl A, **Ashery-Padan R**. Sip1 regulates the generation of the inner nuclear layer retinal cell lineages in mammals. *Development*. 2016;143:2829-41.

Grants

2014-2019 Israel Science Foundation

Dr. Avraham Ashkenazi, Ph.D.

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Tel Aviv University

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Understanding the Cell Biology of Misfolded Proteins That Cause Neurological Disorders

Positions

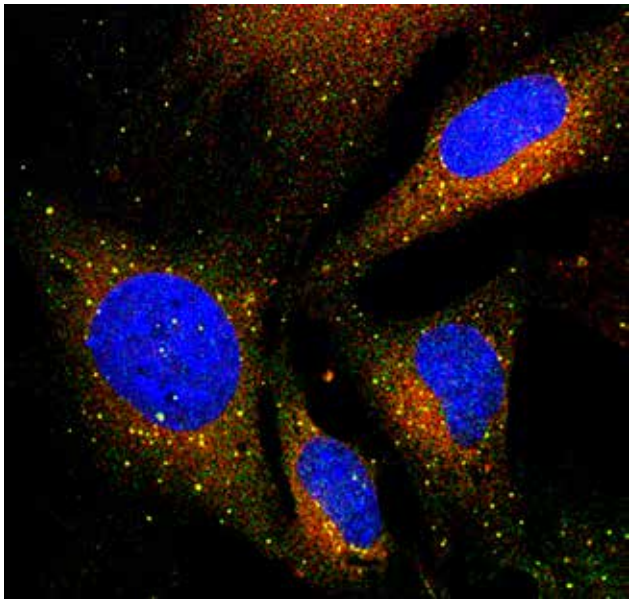
Senior Lecturer, Sackler Faculty of Medicine

Faculty Member, Sagol School of Neuroscience

Director, Biomed@TAU Research Hub, Disorders of the Mind & Brain

Research

Our research utilizes state-of-the-art technologies to elucidate cellular mechanisms of neurological disorders. Some of these disorders progress late in life, such as Huntington's disease and Parkinson's disease. A common characteristic in these disorders is the accumulation of proteins that are not folded properly and can form aggregates in cells. Research in the lab is currently focused on the ubiquitin and autophagy pathways, the main routes by which aggregate-prone proteins are degraded. Also, these pathways are important for cells to cope with various stress conditions. We aim to elucidate novel regulatory pathways of protein homeostasis in cells to better understand the basis of these devastating diseases and to identify future therapeutic targets.



Pre-autophagosomal membrane structures in neuronal cells derived from the mouse striatum detected by the colocalization of the autophagy proteins WIPI2 (red) and ATG16L1 (green) in discrete puncta. Cells were stimulated with nutrient deprivation to induce autophagy.

Publications

Vicinanza, M., Korolchuk, V. I., **Ashkenazi, A.**, Puri, C., Menzies, F. M., Clarke, J. H., and Rubinsztein, D. C. (2015) PI(5)P regulates autophagosome biogenesis. *Molecular Cell* 57, 219-234

Bento, C. F., **Ashkenazi, A.**, Jimenez-Sanchez, M., and Rubinsztein, D. C. (2016) The Parkinson's disease-associated genes ATP13A2 and SYT11 regulate autophagy via a common pathway. *Nature Communications* 7, 11803

Ashkenazi, A., Bento, C. F., Ricketts, T., Vicinanza, M., Siddiqi, F., Pavel, M., Squitieri, F., Hardenberg, M. C., Imarisio, S., Menzies, F. M., and Rubinsztein, D. C. (2017) Polyglutamine tracts regulate beclin 1-dependent autophagy. *Nature* 545, 108–111

Puri, C., Vicinanza, M., **Ashkenazi, A.**, Gratian, M. J., Zhang, Q., Bento, C. F., Renna, M., Menzies, F. M. and Rubinsztein, D. C. (2018) The RAB11A-Positive Compartment Is a Primary Platform for Autophagosome Assembly Mediated by WIPI2 Recognition of PI3P-RAB11A. *Developmental Cell* 45, 114-131

Reviews

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Grants

2018-2019	FEBS Fellowship Follow-up Research Fund
2018-2021	Azrieli Foundation
2020-2025	Koret Foundation Global Collaboration on Neurodegenerative Disease Research

Prof. Hagit Eldar-Finkelman, Ph.D.

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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 ad endocytosis. Research methods combine cell biology, molecular biology and biochemistry disciplines together with bioinformatics and computational biology.

Publications

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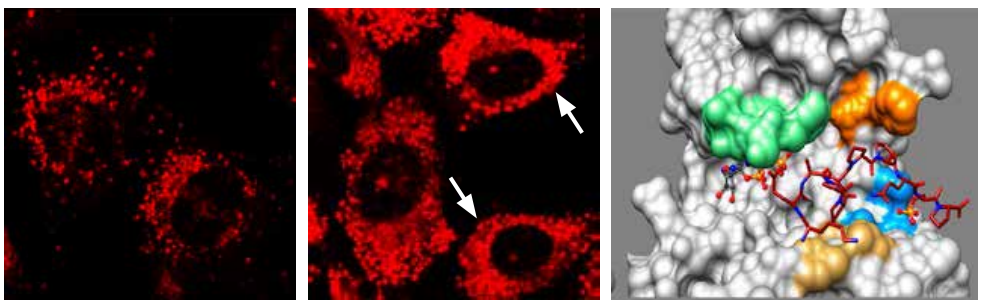
Grants

2017-2020	Israel Science Foundation
2020-2025	Koret Foundation Global Collaboration on Neurodegenerative Disease Research



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).

Dr. Jason Friedman, Ph.D.

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Enhancing Motor Learning and Motor Control in Typically Developing and Clinical Populations

Positions

Senior Lecturer, Sackler Faculty of Medicine

Member, Sagol School of Neuroscience

Head, M.Sc. Program in Physical Therapy

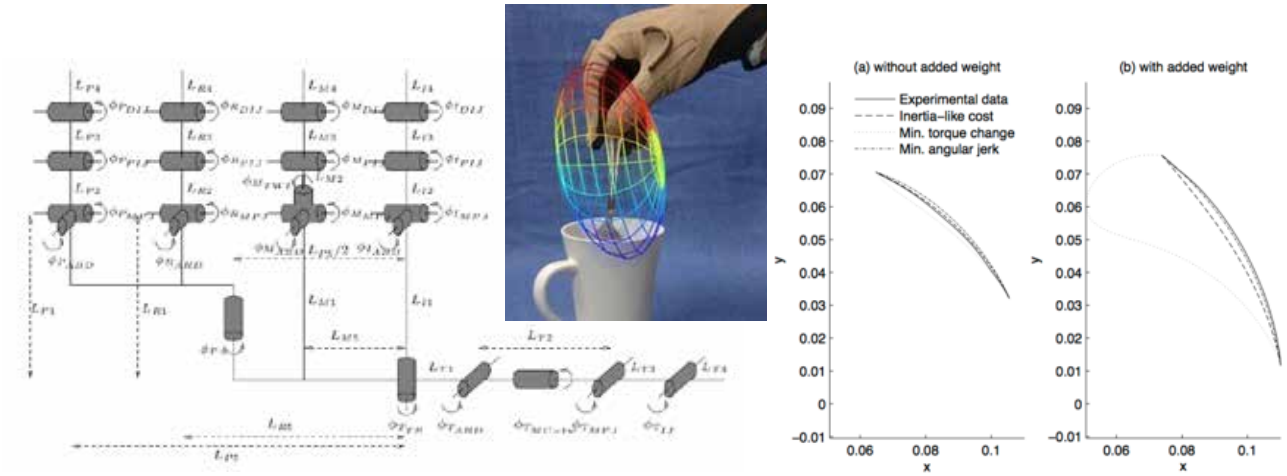
Research

We study human movement in typical and clinical populations, with a focus on arm movements, grasping and finger movements. We are interesting in fundamental questions such as how we learn to make new movements, how children develop motor skills during development, and how our motor function is affected by disorders such as Parkinson's disease, stroke, dystonia or cerebral palsy. We also study the interconnection between decision making and human movements. Our approach is to construct models that describe movement and force generation by the hand and arm, considering 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

J. Friedman and M. Korman. Observation of an expert model induces a skilled movement coordination pattern in a single session of intermittent practice. *Scientific Reports*, 9: 4609, 2019

O. Ezrati, **J. Friedman** and R. Dar. Attenuation of access to internal states in high obsessive-compulsive individuals might increase susceptibility



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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H. Dempsey-Jones, D.B. Wesselink, **J. Friedman**, T.R. Makin. Organised toe maps in extreme foot users. *Cell Reports*, 28(11): 2748 – 2756, 2019

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Zopf, R., **Friedman, J.**, and Williams, M. A. (2015). The plausibility of visual information for hand ownership modulates multisensory synchrony perception. *Experimental Brain Research*, 233, 2311–2321.

Grants

2018-2020 Minducate Science of Learning scholarship, Tel Aviv University – Smart Robotic Device for Enhancing Motor and Cognitive Learning of Children With Special Needs

2019-2021 MILA – Mind and language, Sagol School of Neuroscience, Tel Aviv University – Kinematic factors in the acquisition of sign language

2020-2023 German-Israeli Foundation for Scientific Research and Development (GIF) – Accelerating motor learning with computational scaffolding

Prof. Illana Gozes, Ph.D.

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Neuronal Plasticity and Nerve Cell Protection in Disease

Positions

Professor Emeritus of Clinical Biochemistry, Sackler Faculty of Medicine

Lily and Avraham Gildor Chair for the Investigation of Growth Factors

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

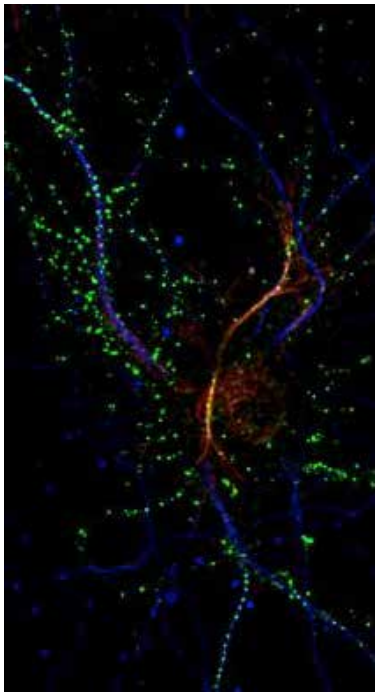
Editor-in-Chief, *Journal of Molecular Neuroscience*

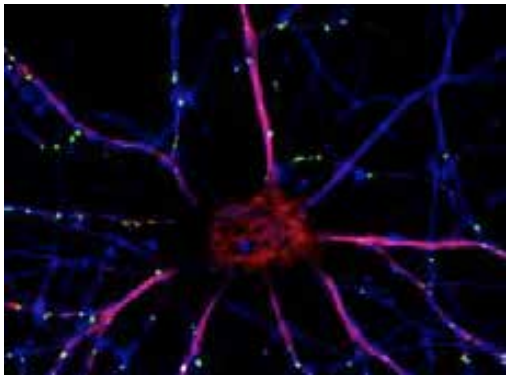
Member, MALAG (Israeli Council of Higher Education)

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 neuroprotetive 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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Gozes I, Ivashko-Pachima Y, Sayas CL. ADNP, a Microtubule Interacting Protein, Provides Neuroprotection Through End Binding Proteins and Tau: An Amplifier Effect. *Front Mol Neurosci*. 2018;11(151).

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Grants

2016-2019 ERA-NET NEURON – Modelling syndromic autism caused by mutations in the ADNP gene (with Frank Kooy, Pierre-Luc Germain, Christopher E. Pearson)

2016-2019 Ministry of Science and Technology, Israel, Eshkol Fellowships (Shlomo Sragovich, Gal Hacohen Kleiman, student fellowships)

2017-2020 NSF-BSF (US-Israel BSF) - Computational Approaches to Assess Replicability of Neurobehavioral, Yoav Benjamini, Ilan Golani, Jackson Labs.

2019-2021 Ministry of Defense Israel, Science Unit, Brain Trauma Biomarkers

2019-2022 ERA-NET Neuron, Pleiotropic Effects of ADNP in Mental Disorders (Ministry of Health)

Dr. Yoni Haitin, Ph.D.

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Sackler Faculty of Medicine
Sagol School of Neuroscience

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

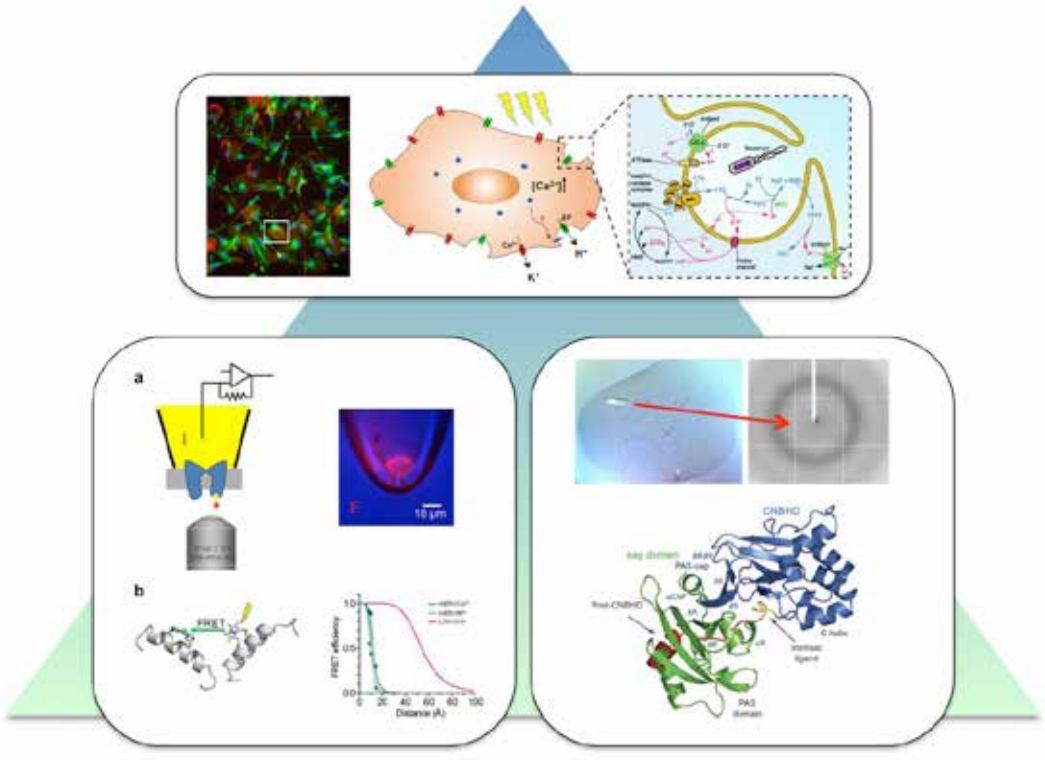
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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

Publications

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Mashahreh B, Hassouna F, Soudah N, Cohen-Kfir E, Strulovich R, **Haitin Y**, Wiener R. Trans-binding of UFM1 to UBA5 stimulates UBA5 homodimerization and ATP binding. FASEB J. 2018;32:2794-2802

Padala P., Soudah N., Giladi M., **Haitin Y**., Isupov M.N., Wiener R. (2017) The crystal structure and conformations of an unbranched mixed tri-ubiquitin chain containing K48 and K63 linkages. *J Mol Biol.,* accepted for publication.

Tobelaim W.S., Dvir M., Lebel G., Cui M., Buki T., Peretz A., Marom M., **Haitin Y**., Logothetis D.E., Hirsch J.A., Attali B. (2017). Ca2+-Calmodulin and PIP2 interactions at the proximal C-terminus of Kv7 channels. *Channels*., accepted for publication.

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Giladi M., Lee S.Y., Ariely Y., Teldan Y., Granit R., Strulovich R., **Haitin Y**., Chung K.Y. and Khananshvili D. (2017). Structure-encoded dynamics of regulatory diversity in sodium-calcium exchanger (NCX) isoforms. *Sci Rep.,* 7, 993.

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Giladi M.*, Edri I., Goldenberg M., Newman H., *Strulovich R.,* Khananshvili D., **Haitin Y.***, Loewenstein A. (2017). Purification and characterization of human dehydrodolychil diphosphate synthase (DHDDS) overexpressed in E. *coli. Protein Expr Purif.,* **132**, 138-142. *Co-corresponding author.

Tobelaim W.S., Dvir M., Lebel G., Cui M., Buki T., Peretz A., *Marom M.,* **Haitin Y**., Logothetis D.E., Hirsch J.A., Attali B. (2017). Competition of calcified calmodulin N lobe and PIP2 to an LQT mutation site in Kv7.1 channel. *PNAS*, **114**, E869–E878.

Grants

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

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

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

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Brain Mechanisms of Human Emotion Generation & Regulation

Laboratory for Brain and Emotion Experience

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

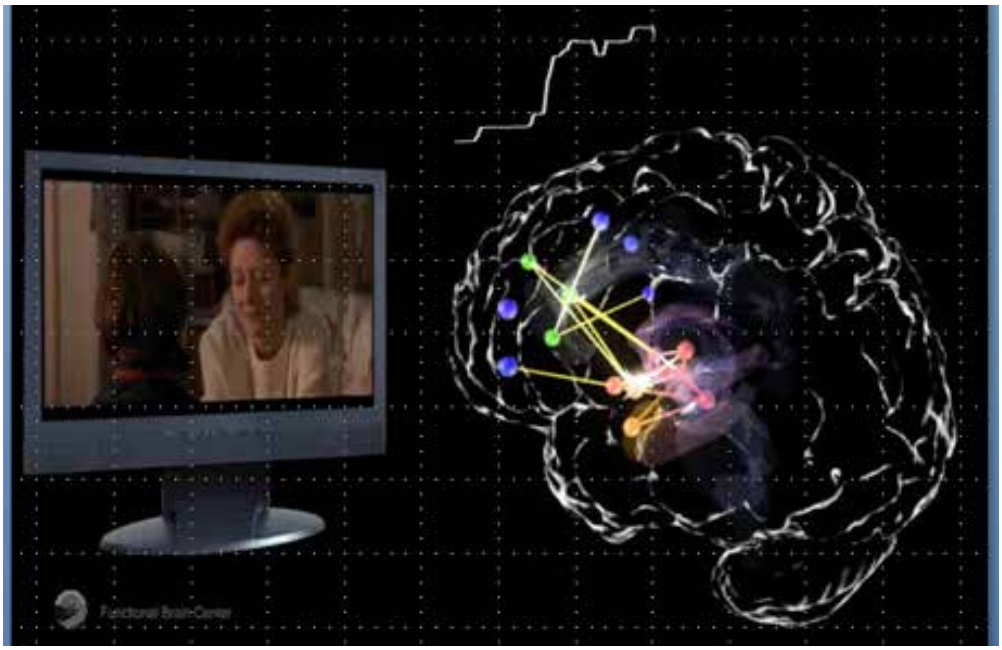
Positions

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

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

Research

Investigating brain mechanisms underlie generation and regulation of the human emotional experience, in healthy and pathological states. The research is based on measuring indices of brain structure and functional dynamics via MRI (functional-MRI, DTI and Volumetric-MRI) and separate or simultaneous recording of electrical signals (scalp-EEG and intracranial-EEG). The characterization of individual brain response is based on correlating neural activity and connectivity with behavioral and physiological measurements of emotionality (e.g. heart rate, hormone secretion, genetic expression, skin conductance, eye movements and verbal output). Induction of emotional states is achieved via film and music media, inter-personal interactions, and interactive social games. Regulation of emotions is modulated via on-line feedback protocols from brain signals in a closed loop set-up (i.e. *NeuroFeedback*). The lab is also involved in studies aim to advance translation while focusing on neural markers of vulnerability and recovery with regard to post



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).

traumatic disorders (e.g. anxiety and depression), developmental disorders (e.g. schizophrenia and personality) and neurodegenerative disorders (e.g. parkinson disease). An essential part of this aspect of our work is the development of advanced new tools for acquiring and analyzing whole brain neural measurements; including applying multi-scale mapping for capturing dynamics of brain networks.

Publications

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Okon-Singer, H., **Hendler, T.,** Pessoa, L., & Shackman, A.J. (2015). The neurobiology of emotion–cognition interactions: fundamental questions and strategies for future research. *Frontiers in Human Neuroscience* 9, 58.

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Raz, G., Hagin, B., & **Hendler, T**. "E-Motion Pictures of the Brain: Recursive Paths between Affective Neuroscience and Film Studies,"Arthur P. Shimamura (editor), Psychocinematics: Exploring Cognition at the Movies (pp. 285-313). (New York: Oxford University Press

Gilam, G., & **Hendler, T**. Deconstructing Anger in the Human Brain. In Current Topics in Behavioral Neurosciences. Springer Berlin Heidelberg, 2016.

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Grants

2020-2024 Israel Precision Medicine Partnership Program (IPMP), with the Israel Science Foundation (with Noam Shomron)

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Neuronal Signaling Dynamics in the Living Brain

Positions

Senior Lecturer, Sackler Faculty of Medicine

Sagol School of Neurosciecne.

Research

Neurons in the brain have a remarkable capacity to undergo changes in function and structure throughout life. How does sensory experience alter neuronal activity and ultimately triggers behavioral adaptations? We address this question by studying the role of neuronal biochemical signaling dynamics in experience dependent plasticity. We use advanced microscopy, gene editing and in vivo imaging to unravel protein signaling dynamics and neuronal activity in awake behaving mice.

Reseach in the lab focuses on:

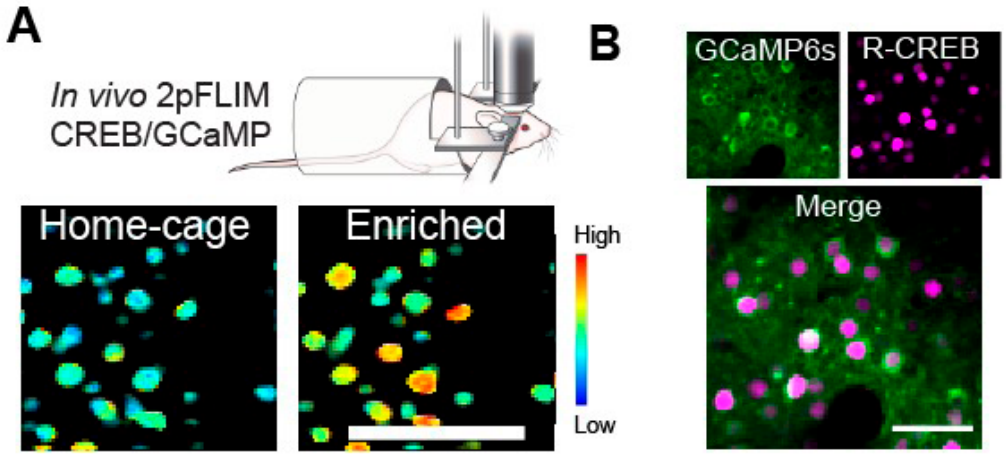
- Experience dependent dynamics of activity dependent transcription factors.
- Synapse to nucleus communication in intact cortical circuits.
- Dynamics of epigenetics regulation in the brain
- Development of new techniques for monitoring and manipulation of neuronal signaling in living mice.

Publications

Laviv, T#., Scholl, B., Parra-Bueno, P., Foote, B., Zhang C., Yan, L., Hayano, Y., Chu, J., Yasuda, R#. (2020). In vivo imaging of the coupling between neuronal and CREB activity in the mouse brain. *Neuron* 105. #Co-corresponding author.

2. **Laviv, T.** *, Kim, B.B. *, Chu, J., Lam, A.J., Lin, M.Z., and Yasuda, R. (2016). Simultaneous dual-color fluorescence lifetime imaging with novel red-shifted fluorescent proteins. *Nature Methods 13.* *Co-first authors.

3. Chu, J., Oh, Y., Sens, A., Ataie, N., Dana, H., Macklin, J.J., **Laviv, T.**, Welf, E.S., Dean, K.M., Zhang, F., et al. (2016). A bright cyan-excitable orange fluorescent protein facilitates dual-emission microscopy and enhances bioluminescence imaging in vivo. *Nature Biotechnology.* 34.



In vivo imaging of CREB activity; (A) Example images of CREB activity, depicted as a lifetime heat map before and after environmental enrichment. (B) *In vivo* image of L2/3 cells dually expressing red-shifted CREB sensor and the calcium indicator GCaMP6s.

Harward, S.C., Hedrick, N.G., Hall, C.E., Parra-Bueno, P., Milner, T.A., Pan, E., **Laviv, T.**, Hempstead, B.L., Yasuda, R., and McNamara, J.O. (2016). Autocrine BDNF-TrkB signalling within a single dendritic spine. *Nature*. 538.

Laviv, T., Vertkin, I., Berdichevsky, Y., Fogel, H., Riven, I., Bettler, B., Slesinger, P.A., and Slutsky, I. (2011). Compartmentalization of the GABAB receptor signaling complex is required for presynaptic inhibition at hippocampal synapses. *Journal of Neuroscience*. 31.

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Grants

2020-2021 KDE-PD Grant for Research on Parkinson's Disease

Prof. Dario G. Liebermann, Ph.D.

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Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Physical Therapy

Movement Science Lab., Department of Physical Therapy

Associate Editor, Journal of Electromyography & Kinesiology

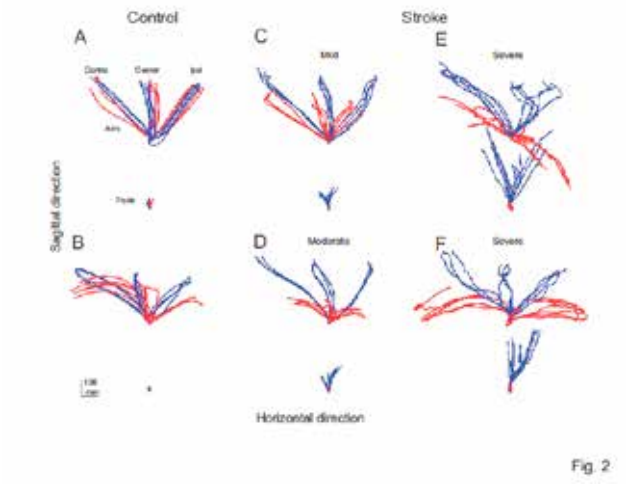
Research

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

Publications

Davidowitz I, Parmet Y, Frenkel-Toledo S, Baniña MC, Soroker N, Solomon JM, **Liebermann DG**, Levin MF, Berman S. Relationship between spasticity and upper-limb movement disorders in individuals with subacute stroke using stochastic spatiotemporal modeling. *Neurorehabil Neural Repair*. 2019;33(2):141-152.

Levin MF, Baniña MC, Frenkel-Toledo S, Berman S, Soroker N, Solomon JM, **Liebermann DG**. Personalized upper limb training combined with anodal-tDCS for sensorimotor recovery in spastic hemiparesis: study protocol for a randomized controlled trial. *Trials*. 2018;19:7.



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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Chapters

Liebermann, D.G. and Franks I.M. "Video-based technologies, substitution of reality and performance feedback"; In M. Hughes and I.M. Franks (Eds.), *The Essentials of Performance Analysis,* Routledge: London, Chapter 4, 2015.

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Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

Position

Professor Emeritus, Sackler Faculty of Medicine

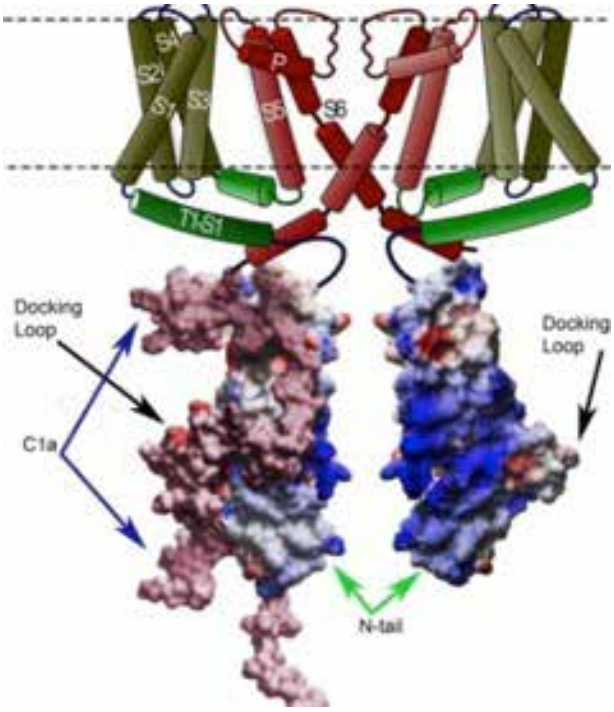
Research

We have a long standing interest in the study the molecular mechanisms of modulation of voltage gated K^+ (Kv) channels by interaction with signaling molecules. We were first to describe modulation of a brain Kv channel by major protein components of the exocytotic machinery. Since then our main focus is the role of Kv channels in transmitter release, finding that it may be far more than just repolarizing the membrane potential: independent of K^+ currents but mediated by protein-protein interactions with the exocytic SNARE proteins. The dual actions of the channel, through its currents and via its interaction with SNAREs, in combination, may reinforce the known activity dependence of dense core vesicle exocytosis.

Main research projects currently in the lab:

1) Study of the novel role of Kv2.1 potassium channel in insulin secretion from pancreatic islet β cells, as a target for novel drug design for the treatment of type-2 diabetes;

2) Study of structure-function and modulations by presynaptic modulators of Kv2.1 and other Kv channels, specifically KCNQ2 and KCNQ3, important in axonal and synaptic excitability.



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

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

Research methods:

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

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

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

Publications

Singer-Lahat D, Barak-Broner N, Sheinin A, Greitzer-Antes D, Michaelevski I, **Lotan I.** The dual function of the polybasic juxtamembrane region of syntaxin 1A in clamping spontaneous release and stimulating Ca2+-triggered release in neuroendocrine cells. *J Neurosci* 2017, 1541-17.

Review

Vertkin I, Styr B, Slomowitz E, Ofir N, Shapira I, Berner D, Fedorova T, Laviv T, Barak-Broner N, Greitzer-Antes D, Gassmann M, Bettler B, **Lotan I**, Slutsky I. GABAB receptor deficiency causes failure of neuronal homeostasis in hippocampal networks. *Proc. Natl Acad Sci USA*. 2015;112:E3291-9.

Siloni S, Singer-Lahat D, Esa M, Tsemakhovich V, Chikvashvili D, **Lotan I**. Regulation of the neuronal KCNQ2 channel by Src – a dual rearrangement of the cytosolic termini underlies bidirectional regulation of gating. *J Cell Sci*. 2015;128, 3489-3501.

Singer-Lahat D, Barak-Broner N, Sheinin A, Greitzer-Antes D, Michaelevski I, **Lotan I**. The dual function of the polybasic juxtamembrane region of syntaxin 1a in clamping spontaneous release and stimulating Ca2+-triggered release in neuroendocrine cells. *J Neurosci*. 2018;38:220-231.

Prof. Yuval Nir, Ph.D.

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Sleep and Its Relation to Cognition

Position

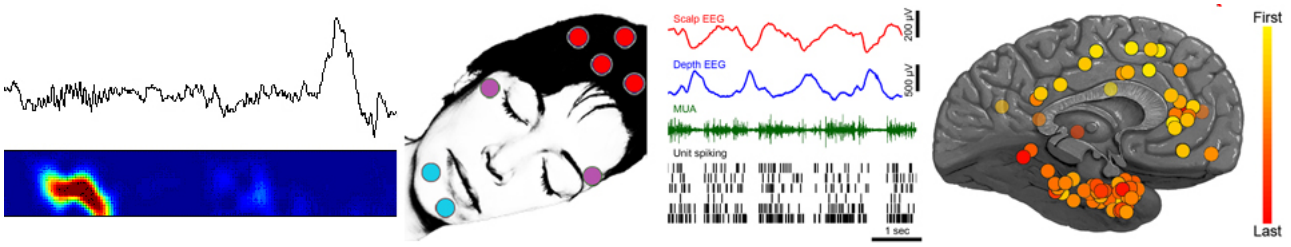
Associate Professor, Sackler Faculty of Medicine

Research

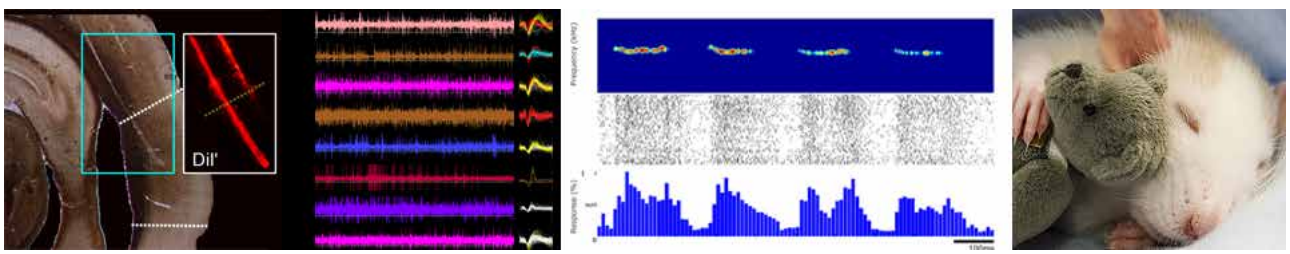
Sleep is a universal behavior that is present across the animal kingdom. We spend a third of our lives sleeping, disconnected from the world around us. Our sleep is closely regulated so that when we are sleep deprived, we ultimately compensate with longer, deeper sleep. Sleep helps our cognitive performance, 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

Magidov E, Hayat H, Sharon O, Andelman F, Katzav S, Lavie P, Tauman R, **Nir Y**. Near-total absence of REM sleep co-occurring with normal cognition: an update of the 1984 paper. *Sleep Med*. 2018;52:134-137.

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Nir Y, Andrillon T, Marmelshtein A, Suthana N, Cirelli C, Tononi G, Fried I. Selective neuronal lapses precede human cognitive lapses following sleep deprivation. *Nat Med.* 2017, doi: 10.1038/nm.4433.

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Andrillon T, **Nir Y**, Cirelli C, Tononi G, Fried I.Single-neuron activity and eye movements during human REM sleep and awake vision. *Nat Commun*. 2015;6:7884.

Nir Y, Vyazovskiy VV, Cirelli C, Banks MI, Tononi G. Auditory responses and stimulus-specific adaptation in rat auditory cortex are preserved across NREM and REM sleep. *Cerebral Cortex*. 2015;25:1362-78.

Grants

2015-2020	Israel Science Foundation grant
2020-2025	ERC Consolidator Grant

Prof. Daniel Offen, Ph.D.

Department of Human Molecular Genetics and Biochemstry
Felsenstein Medical Research Center
Sackler Faculty of Medicine
Sagol School of Neuroscience

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Translational Neuroscience

Positions

Professor, Sackler Faculty of Medicine

Research

We focus on developing **cell-based and gene-based therapies for neurodegenerative diseases**. We use advanced methods, such as CRISPR/Cas9 for *in vivo* gene modification, and take advantage of multiple platforms for the delivery of therapeutics into the CNS, including mesenchymal stem cells, exosomes and peptides. Using cell cultures and animal models, we evaluate the effect of gene modification on cognition and behaviour, as well as on disease-related biochemical and histological features.

Publications

Molcho L ,Ben-Zur T ,Barhum Y ,Angel A ,Glat M ,**Offen D**. Combined gene therapy to reduce the neuronal damage in the mouse model of focal ischemic injury. J Mol Neurosci. 2018

Molcho L, Ben-Zur T, Barhum Y, **Offen D**. DJ-1 based peptide, ND-13, promote functional recovery in mouse model of focal ischemic injury. PLoS One. 2018;13(2):e0192954.

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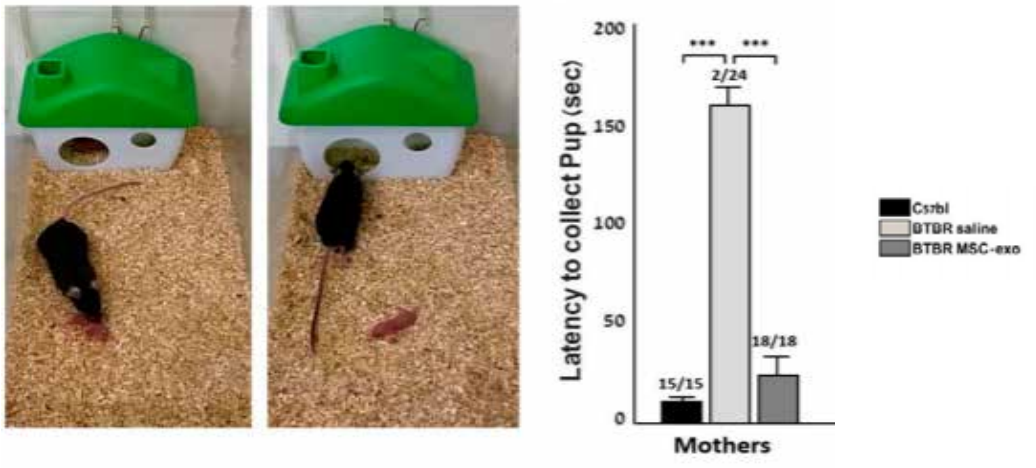
Betzer O, Perets N, Angel A, Motiei M, Sadan T, Yadid G, **Offen D**, Popovtzer R. In vivo neuroimaging of exosomes using gold nanoparticles. ACS Nano. 2017; 11(11):10883-10893.

Fellner A, Barhum Y, Angel A, Perets N, Steiner I, **Offen D**, Lev N. Toll-like receptor-4 inhibitor TAK-242 attenuates motor dysfunction and spinal cord pathology in an Amyotrophic Lateral Sclerosis mouse model. Int J Mol Sci. 2017;18(8).

Segal-Gavish H, Barzilay R, Rimoni O, **Offen D**. Voluntary exercise improves cognitive deficits in female dominant-negative DISC1 transgenic mouse model of neuropsychiatric disorders. World J Biol Psychiatry. 2017:1-10.

Segal-Gavish H, Barzilay R, Rimoni O, **Offen D**. Voluntary exercise improves cognitive deficits in



Intra-nasal delivery of exosomes, delivered from human mesenchymal cells, improves maternal pup retrieval in a mice model of autism (Perets et al 2018).

female dominant-negative DISC1 transgenic mouse model of neuropsychiatric disorders. World J Biol Psychiatry. 2017:1-10.

Segal-Gavish H, Danino O, Barhum Y, Ben-Zur T, Shai E, Varon D, **Offen D**, Fischer B. A multifunctional biocompatible drug candidate is highly effective in delaying pathological signs of Alzheimer's Disease in 5XFAD Mice. J Alzheimers Dis. 2017; 58:389-400.

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Gross A, Benninger F, Madar R, Illouz T, Griffioen K, Steiner I, **Offen D**, Okun E. Toll-like receptor 3 deficiency decreases epileptogenesis in a pilocarpine model of SE-induced epilepsy in mice. Epilepsia. 2017;58(4):586-596.

Barzilay R, Ventorp F, Segal-Gavish H, Aharony I, Bieber A, Dar S, Vescan M, Globus R, Weizman A, Naor D, Lipton J, Janelidze S, Brundin L, **Offen D**. CD44 deficiency is associated with increased susceptibility to stress-induced anxiety-like behavior in mice. J Mol Neurosci. 2016;60(4):548-558.

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Benkler C, Barhum Y, Ben-Zur T, **Offen D**. Multifactorial gene therapy enhancing the glutamate uptake system and reducing oxidative stress delays symptom onset and prolongs survival in the SOD1-G93A ALS mouse model. J Mol Neurosci. 2016;58(1):46-58.

Benninger F, Glat MJ, **Offen D**, Steiner I. Glial fibrillary acidic protein as a marker of astrocytic activation in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis. J Clin Neurosci. 2016;26:75-8.

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Segal-Gavish H, Karvat G, Barak N, Barzilay R, Ganz J, Edry L, Aharony I, **Offen D**, Kimchi T. Mesenchymal stem cell transplantation promotes neurogenesis and ameliorates autism related behaviors in BTBR mice. Autism Res. 2016;9(1):17-32.

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Lev N, Barhum Y, Lotan I, Steiner I, **Offen D**. DJ-1 knockout augments disease severity and shortens survival in a mouse model of ALS. PLoS One. 2015;10(3):e0117190.

Getter T, Zaks I, Barhum Y, Ben-Zur T, Böselt S, Gregoire S, Viskind O, Shani T, Gottlieb H, Green O, Shubely M, Senderowitz H, Israelson A, Kwon I, Petri S, **Offen D**, Gruzman A. A chemical chaperone-based drug candidate is effective in a mouse model of amyotrophic lateral sclerosis (ALS). ChemMedChem. 2015;10(5):850-61.

Aharony I, Ehrnhoefer DE, Shruster A, Qiu X, Franciosi S, Hayden MR, **Offen D**. A Huntingtin-based peptide inhibitor of caspase-6 provides protection from mutant Huntingtin-induced

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Reviews

Volkman R, **Offen D**. Concise review: Mesenchymal stem cells in neurodegenerative diseases. Stem Cells. 2017; 35(8):1867-1880.

Grants

2017-2019 Ministry of Agriculture and Rural Development, A. Helman, co-PI

Dr. Moshe Parnas, Ph.D.

Department of Physiology and Pharmacology
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Sagol School of Neuroscience

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Neural Circuits and Olfactory Perception in Drosophila

Position

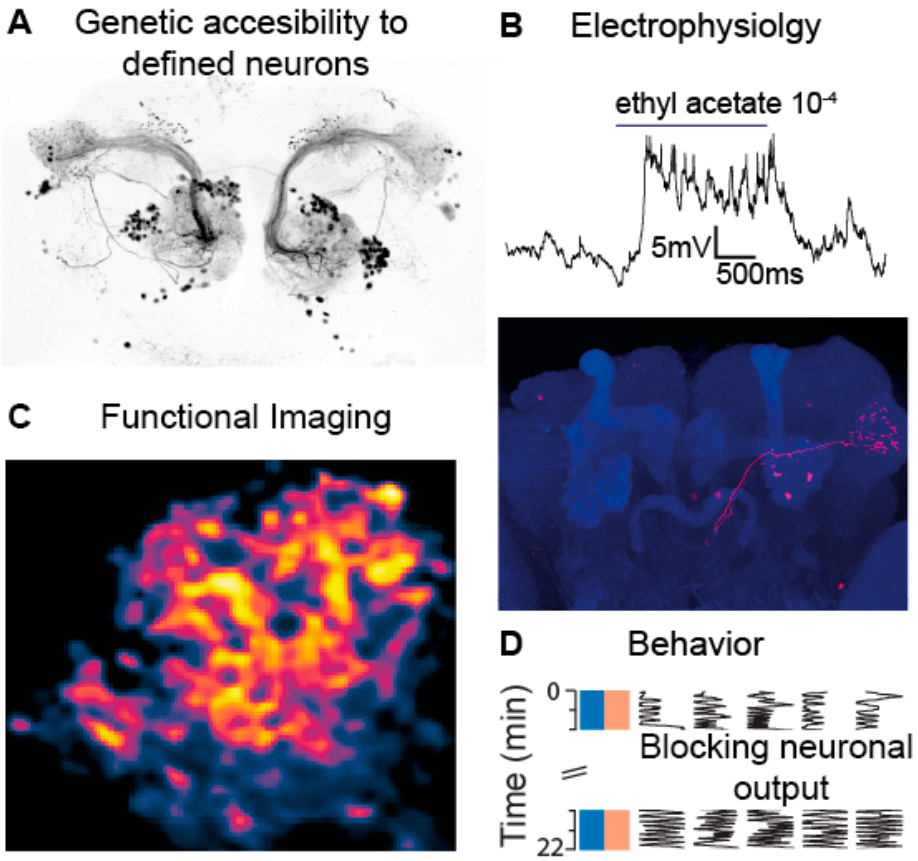
Senior Lecturer, Sackler Faculty of Medicine and Sagol School of Neuroscience

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.



Drosophila as a model system for systems neuroscience. **A.** Using the genetic tools available for *Drosphila* 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 manipulatin of the activity of neural circuits in behaving animals.

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

Lerner H., Rozenman B., Huetteroth W., and **Parnas M.**, (2020). Differential role for a defined lateral horn neuron subset in naïve odor valence in Drosophila. Sci Rep. 2020;10(1):6147.

Rozenfeld E., Lerner H., and **Parnas M.**, (2019). Muscarinic modulation of antennal lobe GABAergic local neurons shapes odor coding and behavior. Cell Reports, 29, 3253-3265.e4.

Bielopolski N., Amin H., Apostolopoulou AA., Rozenfeld E., Lerner H., Huetteroth W., Lin AC. And **Parnas M.** (2019). Inhibitory muscarinic acetylcholine receptors enhance aversive olfactory conditioning in adult Drosophila. eLife, 8: e48264.

Har-Gil H., Golgher L., Israel S., Kain D., Cheshnovsky O., **Parnas M.**, and Blinder P. (2018). PySight: plug and play photon counting for fast continuous volumetric intravital microscopy. Optica, 9:1104-1112.

Bentzur A., Shmueli A., Omesi L., Ryvkin J., Knapp JM., **Parnas M.**, Davis FP., Shohat-Ophir G. (2018). Odorant binding protein 69a connects social interaction to modulation of social responsiveness in Drosophila. PLoS Genetics, 9;14:e1007328.

Grants

2017-2019	United States-Israel Binational Science Foundation
2016-2020	ERC Starting Grant
2018-2023	ISF, Exploring the physiological role of the voltage dependence of muscarinic G protein coupled receptors in Drosophila learning and memory
2019-2022	DFG, Linking the molecular organization of active zones to temporal neural coding
2020	MAFAT, Re-wiring the Drosophila Melanogaster pheromone olfactory system to search and detect specific odor signals

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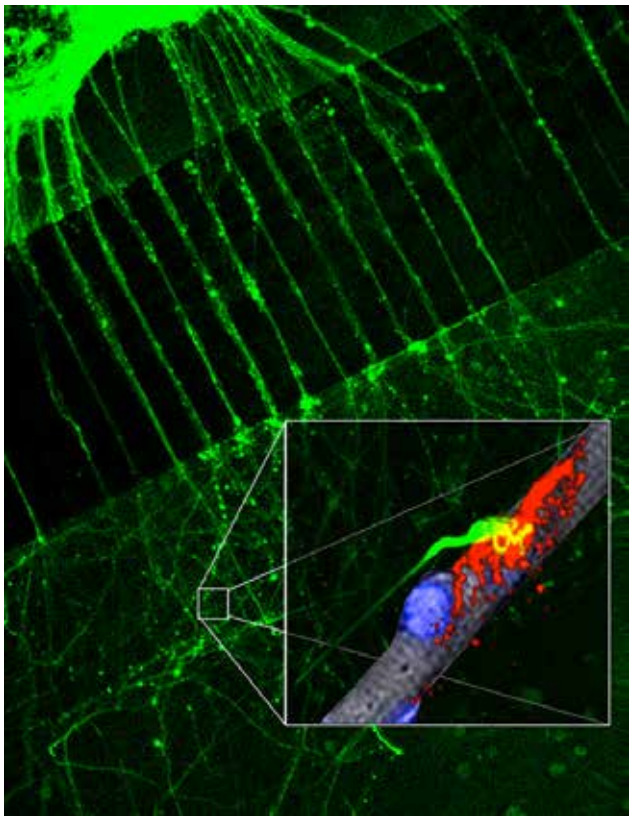
Molecular Mechanisms of Neurodegeneration

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our lab's research is focused on understanding molecular mechanisms of neuro-degeneration using primary rodent cultures, patient's iPSC derived motor neurons and in vivo transgenic mice models. Our lab's main goal, using advanced microscopy, biochemistry, genetic and pharmacological approaches, is to gain knowledge that will elucidate the critical events leading to neuron degeneration and neuromuscular-junction (NMJ) disruption in Amyotrophic Lateral Sclerosis (ALS). This knowledge hopefully will be the basis of future drugs and treatments development. ALS is a lethal adult-onset motor neuron disease, pathologically characterized by motor neuron degeneration. No effective treatment exists for ALS, despite many failed attempts. This is largely because we require a more thorough mechanistic understanding of ALS pathogenesis to rationally develop therapeutics. The lab is taking a fresh approach to this challenge using a novel NMJ-on-a-Chip platform that mimic the human motor unit. This novel Lab-on-a-Chip platform enable to grow patients' neurons and muscles on a silicon chips thus opens new possibilities for experimental studies of neuron degeneration and regeneration process, and provide a strong tool for personalized medicine. Specifically, lab projects are focused to understand key spatial and temporal signaling mechanisms, including axonal transport, receptor organization along the plasma membrane and local protein synthesis events at axons and synapses.



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

- Microfluidic devices: In-house design and fabrication of compartmentalized microfluidic chambers for deciphering spatiotemporal process
- Transgenic mice models: Mechanistic understanding of motor neuron disease using in vitro and in vivo Tg mice model
- Live imaging: High resolution live-cell imaging of axonal transport, NMJ activity, and protein synthesis.
- iPSC-derived muscle and motor neurons: Patient-derived motor neurons for investigating disease mechanisms in familial and sporadic ALS. .

Publications

Maimon R, **Perlson E**. Muscle secretion of toxic factors, regulated by miR126-5p, facilitates motor neuron degeneration in amyotrophic lateral sclerosis. *Neural Regen Res*. 2019;14:969-970.

Gershoni-Emek N, Altman T, Ionescu A, Costa CJ, Gradus-Pery T, Willis DE, **Perlson E**. Localization

of RNAi machinery to axonal branch points and growth cones is facilitated by mitochondria and is disrupted in ALS. *Front Mol Neurosci*. 2018;11:311.

Pathak A, Stanley EM, Hickman FE, Wallace N, Brewer B, Li D, Gluska S, **Perlson E**, Fuhrmann S, Akassoglou K, Bronfman F, Casaccia P, Burnette DT, Carter BD. Retrograde degenerative signaling mediated by the p75 neurotrophin receptor requires p150Glued deacetylation by axonal HDAC1. *Dev Cell*. 2018;46:376-387.e7.

Maimon R, Ionescu A, Bonnie A, Sweetat S, Wald-Altman S, Inbar S, Gradus T, Trotti D, Weil M, Behar O, **Perlson E**. miR126-5p downregulation facilitates axon degeneration and NMJ disruption via a non-cell-autonomous mechanism in ALS. *J Neurosci.* 2018;38:5478-5494.

Zahavi EE, Steinberg N, Altman T, Chein M, Joshi Y, Gradus-Pery T, **Perlson E**. The receptor tyrosine kinase TrkB signals without dimerization at the plasma membrane. *Sci Signal*. 2018;11(529).

Yardeni T, Fine R, Joshi Y, Gradus-Pery T, Kozer N, Reichenstein I, Yanowski E, Nevo S, Weiss-Tishler H, Eisenberg-Bord M, Shalit T, Plotnikov A, Barr HM, **Perlson E**, Hornstein E. High content image analysis reveals function of miR-124 upstream of Vimentin in regulating motor neuron mitochondria. *Sci Rep*. 2018;8(1):59.

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

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Gershoni-Emek, N., Mazza A, Gradus T., Sharan R. and **Perlson E**. (2016) Proteomic analysis of dynein interactors in synaptosomes reveals a role for the RNA-binding protein Staufen1 in Amyotrophic Lateral Sclerosis. *Mol Cell Proteomics*. 15:506-22.

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Zahavi E, Ionescu A, Ben-Yaakov K., Gluska S, and **Perlson E.** (2015) Spatial aspects of GDNF functions revealed in a compartmentalized microfluidic neuromuscular co-culture system. *J Cell Sci*, 128:1241-52.

Bauer A., Nolden T., Nemitz S., **Perlson E**. and Finke S. (2015) A dynein light chain 1 binding motif in RABV polymerase L protein plays a role in microtubule re-organization and viral primary transcription. *J Virol.* 89(18):9591-600.

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Reviews and chapters

Guillermo MA., Gershoni-Emek, N., **Perlson E** and Bronfman FC. (2016). Neurodegeneration and Alzheimer's disease, What can proteomics tell us about the Alzheimer's brain?" Mol Cellular Proteomics. 15:409-25.

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

Grants

2019-2021 Ministry of Science and Technology State of Israel, China-Israel Flagship Projects Brain Sciences. The mechanisms of BDNF-TrkB signaling in neurodegenerative disease

2019-2024 Israel Science Foundation, The Interplay between Local Synthesis

	and Axon/NMJ Maintenance and Degeneration in ALS.	2020-2023	JPND-Multinational research projects on Personalised Medicine for Neurodegerative Diseases, Humanized high-throughput co-culture system for motor neuron diseases
2020-2022	Israel Innovation Authority (Kamin), ALS treatment by miR126-5P manipulations via lentivirsus		

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

Department of Anatomy and Anthropology
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Brain Injuries: Cognitive, Behavioral and Cellular Outcome

Position

Professor, Sackler Faculty of Medicine

Sagol School of Neuroscience faculty member

Dr Miriam and Sheldon G Adelson Chair in Biology of Addictive Diseases

Research

Our 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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Baeta-Corral, R., Defrin, R., **Pick C.G.** and Lydia Giménez-Llort L. Nociception response is preserved in 3xTg-AD mice. *Neurosci. Lett*. 600:158-163 (2015).

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and changes in gene expression are attenuated by treatment with the glucagon-like peptide-1 receptor agonist, exendin-4. *Alzheimer Dement*. 12: 34-48 (2016). *Equal contribution.

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Deselms, H., Maggio, N., Rubovitch, V., Chapman, J. Schreiber, S., Tweedie, D., Kim, D.S, Greig, N.H Pick C.P. Novel pharmaceutical treatments for minimal traumatic brain injury and evaluation of animal models and methodologies supporting their development. *J Neurosci Meth*. (2016). doi:10.1016/j.jneumeth.2016.02.002.

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Tamargo IA, Bader M, Li Y, Yu SJ, Wang Y, Talbot K, DiMarchi RD, **Pick CG**, Greig NH. Novel GLP-1R/*GIPR* co-agonist "twincretin" is neuroprotective in cell and rodent models of mild traumatic brain injury. *Exp Neurol.* 288:176-186 (2017).

Meningher I, Bernstein-Eliav M, Rubovitch V, **Pick CG**, Tavor I. (2020) Alterations in network connectivity following traumatic brain injury in mice. *Journal of Neurotrauma*

Reviews

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

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Molecular Mechanisms of Drugs for Neuropsychiatric Disorders

Positions

Professor Emeritus, Sackler Faculty of Medicine

Research

Main projects in the lab include:

1. Presynaptic monoamine transportes 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

Simchon Tenenbaum Y, Weizman A, **Rehavi M**. (2015)The impact of chronic early administration of psychostimulants on brain expression of bdnf and other neuroplasticity-relevant proteins. *J Mol Neurosci*. 57.

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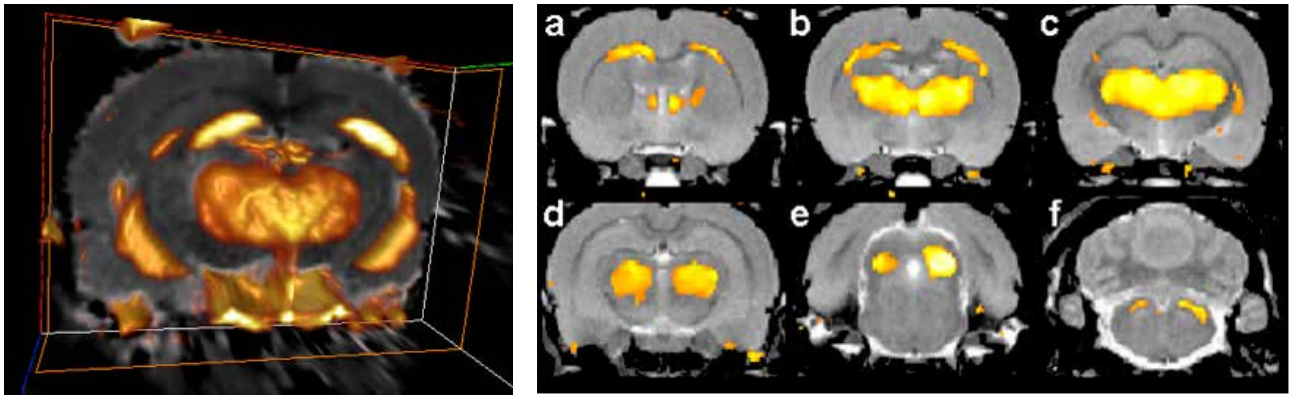

(A) Six representative coronal slices of T_2-weighted MR images from untreated thiamine-deficient rats on day 14. The yellow areas represent abnormalities characterized by a significant increase in signal intensity that occurred on day 14 as compared to day 0 (ANOVA, $p<0.01$). (a,b) thalamus and corpus 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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The Molecular Basis of Epileptic Encephalopathies and Autism

Position

Senior Lecturer, Sackler School of Medicine

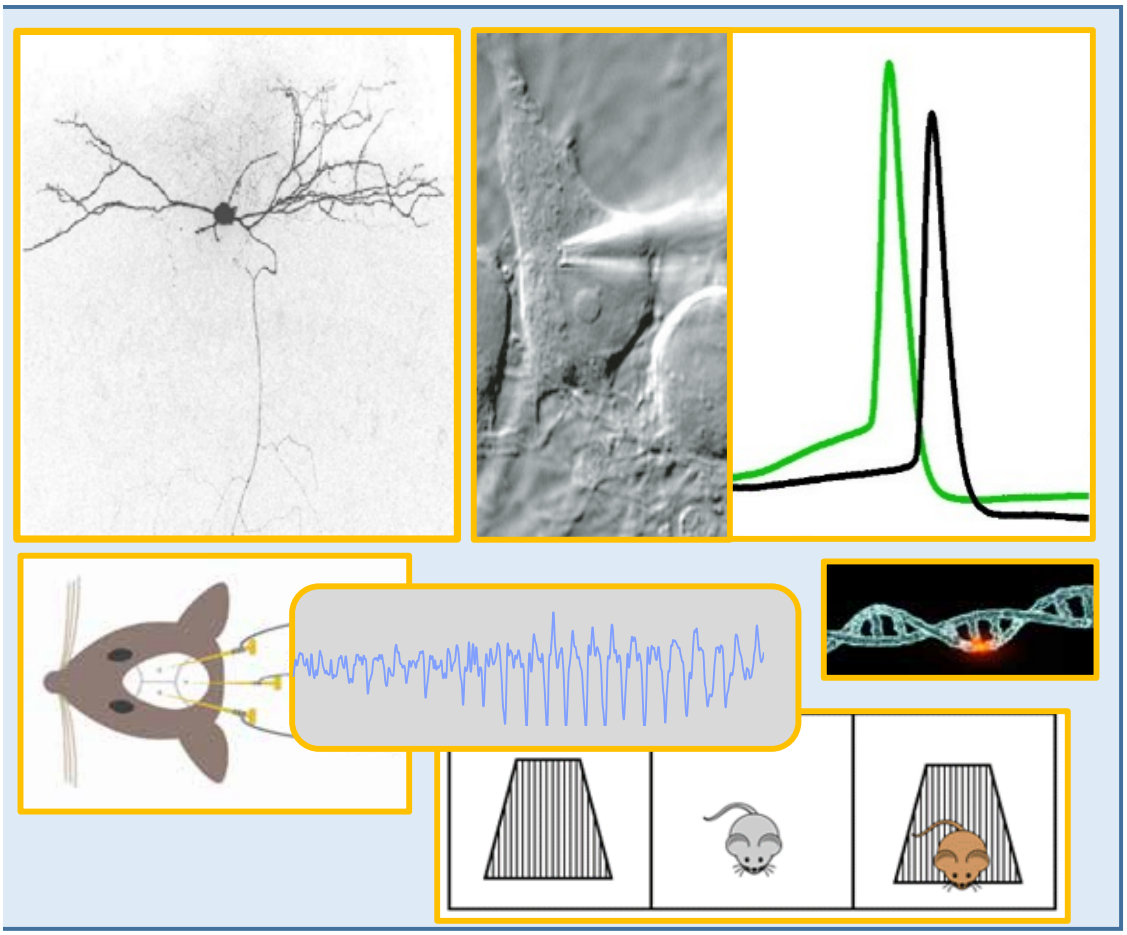
Director, Goldschleger Eye Research Institute

Co-Director, Biomed@TAU Research Hub: Autism & Other Developmental Disorders

Research

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

Visual system abnormalities are often observed in both disorders, ranging from lack of eye contact, through abnormal visual processing, to photosensitive seizures. The tremendous advancement in genetic studies helped to identify the involvement of many genes in the etiology of epilepsy and autism. However,



our understanding of the pathways leading from a genetic mutation to abnormal brain function is still in its infancy.

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

In order to bridge this gap, we harness the strength of mouse genetics, combined with electrophysiological recordings, and behavioral experiments in mice. With this multidisciplinary approach we aim to uncover the neuronal alterations leading to defective information processing in diseased brain, develop early diagnostic tolls as well as novel treatment options.

Publications

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Grants

2018 – 2021 ERA-Net E-Rare – Curing Dravet Syndrome by Gene Therapy

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

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

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Novel Antioxidant for Treatment of Degenerative Diseases

Positions

Professor Emeritus, Sackler Faculty of Medicine

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

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 αIIbβ3–actin cytoskeleton complex. **Thromb. Res.**, 135:114-120, 2015.

M. Levi, M. Tzabari, **N. Savion**, S. M. Stemmer, R. Shalgi, I. Ben- Aharon. Dexrazoxane exacerbates doxorubicin-induced testicular toxicity. *Reproduction* 150:357–366, 2015.

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Stability-Plasticity Balance in Hippocampal Circuits and its Disruption in Alzheimer's Disease

Positions

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Physiology and Pharmacology

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

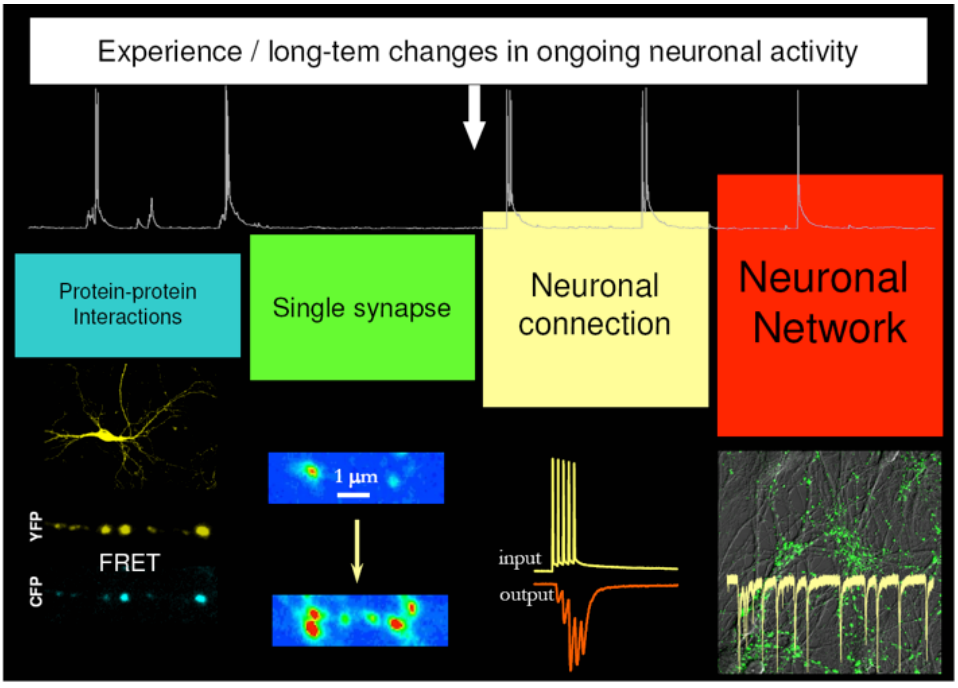
Member, American Federation for Aging Research (AFAR) National Scientific Advisory Council

Member, Azrieli PhD fellowship committee

Member, Managing Committee of Sagol School of Neuroscience

Research

How neuronal circuits maintain the balance between stability and plasticity in a constantly changing environment remains one of the most fundamental questions in neuroscience. Empirical and theoretical studies suggest that homeostatic negative feedback mechanisms operate to stabilize the function of a system at a set point level of activity. While extensive research uncovered diverse homeostatic mechanisms that maintain activity of neural circuits at extended timescales, several key questions remain open. First, what are the basic principles and the molecular machinery underlying invariant population dynamics of neural circuits, composed from intrinsically unstable activity patterns of individual neurons? Second, is homeostatic regulation compromised in Alzheimer's disease (AD) and do homeostatic failures lead to aberrant brain activity and memory decline, the overlapping phenotypes of AD and many other distinct neurodegenerative disorders? And finally, how do homeostatic systems operate in vivo under experience-dependent changes in firing rates and patterns? To target these questions, we have developed an integrative approach combining electrophysiology, advanced optical imaging and molecular biology, together with longitudinal monitoring of activity from large populations of



hippocampal neurons in freely behaving mice. Utilizing these state-of-the-art approaches, we study how firing stability is maintained at different spatial scales and what are the mechanisms leading to destabilization of firing patterns in AD-related context.

Publications

Chen Y, Orr AA, Tao K, Wang Z, Ruggiero A, Shimon LJW, Schnaider L, Goodall A, Rencus-Lazar S, Gilead S, **Slutsky I**, Tamamis P, Tan Za, Gazit E (2020) High-efficiency fluorescence through bioinspired supramolecular self-assembly. ACS Nano 14:2798-2807.

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Styr, B., and **Slutsky, I.** (2018). Imbalance between Firing Instability and Synaptic Plastcity Drives Early-Phase Alzheimer's Disease. Nature Neuroscience, 21(4), 463-473.

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

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

Review

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

Grants

2017–2020	Heritage Legacy Fund and Israel Science Foundation
2017–2022	ERC Consolidator Grant
2020-2023	DFG Grant (with Prof. Silvio Rizzoli, U. GÖTTINGEN)
2019-2022	Lower Saxony – Israel Research Cooperation, Volkswagen Grant (with Prof. Silvio Rizzoli, U. GÖTTINGEN)
2019-2020	Rosetrees Trust Grant
2018-2023	Israel Science Foundation

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Sagol School of Neuroscience

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Basic and Applicative Research of Eye Physiology, Diseases and Function

Positions

Professor, 'Bedimus' (Ret.) 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

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

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Adi Tzameret, Ifat Sher, Vistoria Edelstain, Michael Belkin, Ofra Kalter-Leibovici, **Arieh S. Solomon*** and Ygal Rotenstreich*, *equal contribution. Evaluation of visual function in Royal College of Surgeons rats using a depth perception visual cliff test. *Vis Neuroscience.* 2018.

Ravid Doron, Anna Sterkin, Moshe Fried, Oren Yehezkel, Michael Belkin, Maria Lev, Rosner Mordechai, Yossi Mandel, **Arieh S Solomon**, Uri Polat. Spatial visual function in anomalous trichromats: is less more? *PLoS One*, 2019.

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Hana Ziv H, Sarah Pri-Chen S, **Solomon AS**. Mild carotid sternosis creates gradual progressive,lifelong brainand eye damage: An experimental laboratory rat model. *J Comp Neurol* 2020;528:1672-1682.

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

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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

Kampasi K, English D, Seymour J, **Stark E**, McKenzie S, Vöröslakos M, Wise K, Buzsáki G, Yoon E (2018) Dual color optogenetic control of neural populations using low-noise, multishank optoelectrodes. Microsystems and Nanoengineering, 4(1):1-10

Roux L, Hu B, Eichler R, **Stark E**, Buzsáki G (2017) Sharp wave ripples during learning stabilize hippocampal spatial map. *Nat Neurosci*, 20(6):845-853.

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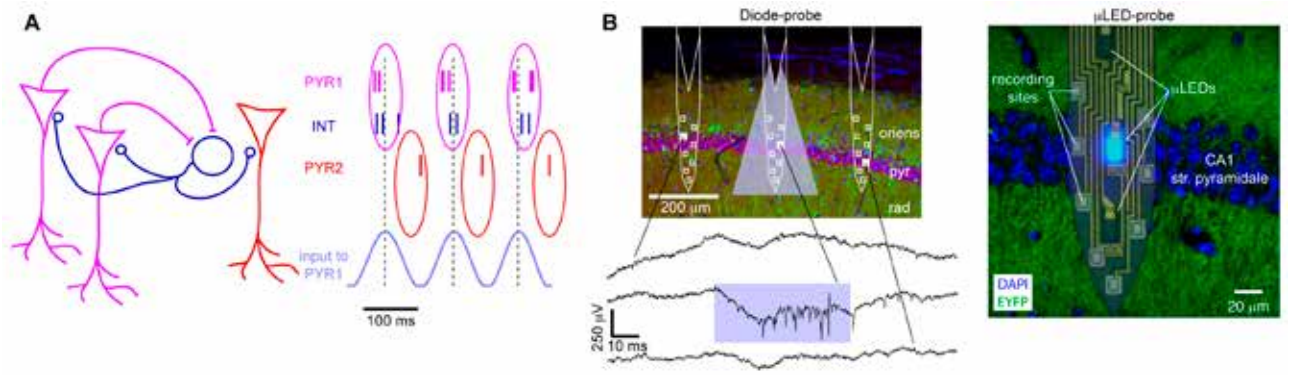

A. Dynamic segregation of neuronal networks into cell assemblies. In the freely-moving mouse, external input is applied to one group of excitatory pyramidal cells (PYR1), which drive inhibitory cells (INT), which then inhibit a second group (PYR2). At certain input frequencies, inhibition actually *induces*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

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.

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.

Grants

2016-2021	ERC Starting Grant
2016-2020	CRCNS (NSF-BSF) Grant
2016-2020	ISF Grant
2017-2020	Rosetrees Grant
2017-2019	ISF Bikura Grant

Dr. Ido Tavor, Ph.D.

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Functional and Structural Brain Connectivity using MRI

Positions

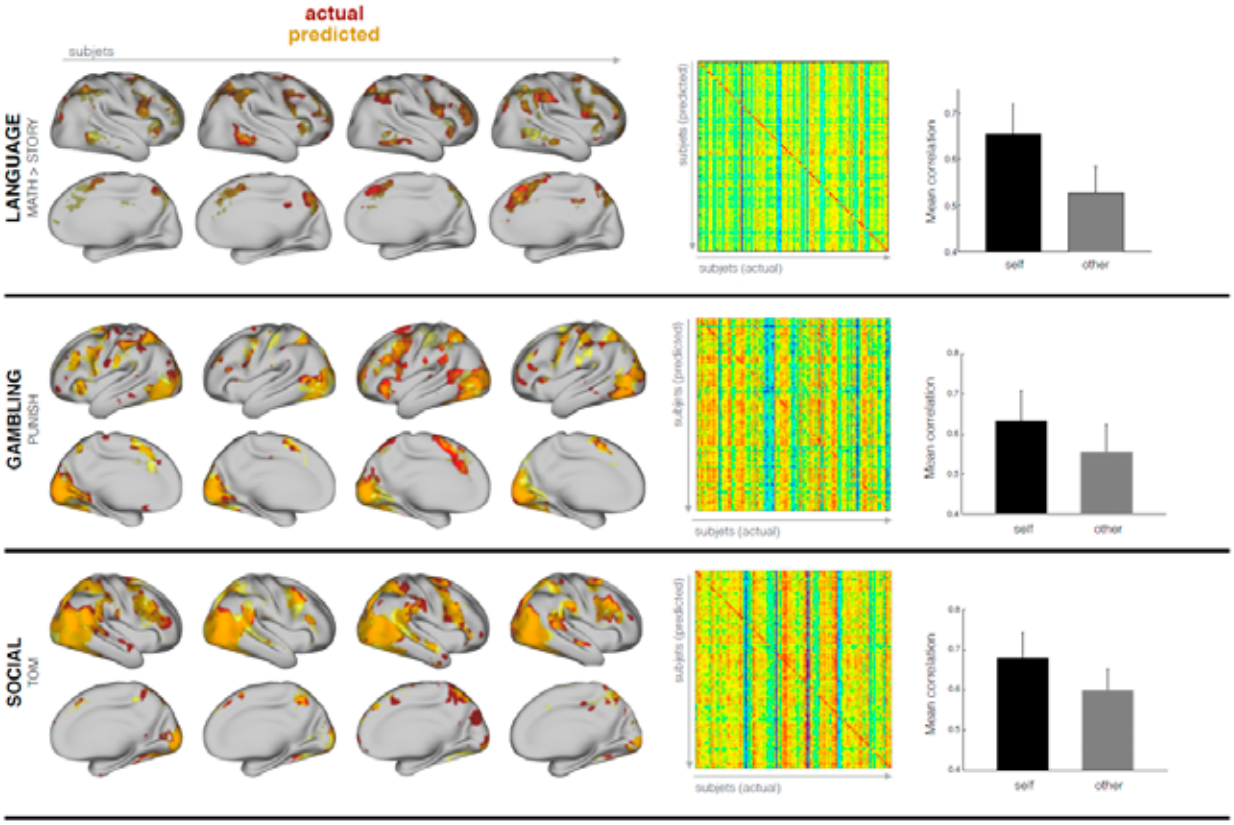
Senior Lecturer, Sackler Faculty of Medicine

Faculty member, Sagol School of Neuroscience

Research

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

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



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

Publications

A. Horowitz, D. Barazany, **I. Tavor**, M. Bernstein, G. Yovel and Y. Assaf. In vivo correlation between axon diameter and conduction velocity in the human brain. *Brain Structure and Function* 220, 1-12, 2015

A. Horowitz, D. Barazany, **I. Tavor**, G. Yovel and Y. Assaf. Response to comments on the paper by Horowitz et al. *Brain Structure and Function* 220, 1791, 2015

D. Joel, Z. Berman, **I. Tavor**, N. Wexler, O. Gaber, Y. Stein, N. Shefi, J. Pool, S. Urchs, D.S. Margulies, F. Liem, J. Hänggi, L. Jäncke, Y. Assaf, 2015. Sex beyond the genitalia: The human brain mosaic. *Proc. Natl. Acad. Sci. USA* 15468-73, 2015

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

Lotan, E., **Tavor, I.**, Barazany, D., Ben-Amitay, S., Hoffmann, C., Tsarfaty, G., ... & Tanne, D. (2019). Selective atrophy of the connected deepest cortical layers following small subcortical infarct. *Neurology*, 92(6), e567-e575.

Tavor, I., Botvinik-Nezer, R., Bernstein-Eliav, M., Tsarfaty, G., & Assaf, Y. (2020). Short-term plasticity following motor sequence learning revealed by diffusion magnetic resonance imaging. *Human Brain Mapping*, 41(2), 442-452.

Meningher I, Bernstein-Eliav M, Rubovitch V, Pick CG, **Tavor I.** (2020) Alterations in network connectivity following traumatic brain injury in mice. *Journal of Neurotrauma*

Grants

2019-2020	Aufzien Family Center for the Prevention & Treatment of Parkinson's Disease Grant
2019-2020	The Goldstein-Goren Center for Mind and Language
2019-2020	The National Institute for Psychobiology in Israel
2018-2022	Israel Science Foundation Grant

Nursing, Occupational and Physical Therapy

Dr. Michal Avrech Bar, Ph.D., O.T.

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

Positions

Lecturer, Sackler Faculty of Medicine

Committee Member, Occupational Science Europe Research Committee

Research

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

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

Publications

Avrech Bar, M., Dao, T. T., Vlodarchyk, L. R., & Backman, C.L. (2020). Fatherhood experiences of men with Inflammatory Arthritis: A preliminary grounded theory. *Arthritis Care & Research*, doi: 10.1002/acr.24189.

Itzhaki, M., Katz Leurer, M., Warshawski, S., & **Avrech Bar, M.** (2020). Preparedness of health professions students for Interprofessional Collaboration: A mixed method study. *Teaching in Higher Education,* doi:10.1080/13562517.2020.1769057.

Strauss, Z., **Avrech Bar, M.**, & Stanger, V. (2019). Fatherhood of a premature infant: "A Rough Roller-Coaster Ride". *Journal of Family Issues*, 40(8), 982-1000.

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D. Rand, N. Givon, & **M. Avrech Bar**. A video-game group intervention: Experiences and perceptions of adults with chronic stroke and their therapists. *Canadian Journal of Occupational Therapy*, Vol 85, pp. 158-168, 2018.

L. Rosenberg, M. Pade, H. Reizis, **M. Avrech Bar**. Associations between meaning of everyday activities and participation among children. *American Journal of Occupational Therapy*, Vol 73, 2018).

Avrech Bar, M., Pade, M., Jarus, T., Gat, S., Kaufman Cohen, Y. & Lipskaya-Velikovsky, L. (2017). Problem-Based learning in occupational therapy curriculum – Implications and challenges. *Disability and Rehabilitation*, 10.1080/09638288.2017.1325942.

Rand, D., Givon, N., & **Avrech Bar, M**. (2017). A video-game group intervention: Experiences and perceptions of adults with chronic stroke and their therapists. *Canadian Journal of Occupational Therapy* (in press).

M. Avrech Bar, M. Katz Leurer, S. Warshawski, M. Itzhaki. The Role of personal resilience and personality traits of healthcare students on their attitudes towards interprofessional collaboration. Nurse Education Today, Vol 61, pp. 36-42, 2017.

Avrech Bar, M., Shelef, L., & Bart, O. (2016). Do participation and self-efficacy of mothers to children with ASD predict their children participation? *Research in Autism Spectrum Disorders, 24*, 1-10.

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Avrech Bar, M., Forwell, S., & Backman, C. (2016). Ascribing meaning to occupation: An example from healthy, working mothers. *OTJR: Occupation, participation and Health, 36, 148-158.*

Avrech Bar, M., Ratzon, N. Z. (2016). Enhancing occupational therapy students' knowledge, competence, awareness, and interest in accessibility. *Hong Kong Journal of Occupational Therapy*, *27*, 18-25.

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Avrech Bar, M., & Jarus, T. (2015). The effect of engagement in everyday occupations, role overload and social support on health and life satisfaction among mothers. *International Journal of Environmental Research and Public Health, 12*, 6045-6065.

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Investigating Sensory Modulation Disorder (SMD) Over Life Span

Positions

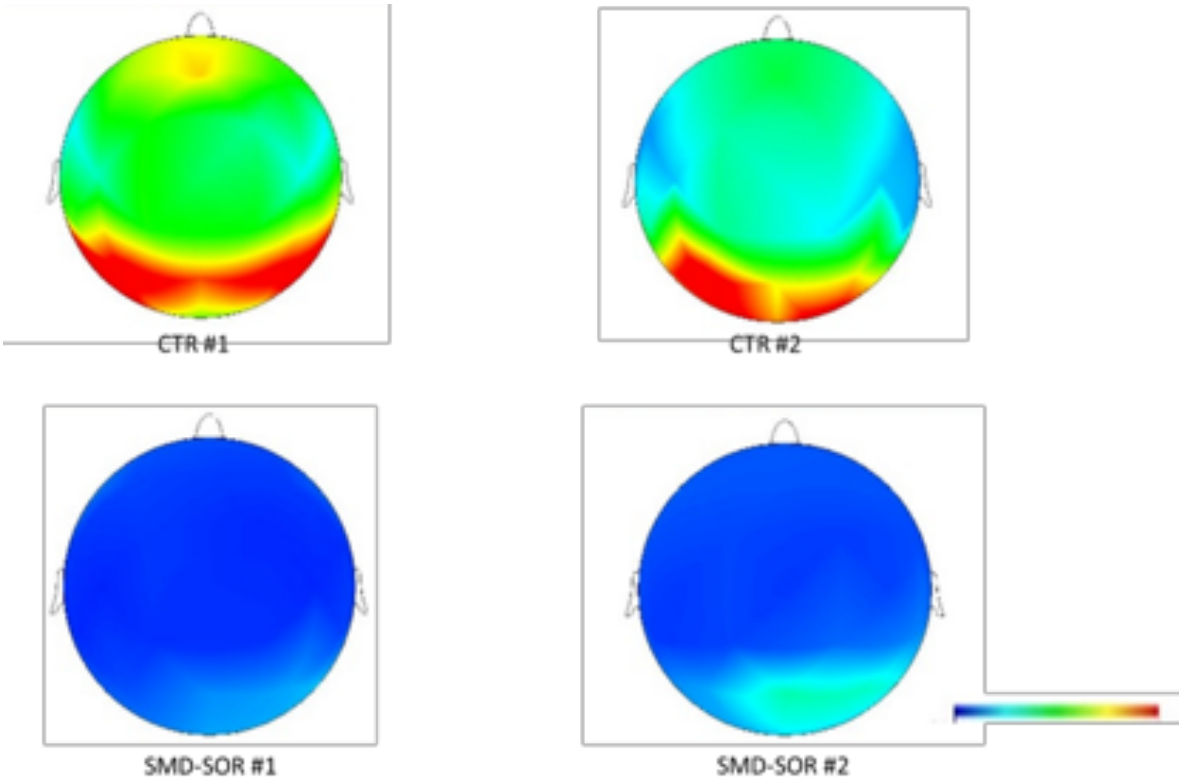
Lecturer, Sackler Faculty of Medicine

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

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

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



Alpha (7.5 – 12 Hz) distribution map of activity (EEG recording) in 2 control and 2 sensory over-responsive subjects. Red color indicates greater alpha power. Control (CTR) but not SOR subjects have high alpha activity, which increases in posterior electrodes.

Publications

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Issachar G, **Bar-Shalita T**, Baruch Y, Horing B, Portnoy S. Design and implementation of a novel subject-specific neurofeedback evaluation and treatment system. *Annals of Biomedical Engineering*. 2019;47:1203-1211

Kalig-Amir M, Berger I, Rigbi A, **Bar-Shalita T**. An exploratory study of parent-child association in sensory modulation disorder involving ADHD related symptoms. *Pediatric Research*. 2019;86:221-226.

Bar-Shalita T, Granovsky Y, Parush S, Weissman-Fogel I. Sensory modulation disorder (SMD) and pain: A new perspective. Special Research Topic: Sensory-Motor Aspects of Nervous Systems Disorders: Insights from Biosensors and smart technology in the dynamic assessment of disorders, their progression, and treatment outcomes. *Frontiers in Integrative Neuroscience*. 2019.

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Bar-Shalita, T., Anatoly Livshitz, A., Yulia Levin-Meltz, Y., Rand, D., Deutsch L., Vatine, J-J. Sensory modulation dysfunction is associated with Complex-Regional-Pain-Syndrome. *PLoS One*. 2018, 13(8):e0201354.

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Hertzog, D., Cermak, S., and **Bar-Shalita, T**. Sensory modulation, physical activity, and participation in daily occupations in young children. The Canadian *Journal of Occupational Therapy*. 2018.

Granovsky, Y., Weissman-Fogel, I., **Bar-Shalita, T**. Resting-state EEG in individuals with sensory over-responsivity: an exploratory study. American *Journal of Occupational Therapy*. 2018.

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

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Bart O., **Bar-Shalita, T**., Darr, R. Relationships among sensory responsiveness, anxiety, and ritual behaviors in children with and without atypical sensory responsiveness. *Phys Occ Ther Ped*. 2016:1-10.

Bar-Shalita, T., Cermak, S. Atypical sensory modulation and psychological distress in the general population. *Am J Occ Ther.* 2016, 70: 1-9.

Lipskaya-Velikovsky, L., **Bar-Shalita, T.,** Bart, O. Sensory modulation and daily-life participation in people with schizophrenia. *Comp Psych*. 2015, 58:130-137

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Grants

2017-2021 Israel Science Foundation (ISF)

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

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Nursing Genetics and Information Technologies

Positions

Associate Professor, Sackler Faculty of Medicine

Research

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

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

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

Information Technologies: Due to the rise of internet technology, medical information is no longer the exclusive property of medical service givers – it is now accessible to everybody – and this new situation has an effect on patient-caregiver relations. Among the research studies we are carrying out, we have investigated the attitudes of nurses towards patients who come forward with information found on the web, what affects those attitudes, and the reactions of nursing teachers to students who bring such information to class. Up to now, most research into this issue has concentrated on the professional caregiver's point of view. We wish to turn the spotlight onto the patient's point of view, and on how they feel after bringing Internet information to an appointment with their doctor or nurse.

Publications

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**. (2016) Patients' attitudes towards disclosure of genetic test results to family members: the impact of patients' sociodemographic background and counseling experience. *J Genet Couns*. 25, 314-324.

Itzhaki, M., Hildesheimer, G., **Barnoy, S**. & Katz, M. (2016) Family involvement in medical decision making: Perceptions of nursing and psychology students. *Nurse Education Today*, 40, 181-187.

Peles-Bortz, A., Bluvstein, I., Bergman, L. & **Barnoy, S.** (2016). Suspicion of gynecologic malignancy: Support resources for women before gynecological surgery. *Women & Health*, 57, 329-341.

Itzhaki, M., Meridian, O., Schifter-Sagiv, T. & **Barnoy, S**. (2016). Nursing students' attitudes and intention to work with mentally ill patients before and after a planned intervention. *Academic Psychiatry*, 41;337-344.

Bar-Tal, Y. and **Barnoy, S**. Factors Influencing Participants' Decision to Comply with Nurse Recommendations. *Nursing Inquiry*. 23: 338–345.

Warshawski, S., Barnoy, S. & Itzhaki, M. Factors associated with nursing students' resilience: communication skills course, use of social media and satisfaction with clinical placement. Journal of Professional Nursing, 33:157.

Niv, G., Bar-Josef, S., Ben Bassat, O., Avni, I., Lichtenshtein, L., Niv, Y., **Barnoy, S.** (2017). Quality

of life and uncertainty in Crohn's disease. *Quality of Life Research*, 26(6),1609–1616.

Barnoy, S., Biton, A., Itzhaki, M. (2017). Social inclusion of children with Down syndrome: Jewish and Muslim mothers' knowledge, attitudes, beliefs, and behavioral intentions. *Journal of Pediatric Nursing*, 35, 50-56.

Kardosh, M., Bar-Tal, Y., **Barnoy, S**. (2017). The relationship between body image, gender, subjective norms and the decision to undergo preventive mastectomy among Arab and Jewish BRCA carriers. *Cancer Nursing*. 41, 255-262.

Warshawski, S., **Barnoy, S**., Kagan, I. Generation, gender and professional differences in perception of organizational values. *Journal of Interprofessional Care*, 31, 696-704.

Asman, O., Melnikov, S., **Barnoy, S**., Tabak, N. (2017). Experiences, behaviors, and perceptions and experiences of registered nurses regarding research ethics and misconduct. *Nursing Ethics*. In press.

Gilbar, R. & **Barnoy, S**. Companions or patients? The impact of family presence in genetic counselling for inherited breast cancer: relational autonomy in practice. Bioethics, 32, 378-387.

Warshawski, S., Katz, O., & **Barnoy, S**. The relationship between test anxiety to academic self-efficacy and social support among nurse students. Nurse Educator, 2019;44, E6-E10.

Warshawski, S., Itzhaki, M. & **Barnoy, S**. Nurses' and nurse students attitudes and self-efficacy perception of icts: professional and cultural differences. *CIN, Computers, Informatics Nursing*, 2019;37:20-28.

Barnoy, S., Melnikov, S. & Bar-Tal, Y. The effect of e-health information on nurse-patient encounters: Mutual feelings and perceptions*. Current Psychology*, 2018.

Warshawski, S., Itzhaki, M. & **Barnoy, S.** The associations between peer caring behaviors and and social support to nurse students' caring perceptions. *Nurse Education in Practice*, 2018;35, 88-94.

Kagan, I., Porat, N. & **Barnoy, S.** The quality and safety culture in general hospitals – patients, physicians and nurses evaluation of its effect on patient satisfaction. *International Journal for Quality in Health Care*, 2018;31, 261-268.

Ohana S, **Barnoy S**. Israeli E-patients' informational needs. *Nursing Outlook*, 2019;67, 190-198.

Lifszyc-Friedlander A, Honovich M, Stolerman E, Madjar B, **Barnoy S**. Family health clinics as a source of social capital. *Journal of Pediatric Nursing*, 2019;47, e2-e7.

Shemesh T, **Barnoy S**. Assessment of the intention to use mobile health applications using a technology acceptance model in an Israeli adult population. *Telemedicine e-Health*; In press

Gilbar, R. and **Barnoy, S**. Facing legal barriers regarding disclosure of genetic information to relatives. *New Genetics and Society*, Accepted for publication, April, 2020.

Grants

2020-2022 Israel National Institute for Health Policy Research

Dr. Orit Bart, Ph.D., OTR

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Sackler Faculty of Medicine

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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

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

L. Lipskaya-Velikovsky**,** T. Bar-Shalita, **O. Bart**. Sensory modulation and daily-life participation in people with schizophrenia. *Comprehensive Psychiatry*. 58, 130-137, 2015.

M. Avrech Bar, L. Shelef, **O. Bart**. Do participation and self-efficacy of mothers to children with ASD predict their children's participation? *Research in Autism Spectrum Disorder.* 24, 1-10, 2016.

M. Avrech Bar, S. Jlole Majadla, **O. Bart**. Managing everyday occupations as a predictor of health and wellbeing among mothers of children with ADHD**.** *Journal of Attention Disorders,* 2015.

L. Rosenberg, **O. Bart**. Different pathways to children's enjoyment of participation in daily activities. *Scandinavian Journal of Occupational Therapy*, 2016.

O. Bart, T. Bar-Shalta, H. Mansour, R. Dar. Relationships among sensory responsiveness, anxiety and ritual behaviors in children with and without Atypical Sensory Responsiveness. *Physical and Occupational Therapy in Pediatrics,* 2016.

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

L. Rosenberg., A. Moran, **O. Bart**. The associations among motor ability, social-communication skills, and participation in daily life activities in children

with low-functioning autism spectrum disorder. *Journal of Occupational Therapy, Schools & Early Intervention.*, 2017.

L. Rosenberg, Shani Jacobi, **O. Bart**. Executive functions and motor ability contribute to children's participation in daily activities. *Journal of Occupational Therapy, Schools, & Early Intervention*, 2017.

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

Prof. Ruth Defrin, Ph.D.

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Investigating Pain Perception and Mechanisms of Chronic Pain

Position

Professor, Sackler Faculty of Medicine

Director, Biomed@TAU Pain Research Hub , Pain Forum

Research

We study the function of the pain system among healthy subjects, individuals with mental disorders and individuals with cognitive impairments. We are interested in the manner with which temporal and spatial aspects of painful events are processed and in changes that occur in pain modulation capacity during various conditions such as stress, distraction and mindfulness.

We also study the underlying mechanisms of chronic pain that develops following 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 interaction between the pain and the stress systems in these conditions and among healthy subjects. We use state of the art methods including quantitative somatosensory testing, evoked related potentials and functional magnetic resonance imaging. The experiments are performed in the pain laboratory at TAU and in hospitals.

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Grants

2015-2019 ISF-Israel Science Foundation

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Emotional Management, Cultural Competence and Decision-Making

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Nursing

Research

Qualitative and quantitative research methods are used to study patients' and caregivers' attempts to structure their emotions through the process of emotional management. We explore the feelings experienced by healthcare workers and patients and how they cope with differences between expected emotions and experienced emotions in life-threatening situations (emergency and disaster) and in the treatment of mental patients and terminal illnesses. Investigation of the emotions experienced by nurses and how they cope with these emotions includes attention to caring and emotional resilience. 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. Moreover, we examine perceptions and knowledge of caregivers and patients concerning chronic illness, end of life, and the effects of treatment on the caregiver, patient, and family members. Understanding these aspects is essential for creating caring environments for nurses, patients and families within today's complex health care organizations.

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Quality of Care and Patient Safety

Positions

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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.

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Epidemiology of Cardiovascular Diseases & Risk Factors

Position

Associate Professor, Sackler Faculty of Medicine

Head of Doctoral Studies, Department of Nursing

Adjunct Associate Professor of Epidemiology, Johns Hopkins University

Research

During the last 18 years, I have been working on cardiovascular diseases epidemiology, focusing mainly in the epidemiology of stroke. The study of triggering risk factors for stroke was the main aim in my PhD thesis. I am especially interested in focusing my research in the study of factors that have a potential effect on short-term risk of stroke, both in persons with known cardiovascular risk factors and those who apparently do not have them and still, at a specific moment, have a stroke. Assessment of this kind of risk factors has a significant potential to contribute to prevention strategies thus reducing the burden of stroke to health systems and society. During my postdoctoral fellowship and afterwards, my research has extended to include differences in stroke characteristics, distribution of risk factors, stroke management and outcome by age, sex, race and other personal characteristics in different populations.

Since the establishment of the ongoing triennial National Acute Stroke Israeli (NASIS) registry in 2004, as a member of the registry's steering and publications committees, I collaborate with specialists in neurology in studies aimed at characterizing stroke at a national level. These studies, based on national unselected data on hospitalized stroke, provide both clinicians and health policy makers with information required for optimizing prevention strategies and care of stroke patients. As consultant epidemiologist at the Comprehensive Stroke Center at the Chaim Sheba Medical Center in the last years, I am aware of the needs of patients and families, as well as physicians and other health professionals, and am able to direct my research efforts towards topics which influence clinical practice.

Publications

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Bio-Psycho-Social Effects of Psychological Trauma

Positions

Visiting Senior Lecturer, Sackler Faculty of Medicine

Research

In our research we aim to uncover the mechanisms at the basis of the relations between exposure to different types of traumatic events (e.g., childhood sexual, physical and emotional abuse, domestic violence), and various outcomes, including psychological distress and psychopathology (e.g., PTSD, depression, suicidality), somatic and physical health difficulties (e.g., chronic pain, morbidity, somatization) as well as functional difficulties (e.g., vocational, social, and familial functioning). We use an interdisciplinary approach, advanced research methods and rigorous statistical analyses to understand the underlying dynamics of the questions at hand, and to promote the development of clinical intervations.

Publications

Y. Lahav, Y. Kanat-Maymon, Z. Solomon. Secondary traumatization and attachment among wives of former POWs: A longitudinal study. Attachment & Human Development, 18(2), 1-13, 2015.

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Dr. Lena Lipskaya-Velikovsky, Ph.D., O.T.

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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, sence 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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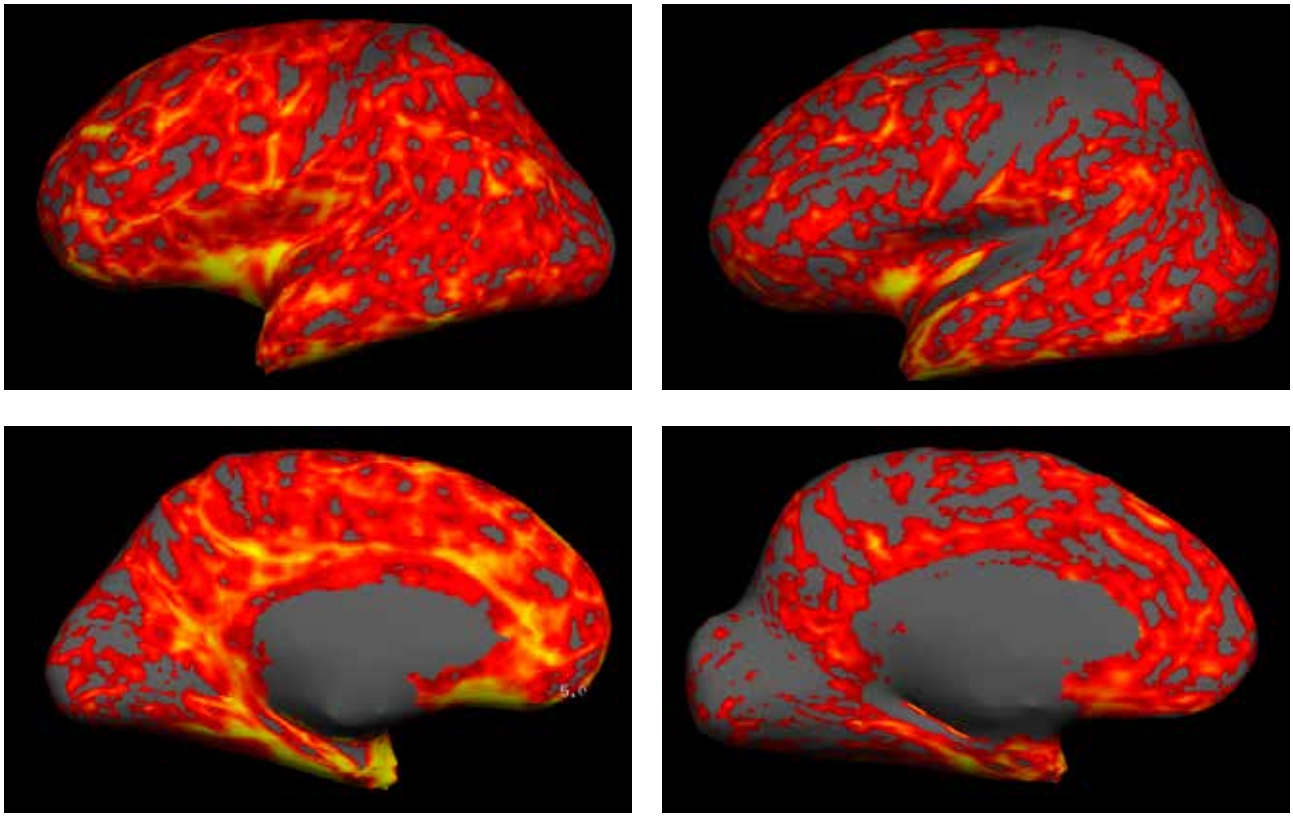
Physical Activity, Gait and Posture in People with Neurological Diseases

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our main research focuses on physical activity, gait and balance measurements, predictors, and outcomes in persons with neurological diseases, specifically multiple sclerosis (MS). Currently we are examining the relationship between various physical and mobility parameters with brain damage, determined by MRI methods in different neurological patient groups. Special interest is placed on aerobic function capabilities during various daily and challenging situations. We anticipate that our research will result in quantifying differences in physical activity, particularly in the rates of moderate-to-vigorous physical activity in several neurological patient groups vs. non-diseased controls. The interest in this research is based on the rationale that a better understanding of these mechanisms will facilitate the development of practical interventions, thus minimizing the negative aspects of the disease process. Overall, the research questions range from theoretical exploration to clinical application and are often multi-disciplinary in nature.



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

Publications

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Grants

2019-2022 Ministry of Science and Technology

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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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Hay O, Dar G, Abbas J, Stein D, May H, **Masharawi Y**, Peled N, Hershkovitz I. The lumbar lordosis in males and females, revisited. PLoS One. 10:e0133685, 2015.

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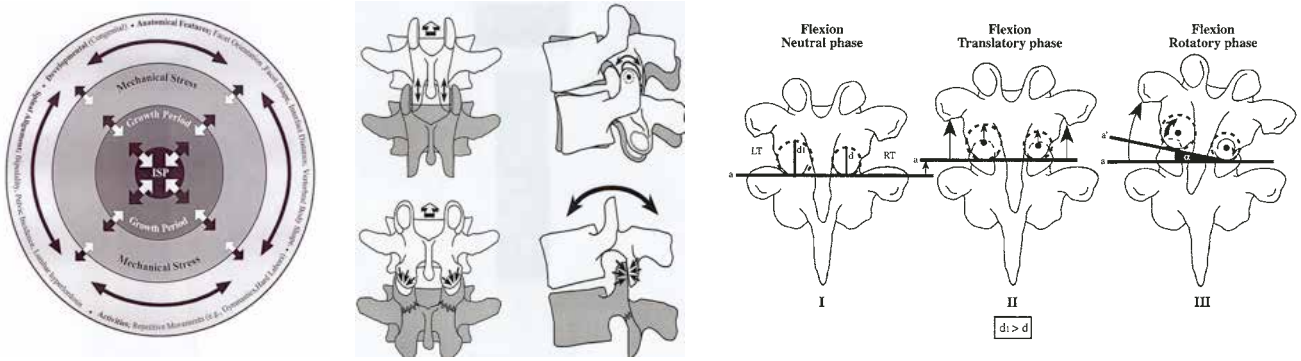

A B C

The suggested pathogenesis (A) and kinematics (B-C) in isthmic spondylolysis (ISP).

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Weisman A, Yona T, **Masharawi Y**. An act of man or a caprice of nature? Mil Med. 2019;184:22.

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Weisman A, Quintner J, Galbraith M, **Masharawi Y**. Why are assumptions passed off as established knowledge? Med Hypotheses. 2020;140:109693.

Dr. Semyon Melnikov, R.N. Ph.D.

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

Position

Head, Short-day studies BA Nursing Program Senior

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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

Publications

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Kagan I, Friedman S, Shalom E, **Melnikov S**. (2017). The effect of working in an infection isolation room on hospital nurses' job satisfaction. *Journal of Nursing Management*

Kagan I, Itzhaki M, **Melnikov S**. (2017). Patriotism, organizational commitment and Israeli nurses' intention to report to work in emergencies. *International Nursing Review*, DOI: 10.1111/inr.12395

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Melnikov S, Itzhaki M, Koton S. (2016). Differences between new immigrants from the Former Soviet Union and veteran residents in knowledge, perception, and risk factors of stroke. *Journal of Cardiovascular Nursing*, 31(6), 500-506

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Computational Biomechanics in Motor Rehabilitation

Position Senior

Senior 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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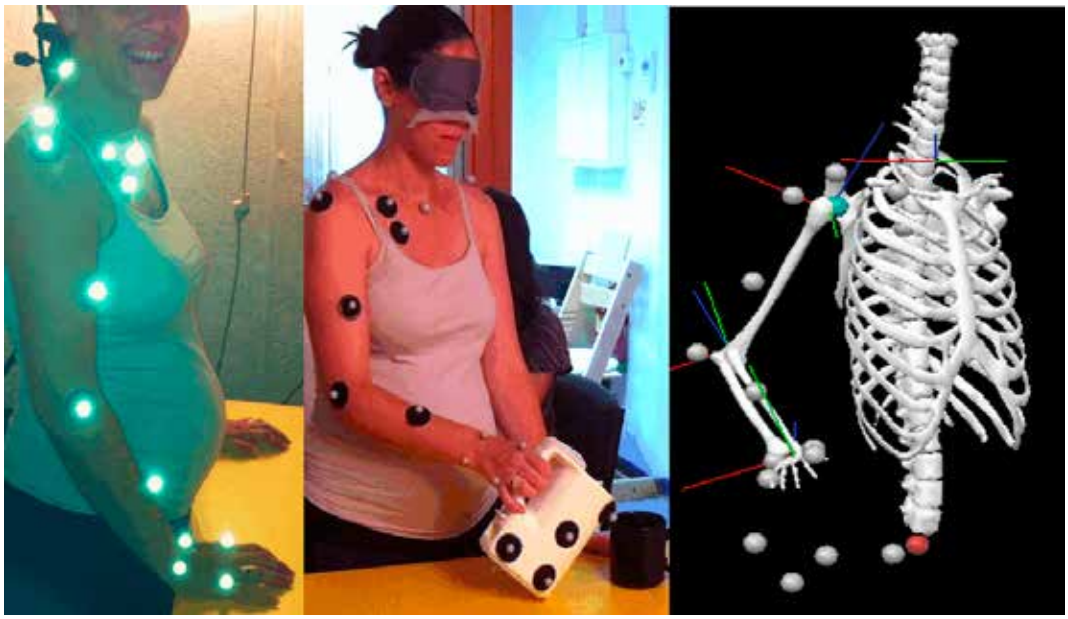

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Gaming for Rehabilitation of Neurological and Geriatric Populations

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Publications

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Grants

2017–2019	Maccabi Healthcare Services Research Fund
2017–2019	Israel National Institute for Health Policy Research

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Investigating the Ergonomics of Occupational Tasks and Driving Rehabilitation

Position

Professor, Sackler Faculty of Medicine

Research

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

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

Publications

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Grants

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

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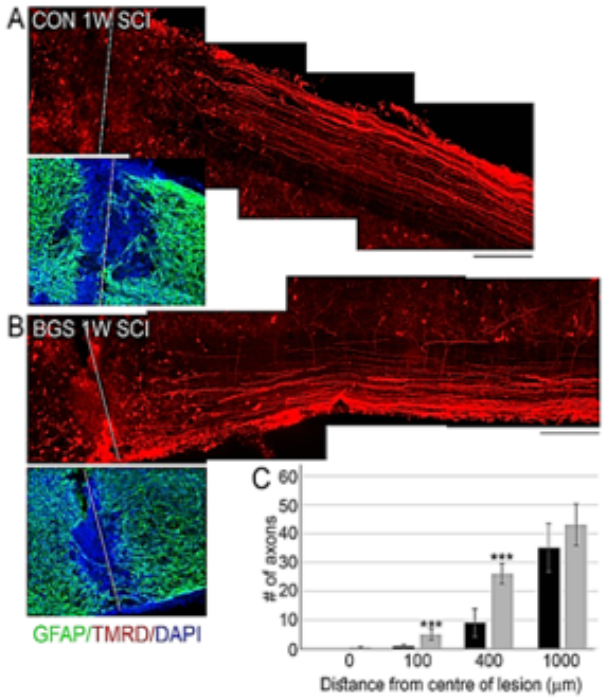
The Role of Glutamate Excitotoxicity in Neurodegenerative and Malignant Diseases

Position

Lecturer, Sackler Faculty of Medicine

Research

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



BGS treatment decreased axonal degeneration and increased GAP-43 expression on neurons at the lesion site. One week after SCI (A) TMRD axonal tracing of the descending axons of vehicle –control- and BGS-treated animals. The center of the lesion is indicated by the line. Glial scarring appears in the lower panel of the same lesion site of the upper panel immunostained with GFAP. The scale bar in A and B is 200µm. (B) Quantitation of the number of axons at different distances from the center of the lesion site (0µm).

Publications

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functional recovery in mice with spinal cord injury. *J Neurosurgery: Spine*. 2020.

Grants

2018 – 2020 Medical Research, Israel Defense Forces (IDF) "Blood glutamate scavenging as Novel neuroprotective treatment for spinal cord injury".

2017 – 2019 California Breast Cancer Research Program (CBCRP) "Targeting metastatic triple negative breast cancer by scavenging blood glutamate".

2016 – 2019 Israel Science Foundation (ISF) Individual Research Grant and New Faculty Equipment, "Blood glutamate scavenging in the prevention of melanoma invasiveness".

2019- 2021 AFTAM Research Collaboration Awards, "Spinal cord trauma amelioration by GOT1-mediated glutamate scavenging".

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

Positions

Lecturer, Sackler Faculty of Medicine

Research

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

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

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

Publications

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Theilla M, Ławiński M, Cohen J, Hadar E, Kagan I, Perkewick M, Singer P. Safety of home parenteral nutrition during pregnancy. Clin Nutr. 2015 Dec 12. [Epub ahead of print]

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Zusman O, **Theilla M**, Cohen J, Kagan I, Ben-David I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: A retrospective cohort study. Crit Care 2016; 20: 367.

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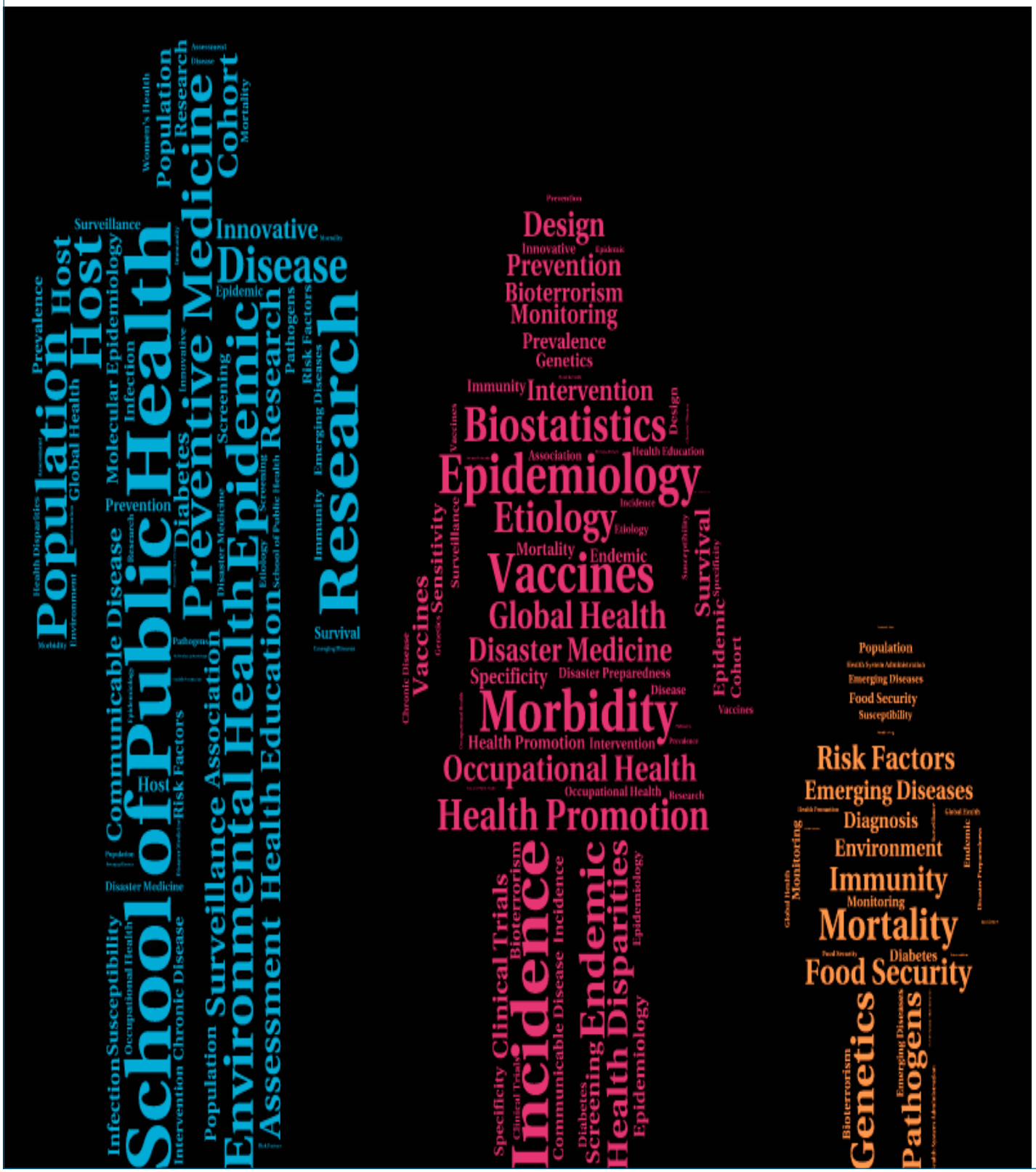
Public Health



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Emergency & Disaster Management

Positions

Senior Lecturer, Faculty of Medicine

Chair, Department of Emergency Management & Disaster Medicine

Chair, Teaching Committee, Dept of Emergency Management & Disaster Medicine

Member, Board, World Association of Disaster & Emergency Medicine (WADEM)

Research

Our research agenda encompasses a wide array of topics relevant to emergency & disaster management and medicine including perceptions of the public and the first responders concerning varied threats; psycho-social characteristics of response; evaluation of emergency readiness; factors that impact on personal and community resilience; effectiveness of risk communication and its effect on the population behavior; efficacy of humanitarian action; impact of innovative methods of risk management, and more. Methodologies for cross-border response to natural disasters are proposed and their effectiveness investigated; utilization of conventional and new (social) media during disasters is studied within the responders' realm and between them and the public. "Wisdom of the crowd" (involving the public) in enhancing response capacity is researched.

Publications

Tennenbaum-Baruchi C, Feder-Bubis P, **Adini B**, Aharonson-Daniel L. Emergency Situations and Deaf People in Israel: Communication Obstacles and Recommendations. Disaster Health. 2(2):106-111. 2015.

Adini B, Aharonson-Daniel L, Israeli A. Load index model: An advanced tool to support decision-making during mass casualty incidents. J Trauma Acute Care Surg. 78(3):622-7, 2015.

Tomer S, Aharonson-Daniel L, El-Hadid M, **Adini B**. Cross-border emergency coordination and communications using social media: developing a joint Israeli–Jordanian standard operating procedure for leveraging social media in emergencies. Int J Emergency Management. 11(2):169-190. 2015.

Cohen O, Feder-Bubis P, Bar-Dayan Y, **Adini B**. Promoting Public Health Legal Preparedness for Emergencies: Review of Current Trends and their Relevance in Light of the Ebola Crisis. Global Health Action. 8:28871. 2015.

Simon T, Goldberg A, **Adini B**. Socializing in Emergencies - A Review of the Use of Social Media in Emergency Situations. International Journal of Information Management. 35(5):609-619. 2015.

Madar R, Aharonson-Daniel L, Plecht I, **Adini B**. Methodologies to train general hospital teams to manage a chemical warfare event. Journal of Israeli Military Medicine. 13(3): 13-17. 2016.

Shapira S, Aharonson-Daniel L, Bar-Dayan Y, Sykes D, **Adini B**. Knowledge, perceptions, attitudes and willingness to report to work in an earthquake: A pilot study comparing Canadian versus Israeli hospital nursing staff. International Emergency Nursing. 25:7-12. 2016.

Simon T, Goldberg A, Leykin D, **Adini B**. Kidnapping WhatsApp – Rumors during the search and rescue operation of three kidnapped youth. Computers in Human Behavior 64:183-190, 2016.

Simon T, Goldberg A, **Adini B**. Are Ethical norms and current policies still relevant in face of the recent mass terror events? Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 24:118, 2016.

Adini B, Ohana A, Furman E, Ringel R, Golan Y, Fleshler E, Keren U, Reisner S. Learning lessons in emergency management – the 4th International Conference on Healthcare System Preparedness and Response to Emergencies and Disasters. 2016.

Adini B, Bodas M, Nilsson H, Peleg K. Policies for managing Emergency Medical Services in mass casualty incidents. Injury. S0020-1383(17)30359-5. 2017.

Keret S, Nahari M, Merin O, Aharonson-Daniel L, Goldberg S, **Adini B**. Facilitating hospital emergency evacuation through uniform criteria. American Journal of Emergency Medicine. 35(5):681-684. 2017.

Adini B, Cohen O, Eide AW, Nilsson S, Aharonson-Daniel L, Herrera IA. Striving to be resilient: What concepts, approaches and practices should be incorporated in resilience management guidelines? Technological Forecasting & Social Change. 121:39-49. 2017

Adini B, Israeli A, Bodas M, Peleg K. Increasing perceived emergency preparedness by participatory policy-making (Think-Tanks). Disaster medicine and public health preparedness. 2018 Feb:1-6.

Yafe J, Walker BB, Amram O, Schuurman N, Randall E, Friger M, **Adini B**. EMS Volunteer first responders for optimizing management of mass casualty incidents. Disaster Medicine and Public Health Preparedness.1-8. 2018.

Madar R, **Adini B**, Greenberg D, Waisman Y, Goldberg A. Perspectives of health professionals on the best care settings for pediatric trauma casualties: a qualitative study. Israel Journal of Health Policy Research. 7(1): 12. 2018.

Peleg K, Bodas M, Shenhar G, **Adini B**. Wisdom of (using) the crowds: Enhancing disasters preparedness through public training in Light Search and Rescue. International Journal of Disaster Risk Reduction. 31:750-757. 2018.

Bodas M, Peleg K, Shenhar G, **Adini B**. Light Search and Rescue Training of High School Students in Israel – Longitudinal Study of Effect on Resilience and Self-Efficacy. International Journal of Disaster Risk Reduction. 2019.

Prof. Daniel I. Cohen, Ph.D.

Department of Epidemiology and Preventive Medicine
School of Public Health
Sackler Faculty of Medicine

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Epidemiology of Infectious Diseases

Positions

Professor of Epidemiology and Preventive 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

Member, Executive Committee (Hamerakezet), Tel Aviv University Senate

Chair, Middle East Consortium for Infectious Diseases Surveillance (MECIDS)

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

Tobias J, Kassem E, Rubinstein U, Bialik A, Vutukuru S, Navaro A, Rokney A, Valinsky L, Ephros M, **Cohen D**, Muhsen K. Involvement of main diarrheagenic Escherichia coli, with emphasis on enteroaggregative E. coli, in severe non-epidemic pediatric diarrhea in a high-income country. BMC Infect Dis. 2015;15(1):79

Muhsen K, Goren S. **Cohen D**. Helicobacter pylori Infection in Early Childhood and Growth at School Age. Helicobacter. 2015 ;20(6):410-7.

Muhsen K, Rubenstein U, Kassem E, Goren S, Schachter Y, Kremer A, Shulman L.M, Ephros M, **Cohen D**. A significant and consistent reduction in rotavirus gastroenteritis hospitalization of children under five years of age, following the introduction of universal rotavirus immunization in Israel. Hum Vaccin Immunother. 2015;11(10):2475-82

Muhsen K, Chodick G, Goren S, Anis E, Ziv-Baran T, Shalev V, **Cohen D.** Change in incidence of clinic visits for all-cause and rotavirus gastroenteritis in young children following the introduction of universal rotavirus vaccination in Israel. *Euro Surveill*. 2015;20(42).

Mor O, Bassal R, Michaeli, M, Wax M, Ram D, Cohen-Ezra O, **Cohen D**, Mendelson E, Ben-Ari Z, Shohat T. Prevalence of Hepatitis E virus antibodies in Israel. *Emerg Infect Dis*. 2015; 21: 692-694.

Behar A, Fookes MC, Goren S, Thomson NR, **Cohen D**. Whole genome analysis to detect potential vaccine-induced changes on Shigella sonnei genome. *Vaccine.* 2015;33:2978-83.

Bassal R, Schejter E, Bachar R, Perri T, Korach J, Jakobson-Setton A, Ben-David LH, **Cohen D**, Keinan-Boker L. Risk factors for cervical cancer and cin3 in Jewish women in israel – two case control studies. *Asian Pac J Cancer Prev*. 2016;17:2067-73.

Bassal R, Lerner L, Valinsky L, Agmon V, Peled N, Block C, Keller N, Keness Y, Taran D, Shainberg B, Ken-Dror S, Treygerman O, Rouach T, Lowenthal S, Shohat T, **Cohen D**. Trends in the epidemiology of *Campylobacteriosis* in Israel (1999-2012). *Foodborne Pathog Dis*. 2016;13:448-55.

Baker KS, Dallman TJ, Behar A, Weill FX, Gouali M, Sobel J, Fookes M, Valinsky L, Gal-Mor O, Connor TR, Nissan I, Bertrand S, Parkhill J, Jenkins C, **Cohen D**, Thomson NR. Travel- and community-based transmission of multidrug-resistant shigella sonnei lineage among international orthodox Jewish communities. *Emerg Infect Dis*. 2016;22:1545-53.

Glatman-Freedman A, Kaufman Z, Kopel E, Bassal R, Taran D, Valinsky L, Agmon V, Shpriz M, **Cohen D**, Anis E, Shohat T. Near real-time space-time cluster analysis for detection of enteric disease outbreaks in a community setting. *J Infect*. 2016;73:99-106.

Muhsen K, Kassem E, Rubenstein U, Goren S, Ephros M, **Cohen D,** Shulman LM. Incidence of rotavirus gastroenteritis hospitalizations and genotypes, before and five years after introducing universal immunization in Israel. *Vaccine*. 2016; 34:5916-5922.

Miller-Roll T, Na'amnih W, **Cohen D**, Carmeli Y, Adler A. Molecular types and antimicrobial susceptibility patterns of Clostridium difficile isolates in different epidemiological settings in a tertiary care center in Israel. *Diagn Microbiol Infect Dis*. 2016; 86:450-454.

Bassal R, Weil M, **Cohen D**, Mendelson E, Shohat T. Seroprevalence of Hepatitis A 12-years following the implementation of toddlers' vaccination: A population based study in Israel. *Pediatr Infect Dis J.* 2017 May 11. (in press).

Na'amnih W, Adler A, Miller-Roll T, **Cohen D**, Carmeli Y. Incidence and Risk Factors for Community and Hospital acquisition of Clostridium Difficile Infection in Tel Aviv Sourasky Medical Center. *Infect Cont Hosp Epidemiol* 2017.

Muhsen M, Anis E, Rubinstein U, Kassem E, Goren S, Shulman L, Ephros M, **Cohen D**. Effectiveness of rotavirus pentavalent vaccine under a universal immunization program in Israel, 2011-2015: a case-control study. *Clin Microbiol Infect* 2017 (in press).

Launay O, Lewis DJM, Anemona A, Loulergue P, Leahy J, Sciré AS, Maugard A, Marchetti E, Zancan S, Huo Z, Rondini S, Marhaba R, Finco O, Martin LB, Auerbach J, **Cohen D**, Saul A, Gerke C, Podda A. Safety profile and immunologic responses of a novel vaccine against shigella sonnei administered intramuscularly, intradermally and intranasally: results from two parallel randomized phase 1 clinical studies in healthy adult volunteers in Europe. *EBioMedicine.* 2017.

Bassal R, Shohat T, Kaufman Z, Mannasse B, Shinar E, Amichay D, Barak M, Ben-Dor A, Bar Haim A, **Cohen D**, Mendelson E, Lustig Y. The seroprevalence of West Nile Virus in Israel: A nationwide cross sectional study. *PLoS One.* 2017.

Muhsen K, Sinnreich R, Beer-Davidson G, Nassar H, **Cohen D**, Kark JD. Sero-prevalence of Helicobacter pylori CagA immunoglobulin G antibody, serum pepsinogens and haemoglobin levels in adults. *Sci Rep.* 2018;8:17616.

Behar A, Baker KS, Bassal R, Ezernitchi A, Valinsky L, Thomson NR, **Cohen D**. Microevolution and patterns of transmission of Shigella sonnei within cyclic outbreaks Shigellosis, Israel. *Emerg Infect Dis*. 2018;24:1335-1339.

Katz D, Ben-Chetrit E, Sherer SS, **Cohen D**, Muhsen K. Correlates of non-typhoidal Salmonella bacteraemia: a case-control study. *Int J Infect Dis.* 2019. pii: S1201-9712(19)30039-6.

Reviews

Muhsen K, **Cohen D**. Rotavirus vaccines in Israel: uptake and impact. *Hum Vacc Immunotherap*. 2017; 13 (7).

Green MS, LeDuc J, **Cohen D**, Franz DR. Confronting the threat of bioterrorism: realities, challenges and defensive strategies. *Lancet Inf Dis* 2018.

Grants

2017-2019	Ministry of Agriculture, Development of a New vaccine Against Brucellosis
2018-2019	Connecting Organizations for Regional Disease Surveillance (CORDS), PI: InterNetwork Project on “Digital event information and data collection at community-level in cross-border areas”
2918-2020	Bill and Melinda Gates Foundation PI: Extended Shigella Vaccine Immunogenicity Studies

Prof. Jiska Cohen-Mansfield, Ph.D.

Department of Health Promotion
School of Public Health
Sackler Faculty of Medicine

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Email: jiska@post.tau.ac.il

Aging and End of Life

Positions

Professor, Department of Health Promotion, Sackler Faculty of Medicine

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

Dr Igor Orshtein Chair for Research in Aging

Research

Health and Mental Health Promotion in older persons:

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

End of Life

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

Publications

Cohen-Mansfield J, Perach R. (2015) Interventions for alleviating loneliness among older persons: a critical review. Am J Health Promot. 29:e109-25.

Cohen-Mansfield J, Ray CA. Whose responsibility is it to make life worth

Cohen-Mansfield J, Cohen R, Buettner L, Eyal N, Jakobovits H, Rebok G, Rotenberg-Shpigelman S, Sternberg S. Interventions for older persons reporting memory difficulties: a randomized controlled pilot study. Int J Geriatr Psychiatry. 2015;30(5):478-86.

Cohen-Mansfield J, Marx MS, Dakheel-Ali M, Thein K. The use and utility of specific nonpharmacological interventions for behavioral symptoms in dementia: an exploratory study. Am J Geriatr Psychiatry. 2015;23(2):160-70.

Kenigsberg PA, Aquino JP, Bérard A, Gzil F, Andrieu S, Banerjee S, Brémond F, Buée L, **Cohen-Mansfield J**, Mangialasche F, Platel H, Salmon E, Robert P. Dementia beyond 2025: Knowledge and uncertainties. Dementia (London). 2016;15:6-21.

Cohen-Mansfield J, Jensen B. Intergenerational programs in schools: Prevalence and perceptions of impact. J Appl Gerontol. 2015 Feb 19. pii: 0733464815570663

Cohen-Mansfield J, Dakheel-Ali M, Marx MS, Thein K, Regier NG. Which unmet needs contribute to behavior problems in persons with advanced dementia? Psychiatry Res. 2015;228(1):59-64.

Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Jensen B. Sources of discomfort in persons with dementia: Scale and initial results. Behavioural Neurology, 2015, Article ID 732832.

Ray CA, Ingram V, **Cohen-Mansfield J**. Systematic review of planned care transitions for persons with dementia. Neurodegener Dis Manag. 2015;5(4):317-31.

Cohen-Mansfield J, Hazan H, Lerman Y, Shalom V. Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. Int Psychogeriatr. 2016 Apr;28(4):557-76. doi: 10.1017/S1041610215001532. Epub 2015 Oct 1. PubMed PMID: 26424033.

Cohen-Mansfield J. Non-pharmacological interventions for agitation in dementia: various strategies demonstrate effectiveness for care home residents; further research in home settings is needed. Evid Based Nurs. 2016;19(1):31.

Cohen-Mansfield J. Predictors of smoking cessation in old-old age. Nicotine Tob Res. 2016 Jan 17.

Cohen-Mansfield J, Cohen R, Golander H, Heinik J. The impact of psychotic symptoms on the persons with dementia experiencing them. Am J Geriatr Psychiatry. 2016;24(3):213-20.

Cohen-Mansfield J, Shmotkin D, Hazan H. Changes in religiosity in old age: an exploratory study. Int J Aging Hum Dev. 2016

Cohen-Mansfield, J, and Regev, I. Retirement preparation programs: An examination of retirement perceptions, self-mastery, and well-being. Research on Social Work Practice. 2016,

Cohen-Mansfield, J., Perach, R. Kadmon Stern, T., Albeck, S., Rotem, D., Arnow, TL, Lerma, Y. Telephone hotline for aging: Information needs, quality of service, and insights *International Social Work* 2016

Cohen-Mansfield J, Gavendo R, Blackburn E. Activity preferences of persons with dementia: An examination of reports by formal and informal caregivers. Dementia (London). 2017;1471301217740716.

Cohen-Mansfield J, Sela AH, Iecovich E, Golander H. Quality of care for frail older persons in a homecare setting: what is it and how can it be measured? Int Psychogeriatr. 2017;2:1-9.

Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, **Cohen-Mansfield J**, Ismail Z, Lyketsos C, Miller DS, Musiek E, Osorio RS, Rosenberg PB, Satlin A, Steffens D, Tariot P, Bain LJ, Carrillo MC, Hendrix JA, Jurgens H, Boot B. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimers Dement (N Y). 2017;3:440-449.

Cohen-Mansfield J, Cohen R, Skornick-Bouchbinder M, Brill S. What is the End of Life period? Trajectories and characterization based on primary caregiver reports. J Gerontol A Biol Sci Med Sci. 2017 Oct 12.

Cohen-Mansfield J. Activity groups for persons with dementia: Personal predictors of participation, engagement and mood. Psychiatry Res. 2017;257:375-380.

Cohen-Mansfield J, Skornick-Bouchbinder M, Hoshen M, Brill S. The relationship between health services standardized costs and mortality is non-linear: Results from a large HMO population. Health Policy. 2017;121:1008-1014.

Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S, Burns A, **Cohen-Mansfield J**, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care. Lancet. 2017;pii: S0140-6736(17)31363-6.

Cohen-Mansfield J, Skornick-Bouchbinder M, Cohen R, Brill S. Treatment and communication-that is what matters: an analysis of complaints regarding end-of-life care. J Palliat Med. 2017;20:1359-1365.

Cohen-Mansfield J, Ray CA, Hai T, Marcu C, Callahan BL, Freedman M. The ultimate outlier: transitional care for persons with dementia and BPSD. Curr Alzheimer Res. 2017;14:969-977.

Cohen-Mansfield J, Golander H, Iecovich E, Jensen B. Social engagement care for frail older persons: desire for it and provision by live-in migrant caregivers. J Gerontol B Psychol Sci Soc Sci. 2017.

Cohen-Mansfield J, Golander H, Cohen R. Rethinking psychosis in dementia: an analysis of antecedents and explanations. Am J Alzheimers Dis Other Demen. 2017;32:265-271.

Cohen-Mansfield J, Hai T, Comishen M. Group engagement in persons with dementia: The concept and its measurement. Psychiatry Res. 2017;251:237-243

Berenbaum R, Tziraki C, **Cohen-Mansfield J**. The right to mourn in dementia: To tell or not to tell when someone dies in dementia day care. Death Stud. 2017;41:353-359.

Cohen-Mansfield J, Sela AH, Iecovich E, Golander H. Quality of care for frail older persons in a homecare setting: what is it and how can it be measured? *Int Psychogeriatr*. 2017:1-9.

Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, **Cohen-Mansfield J**, Ismail Z, Lyketsos C, Miller DS, Musiek E, Osorio RS, Rosenberg PB, Satlin A, Steffens D, Tariot P, Bain LJ, Carrillo MC, Hendrix JA, Jurgens H, Boot B. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. *Alzheimers Dement* (NY). 2017;3(3):440-449.

Cohen-Mansfield J. Do reports on personal preferences of persons with dementia predict their responses to group activities? *Dement Geriatr Cogn Disord*. 2018;46(1-2):100-108.

Cohen-Mansfield J, Jensen B. Attendance in recreational groups for persons with dementia: the impact of stimulus and environmental factors. *Am J Alzheimers Dis Other Demen*. 2018:1533317518788158.

Cohen-Mansfield J. The impact of group activities and their content on persons with dementia attending them. *Alzheimers Res Ther*. 2018;10(1):37.

Cohen-Mansfield J. Non-pharmacological interventions for persons with dementia: what are they and how should they be studied? Int Psychogeriatr. 2018;30(3):281-283. Cohen-Mansfield J, Hazan H, Lerman Y, Shalom V, Birkenfeld S, Cohen R. Efficacy of the I-SOCIAL intervention for loneliness in old age: Lessons from a randomized controlled trial. *J Psychiatr Res*. 2018.

Cohen-Mansfield J, Gavendo R, Blackburn E. Activity Preferences of persons with dementia: An examination of reports by formal and informal caregivers. *Dementia* (London). 2017:1471301217740716.

Cohen-Mansfield J, Cohen R, Skornick-Bouchbinder M, Brill S. What Is the End of Life Period? Trajectories and Characterization Based on Primary Caregiver Reports. *J Gerontol A Biol Sci Med Sci*. 2018;73(5):695-701.

Cohen-Mansfield, J., Perach, R. Kadmon Stern, T., Albeck, S., Rotem, D., Arnow, TL, Lerma, Y. Telephone hotline for aging: Information needs, quality of service, and insights International Social Work, 2018, 61(5), 681-691

Cohen-Mansfield, J., & Regev, I. (2018). Retirement preparation programs: An examination of retirement perceptions, self-mastery, and well-being. Research on Social Work Practice, 28(4), 428-437.

Teshuva, K., **Cohen-Mansfield, J.**, Iecovich, E., Golander, H. Like one of the family? Understanding relationships between migrant live-in care workers and older care recipients in Israel. *Ageing & Society.* 2018:1-22.

Chapters

Cohen-Mansfield, J. (2015). Behavioral and Psychological Symptoms of Dementia In: P.A. Lichtenberg, B.T. Mast (Eds.) APA Handbook of Clinical Geropsychology. Vol 2. Chapter 11, pp. 271-317. American Psychological Association.

Cohen-Mansfield, J. (2017) Notes on the Israeli National Program for Addressing Alzheimer's Disease and Other Types of Dementia. In Schmidhuber, Bergemann, and Frewer (Eds.) Ethical Dimentions of International Dementia Plans. New Strategies for Human Rights. pp. 67-76. Verlag Königshausen & Neeumann – Würzburg.

Cohen-Mansfield J, Skornick-Bouchbinder M, Brill S. Trajectories of end of life: a systematic review. J Gerontol B Psychol Sci Soc Sci. 2018;73(4):564-572.

Grants

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

Dr. Yftach Gepner, Ph.D.

School of Public Health,
Sackler Faculty of Medicine
and Sylvan Adams Sports Institute

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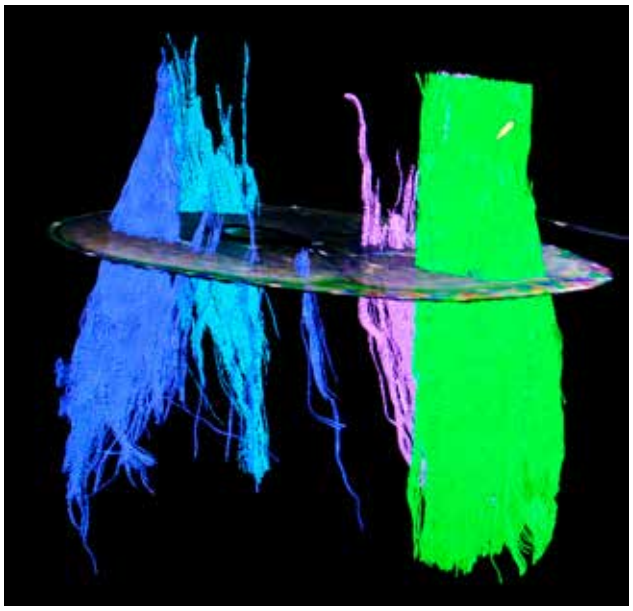
The Effect of Physical Activity and Exercise Inteventions on Cardiometabolic Health

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

The physiology response to exercise is complex, highly variable, and involves a myriad of adaptive responses in multiple organ systems. The lab is mainly interested in studying the health benefits of exercise on disease prevention and the improvement of physical health, fitness, and muscle strength. Our research focuses on better understanding the extent, intensity, and type of physical activity needed to improve health under a wide range of clinical conditions in a personal manner using cutting-edge technologies, including magnetic resonance imaging (MRI) for assessing muscle damage and adipose tissue distribution, body composition, as well as markers of cardiometabolic health. Our multi-disciplinary research in the area of physical activity and the public health domain, using a large-scale randomized clinical trial design is aimed to develop, test, and implement lifestyle interventions that promote health and prevent human diseases. We also collaborate with other research groups to better understand the mechanism underlying the acute and chronic adaptive response to exercise training.



Muscle volume and integrity assesment using diffusion tensor imaging (DTI), a sensitive magnetic resonance imaging (MRI) technique used to assess subclinical signs of muscle injury. DTI assessment is predicated on cell membranes and other structures constraining water diffusion. Water movement is evaluated by determining the three orthogonal directions of water diffusion, called eigenvectors, and their intensities, called eigenvalues. An axial slice of the middle hip was used to determine DTI in four muscles: Light blue- rectus femoris; Dark blue- vastus lateralis; Green- adductor magnus; and Pink- semitendinosus.

Publications

Gepner Y*, Bril N*, Shelef I*, Schwarzfuchs D, Serfaty D, Rein M, Cohen N, Shemesh E, Tangi-Rosental O, Sarusi B, Goshen E, Kenigsbuch S, Chassidim Y, Golan R, Witkow S, Henkin Y, Stampfer MJ, Rudich A, Shai I. Higher visceral adiposity is associated with an enhanced early thermogenic response to carbohydrate-rich food. Clinical Nutrition. 2015. 35(2):422-427. *equal contribution.

Henkin Y, Kovsa J, **Gepner Y**, Shai I. Diets and morbid tissues - history counts, present counts. British Journal of Nutrition. 2015. 113 Suppl 2:S11-8.

Gepner Y, Henkin Y, Schwarzfuchs D, Golan R, Durst R, Shelef I, Harman-Boehm I, Spitzen S, Witkow S, Novack L, Friger M, Tangi-Rosental O, Sefarty D, Bril N, Rain M, Cohen N, Chassidim Y, Sarusi B, Wolak T, Stampfer J M, Rudich A, Shai I. Differential effect of initiating moderate red wine consumption on 24-h blood pressure by alcohol dehydrogenase genotypes; Randomized trial in type 2 diabetes. American Journal of Hypertension. 2016. 29(4):476-83.

Haim Y, Blüher M, Slutsky N, Goldstein N, Klöting N, Harman-Boehm I, Kirshtein B, Ginsberg D, Gericke M, Guiu Jurado E, Kovsan J, Tarnovscki T, Kachko

L, Bashan N, **Gepner Y**, Shai I, Rudich A. Obesity-associated elevated adipose tissue autophagy gene expression in humans: a potential non-cell-cycle –dependent function of E2F1. Autophagy. 2015. 2;11(11):2074-2088.

Gepner Y*, Golan R*, Harman-Boehm I, Henkin Y, Schwarzfuchs D, Shelef I, Durst R, Kovsan J, Bolotin A, Leitersdorf E, Spitzen S, Blag S, Shemesh E, Witkow S, Tangi-Rosental O, Chassidim Y, Liberty F L, Sarusi B, Ben-Avraham S, Helander A, Ceglarek U, Stumvoll M, Blüher M, Thiery J, Rudich A, Stampfer J M, Shai I. Effects of moderate alcohol intake on cardiometabolic para meters in adults with type 2 diabetes mellitus: a randomized controlled trial. Annals of Internal Medicine. 2015. 20;163(8):569-79. *equal contribution.

Slutsky N, Vaterescu M, Haim Y, Goldstein N, Kirshtein B, Harman-Boehm I, **Gepner Y**, Shai I, Bashan N, Blüher M, Assaf A. Decreased adiponectin links elevated adipose tissue autophagy with adipocyte endocrine dysfunction in obesity. International Journal of Obesity. 2016. 40(6):912-20.

Serfaty D, Rein M, Schwarzfuchs D, Shelef I, **Gepner Y**, Bril N, Cohen N, Shemesh E, Tangi-Rosental O, Sarusi B, Kovsan J, Kenigsbuch S, Chassidim Y, Golan R, Witkow S, Henkin Y, Stampfer M J, Rudich A, Shai I. Abdominal fat sub-depots, energy expenditure, and resting metabolic rate: Magnetic resonance imaging study. Clinical Nutrition. 2016. 5614(16)30103-0.

Hoffman J R, **Gepner Y**, Stout R J, Hoffman W M, Ben-Dov D, Funk S, Daimont I, Jajtner R A, Townsend R J, Church D D, Shelef I, Rosen P, Avital G, Chen Y, Frankel H, Ostfeld I. β-Hydroxy-β-methylbutyrate attenuates the cytokine response during sustained military training. Nutrition research. 2016. 36(6):553-63.

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Cardiovascular Disease Epidemiology

Positions

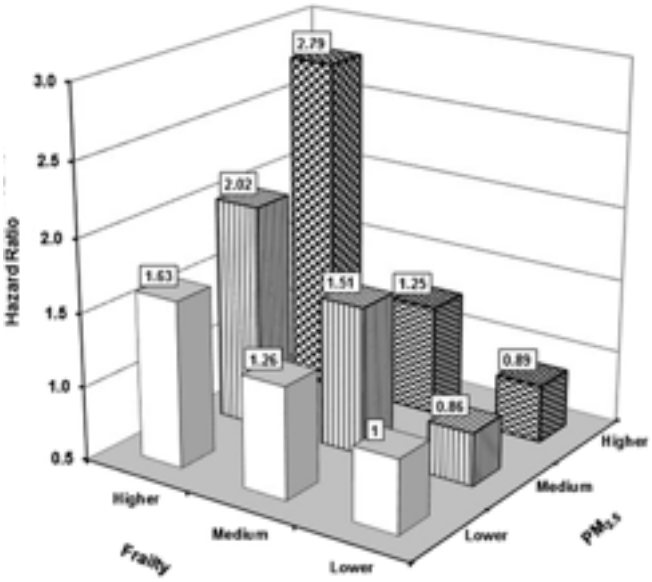
Professor, Sackler Faculty of Medicine

Adjunct Faculty, Health Sciences Research, College of Medicine, Mayo Clinic, Minnesota

Chair, Dept. of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine

Research

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



Effect modification of the association between chronic exposure to PM2.5 and post-myocardial infarction mortality by frailty status. A positive dose-response relationship between chronic exposure to PM2.5 and mortality is evident among frailer participants only. PM2.5, particulate matter ≤2.5 μm in diameter. Figure created by authors from data in Gerber et al. *J Am Coll Cardiol*. 2014;63:1698–99.

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Grants

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

Positions

Professor Emeritus, Sackler Faculty of Medicine

Honorary Member, Israeli Heart Society

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

Research

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

Current involvement:

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

Epidemiology of stroke.

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

Cancer incidence in the IIHD.

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

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

Publications

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Enhancing Performance and Motor Learning Through Coaching Strategies

Position

Senior Lecturer

Research

We study ways to optimize coaching interventions rooted in motor learning and sports science to enhance physical performance, increase learning processes of new motor skills and motivation to exercise, and to reduce sport injuries. I take a special interest in the effects of directing one's attention to a particular aspect of a motor task: self-observation techniques, including mirrors and videos of motor task execution, and the restructuring of training and rehabilitation programs in view of individual preferences. On the one hand, we study athletes to improve performance in their related disciplines, and on the other hand, we study sedentary and injured populations to probe public health issues.

Publications

I. Halperin, D. Copithrone, and D.G. Behm. Unilateral isometric muscle fatigue decreases force production and activation of contralateral knee extensors but not elbow flexors. Applied Physiology, Nutrition and Metabolism 2015; 39, 1338-1344.

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Reviews

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I. Halperin and A. Vigotsky. Letter to editor: The mind-muscle connection in resistance training: friend or foe? European Journal of Applied Physiology 2016; 116, 863-4.

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Reproductive Epidemiology

Positions

Professor, Sackler Faculty of Medicine

Chair, Teaching Committee, School of Public Health

Director, National Registry for In Vitro Fertilization (IVF) Treatments

Research

Our research agenda is focused on women and children's health with a special emphasis on reproductive epidemiology in multi-center and national and international studies related to health policy. We investigate the short- and long-term effects of exposure to assisted reproductive technologies in women and children including obstetric outcomes, congenital malformations, cancer and motor and cognitive development. In addition, we evaluate the role of various predictive factors that might influence the outcome of IVF treatments including age, environmental exposures and stress. Our research involves population-based studies in which we integrate epidemiological and biostatistical methods to analyze data from multiple sources including interviews, medical records' data, biosamples and national registries.

Publications

Pinhas-Hamiel O, Levek-Motola N, Kaidar K, Boyko V, Tisch E, Mazor-Aronovitch K, Graf-Barel C, Landau Z, **Lerner-Geva L**, Frumkin Ben-David R. Prevalence of overweight, obesity and metabolic syndrome components in children, adolescents and young adults with type 1 diabetes mellitus. Diabetes Metab Res Rev. 31:76-84, 2015.

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

Positions

Associate Professor Sackler Faculty of Medicine

Research

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

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

Publications

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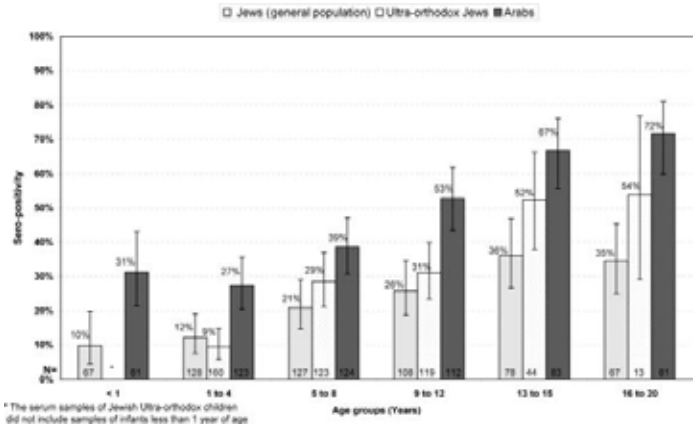

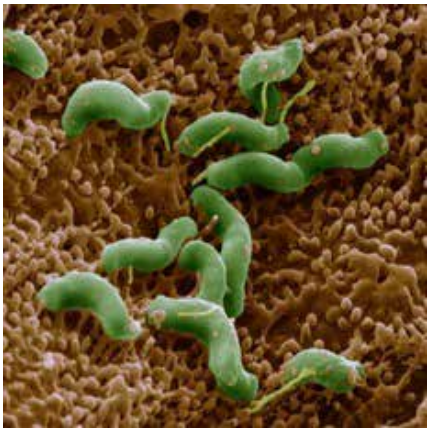

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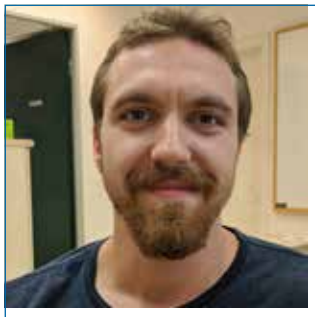
Grants

2016-2019	BSF (PI with Prof. MM Levine, USA)
2018-2019	Stlotz Fund, Sackler Faculty of Medicine, Tel Aviv University
2018-2021	Israel National Institute for Health Policy and Health Services Research



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Computational Epidemiology of Infectious Diseases

Positions

Senior Lecturer, Sackler Faculty of Medicine and Raymond & Beverly Sackler Faculty of Exact Sciences

Research

In our research we aim to tackle major topics in infectious diseases and how they are affected by environmental factors, using computational tools and insights from evolutionary and ecological processes. In particular, we are interested in changes of antibiotic resistance frequencies, due to antibiotic misuse, and in the effect of climate on the dynamics of mosquito-borne diseases. We use an interdisciplinary approach that combines mathematical models and statistical methods to understand the underlying dynamics of the questions at hand, and to predict the outcomes of possible interventions

Publications

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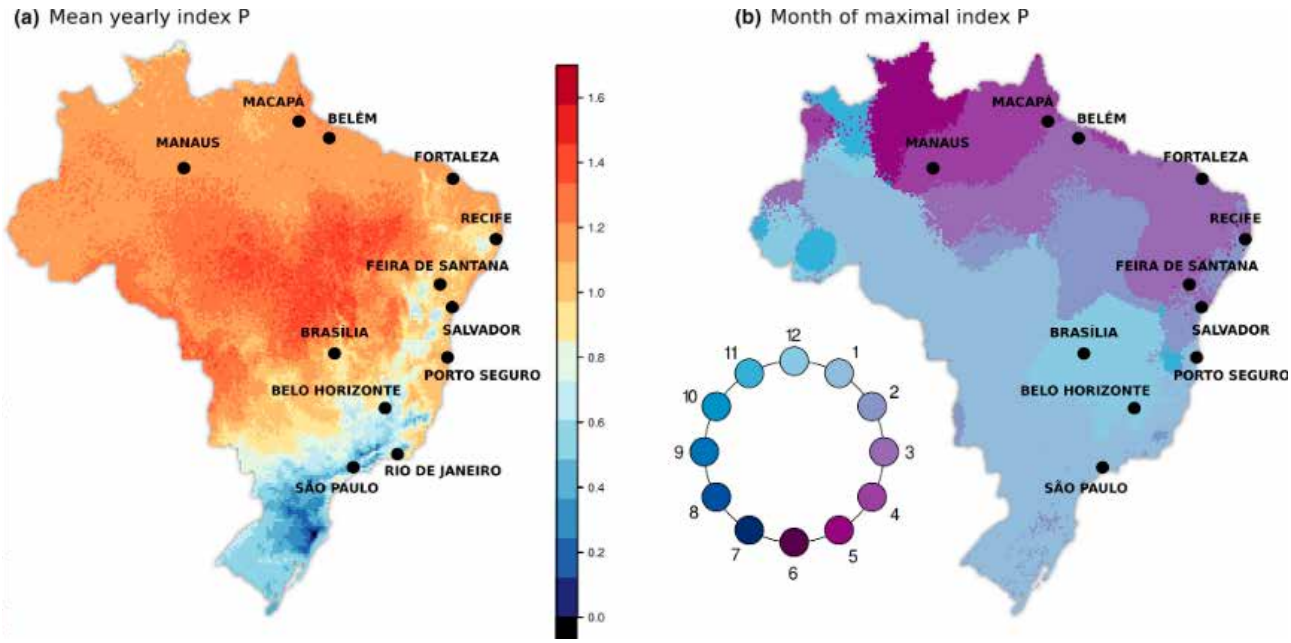

Spatiotemporal characterization of index P, representing the potential of Dengue transmission across Brazil. (a) Map presents the mean index P per pixel. Values coloured according to scale on the right. (b) Using the estimated index P of each pixel, with 12 points representing months, the month with highest index P is identified. Each pixel is coloured according to that month, with the colour scale represented in a circle.

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Epidemiology of Parkinson's Disease and Environmental Epidemiology

Positions

Associate Professor 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

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

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Rosenberg A, Weinberger M, Paz S, Valinsky L, Agmon V, **Peretz C**. Ambient temperature and age-related notified Campylobacter infection in Israel: A 12-year time series study. *Environ Res.* 2018;164:539-545.

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Prof. Laura (Leah) J. Rosen Ph.D.

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Improving Public Health, and Control Tobacco Use and Exposure

Positions

Associate Professor Sackler Faculty of Medicine

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

Affiliated Faculty, Harvard Global Center for Tobacco Control

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

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

External Steering Committee Member, World Health Organization EvipNet

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

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

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Rosen L, Galili T, Kott J, Goodman M, Freedman L. Diminishing effect of smoking cessation medications during the first year: A meta-analysis of randomized controlled trials. Addiction 2018;113(5):805-816.

Berman T, Mery N, Keinan-Boker L, Shimony T, Goldsmith R, Geva H, Barnett-Itzhaki Z., **Rosen L**. Exposure to environmental tobacco smoke in non-smoking adults in Israel. Israel Journal of Health Policy Research 2018;7:33.

Myers V, Shiloh S, **Rosen L**. Parental perceptions of children's exposure to tobacco smoke: Development and validation of a new measure. BMC Public Health. 18:1031.

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Berman T, Barnett-Itzhaki1 Z, Axelrod R, Keinan-Boker L, Shimony T, Goldsmith R, Göen T, **Rosen L**. Socioeconomic inequalities in exposure to environmental tobacco smoke in children in Israel: Results of the second Israel biomonitoring survey. *Environ Int.* 2018;121(Pt 1):643-648.

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Reviews and Chapters

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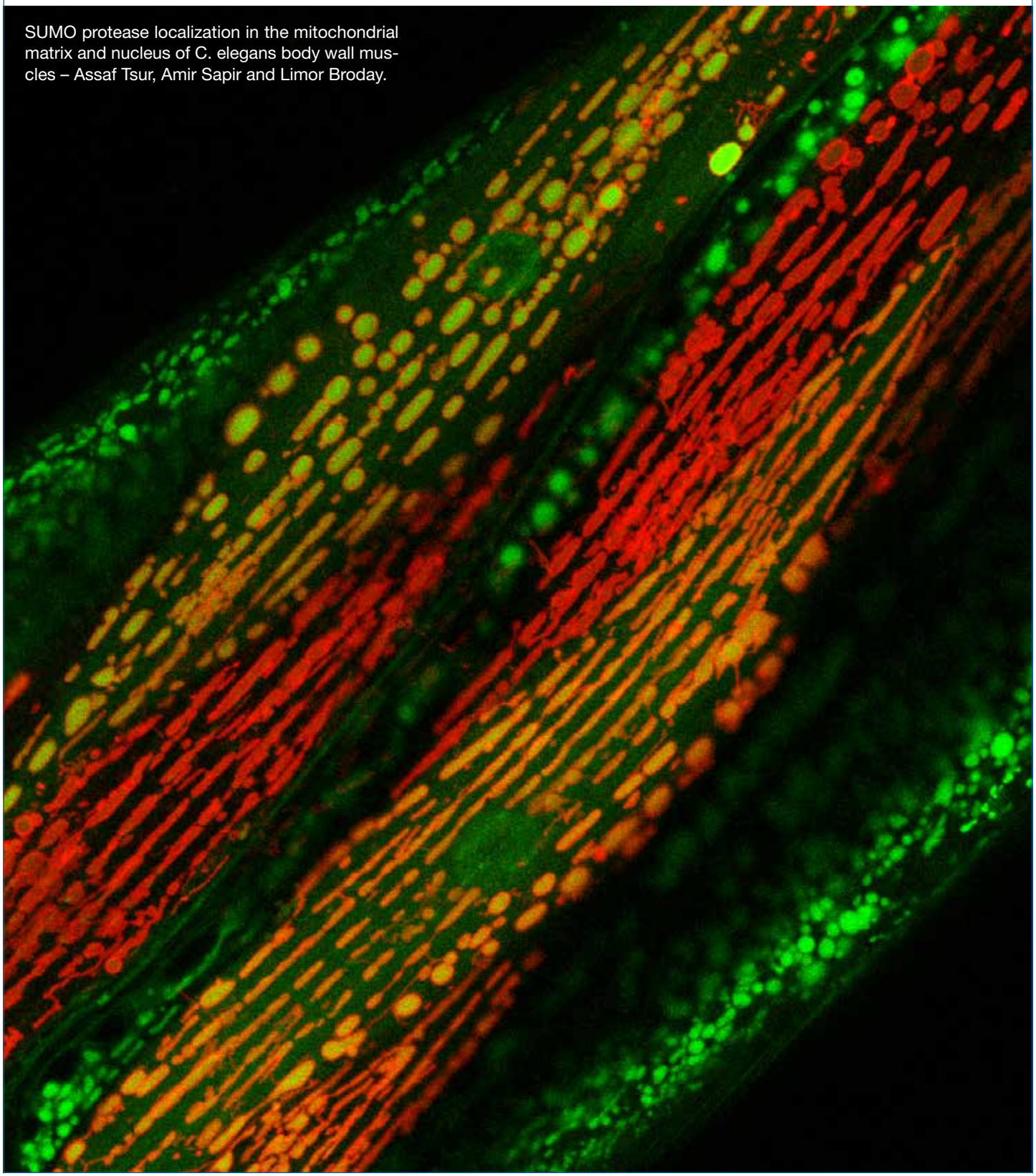
Reproduction, Development and Evolution



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

Dr. Limor Broday, Ph.D.

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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

Tsur, A., Bening Ab-Shach, U., and **Broday, L.** 2015. ULP-2 SUMO protease regulates E-cadherin recruitment to adherens junctions. *Developmental Cell.* 35:1-15, 2015. *Preview:* Adhesion with a SUMO. Developmental Cell. 35, 2015. *Featured in Research Highlight:* SUMO controls a tug of war at junctions. Nature Rev. Mol. Cell. Biol. 16:641, 2015.

Sagi D, Rak R, Gingold H, Adir I, Maayan G, Dahan O, **Broday L**, Pilpel Y, Rechavi O. 2016. Tissue- and time-specific expression of otherwise identical tRNA genes. *PLoS Genet.* 25;12(8):e1006264.

Surana, P., Gowda, C., Tripathi, V., **Broday, L.**, and Das, R. Structural and functional analysis of SMO-1, the SUMO homolog in *Caenorhabditis elegans. PLoS One*. 2017

Savion N, Levine A, Kotev-Emeth S, Bening Abu-Shach U, **Broday L**. S-allylmercapto-N-acetylcysteine protects against oxidative stress and extends lifespan in *Caenorhabditis elegans*. *PLoS One.* 2018;13:e0194780.

Thiruvalluvan M, Barghouth PG, Tsur A, **Broday L**, Oviedo NJ. SUMOylation controls stem cell proliferation and regional cell death through Hedgehog signaling in planarians. *Cell Mol Life Sci*. 2018;75:1285-1301.

Reviews

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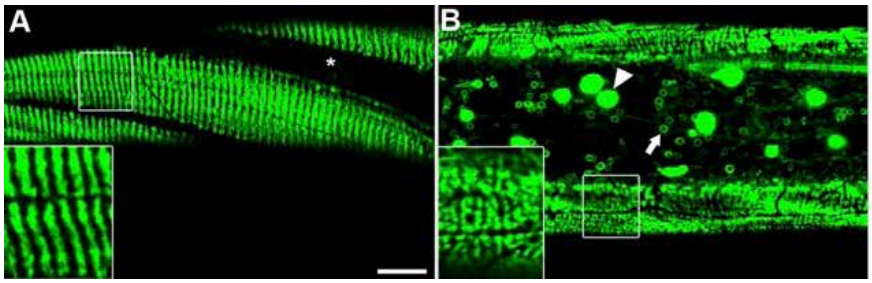

(A) Organization of the *C. elegans* epidermal intermediate filament protein IFB-1 in circumferential bands in wild-type animal.
(B) Abnormal filaments and formation of inclusions in *smo-1* deleted worms.

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Genetic and Hormonal Regulation of Bone Metabolism

Position

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Anatomy & Anthropology

Research

Genetics: Our laboratory focuses on the genetic and hormonal regulation of bone remodeling, microarchitecture and strength. These traits have a high degree of heritability, and one aspect of our research is to characterize new genetic determinants of bone remodeling as well as elucidate the mechanism of action of selected genes. Our GWAS confirmed the role of AVP (vasopressin) and OXT (precursor of oxytocin) in bone and identified for the first time Rhbdf2 as a significant determinant of bone structure.

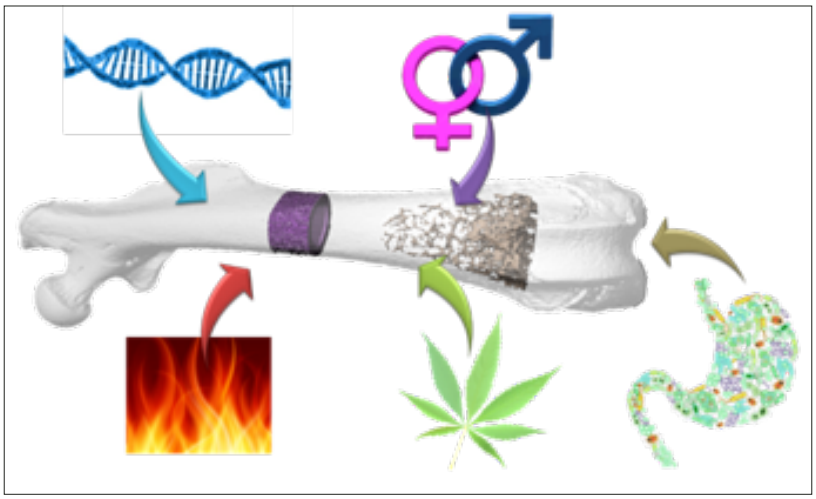
Erythropoietin: Epo is the main hormone that regulates blood cells production. We investigated the role of Epo in bone remodeling in general and on the bone cells in particular.

Inflammation-induced osteolysis: Today, most dental implants undergo surface roughening to enhance osseointegration. However, ultrasonic scaling performed routinely for oral hygiene releases particles from titanium implants. We found that these particles stimulate the secretion of inflammatory cytokines and induce osteoclastogenesis in vitro and in vivo.

Gut microbiota: The variety and number of bacteria in our gastro-intestinal tract is greater than our own genome. Studying their roles in regulating physiological and pathological processes is in the forefront of biomedical research. In a collaboration with the Weizmann Institute and the Technion, we are conducting a large-scale study aimed at identifying the bacterial strains that affect or benefit our bone density.

Cannabinoids: Cannabis-derived and endogenous cannabinoids are important regulators of bone cells. We investigate the beneficial actions of cannabinoids in bone fracture healing, osteoporosis, Osteogenesis Imperfecta, and inflammation-induced bone destruction.

Recently, we started investigating a possible role for endocannabinoids in the regulation of immune cells by bone cells.



Regulation of bone turnover and microstructure by genetic determinants, inflammation, sex hormones and cannabis/endocannabinoids.

Publications

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Kogan NM, Bajayo A, Wasserman E, Raphael B, Breuer A, Stok KS, Villarreal Escudero AV, Sondergaard R, Attar-Namdar M, Friedlander-Barenboim S, Mechoulam R, Müller R, Melamed E, **Gabet Y***, Bab I*. (2015) Cannabidiol, a major non-psychotrophic cannabis constituent enhances fracture healing and stimulates lysil hydroxylase activity in osteoblasts. *J Bone Min Res.* 30(10):1905-1913. * Equal contribution, corresponding author

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* **Equal contribution**

Hershkovitz I, Weber GW, Fornai C, Gopher A, Barkai R, Slon V, Quam R, **Gabet Y** and Sarig R. (2015) New Middle Pleistocene dental remains from Qesem Cave (Israel). *Quaternary International*; 398, 148-158.

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Masarwi M, **Gabet Y**, Dolkart O, Brosh T, Shamir R, Phillip M, Gat-Yablonski G. (2016) Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats. *Br J Nutr*. 116(1):59-69.

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* Equal contribution

Rauner M, Franke K, Murray M, Singh RP, Hiram-Bab S, Platzbecker U, Gassmann M, Socolovsky M, Neumann D, **Gabet Y**, Chavakis T, Hofbauer LC, Wielockx B. (2016) Increased EPO Levels Are Associated with Bone Loss in Mice Lacking PHD2 in EPO-Producing Cells. *J Bone Miner Res*, 31(10):1877-87.

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in Cognitive/Motor Delayed ADNP-Mutated Children, *Translational Psychiatry*, 7(2):e1043.

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van den Bosch MH, Blom AB, Kram V, Maeda A, Sikka S, **Gabet Y**, Kilts TM, van den Berg WB, van Lent PL, van der Kraan PM, Young MF. (2017) WISP1/CCN4 aggravates cartilage degeneration in experimental osteoarthritis. *Osteoarthritis Cartilage*. 25(11):1900-1911. doi: 10.1016/j.joca.2017.07.012.

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Vinik Y, Shatz-Azoulay H, Hiram-Bab S, Kandel L, **Gabet Y**, Rivkin G, Zick Y. (2017) Ablation of the mammalian lectin galectin-8 induces bone defects in mice. *FASEB J*. pii: fj.201700716R.

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Sabag E, Halperin E, Liron T, Hiram-Bab S, Frenkel B, **Gabet Y**. Hormone-independent sexual dimorphism in the regulation of bone resorption by Krox20. J Bone Miner Res. 2019;34:2277-2286.

Baraghithy S, Smoum R, Drori A, Hadar R, Gammal A, Hirsch S, Attar-Namdar M, Nemirovski A, **Gabet Y**, Langer Y, Pollak Y, Schaaf CP, Rech ME, Gross-Tsur V, Bab I, Mechoulam R, Tam J. Magel2 modulates bone remodeling and mass in prader-willi syndrome by affecting oleoyl serine levels and activity. J Bone Miner Res. 2019;34:93-105.

Levy R, Levet C, Cohen K, Freeman M, Mott R, Iraqi F, **Gabet Y**. A genome-wide association study in mice reveals a role for Rhbdf2 in skeletal homeostasis. Sci Rep. 2020;10:3286

Kolomansky A, Hiram-Bab S, Ben-Califa N, Liron T, Deshet-Unger N, Mittelman M, Oster HS, Rauner M, Wielockx B, Neumann D*, **Gabet Y***. Erythropoietin mediated bone loss in mice is dose-dependent and mostly irreversible. Int J Mol Sci. (2020)

Grants

2017-2021	Israel Science Foundation
2018-2021	German-Israeli Foundation (GIF)
2019-2021	Emerson Collective
2019-2022	Israel Ministry of Science and Space
2019-2020	Gassner Fund
2020-2021	Israel Cancer Association (with Drorit Neumann)
2020-2022	Dotan Research Center (with Drorit Neumann)

Prof. Israel Hershkovitz, Ph.D.

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Evolutionary Medicine, Paleopathology and Bio-history

Position

Professor Emeritus

Director, The Shmunis Family Anthropology Institute
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 'agriculuture 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.

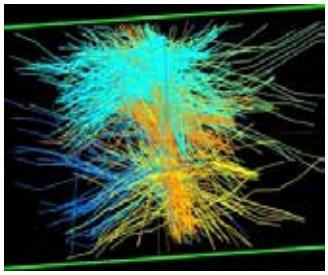
Human evolution: Searching for the origin of anatomically modern humans. The origin of anatomically modern *Homo sapiens* and the fate of the Neanderthals have been fundamental questions in human evolutionary studies for over a century. New fossils excavated at Qesem, Misliya and Manot caves, may shed 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.

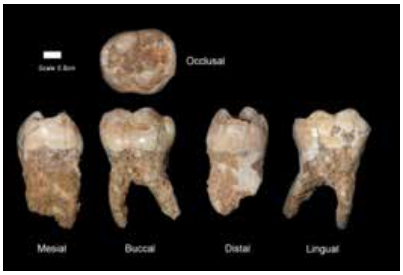
Publications

Hershkovitz I, Marder O, Ayalon A, Bar-Matthews M, Yasur G, Boaretto E, Caracuta V, Alex B, Frumkin A, Goder-Goldberger M, Gunz P, Holloway RL, Latimer B, Lavi R, Matthews A, Slon V, Mayer DB, Berna F, Bar-Oz G, Yeshurun R, May H, Hans MG, Weber GW, Barzilai O. Levantine cranium from Manot Cave (Israel) foreshadows the first European modern humans. *Nature*. 520(7546):216-9, 2015.

Hershkovitz I, Donoghue HD, Minnikin DE, May H, Lee OY, Feldman M, Galili E, Spigelman M, Rothschild BM, Bar-Gal GK. Tuberculosis origin: The Neolithic scenario. *Tuberculosis (Edinb).* 95 Suppl 1:S122-6, 2015.



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).

Slon V, Stein D, Cohen H, Sella-Tunis T, May H, **Hershkovitz I**. Vertebral hemangiomas: their demographical characteristics, location along the spine and position within the vertebral body. *Eur Spine J*. 24(10):2189-95, 2015.

Sarig R, **Hershkovitz I**, Shpack N, May H, Vardimon AD. Rate and pattern of interproximal dental attrition. *Eur J Oral Sci*. 123(4):276-81, 2015.

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Cohen H, Kugel C, May H, Medlej B, Stein D, Slon V, **Hershkovitz I**, Brosh T. The impact velocity and bone fracture pattern: Forensic perspective. *Forensic Sci Int*. 7;266:54-62, 2016.

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Alex B, Barzilai O, **Hershkovitz I**, Marder O, Berna F, Caracuta V, Abulafia T, Davis L, Goder-Goldberger M, Lavi R, Mintz E, Regev L, Bar-Yosef Mayer D, Tejero JM, Yeshurun R, Ayalon A, Bar-Matthews M, Yasur G, Frumkin A, Latimer B, Hans MG, Boaretto E. Radiocarbon chronology of Manot Cave, Israel and Upper Paleolithic dispersals. *Sci Adv.* 3:e1701450, 2017.

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Reviews

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Grants

2018-2019 Leakey Foundation

2018-2019 Wenner Gren Foundation

2016-2019 Dan David Foundation

Prof. Michael M. Kozlov, Ph.D.

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Theoretical Biophysics of Membranes and Cytoskeleton

Position

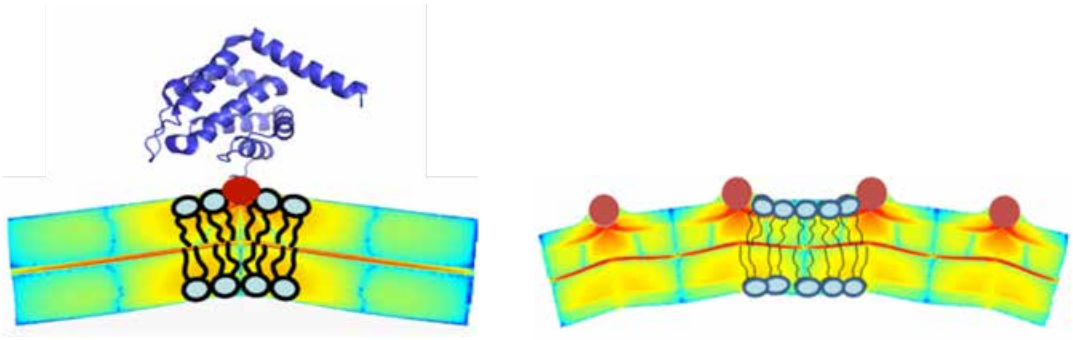
Professor, Sackler Faculty of Medicine

Joseph Klafter Chair in Biophysics

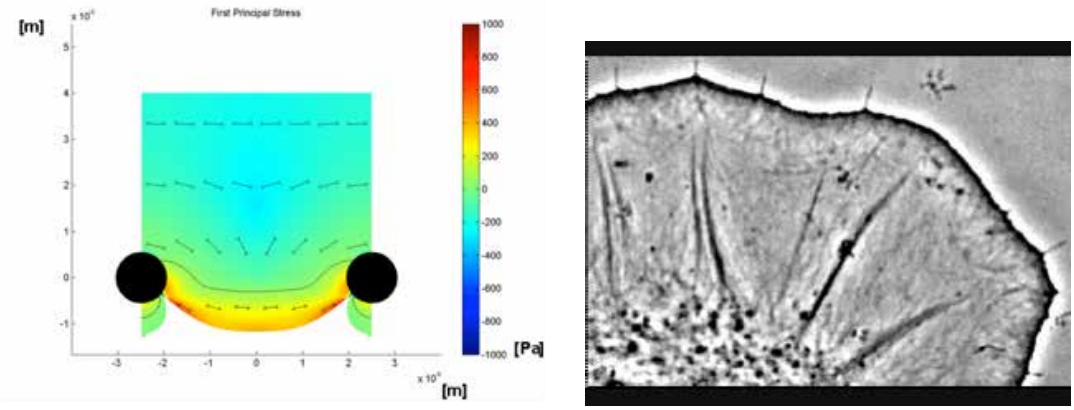
Research

We model the mechanisms of shaping and remodeling of intracellular membranes by specialized proteins that includes generation of large membrane curvatures, membrane fission and fusion. Our goal is to reveal the common mechanistic themes in the function of membrane shaping proteins acting in different intracellular systems. In this way, we hope to be able to understand whether every stage of membrane shaping needs a special protein or the same protein machinery can enable both membrane curvature generation and fission and/or fusion. Specifically, we model the action of BAR domain proteins, Epsins and Dynamins in endocytosis, Reticulons and their partners in shaping the Endoplasmaic Reticulum, and ESCRT-III complexes in fission of cytokinetic tubes.

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



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).

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Laboratory for Bio-History and Evolutionary Medicine

Position

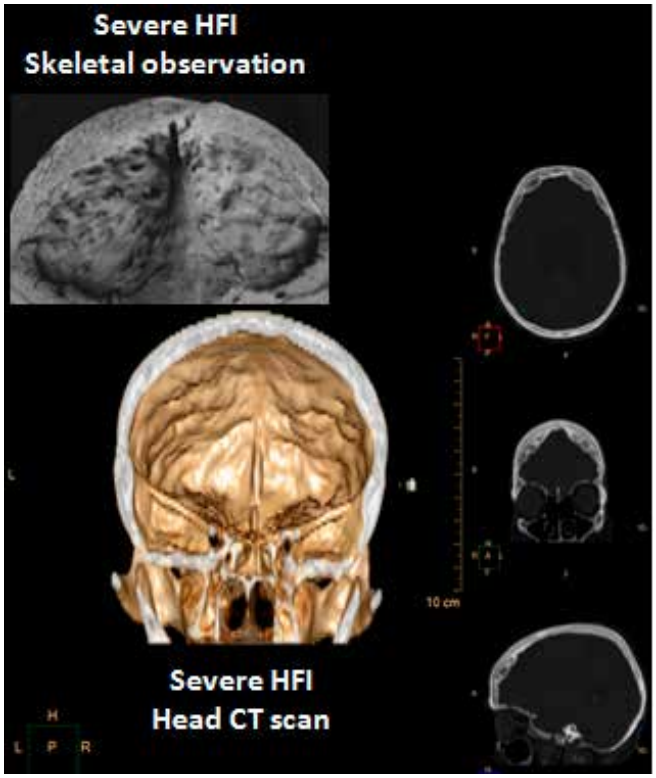
Lecturer

Research

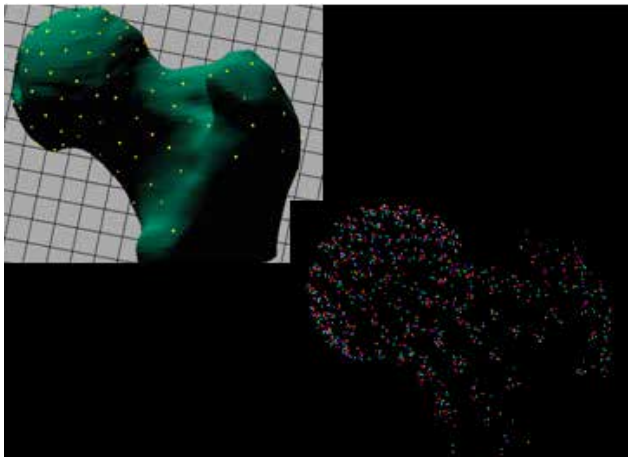
Inter-disciplinary laboratory focusing on two major topics: evolutionary history of anatomical systems and their impact on current population health, and reconstruction of ancient populations' daily life, based on their skeletal remains, with emphasis on the interaction between genetic and socio-cultural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

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

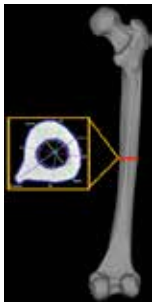
Reconstructing past population daily life: revealing daily activities of prehistoric and historic populations is a challenging task considering the evidence at hand (bones). Nevertheless, bones may furnish us with information otherwise not available, e.g., division of labor, social stratification, intensity 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

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M Feldman, E Fernández-Domínguez, L Reynolds, D Baird, J Pearson, I Hershkovitz, **H May**, N Goring-Morris, M Benz, J Gresky, R.A. Bianco, A Fairbair, G Mustafaoğlu, P.W. Stockhammer, C Posth, W Haak, C Jeong, J Krause. Late Pleistocene human genome suggests a local origin for the first farmers of central Anatolia. *Nat Commun* 10 (1), 2019.

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Rothschild BM, Tanke D, Rühli F, Pokhojaev A, **May H**. Suggested case of Langerhans Cell Histiocytosis in a Cretaceous dinosaur. *Sci Rep*. 2020;10(1):2203.

Grants

2016-2019 Israel Science Foundation: From Hunting to Farming: Exploring Micro-Evolutionary Trends in the Human Masticatory System and their Implications at the Terminal Pleistocene Levant

2016-2019 ISF Equipment Grant

2018-2019 Leakey Foundation, National Geographic Foundation

2018-2019 The Wenner-Gren Foundation

2018-2021 Broad-ISF

Prof. Ruth Shalgi, Ph.D.

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Reproduction in Animal Models and in Humans

Positions

Professor Emeritus, Sackler Faculty of Medicine

Research

Our research focuses on Reproductive Physiology in animal models and in humans. The current research directions investigated in the laboratory are:

- The role of Fyn kinase, member of the Src family kinases, during meiosis and early events of oocyte activation, as well as in cancer cells (Figure-left panel).
- Fertility preservation – the signaling pathway leading to apoptosis in aging oocytes and in oocytes exposed to chemotherapeutic treatments and potential protectants (Figure -right panel).
- Regulation of angiogenesis in reproductive organs by Pigment epithelium derived factor (PEDF) and treatment of reproductive angiogenic-related pathologies.

Various research methods are routinely used in the laboratory, ranging from *in vivo* animal studies and cells cultures to an array of protein methodologies such as western blotting, immunohistochemistry, molecular biology techniques as well as cellular and molecular imaging.

Publications

Bar-Joseph, H., Stemmer, S.M., Tsarfaty, I., **Shalgi, R.** and Ben Aharon, I. Chemotherapy -induced vascular toxicity – Real-time in vivo imaging of vessel impairment. *J Vis Exp*. e51650, http://www.jove.com/video/51650, 2015.

Hasky, N., Uri-Belapolsky S., Goldberg, K., Miller, I., Grossman, H., Stemmer, S.M. Ben-Aharon, I*. and **Shalgi, R*.** Gonadotropin-releasing hormone agonists for fertility preservation – unraveling the enigma? *Hum Reprod*. 30:1089–1101, 2015.

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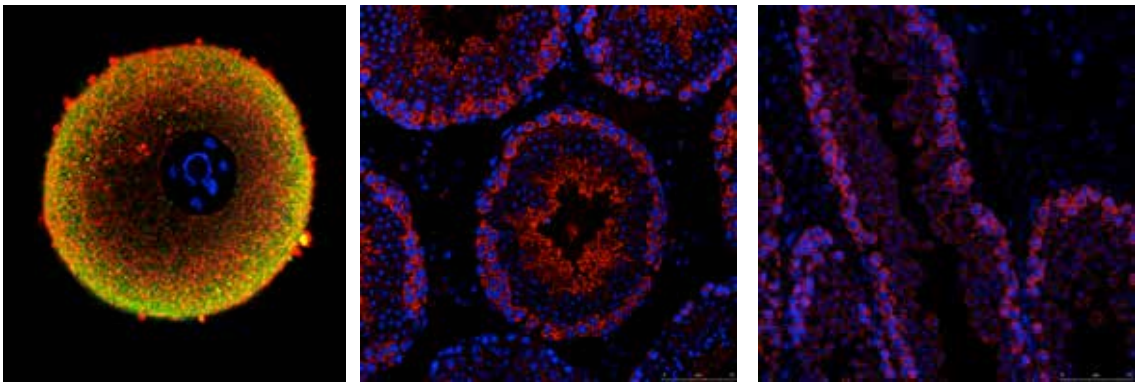

Left panel- Human oocyte stained for DNA (blue); cytoskeleton (tubulin; red); protein (Fyn kinase; green). Arrow – Germinal vesicle (genetic material); C- Cytoplasm. Confocal microscopy. Right panels -Section of sperm producing tubules in mouse testis before (left) and after treatment with chemotherapy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

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Grants

2020-2022 Ministry of Health Grant

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Genetic Study of Ancient Populations

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

We study the genetic makeup of prehistoric and proto-historic populations, with a focus on the Levant – a major corridor for migrations throughout human evolution and one of the earliest centres of agriculture in the world. To do so, we implement and pursue the development of state-of-the-art methodology suited to face the challenges of DNA preservation over time in warm climates. In our laboratory, we strive to recover DNA of ancient individuals both from skeletal remains and from sediments deposited at archaeological sites. The genetic data we obtain is analyzed by comparing it to existing datasets of ancient and present-day genomes world-wide; and contextualized by integrating it with data from other research fields, such as archaeology, physical anthropology, geology and chronometry. The study of ancient genomes allows to elucidate relationships between populations, infer demographic histories, retrace migrations, reconstruct social structures, search for signs of local adaptation to varying environments, and investigate the effect of past events on our own genomes today.

Publications

Parush, Y., Assaf, E., **Slon, V.**, Gopher, A. and Barkai, R. (2015), Looking for sharp edges: Modes of flint recycling at Middle Pleistocene Qesem Cave, Israel, *Quaternary International* 361: 61-87

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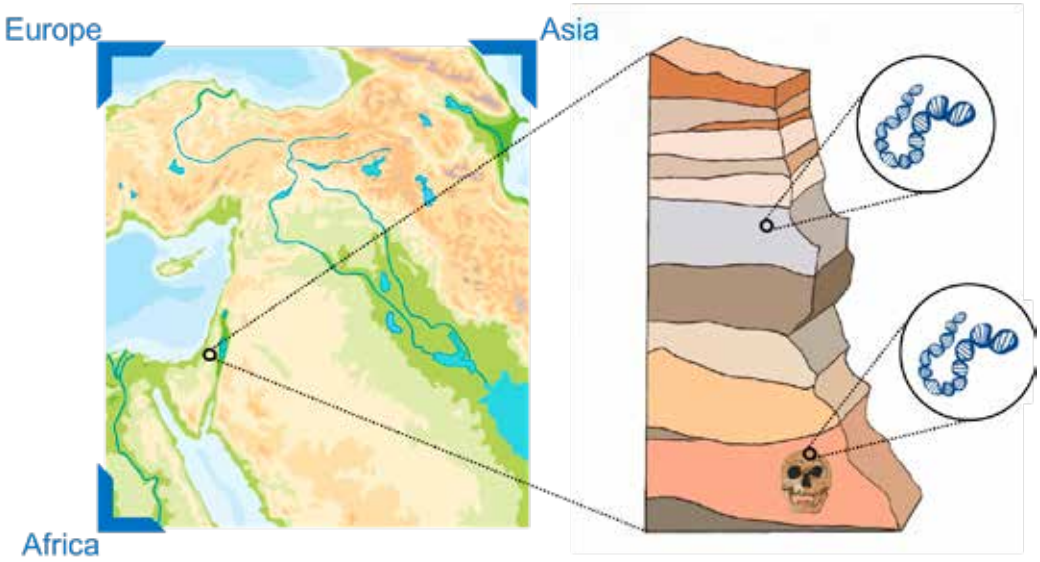

At the crossroad between Africa, Asia and Europe, the region of the Levant is of particular interest for the study of ancient human populations. In our laboratory, we analyze ancient DNA recovered from skeletal remains and from sediments collected at archaeological sites. (Illustration courtesy of S. Peyrégne).

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Reviews

Slon, V. and Hershkovitz, I. (2018), Levantine fossil record, *The International Encyclopedia of Biological Anthropology*, DOI: 10.1002/9781118584538.ieba0548

Swift, J.A., Bunce, M., Dortch, J., Douglass, K., Faith, J.T., Fellows Yates, J.A., Field, J., Haberle, S., Jacob, E., Johnson, C.N., Lindsey, E., Lorenzen, E.D., Louys, J., Miller, G., Mychajliw, A., **Slon, V.**, Villavicencio, N., Waters, M., Welker, F., Wood, R., Petraglia, M., Boivin, N. and Roberts, P. (2019), Micro-Methods for Megafauna: Novel approaches to the study of Late Quaternary extinctions and their contributions to faunal conservation in the Anthropocene.*BioScience* 69(11): 877-887

Grants

2020-2023 Alon Fellowship

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Cellular Mechanics and Tissue Morphogenesis

Positions

Associate Professor, Sackler Faculty of Medicine

Director, Sackler Cellular and Molecular Imaging Center (SCMIC)

Research

Our main interest is in understanding how mechanical forces are generated by cells and how cells use these forces to change shape and move, as happens during cell division, cell migration and tissue morphogenesis. We focus on distinct cellular structures that mediate cell adhesion and contractility: cell-matrix and cell-cell junctions and the actomyosin cytoskeleton. Together, these structures are responsible for the dynamic control of cell and tissue shape during development and homeostasis and their mis-regulation is associated with various diseases.

We take a multi-scale approach in our investigations, from single proteins to an entire organism, and employ a variety of tools, including genetic engineering, proteomics, biochemistry and bioinformatics, but primarily relying on live imaging with fluorescence microscopy.

Our findings, both in mammalian cells and in the nematode *C. elegans*, are defining the protein network regulating cell adhesion and contractility in vivo and elucidating molecular mechanisms of mechanosensing and mechanotransduction.

Publications

Priti A, Ong H-T, Toyama Y, Padmanabhan A, Dasgupta S, Krajnc M, **Zaidel-Bar R**. Syncytial germline architecture is actively maintained by contraction of an internal actomyosin corset (2018) Nature Communications, 2018.

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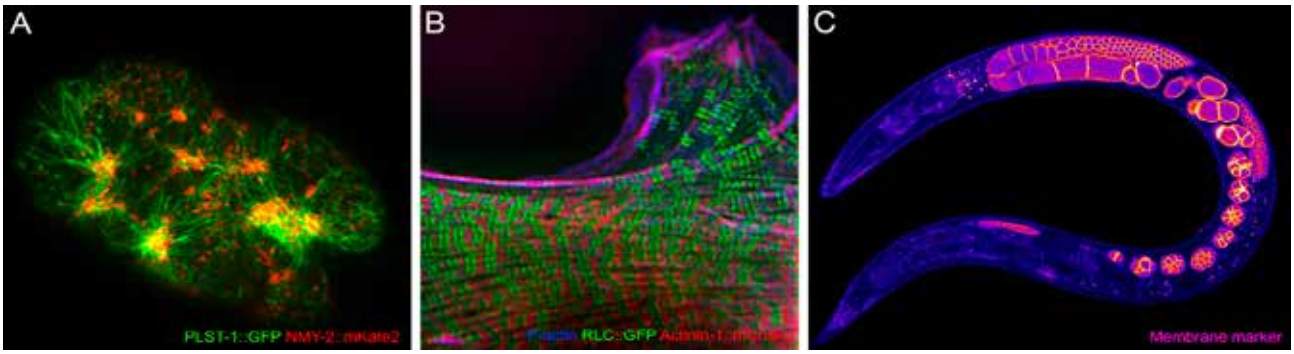
Ding W-Y, Ong H-T, Hara Y, Wongsantichon J, Toyama Y, Robinson R, Nédélec F, **Zaidel-Bar R.** Plastin increases cortical connectivity to facilitate robust



Actomyosin-generated forces shape cells and tissues: (A) A contractile actomyosin network at the cortex of a *C. elegans* early embryo. It is essential for cell polarization and division. **(B)** Actin and myosin self-organize into arrays of parallel stress fibers in a REF52 fibroblast. They are required for cell spreading and adhesion. **(C)** The germline of *C. elegans*, highlighted by a membrane marker, is like an assembly line for embryos. Actomyosin contractility is essential for maintaining germline architecture and for moving oocytes and embryos along.

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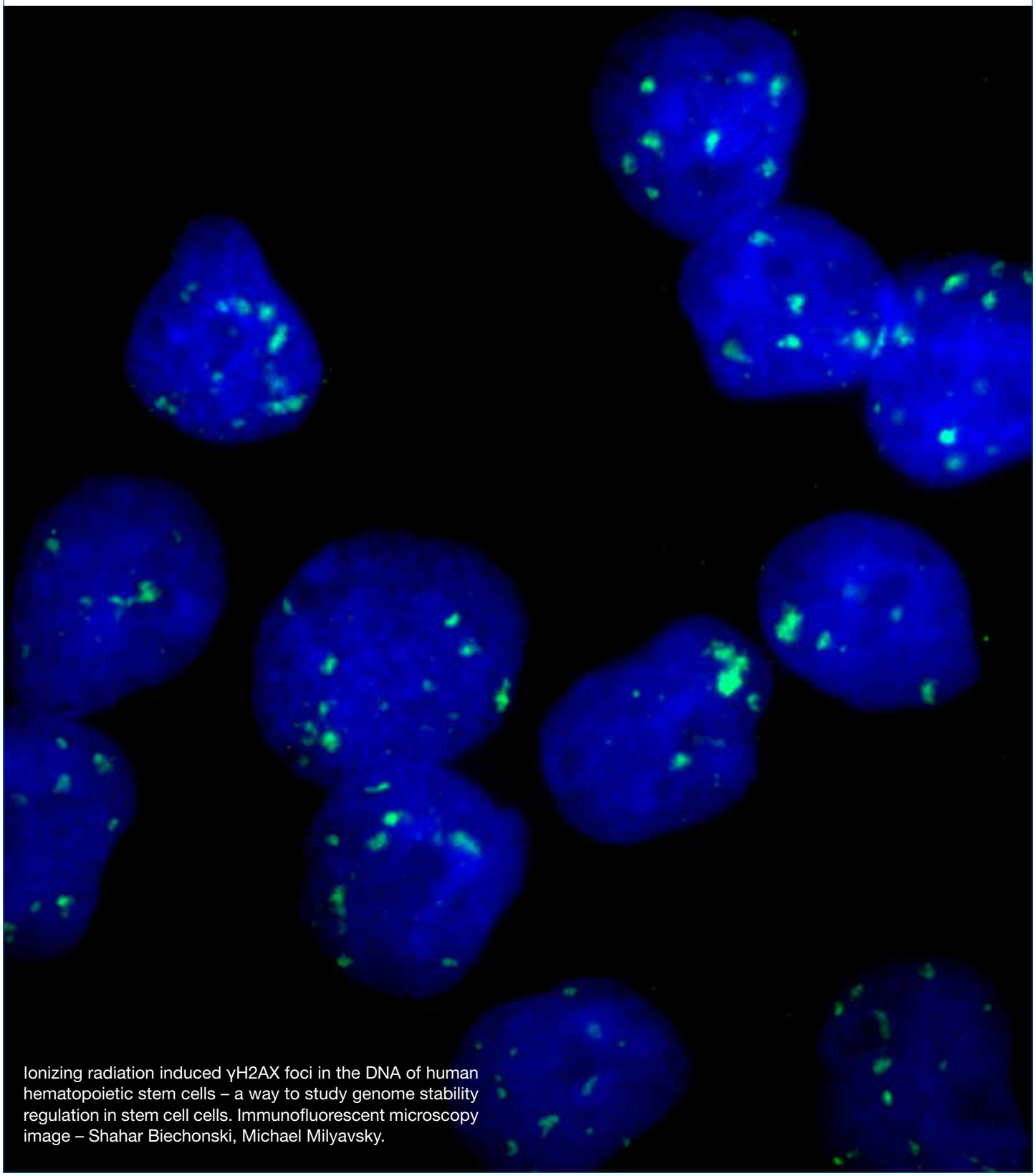
Grants

2017 –2020	Israel Science Foundation Research grant: Mechanotransduction in contractile tubes: using the *C. elegans* spermatheca as a model to study the regulation of RHO-1- and Ca2+-dependent actomyosin contractility in response to stretching.
2017 –2020	Israel Science Foundation Equipment Grant
2018-2020	Israel Cancer Research Fund Acceleration grant: Elucidating the role of the upstream partner in oncogenic ALK gene fusions
2018-2022	United-States – Israel Bilateral Science Foundation: Elucidating the role of ERM proteins in cytoskeletal orientation in a contractile tissue

Stem Cells, Regenerative Medicine and Aging



Ionizing radiation induced γH2AX 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.

Dr. Daniel Zvi Bar, Ph.D.

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Molecular Biology of Aging

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Aging is the leading risk factor for most causes of death in the western world, including cardiovascular disease, cancer and diabetes. The aging process can be slowed down, as was shown in multiple model organisms. This slowdown is accompanied by delayed onset of multiple common chronic diseases and an inhibition of tumorigenesis. However, translating these findings to humans is not straightforward. We have developed a method to identify the protein composition of organelles and subcellular structures directly from primary tissues. We apply this method to study how subcellular structures, like the mitochondria and the nuclear envelope, that have key roles in the aging process, change with age. Our lab is located at the Schools of Dental medicine, thus enabling us the access to fresh oral tissue samples from live and consenting participants. By tracking the aging process at a subcellular level, we will gain insights into human aging and highlight tissue specific processes.

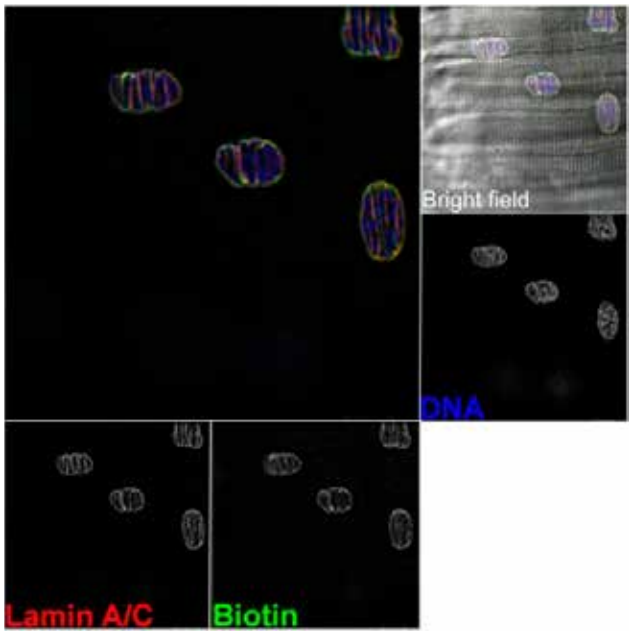

Fig. 1: Nuclear envelope labeling in primary human muscle samples. The shape of the nuclear envelope in primary muscles deviates from the classical view of a round smooth circle. Similarly, significant changes in protein content were seen between primary muscle sample and cell culture.

Publications

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Musculoskeletal and Adipose Stem Cells Lineage Fate and Usage in Regenerative Medicine

Position

Professor, Sackler Faculty of Medicine

Head, Marian Gertner Institute for Medical Nanosystems

Research

Our interest is to follow the differentiation of mesenchymal stem cells and their lineage fate. We study the balance between skeletal stem cells and the adipose fate lineage in vitro and vivo in various animal models in health and disease. The role of stem cells function is followed at the cellular and molecular biology levels. In silico characterization, using bioinformatics of genes profiling and identification of biomarkers networks, allow is to identify markers for stem cells.

In recent projects we have shown that the cell niche affects their activity from factors secreted and the effect of extracellular matrix that play a role in the stem cells activation and function under normal physiology, diabetes and with 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 or fat tissue function due to aging or change in metabolic conditions. The use of stem cells 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 imaging techniques of immunofluorescence, scanning electron microscopy and biochemistry. Nanotechnology and nano-scaping combines the cell fate differentiation with multidisciplinary approaches for the development of new platforms for cell analysis.

Publications

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Reviews

Benayahu D, Wiesenfeld Y, Sapir-Koren R. How is mechanobiology involved in mesenchymal stem cell differentiation toward the osteoblastic or adipogenic fate? *J Cell Physiol.* 2019.

Grants

2016-2019	Ministry of Science Cooperation, Jointly with Prof. R. Haj-Ali
2016-2020	Israel Science Foundation, Jointly with Prof. A. Gefen

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Cytoskeletal Regulation of Epidermal Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

Head, Graduate School International Program

Director, Biomed@TAU Research Hub, Developmental Biology

Research

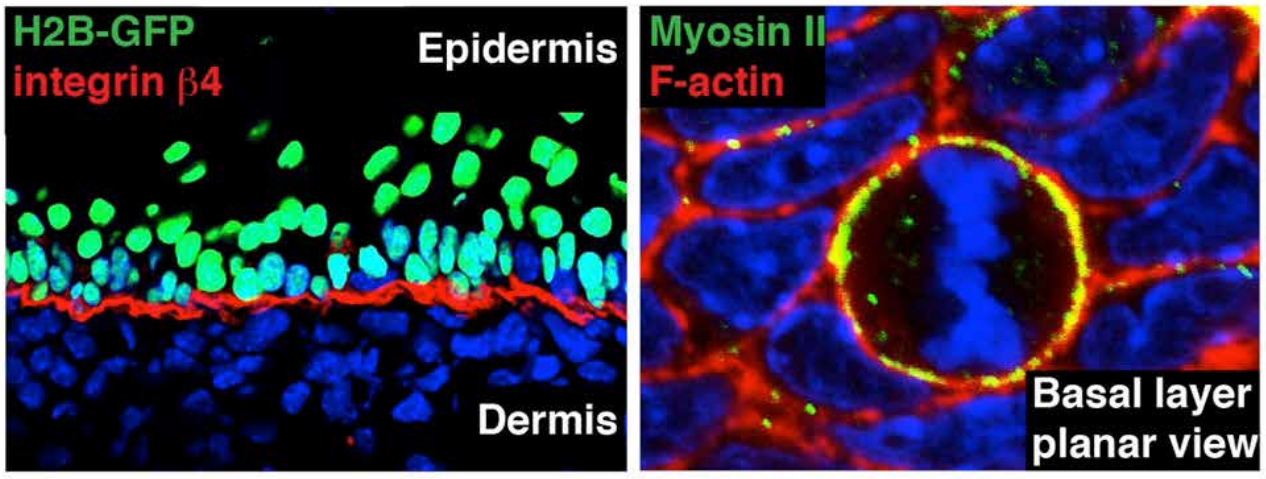
Our laboratory studies how cytoskeleton-derived signals control stem cell's ability to give rise to a functional tissue during development, to maintain it throughout life and repair it upon wounding.

The actomyosin cytoskeleton is a complex cellular structure that plays a role in many biological processes. Classic studies established its role in cell structural organization. However, new studies demonstrate that the cytoskeleton plays a major role in regulatory processes that control signal transduction, gene expression and stem cell lineage specification.

Our laboratory uses the skin epidermis as its main model system. Projects in the lab explore both skin development and skin common diseases such as cancer and psoriasis. In addition to classic genetic tools and in vivo models we also use state of the art technology to manipulate stem cells in utero. Genome wide analysis of gene expression, quantitative digital microscopy and a variety of molecular and cellular methods are all commonly used in our lab.

Publications

Luxenburg C, Heller E, Pasolli HA, Chai S, Nikolova M, Stokes N, Fuchs E. Wdr1-mediated cell shape dynamics and cortical tension are essential for epidermal planar cell polarity. *Nat Cell Biol*. 2015;17:592-604.



Left hand side**:** We use state of the art *in utero* injections of lentivirus (H2B-GFP+ cells in the epidermis) to manipulate gene expression in epidermal stem cells/progenitors early in embryonic development, before cell fate specification.
Right hand side**:** Whole mount image of embryonic epidermis showing an early mitotic cell and its interphase neighbors in planar view. Note the dramatic differences in cell shape. We demonstrated that mitotic rounding is important for cells ability to orient their spindle and undergo asymmetric cell division.

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Reviews

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Grants

2015-2020 Israel Science Foundation (ISF) Grant

Dr. Michael Milyavsky, Ph.D.

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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

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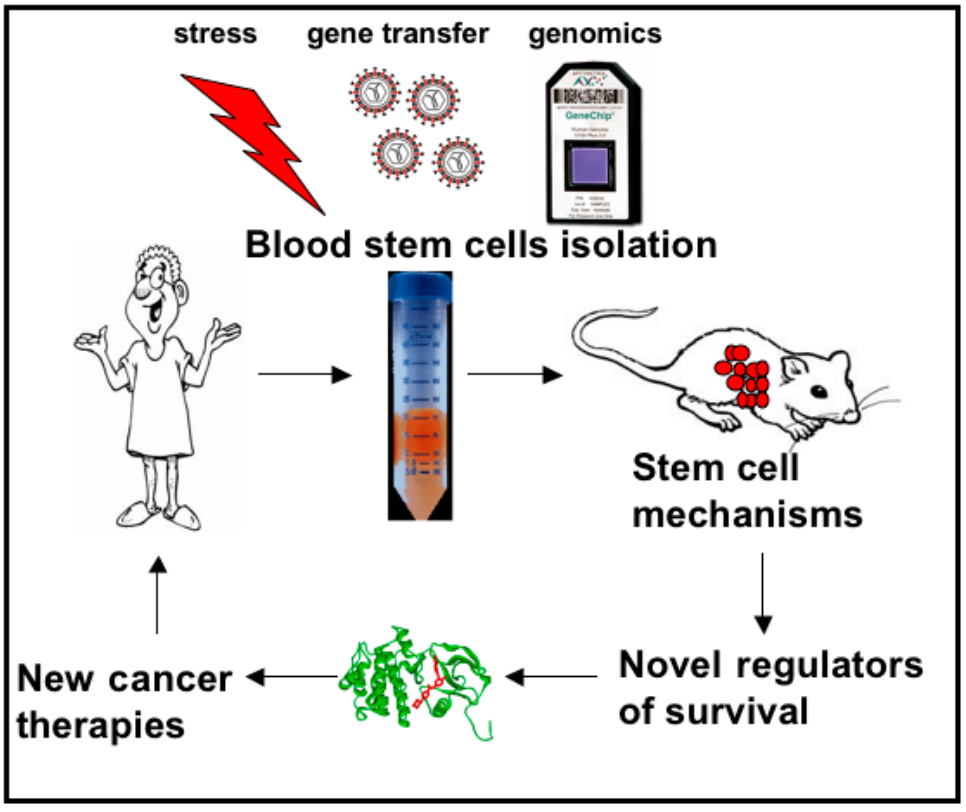

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Biechonski S, Olender L, Zipin-Roitman A, Yassin M, Aqaqe N, Marcu-Malina V, Rall-Scharpf M, Trottier M, Meyn MS, Wiesmüller L, Beider K, Raz Y, Grisaru D, Nagler A, **Milyavsky M**. *Sci Rep*. 2018;8:6071.

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Gold A, Eini L, Nissim-Rafinia M, Viner R, Ezer S, Erez K, Aqaqe N, Hanania R, **Milyavsky M**, Meshorer E, Goldberg M. Spironolactone inhibits the growth of cancer stem cells by impairing DNA damage response. *Oncogene*. 2019.

Reviews

Flach J, **Milyavsky M.** Replication stress in hematopoietic stem cells in mouse and man. Mutat Res. 2018;808:74-82.

Grants

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

updated KBA October 27