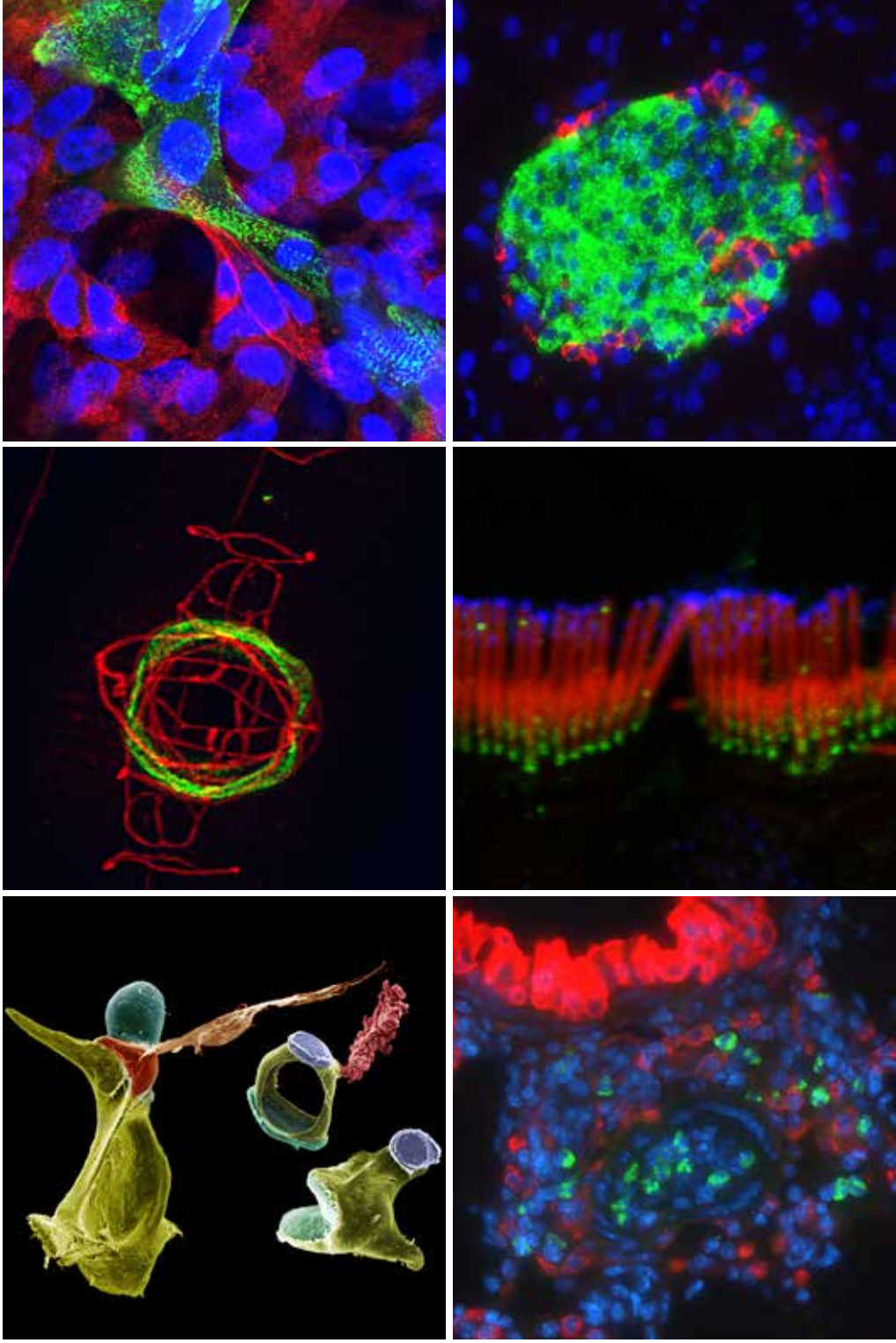

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine

Preclinical Research 2017

TEL AVIV UNIVERSITY

Sections

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

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Editor: Prof. Karen Avraham
Graphic design: Michal Semo Kovetz, TAU Graphic Design Studio
August 2016

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. Meir Lahav, Prof. Ami Fishman, Prof. Moshe Kotler; and Assistant to the Dean, Ms. Yael Keilin.

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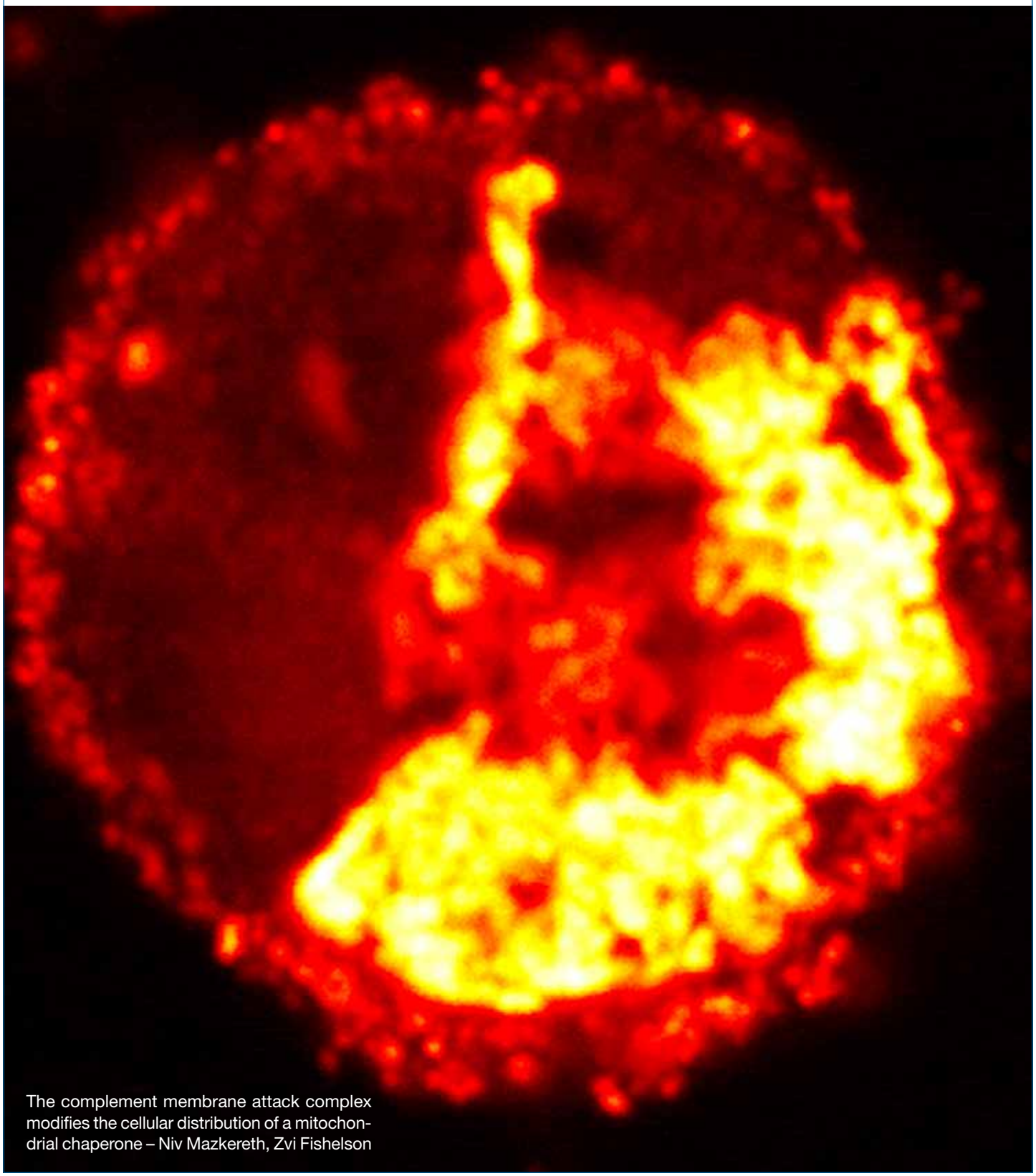

The complement membrane attack complex modifies the cellular distribution of a mitochondrial chaperone – Niv Mazkereth, Zvi Fishelson

Dr. Yaron Carmi, Ph.D.

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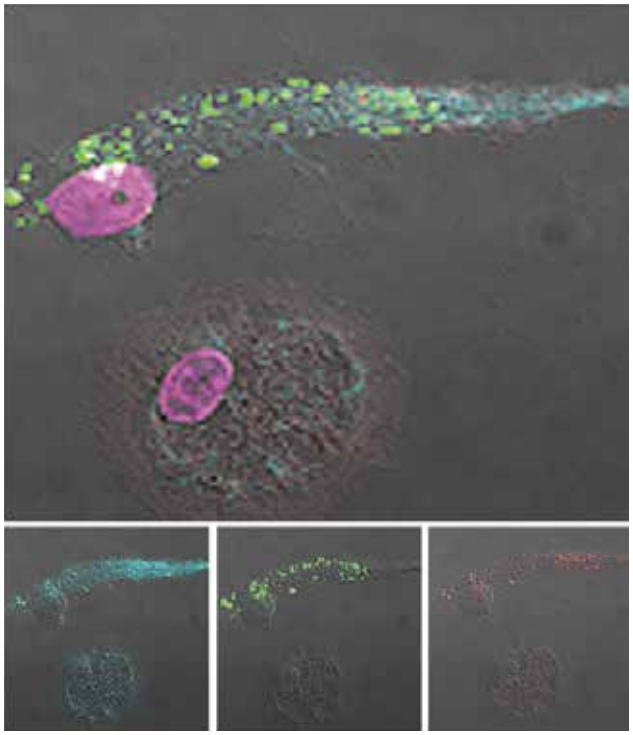
Cellular and Molecular Mechanisms of Antigen-Restricted Rumor Immunity

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.

Publications

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Carmi Y, Dotan S, Rider P, Kaplanov I, White MR, Baron R, Abutbul S, Huszar M, Dinarello CA, Apte RN, et al. The role of IL-1b in the early tumor cell induced angiogenic response. *J Immunol*. 2013, 190:3500-3509.

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Patents

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Prof. Malka Cohen-Armon, D.Sc.

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PARP Proteins in Health and Disease

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

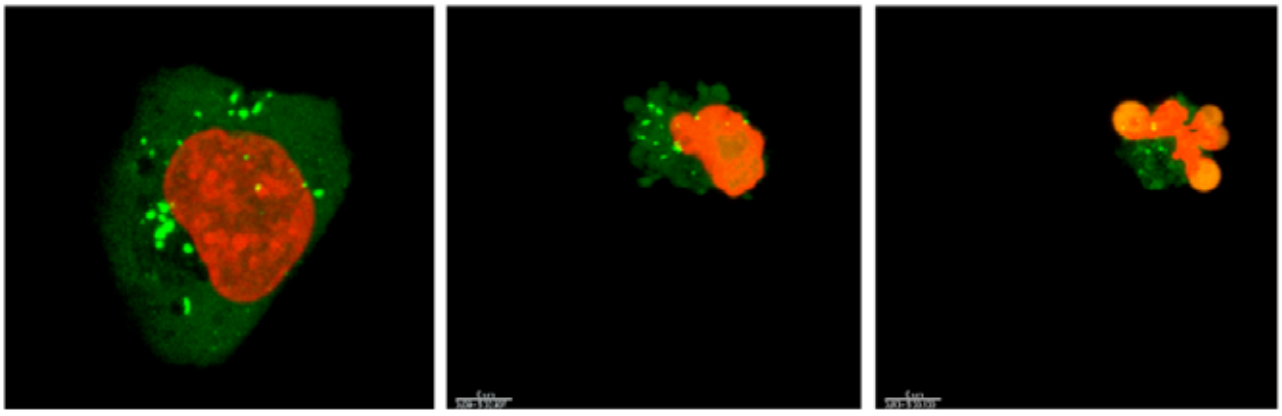
One of our contributions to this field was the discovery of alternative mechanisms activating PARP-1 in the absence of DNA breaks. This unveiled a variety of extra-nuclear signals activating PARP proteins in a variety of processes regulating gene expression.

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

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

Publications

Geistrikh I., Visochek L., Klein R., Miller L., Mittelman L., Shainberg A. and **Cohen-Armon M.** 2011. Ca^{2+} induced PARP-1 activation and *ANF* expression are coupled events in cardiomyocytes. *Biochem J.* 438: 337–347.



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

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Review

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Patents

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

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

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Cancer Related Inflammation in Tumor Progression and Metastasis

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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

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

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

Publications

Klein A, Sagi-Assif O, Izraely S, Meshel T, Pasmanik-Chor M, Nahmias C, Couraud PO, **Erez N**, Hoon DS, Witz IP. The metastatic microenvironment: Brain-derived soluble factors alter the malignant phenotype of cutaneous and brain-metastasizing melanoma cells. *Int J Cancer*. 2012; 131:2509-2518.

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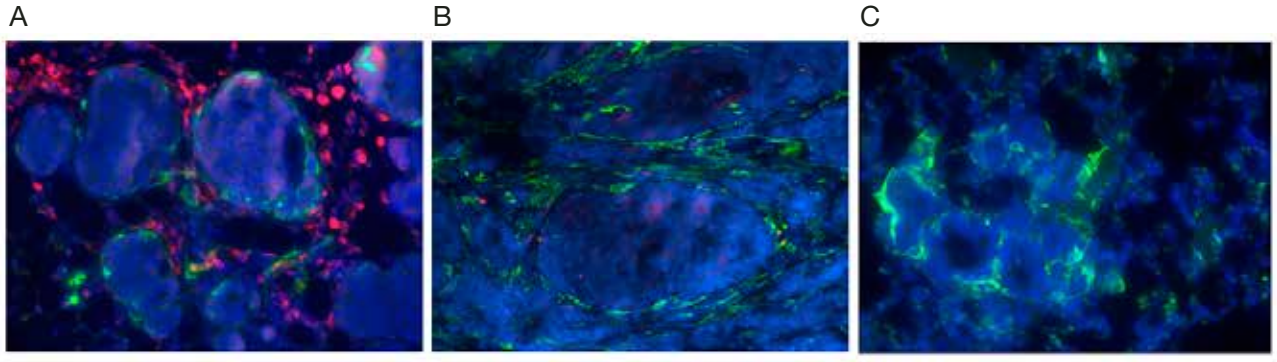

A, B: Cancer Associated Fibroblast (CAFs) accumulate around mammary tumors in tissue Sections from the MMTV-PyMT transgenic mouse model. Green-aSMA, Blue-DAPI, Red-FSP-1. **C**: Immunofluorescent staining showing activated fibroblasts in lung metastases in MMTV-PyMT mice. Blue- DAPI. Green –aSMA.

Raz, Y. and **Erez N.** An inflammatory vicious cycle: fibroblasts and immune cell recruitment in cancer. *Exp Cell Res*. 2013 pii: S0014-4827:00130-4.

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Klein A, Schwartz H, Sagi-Assif O, Meshel T, Izraely S, Ben Menachem S, Ben-Shmuel A, Nahmias C, Couraud P, Witz IP and **Erez N.** Astrocytes facilitate melanoma brain metastasis via secretion of IL-23. J Pathol. 2015 doi: 10.1002/path.4509.

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Reviews

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Erez N. Cancer: Opening LOX to metastasis. Nature. 2015. doi: 10.1038/nature14529.

Erez N. Fibroblasts form a hospitable metastatic niche in the liver. Nat Cell Biol. 2016, 18:465-6. doi: 10.1038/ncb3352

Grants

2012–2016	Israel Science Foundation (ISF) Grant
2014 – 2016	Israel Cancer Association (ICA)
2014 – 2016	The Eva and Henry Frænkel Mindefond-Denmark
2014–2017	Association for International Cancer Research (AICR)
2014 – 2017	Melanoma Research Alliance SABAN FAMILY FOUNDATION-TEAM SCIENCE AWARD
2014 – 2017	Israel Cancer Research Foundation (ICRF). Research Career Development Award
2015–2019	European Research Council (ERC) Starting Grant

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Molecular Analysis of Cancer Immunoresistance

Positions

Professor, Sackler Faculty of Medicine

President, International Complement Society

President, European Complement Network

Advisory Editor, *Molecular Immunology*

Associate Editor, *Frontiers in Molecular Innate Immunity*

Research

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

Publications

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Moskovich O, Herzog L-O, Ehrlich M and **Fishelson Z**. Caveolin-1 and dynamin-2 are essential for removal of the complement C5b-9 complex via endocytosis. *J. Biol. Chem*. 287: 19904-19915, 2012.

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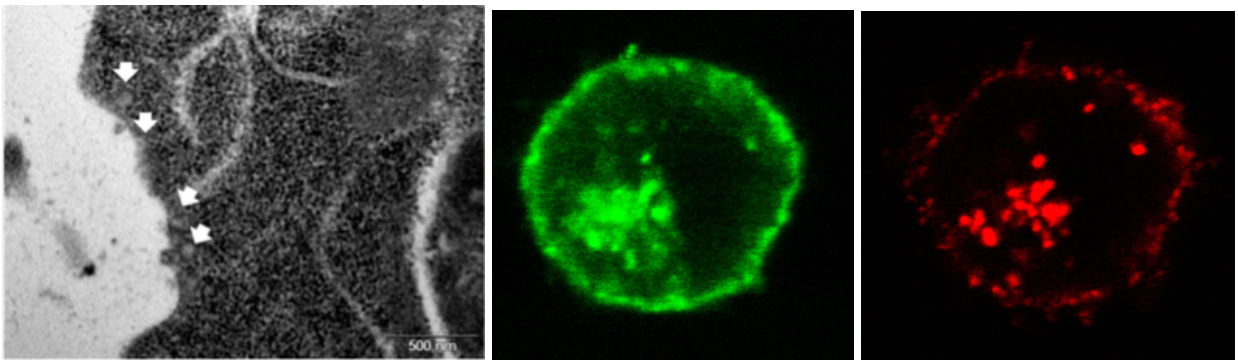
Rozenberg P, Kocsis J, Saar M, Prohászka Z, FÜst G and **Fishelson Z**. Elevated levels of mitochondrial mortalin and cytosolic HSP70 in blood as risk factors in colorectal cancer patients. *Int. J. Cancer*. 133: 514-519, 2013.

Gurevich M and **Fishelson Z**. Construction and characterization of recombinant human C9 or C7 linked to single Chain Fv directed to CD25. *Mol. Immunol*. 55: 400-408, 2013.



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).

Saar Ray M., Moskovich O. Iosefson O. and **Fishelson Z.** Mortalin/Grp75 binds to complement c9 and plays a role in resistance to complement-dependent cytotoxicity, *J. Biol. Chem*. 2014, 289:15014-22.

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.

Mazkereth N., Rocca F., Schubert J.-R., Geisler C., Hillman Y., Egner A. and **Fishelson Z**., Complement triggers relocation of mortalin/GRP75 from mitochondria to the plasma membrane, *Immunobiology* 2016 (in press, doi:10.1016/j.imbio.2016.07.005)

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Moskovich O. and **Fishelson Z.,** Quantification of complement C5b-9 binding to cells by Flow Cytometry, in 'Methods in Molecular Biology; Complement System: Methods and Protocols' Gadjeva M. ed., Springer Science+Business Media New York, 2014, pp103-108.

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

Grants

2015-2020	Complement-dependent cytotoxicity of cancer cells: toxic and evasion mechanisms (ISF)
2015-2016	Combined therapy of leukemia/lymphoma with Rituximab and mortalin (ICA)
2016-2018	The mitochondrion-plasma membrane interaction at super-resolution microscopy (VW Lower Saxony grant, binational with Germany (Dr. Alex Egner, Goettingen))
2015-2016	A novel minibody for cure of chronic lymphocytic leukemia (Kamin)

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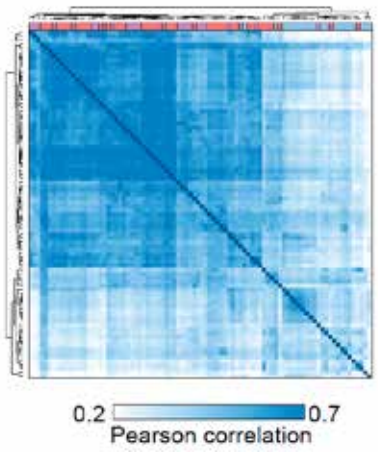
Cancer Proteomics

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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



Correlation matrix of proteomes of breast cancer and healthy tissue

Publications

Pozniak, Y., Lahat, N., Rudolph, J.D., Katzir, R., Avivi, C., Ruppin, E., Barchack, I. & **Geiger, T***. System-wide clinical proteomics of breast cancer reveals global remodeling of cellular homeostasis. Cell Systems, 2:172-84 (2016). *Corresponding author.

Tyanova, S., Albrechsten, R., Kronqvist, P., Cox, J.*, Mann, M.* & **Geiger, T.*** Quantitative clinical proteomics reveals functional maps of breast cancer subtypes. Nat Communications 7:10259 (2016). *Corresponding author

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Aviner, R., Shenoy, A., Elroy-Stein, O.* & **Geiger, T.*** (2015). Uncovering hidden layers of cell cycle regulation through integrative multi-omic analysis. PLoS Genetics 11, e1005554. *Corresponding author.

Darr, J. **Geiger, T.**, Gordon, J., Isacc, S. & Eden, A. Phosphoprotemic Analysis of Snf5 Deficient Tumor Cells Reveals Activation of EGFr Signaling Which Is Dependent Upon Snf5 Expression. Cancer Genetics 207, 446 (2015).

Elbaz-Alon, Y., Eisenberg-Bord, M., Shinder, V., Stiller, S. B., Shimoni, E., Wiedemann, N., **Geiger, T.** & Schuldiner, M. Lam6 regulates the extent of contacts between organelles. Cell reports 12, 7-14 (2015).

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Harel, M., Oren-Giladi, P., Kaidar-Person, O., Shaked, Y., & **Geiger, T.*** Proteomics of Microparticles with SILAC Quantification (PROMIS-Quan): A Novel Proteomic Method for Plasma Biomarker Quantification. Mol Cell Proteomics 14, 1127-1136 (2015). *Corresponding author.

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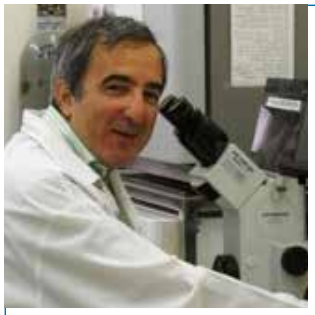
Grants

2012-2017	Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease
2012-2017	Israel Science Foundation (ISF) Grant: The role of metabolic pathways in the regulation of breast cancer progression.
2015-2020	European Research Council- ERC starting grant: Topoproteomic profiling of breast cancer heterogeneity
2014-2017	Israel Ministry of Science and Technology: Proteogenomic analysis of breast cancer



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Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions

Professor, Sackler Faculty of Medicine

Chair, MD-PhD program

Research

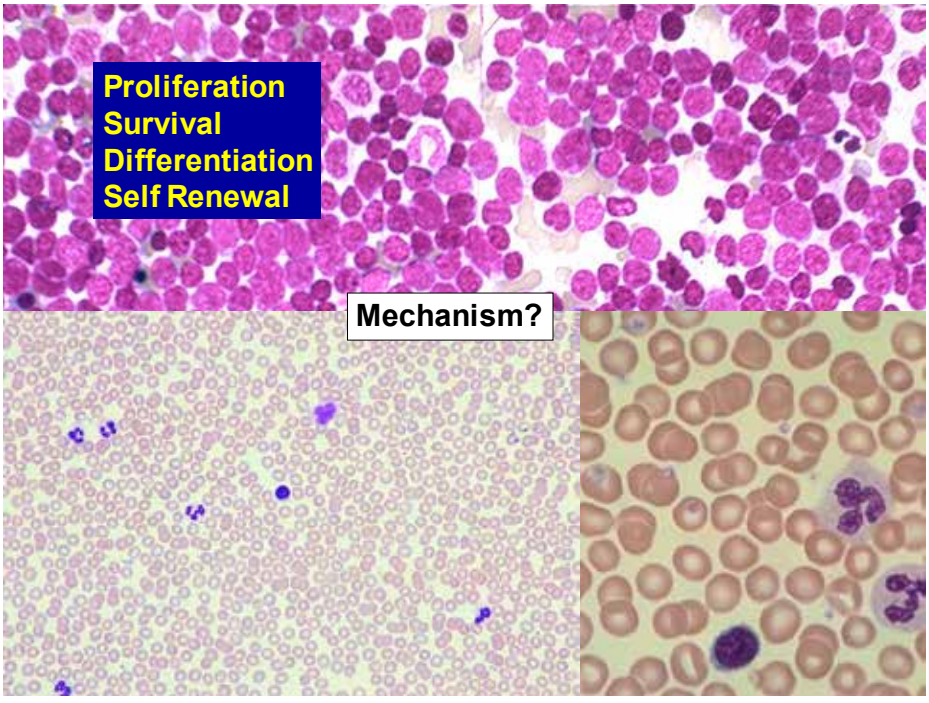
We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

Our research is divided into two major topics:

1. Basic, translational and clinical research of leukemia.

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

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



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

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.

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

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Tal, N., C. Shochat, I. Geron, D. Bercovich, and **S. Izraeli**. Interleukin 7 and thymic stromal lymphopoietin: from immunity to leukemia. *Cell Mol Life Sci*, 2014. 71:365-78.

Grants

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

Prof. Yona Keisari, Ph.D.

Department of Clinical Microbiology and Immunology
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Development of Cancer Treatments Integrating Radiotherapy or Electrochemical Ablation and Immunotherapy

Positions

Professor, Sackler Faculty of Medicine

Roberts-Guthman Chair in Immunopharmacology

President, Israeli Society for Cancer Research

Associate Editor, *Mediators of Inflammation*

Research

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

In order to achieve efficient primary tumor ablation we developed two novel and powerful treatment modalities for solid cancer, which can be used instead or in combination with surgery. The first treatment, developed with Prof. Rafi Korenstein (Dept. Physiology & Pharmacology), is 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

Greenberg E, Hershkovitz L, Hajdu S, Nemlich Y, Itzhaki O, Ortenberg R, Gefen N, Edry L, Barschak I, **Keisari Y**, Besser MJ, Schachter J, Shomron N, Markel G. Regulation of cancer aggressive features in melanoma cells by microRNA molecules. *Plos One*, 6:e18936, 2011.

Cafri G, Amram E, Rinot G, Koifman G, Fishman S, **Keisari Y**, Tzehoval E, Eisenbach L, Margalit A, Gross G. Coupling presentation of MHC class I peptides to constitutive activation of antigen-presenting cells through the product of a single gene. *Int Imm*, 23:453-61, 2011.

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cancer cells exposed to alpha particles. *Radiat Res*, 177:280-7, 2011.

Horev-Drori G, Cooks T, Bittan H, Lazarov E, Schmidt M, Arazi L, Efrati M, Kelson I, **Keisari Y**. Local control of malignant pancreatic tumors by a combined treatment with intratumoral ^{224}Radium-loaded wires releasing alpha-emitting atoms and chemotherapy. *Transl Res* 159:32-41, 2012.

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Cooks, T., Tal, M., Raab, S., Efrati, M., Reitkopf, S., Lazarov, E., Etzyoni, R., Schmidt, M., Arazi, L., Kelson, I., **Keisari, Y**. Intratumoral Ra-224-loaded wires spread alpha emitting atoms inside solid human tumors in athymic mice and can achieve local tumor control. *Anticancer Res*. 32:5315-21, 2012.

Milrot, E., Jackman, A., Flescher, E., Gonen, P., Kelson, I., **Keisari, Y**., Sherman, L. Enhanced killing of cervical cancer cells by combinations of methyl jasmonate with cisplatin, X or alpha radiation. Invest. *New Drugs*. 31:333-44, 2013.

Tepper, M., Shoval, A., Hoffer, O., Confino, H., Kelson, I., **Keisari, Y**., Gannot, I. Thermographic investigation of tumor size, and its correlation to tumor relative temperature, in mice with transplantable solid breast carcinoma. *J Biomed Optics*. 18:111410, 2013.

Keisari, Y., Hochman, I., Confino, H., Korenstein, R., Kelson, I. Activation of local and systemic anti-tumor immune responses by ablation of solid tumors with intra-tumoral electrochemical or alpha radiation treatments. *Cancer Immunol Immunother*. 63:1-9, 2014.

Reitkopf-Brodutch, S., Confino, H., Schmidt, M., Cooks, T., Efrati, M., Arazi, L., Rath-Wolfson, L., Marshak, G., Kelson, I., **Keisari Y**. Ablation of experimental colon cancer by intratumoral ^{224}Radium Loaded wires is mediated by alpha particles released from atoms which spread in the tumor and can be augmented by chemotherapy. *Int J Radiation Biol*. 2014 2:1-15.

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Chapters and Reviews

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Keisari Y. Tumor abolition and antitumor immunostimulation by physico-chemical tumor ablation. *Frontiers Biosc. Landmark*, 22: 310-347, 2017. In press.

Books

Keisari Y. Tumor Ablation: effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Springer, 2013.

Grants

2016 2018 Ramot- Alpha Tau Medical Research Contract

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Interaction of Nanomaterials and Electromagnetic Fields with Cells

Positions

Professor, Sackler Faculty of Medicine

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

Editorial Board, *Bioelectromagnetics*

Research

The research activity addresses the following lines of research:

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

Publications

Toropova, A.P., Toropov, A.A., Benfenati, E., **Korenstein, R.**, Leszczynska, D., Leszczynski, J. (2015) Optimal nano-descriptors as translators of eclectic data into prediction of the cell membrane damage by means of nano metal-oxides. *Environ Sci Pollut Res Int* 22, 745-757.

Turko, N.A., Barnea, I., Blum, O., **Korenstein, R.,** Shaked, N.T. (2015) Detection and controlled depletion of cancer cells using photothermal phase microscopy. *J Biophotonics* 8, 755-763.

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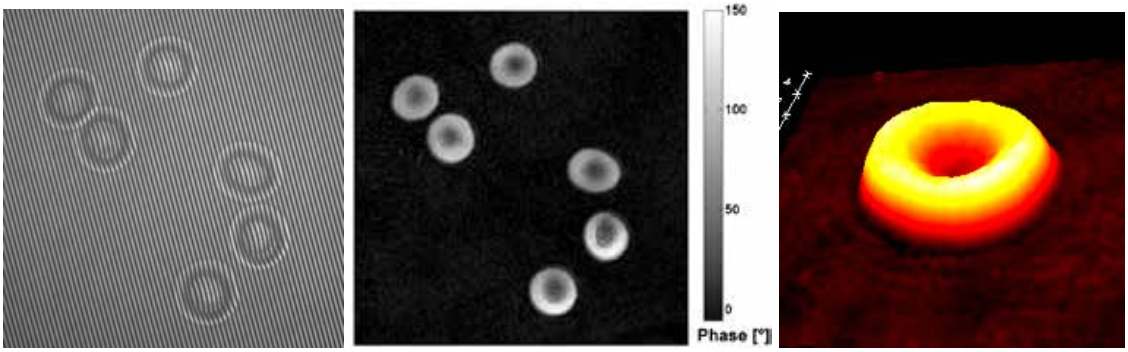

Hologram image of red blood cells (left), reconstructed phase image (middle) and 3D reconstruction of a single red blood cell (right)

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Hole P., Sillence K., Hannell C., Maguire CM Roesslein M, Suarez G, Capracotta S, Magdolenova Z, Horev-Azaria L, Dybowska A, Cooke L, Haase A, Contal S, Manø S, Vennemann A, Sauvain J-J, Staunton KC, Anguissola S, Luch A, Dusinska M, **Korenstein R**, Gutleb AC, Wiemann M, Prina-Mello A, Riediker M, Wick P., (2013) Interlaboratory comparison of size measurements on nanopartcles using Nanoparticle Tracking Analysis (NTA). *J Nanopart Res* 15, 2101.

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Shock, I., Barbul, A., Girshovitz, P. Nevo, U., **Korenstein, R.**, Shaked N.T. (2012) Optical phase nanoscopy in red blood cells using low-coherence spectroscopy. *J Biomed Optics* 17, 101509

Ben-Dov N. and **Korenstein R**. (2012) Enhancement of cell membrane invaginations, vesiculation and uptake of macromolecules by protonation of the cell surface. *PLoS One* 7, E35204

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Horev-Azaria L, Kirkpatrick CJ, **Korenstein R** et al., (2011) Predictive toxicology of cobalt nanoparticles and ions: comparative in-vitro study of different cellular models using methods of knowledge discovery from data. *Toxicol Sci* 122:489-501

Chapter

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Grants

2015-2018	European Commission – Horizon 2020 ERA-NET funded consortium on "Establishing nanomaterial grouping/ classification strategies according to toxicity and biological effects for supporting risk assessment" (achronym "NanoToxClass").
2016-2019	European Commission – Horizon 2020 EC funded consortium on "High level Integrated Sensor for Nanotoxicity Screening (achronym "HISENTS").

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The Wnt Signaling Pathway and Colorectal Cancer

Position

Senior Lecturer, Sackler Faculty of Medicine

Chair, Search Committee

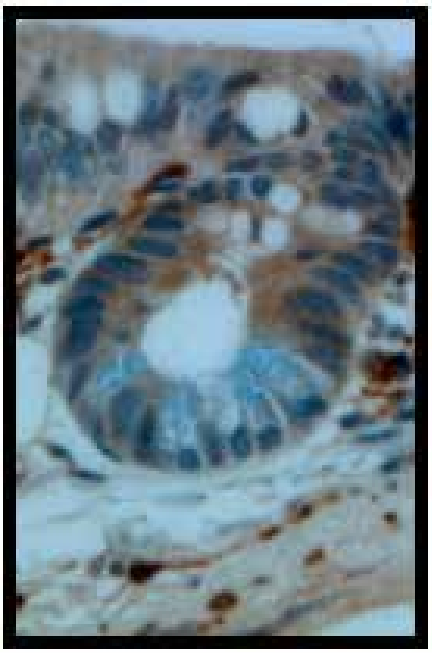
Research

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

Current projects in the lab include:

1. Identifying and characterizing new Wnt signaling components.

2. Developing new anti-colorectal cancer treatment strategies.



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

Publications

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Raviv, Z., Zilberberg, A., Cohen, S., Reischer-Pelech, D., Horrix, C., Berger, M.R., **Rosin-Arbesfeld, R**. and Flescher, E. Methyl jasmonate downregulates surviving expression and sensitizes colon carcinoma cells towards TRAIL-induced cytotoxicity. *Br J Pharmacol*. 10, 1476-5381, 2011.

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Dovrat S, Caspi M, Zilberberg A, Lahav L, Firsow A, Gur H, **Rosin-Arbesfeld R**. 14-3-3 and β-catenin are secreted on extracellular vesicles to activate the oncogenic Wnt pathway. *Mol Oncol*. pii: S1574-7891(14)00059-3, 2014.

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Raviv S, Bharti K, Rencus-Lazar S, Cohen-Tayar Y, Schyr R, Evantal N, Meshorer E, Zilberberg A, Idelson M, Reubinoff B, Grebe R, **Rosin-Arbesfeld R**, Lauderdale J, Lutty G, Arnheiter H, Ashery-Padan R. (2014) PAX6 regulates melanogenesis in the retinal pigmented epithelium through feed-forward

regulatory interactions with MITF. *PLoS Genet*. 10(5):e1004360.

Domke LM, Rickelt S, Dörflinger Y, Kuhn C, Winter-Simanowski S, Zimbelmann R, **Rosin-Arbesfeld R,** Heid H, Franke WW. (2014) The cell-cell junctions of mammalian testes: I. The adhering junctions of the seminiferous epithelium represent special differentiation structures. *Cell Tissue Res*. 8(5):894-911.

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Oz S, Kapitansky O, Ivashco-Pachima Y, Malishkevich A, Giladi E, Skalka N, **Rosin-Arbesfeld R**, Mittelman L, Segev O, Hirsch JA, Gozes I. (2014) The NAP-motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through microtubule end binding proteins. *Mol Psyc*h 19(10):1115-24.

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Franke WW, Zimbelmann R, Dörflinger , Kuhn C, Frey N, Heid H, **Rosin-Arbesfeld R.** (2015) Striatin family proteins, near-ubiquitous in mammalian cells, as constitutive components of the cytoplasmic plaques of the zonulae adhaerentes of simple epithelia, specific domains in the tessellate junctions of stratified epithelia and the myocardiac composite junctions. *Cell Tissue Res* 359(3):779-97.

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Skalka N, Caspi M, Lahav-Ariel L, Loh YP, Hirschberg K and **Rosin-Arbesfeld R.** (2016) Carboxypeptidase E (CPE) inhibits the secretion and activity of Wnt3a. Oncogene. Jul 4. doi: 10.1038/onc.2016.173.

Yedid N, Kalma Y, Malcov M, Amit A, Kariv R; Caspi M **Rosin-Arbesfeld R***, Ben-Yosef D (2016) The effect of a germline mutation in the APC gene on ß-catenin in human embryonic stem cells. BMC Cancer. *Equally corresponding authors.

Grants

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

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Angiogenic Switch Using Rationally-Designed Theranostic Nanomedicines

Positions

Chair, Department of Physiology and Pharmacology

Professor, Sackler Faculty of Medicine

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

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

Faculty Coordinator, Postgraduate Program in Nanotechnology

Associate Editor, *Advanced Drug Delivery Reviews*

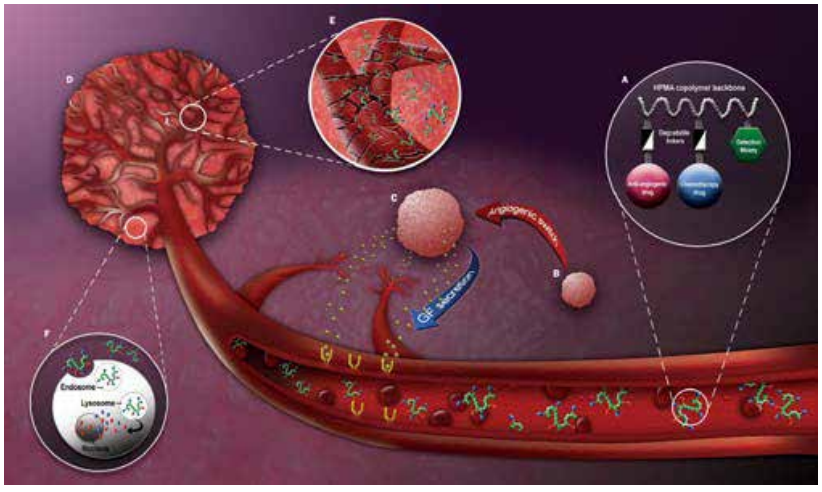
Associate Editor, *Nanomedicine: Nanotechnology, Biology and Medicine*

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

Research

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

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



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

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

Publications

Polyak D, Ryppa C, Ofek P, Licha K, Many A, Kratz F and **Satchi-Fainaro R**, Development of PEGylated doxorubicin-E-[c(RGDfK)$_2$] conjugate for integrin-targeted cancer therapy, *Polymers for Advanced Technology*, 22, 103–113 (2011).

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Miller K, Eldar-Boock A, Polyak D, Segal E, Benayoun L, Shaked Y and **Satchi-Fainaro R**, Antiangiogenic Antitumor Activity of HPMA Copolymer-Paclitaxel-Alendronate Conjugate on Breast Cancer Bone Metastasis Mouse Model, *Molecular Pharmaceutics*, 8,1052-1062 (2011).

Clementi C, Miller K, Mero A, **Satchi-Fainaro R** and Pasut G, Dendritic Poly(ethylene glycol) Bearing Paclitaxel and Alendronate for Targeting Bone Neoplasms, *Molecular Pharmaceutics*, 8:1063-1072 (2011).

Segal E, Pan H, Benayoun L, Kopečková P, Shaked Y, Kopeček J and **Satchi-Fainaro R**, Enhanced anti-tumor activity and safety profile of targeted nano-scaled HPMA copolymer-alendronate-TNP-470 conjugate in the treatment of bone malignances, *Biomaterials,* 32:4450-4463 (2011).

Scomparin A, Salmaso S, Bersani S, **Satchi-Fainaro R**, Caliceti P, Novel folated and non-folated pullulan bioconjugates for anticancer drug delivery, *European Journal of Pharmaceutical Sciences*, 42, 547-558 (2011).

Karton-Lifshin N, Segal E, Omer L, Portnoy M, **Satchi-Fainaro R***, Shabat D*, A unique paradigm for a turn-on near-infrared cyanine-based probe: non-invasive intravital optical imaging of hydrogen peroxide, *Journal of the American Chemical Society (JACS)*, 133, 10960-10965 (2011). *Corresponding authors.

Fante C, Eldar-Boock A, **Satchi-Fainaro R**, Osborn H, Greco F, Synthesis and biological evaluation of a polyglutamic acid-dopamine conjugate: a new anti-angiogenic agent, *Journal of Medicinal Chemistry*, 54, 5255-5259 (2011).

Satchi-Fainaro R*, Ferber S*, Segal E, Ma L, Dixit N, Ijaz A, Hlatky L, Abdollahi A, Almog A, Prospective identification of glioblastoma cells generating dormant tumors, *PLoS One,* 7: e44395. (2012).

Herzog IM, Green KD, Berkov-Zrihen Y, Feldman M, Vidavski RR, Eldar-Boock A, **Satchi-Fainaro R**, Eldar A, Garneau-Tsodikova S and Fridman M, 6"-Thioether tobramycin analogues: Towards selective targeting of bacterial membranes, *Angewandte Chemie*, **51**, 5652-5656 (2012)**.**

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2012-2016	MAGNET Rimonim Consortium, Office of the Chief Scientist of the Ministry of Industry, Trade & Labor: “siRNA delivery to ovarian cancer”
2012-2017	Israel National Nanotechnology Initiative (INNI), Focal Technology Area in nanotechnology, “Theranostic Nanomedicines for Personalized Medicine”
2014-2019	European Research Council (ERC) Consolidator Award. PolyDorm: “Uncovering the molecular and cellular mechanism of tumor dormancy for the rational design of theranostic nanomedicines”
2014–2018	Israel Science Foundation (ISF) Grant
2014 – 2016	Israel Cancer Association (ICA)
2014 – 2017	Melanoma Research Alliance SABAN Family Foundation-Team Science Award

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The ATM-Mediated DNA Damage Response

Positions

Professor, Sackler Faculty of Medicine

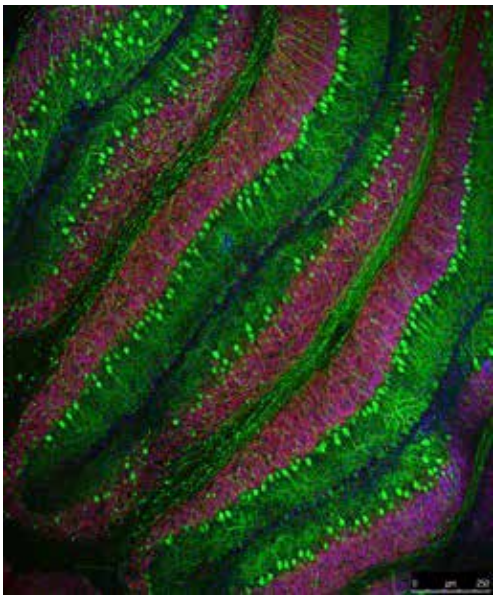
David and Inez Myers Chair in Cancer Genetics

ICRF Research Professorship

Research

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

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

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premature ageing. *Ageing Research Reviews* (in press).

Grants

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

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

Position

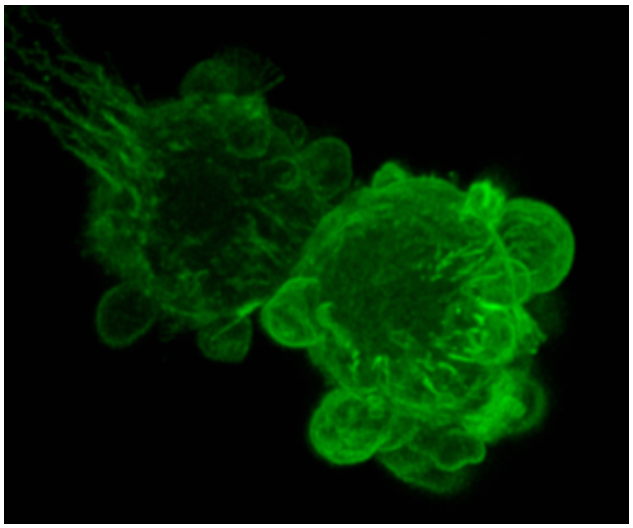
Associate Professor, Sackler Faculty of Medicine

Director, Sackler Cellular and Molecular Imaging Center (SCMIC)

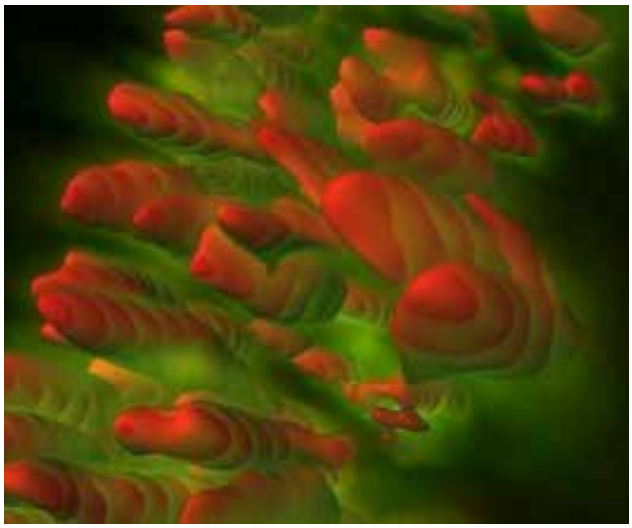
Research

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

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



Met localization in blebbing cells



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

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

To study Met activation by HGF/SF *in vivo*, we used a xenograft mouse model in which DA3 cells expressing the fluorescent protein mCherry (DA3-mCherry) are injected 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.

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Review

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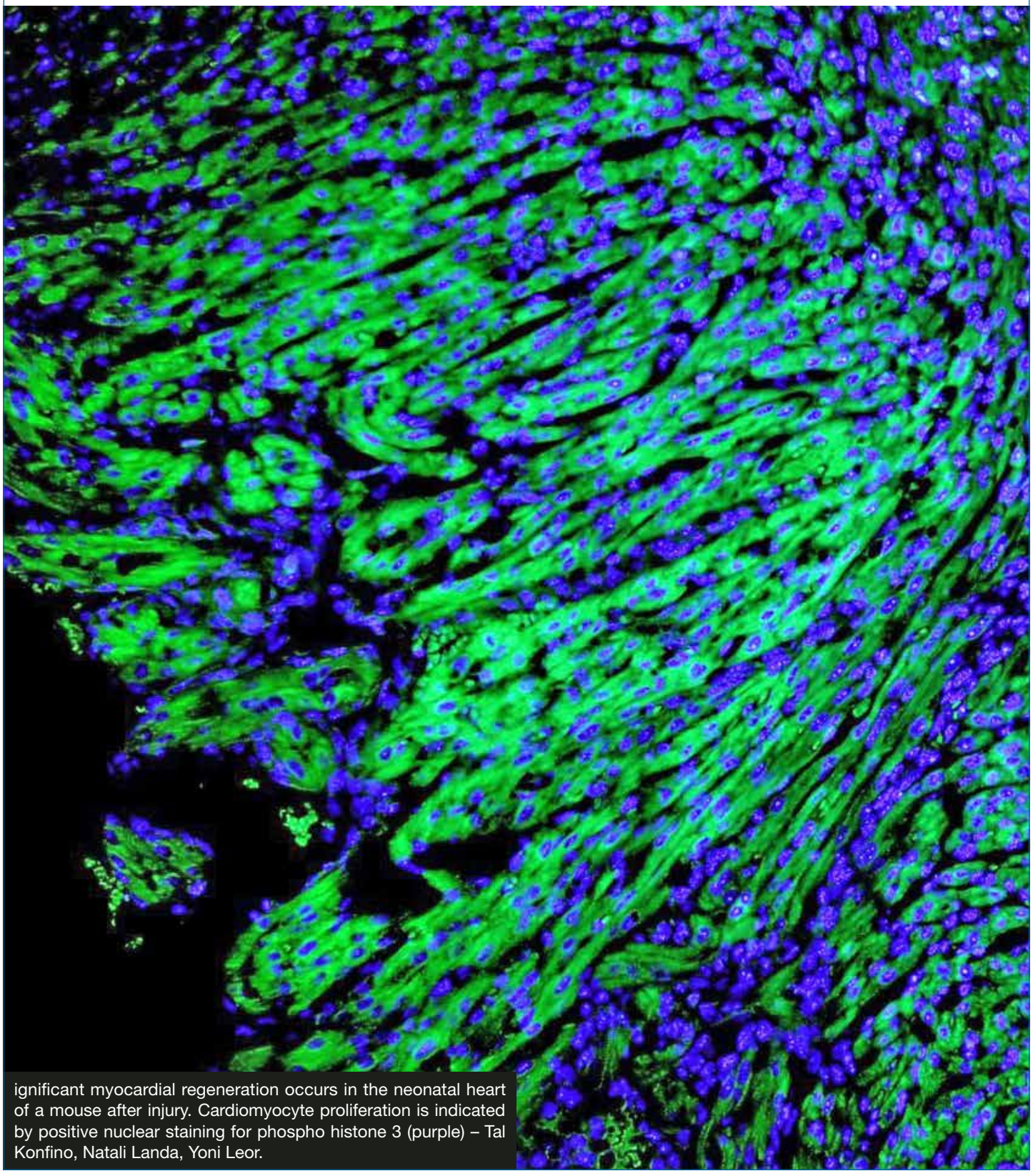
Cardiovascular Research and Diseases



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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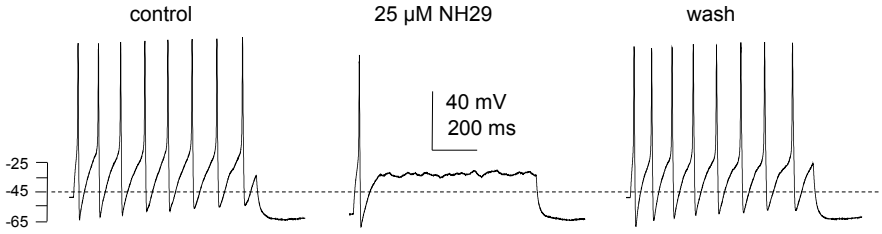
Normal and Diseased Potassium Channels in Human Brain and Heart

Position

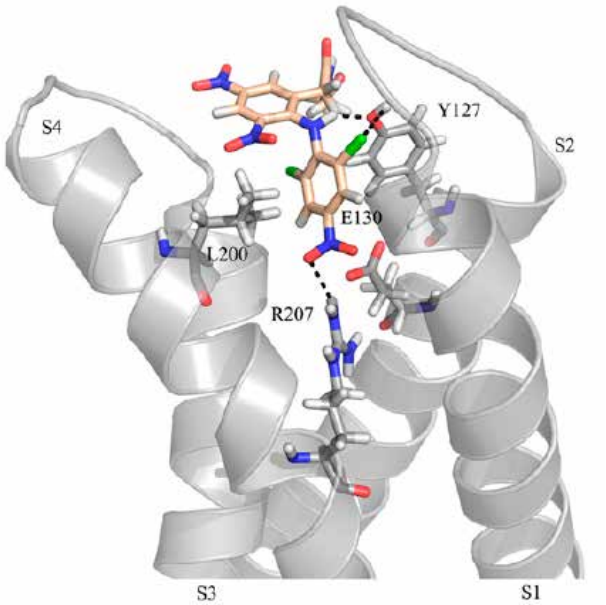
Professor, Sackler Faculty of Medicine

Research

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



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



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

Publications

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Grants

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

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

2014-2017 Israel Science Foundation-China (The ISF-NSFC joint program, 2092/14)

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

Position

Professor of Physiology, Sackler Faculty of Medicine

Research

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

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

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

Publications

Oz S, Tsemakhovich V, Christel CJ, Lee A & **Dascal N**. (2011). CaBP1 regulates voltage dependent inactivation and activation of $Ca_V1.2$ (L-type) calcium channels. *J Biol Chem* 286, 13945-13953.

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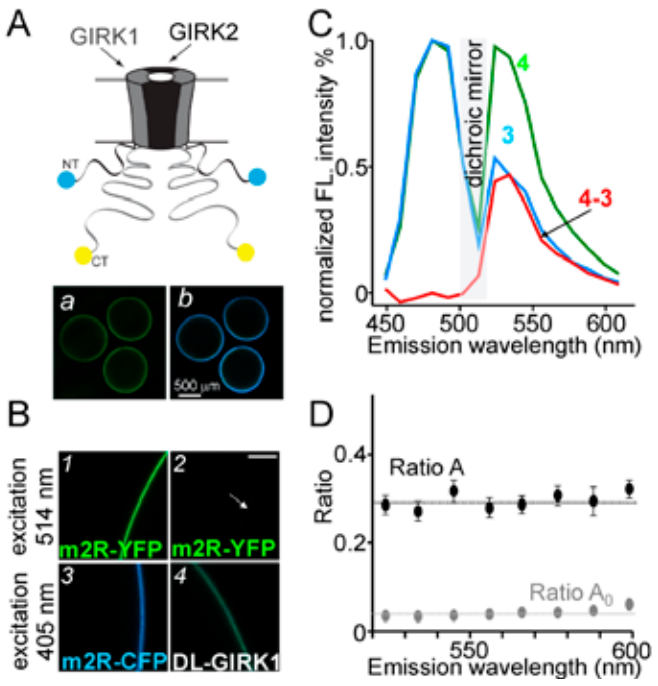

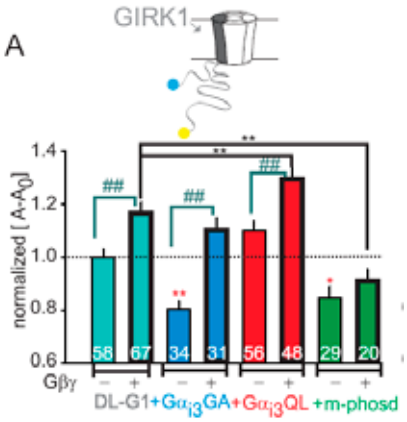

Studying GIRK channels expressed in a heterologous system (*Xenopus* oocytes). Intramolecular fluorescence resonance energy transfer (i-FRET) shows interactions of cytosolic N- and C-termini of the channel. **A**, GIRK channel labeled with two fluorescent proteins. **B**, Imaging the expressed fluorescent 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.

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Grants

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

Dr. Michal Katz-Leurer, Ph.D.

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

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Investigating the Cardiac Autonomic System Among Brain Damaged Patients

Position

Senior Lecturer

Chair, Department of Physical Therapy

Research

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

Publications

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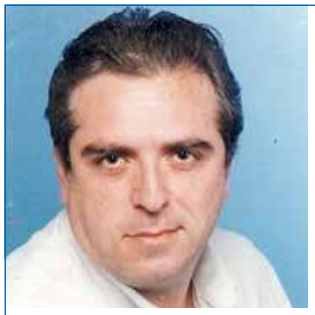

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Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

Positions

Professor, Sackler Faculty of Medicine

Research

Calcium (Ca^{2+}) is a major regulator in the living cell. In many cell-types the 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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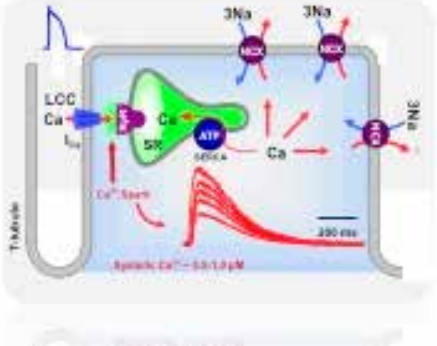

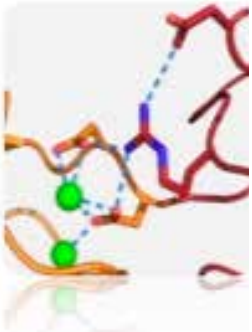

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Reviews

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Grants

2013-2017 Fields Center of Molecular Cardiology

2014-2018 Israeli Science Foundation

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

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Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions

Professor of Cardiology, Sackler Faculty of Medicine

Director, Neufeld Cardiac Research Institute, Tel Aviv University

Director, Tamman Cardiovascular Research Institute, Sheba Medical Center

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

Research

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

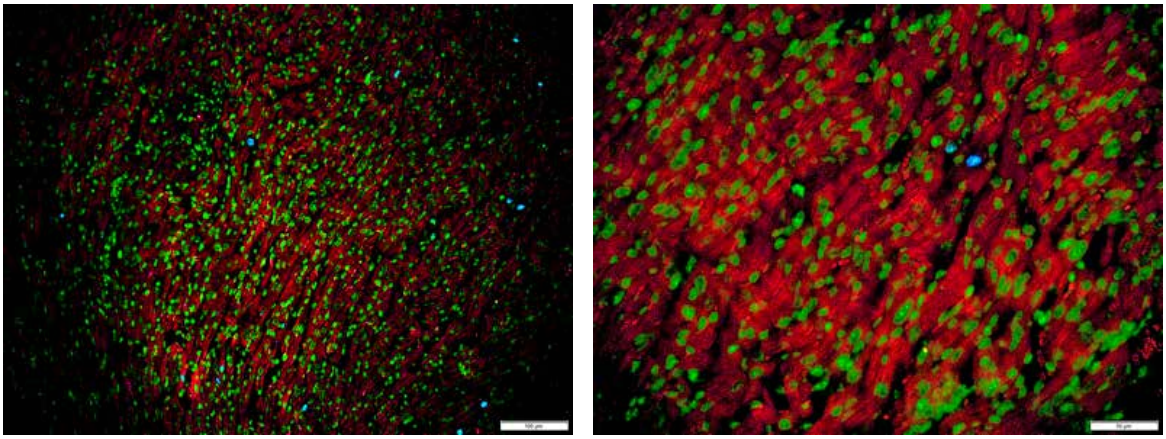
Publications

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

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

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

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



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

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

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

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Overgaard CB, Dzavik V, Buller CE, Liu L, Banasiak W, Devlin G, Maggioni AP, **Leor J**, Burton JR, Reis G, Ruzyllo W, Forman SA, Lamas GA, Hochman JS and Investigators OAT. Percutaneous revascularization and long term clinical outcomes of diabetic patients randomized in the Occluded Artery Trial (OAT). *Int J Cardiol*. 2013;168:2416-22.

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

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

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Grants

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

Dental Health and Medicine

Prof. Tamar Brosh, Ph.D.

Department of Oral Biology
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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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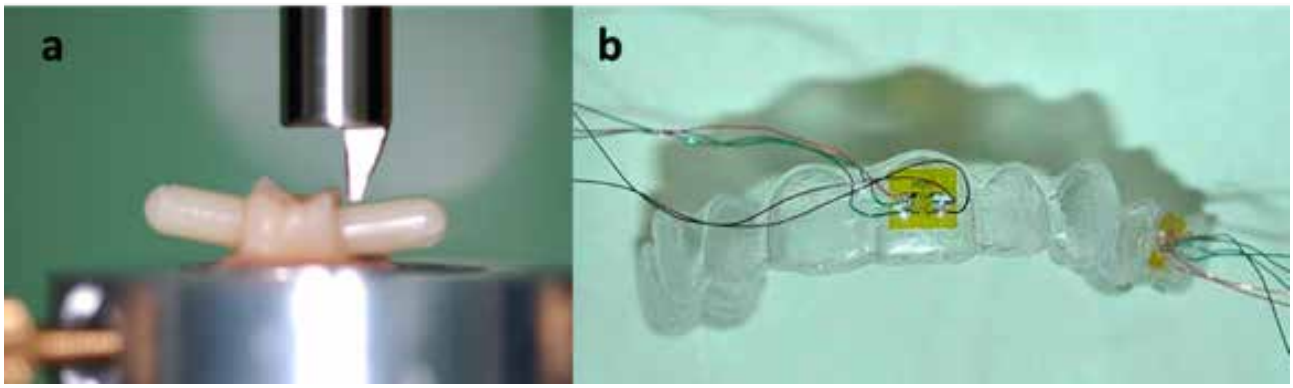

a. Shear bond test experiment. b. Transparent aligner equipped with strain gauges

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Brosh T, Yekaterina BE, Pilo R, Shpack N, Geron S. Can cone beam CT predict the hardness of interradicular cortical bone? *Head & Face Medicine,* 2014, 15;10:12.

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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 and imaging study in rats. *Am J Sports Med*. 2016 44:177-82.

Grants

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

Prof. Ilana Eli, D.M.D.

Department of Oral Biology
Goldschleger School of Dental Medicine
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Behavioral Sciences in Dentistry

Positions

Professor, Sackler Faculty of Medicine

Head, School of Dental Medicine

Research

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

Research topics:

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

Publications

E. Winocur , N. Uziel , T. Lisha, C. Goldsmith, **I. Eli..** Self-reported bruxism – associations with perceived stress, motivation for control, dental anxiety and gagging .*Journal of Oral Rehabilitation*, 38, 3-11, 2011

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

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I. Eli. Stress and patients' ability to comply with or adhere to treatment regimens. *J Oral Facial Pain Headache*, 28, 297, 2014.

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Chapters

I. Eli. Pain, placebo and hypnosis – how words and suggestions affect patients. In: *Hypnosis: Psycho-philosophical Perspectives and Therapeutic Relevance,* Renu Sharma, Bhupendra M. Palan (eds.), *Concept Publishing Co. Pvt. Ltd*., New Delhi, India, 2011 (pp.64-72)

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Prof. Sandu Pitaru, D.M.D.

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

Position

Professor of Oral Biology, School of Dental Medicine

Research

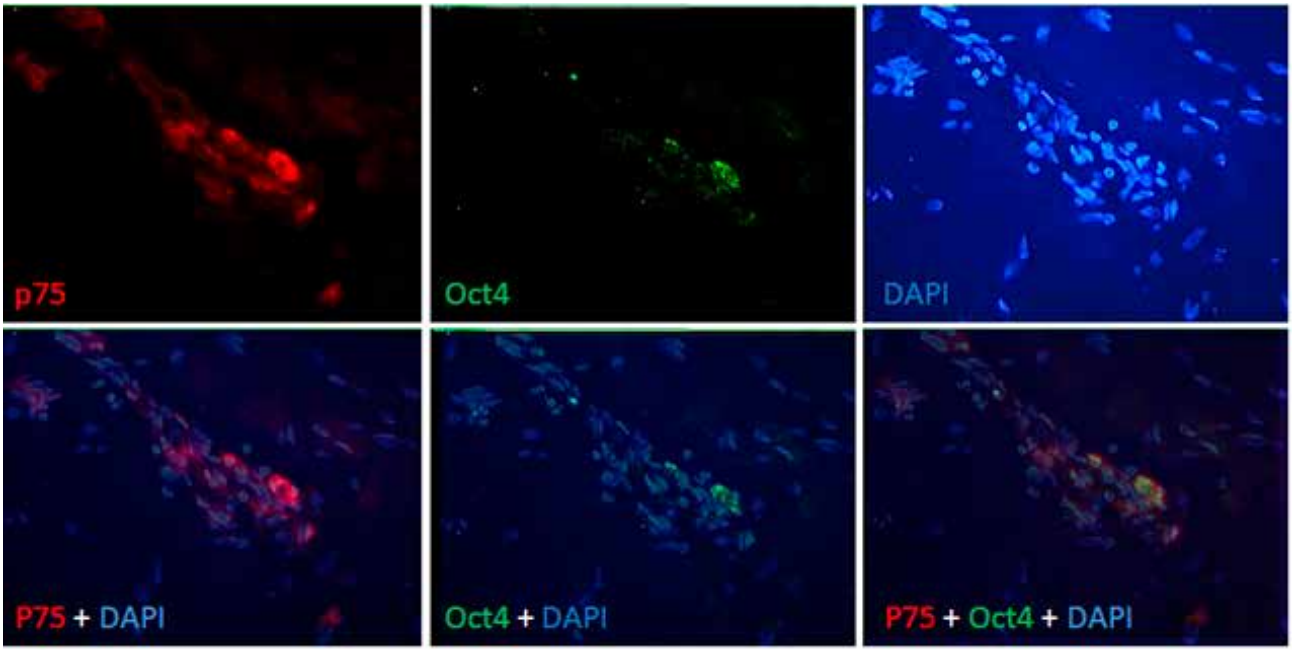
Our research focuses on the biology of a new stem cell population recently discovered in our laboratory. We found, that in contrast to other tissues, the oral mucosa of the adult and elderly organism harbors a primitive neural crest-like stem cell population, which is capable of expressing embryonic associated markers and of differentiating into cell lineages of the 3 germ layers – ectoderm, mesoderm and endoderm. We term this population "oral mucosa derived stem cells – OMSC". Using cutting edge technologies, we are investigating the genetic and epigenetic mechanisms that maintain such a fetal-like stem cell population in the adult and aging oral mucosa, and study how these mechanisms and OMSC are affected by chronic and neurodegenerative diseases as diabetes and Parkinson's Disease. By elucidating these mechanisms, we aim to develop new therapeutic approaches for treating chronic diseases associated with ageing.

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

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

Publications

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



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

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Grants

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

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

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

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

Position

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

Research

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

Understanding the evolutionary 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

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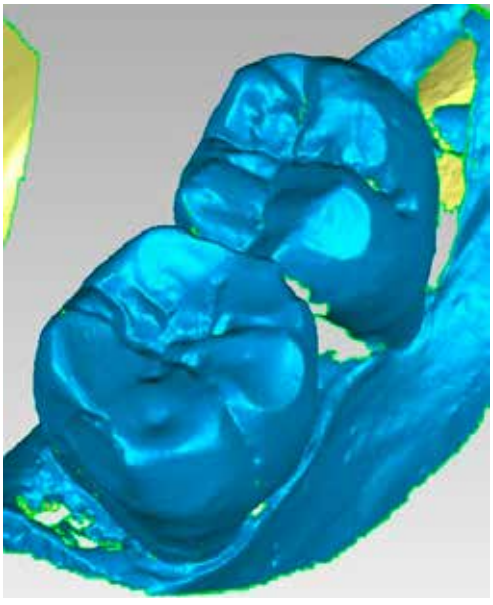
J. Abbas, K. Hamoud, H. May, N. Peled, **R. Sarig**, D. Stein, D. Alperovitch-Najenson, I. Hershkovitz. Socioeconomic and physical characteristics of



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Grants

2016-2019 Israel Science Foundation

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

Department of Periodontology and Oral Implantology
Goldschleger School of Dental Medicine
Sackler Faculty of Medicine

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Bone Regeneration in the Jaws

Positions

Professor

Chair, Department of Periodontology and Oral Implantology

Gerald Niznick Chair of Implantology

Research

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

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

Publications

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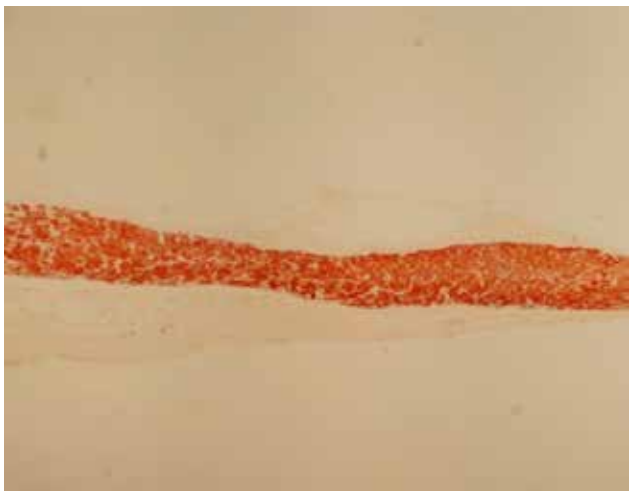

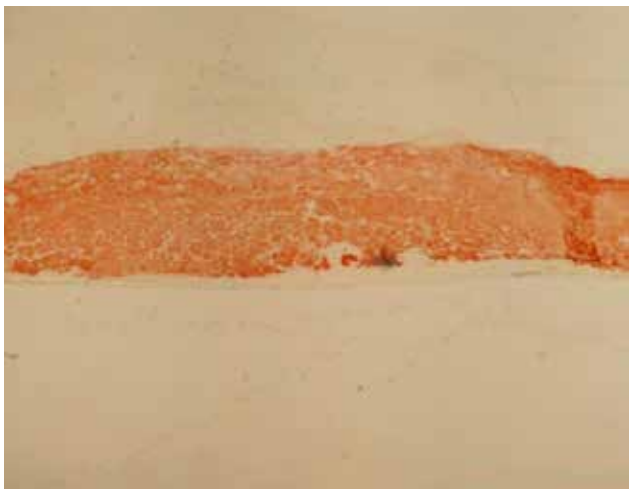

Stabilizing collagen membrane used in guided bone regeneration procedures.

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

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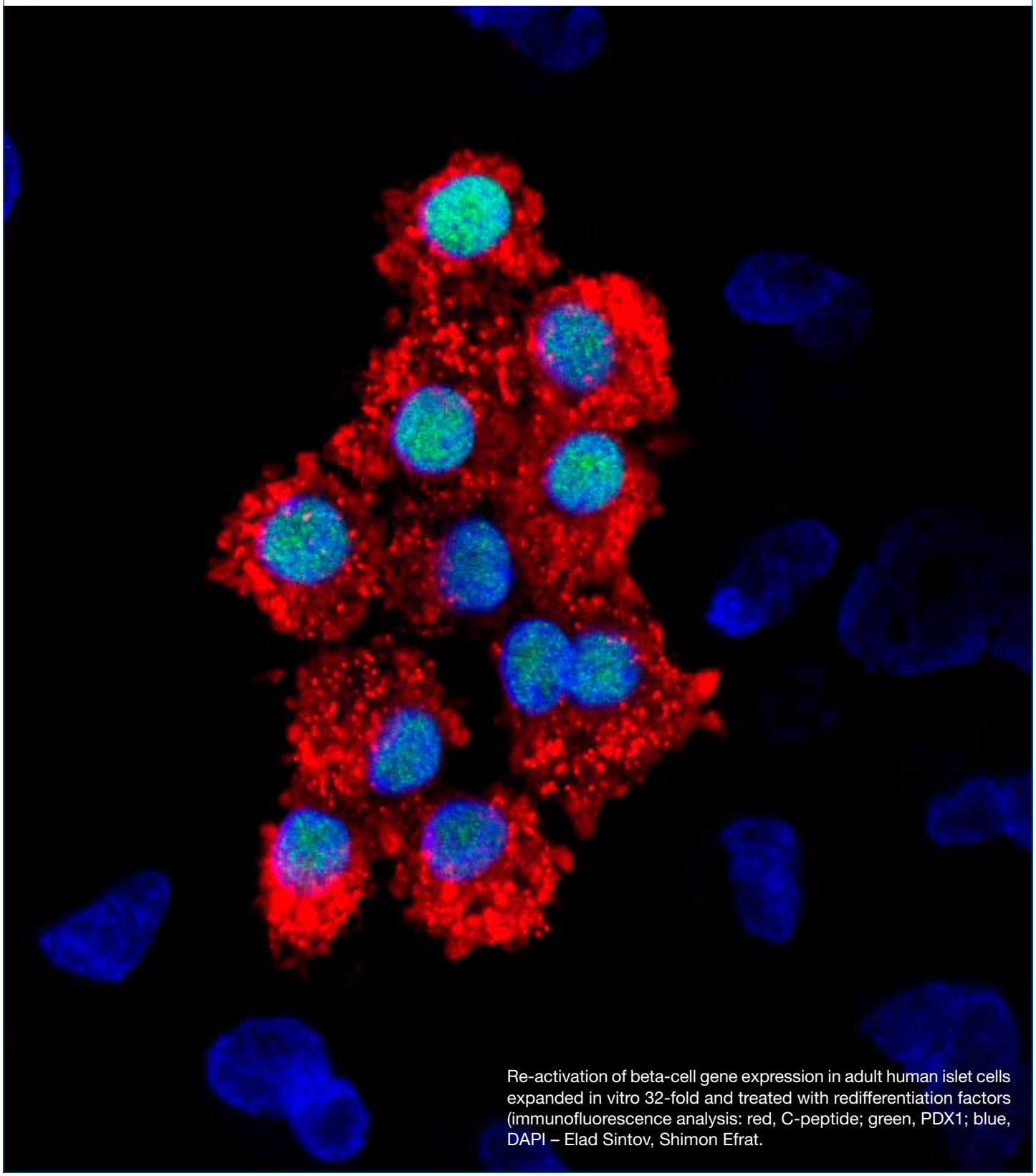
Diabetes, Metabolic and Endocrine Diseases



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

Prof. Shimon Efrat, Ph.D.

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Cell Replacement Therapy for Diabetes

Position

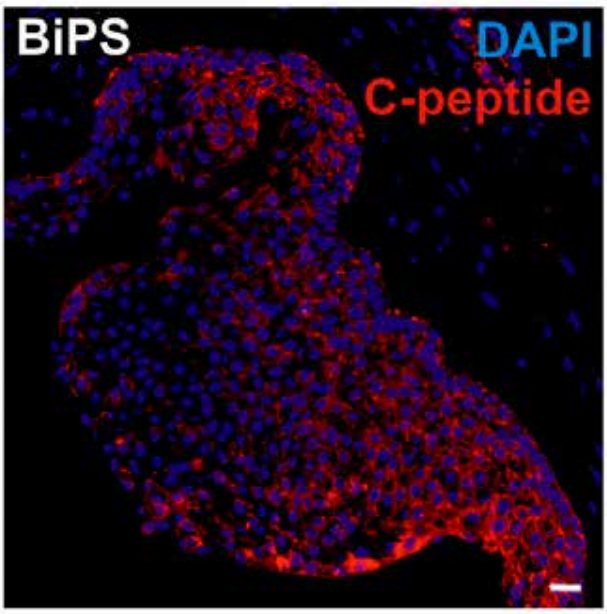
Professor, Sackler Faculty of Medicine

Nancy Gluck Regan Chair in Juvenile Diabetes

Research

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

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



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

Publications

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

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Grants

2012-2017 Innovative Medicines Initiative (IMI)

2013-2017 Israel Science Foundation (ISF)

2015-2017 Kadimastem Ltd.

2015-2018 Rosetrees Trust

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Intracellular Membrane Trafficking

Position

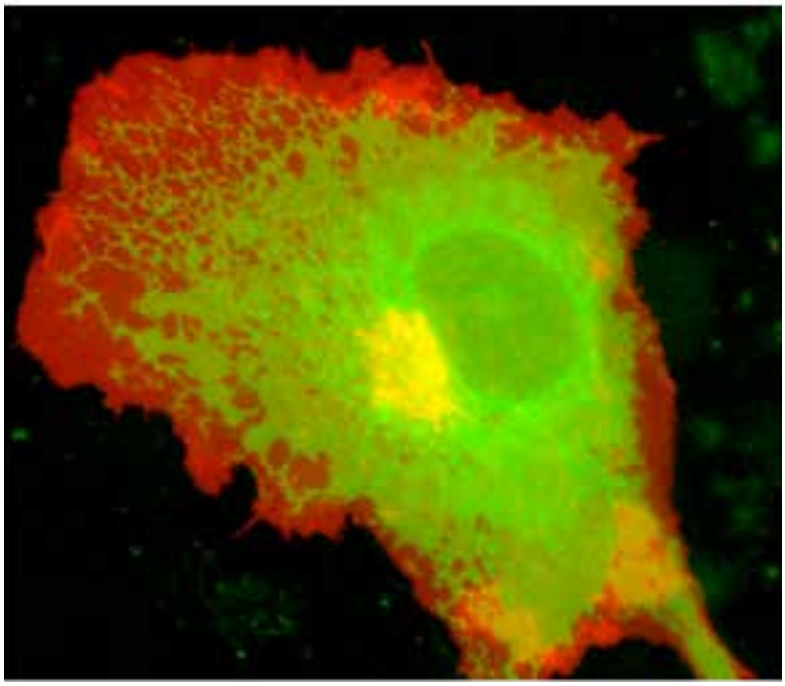
Professor, Sackler Faculty of Medicine

Research

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

To understand these processes in detail, one must recognize that protein–protein as well as protein-lipid interactions are involved. Studying the 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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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**. The myelin proteolipid Plasmolipin, forms oligomers and induces liquid ordered membranes in the Golgi apparatus. *J. Cell Science* 128, 2293-302. 2015

Grants

2012-2016	Israel Science Foundation (ISF) Grant, Surface expression of proteins is regulated by sorting and selection in endoplasmic reticulum exit sites and in the Golgi apparatus
2016	Jerome Lejeune Foundation

Dr. Limor Landsman, Ph.D.

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Sackler Faculty of Medicine

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Pancreas Development and Function: the Role of Microenvironmental Cues

Position

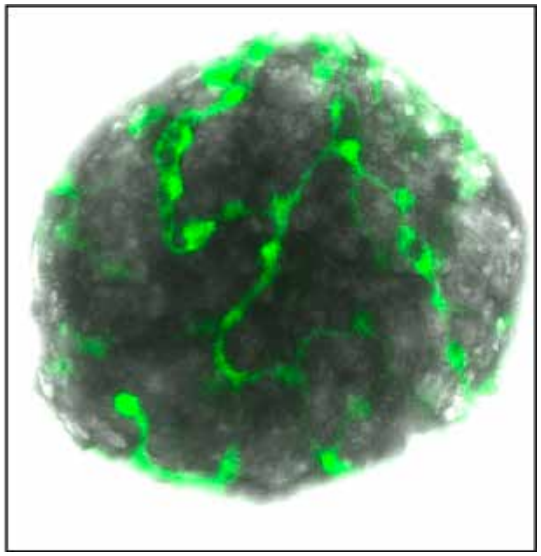
Senior Lecturer, Sackler Faculty of Medicine

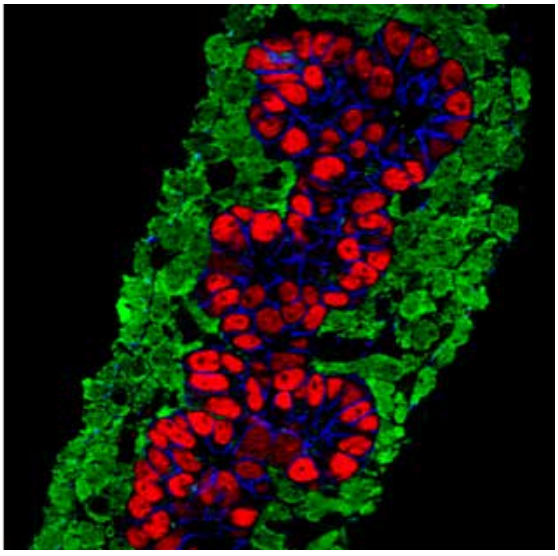
Research

Maintenance of blood glucose levels is dependent upon the tight regulation of insulin secretion from pancreatic beta-cells. Insufficient insulin secretion, whether due to reduced beta-cell numbers, or impaired beta-cell function, leads to diabetes. Our group studies how insulin-producing beta-cells maintain their functionality in health, and how it is lost in diabetes. To this end, we research the cross talk between insulin-producing cells and 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 mesenchymal and other pancreatic cell types in both healthy and diseased mouse models.





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

Publications

Avraham-Davidi I, Yona S, Grunewald M, **Landsman L**, Cochain C, Silvestre JS, Mizrahi H, Faroja M, Strauss-Ayali D, Mack M, Jung S, Keshet E. (2013) On-site education of VEGF-recruited monocytes improves their performance as angiogenic and arteriogenic accessory cells. *J Exp Med* 210, 2611-25.

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

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Sasson A., Rachi E., Sakhneny L, Baer D., Lisnyansky M., Epshtein A. and **Landsman L**. (2016) Islet pericytes are required for beta-cell maturity. *Diabetes*, In press.

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

Grants

2012–2016	Marie Curie Career Integration grant (CIG)
	Cellular composition of the pancreas: elucidating the role of mesenchymal signaling pathways
2013–2018	European Research Council (ERC) Starter Grant
	ß-cell dysfunction in diabetes: elucidating the role of islet-associated mesenchymal cells
2014-2017	Israel Ministry of Health
	Elucidating the role of pancreatic mesenchyme secreted factors in beta-cell function and diabetes progression
2016 – 2018	German-Israeli Foundation (GIF), with Dr. Francesca Spagnoli

Prof. Drorit Neumann, Ph.D.

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

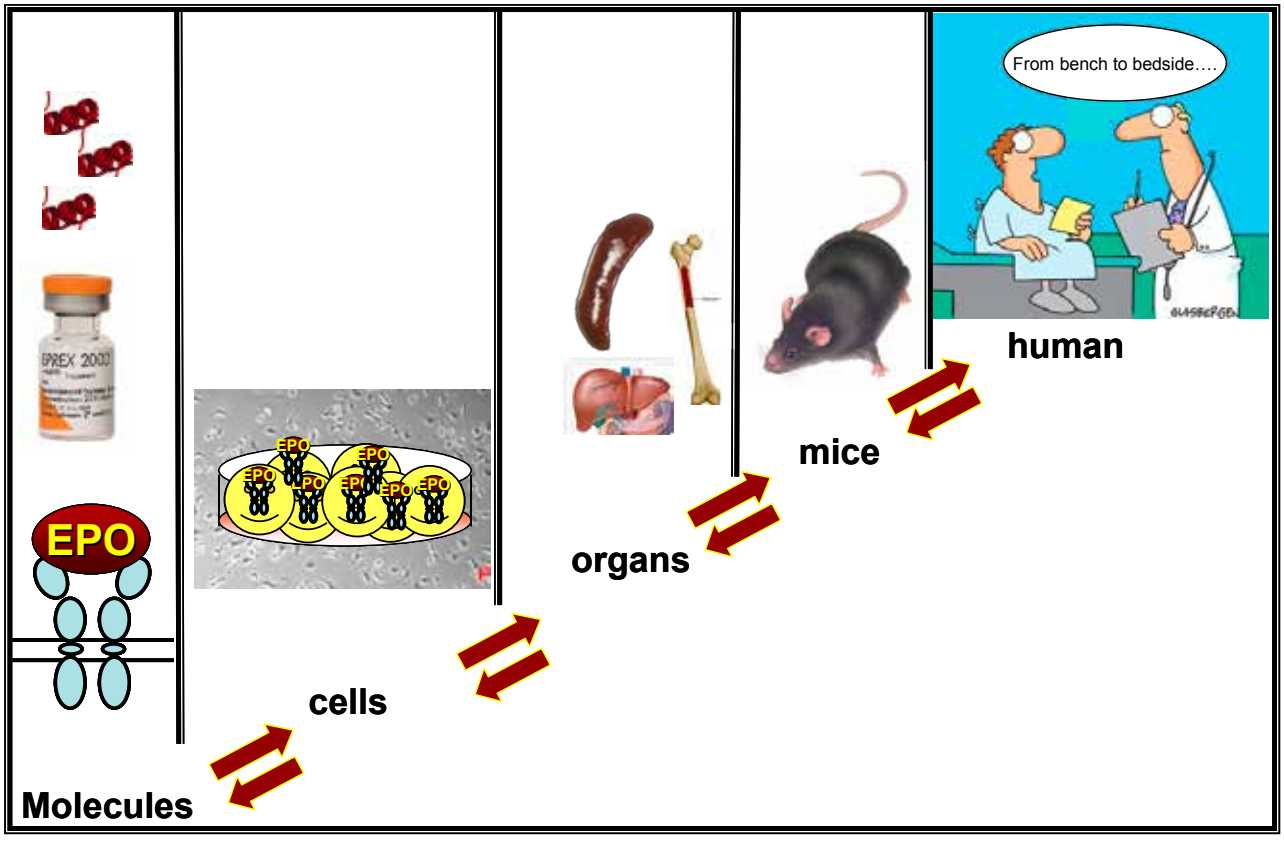
Positions

Professor, Sackler Faculty of Medicine

Chair, M.Sc. Studies, Dr. Miriam and Sheldon Adelson Graduate School of Medicine, Sackler Faculty of Medicine

Research

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



of *in-vitro* and murine experimental models, and include also an avenue of elucidating the relevance and possible clinical application of the results.

Publications

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Inbar D., M. Cohen-Armon and **D. Neumann.** Erythropoietin driven signaling and cell migration mediated by polyADP-ribosylation, *Brit. J. Cancer* 107: 1317-1326 (2012).

Oster H. S., S. Prutchi-Sagiv, O. Halutz, E. Shabtai, M. Hoffman, **D. Neumann**, M. Mittelman. Erythropoietin treatment is associated with an augmented immune response to the influenza vaccine in hematologic patients. *Exp. Hematol*. 41:167-71 (2013).

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

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Chapters and Reviews

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Oster H. S., **D. Neumann**, M. Hoffman and M. Mittelman. Erythropoietin: the swinging pendulum. *Leukemia Res* 36:939-44 (2012)

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

Hiram-Bab S, **Neumann D,** Gabet Y. Erythropoietin in bone - Controversies and consensus. *Cytokine*. 2016 *in press*

Grants

2015-2017 Israel Cancer Association –

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

Position

Professor Emeritus, Sackler Faculty of Medicine

Julius Friedrich Cohnheim Laboratory of Phagocyte Research

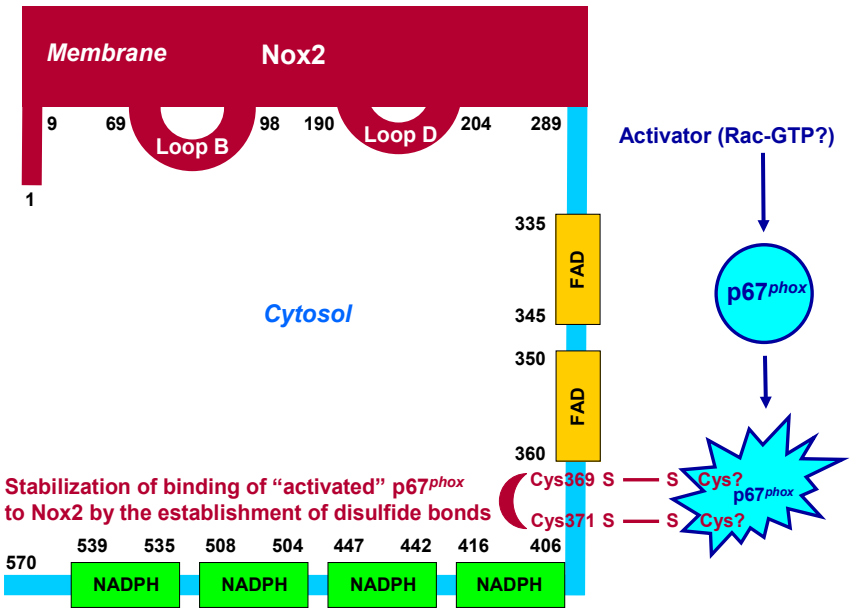
Member, Editorial Board, *The FASEB Journal*

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

Research

We are studying the production of reactive oxygen species (ROS) by phagocytes. ROS are generated by an enzyme complex, known as the NADPH oxidase. Our group is responsible for many of the seminal advances in the biochemistry and molecular biology of the NADPH oxidase complex, including: the standard micro-assay for the measurement of ROS (991 citations); the development of the first cell-free system of ROS production; the discovery of the cytosolic oxidase components (673 citations); the discovery of the role of the small GTPase Rac in oxidase activation (832 citations); the introduction of "peptide walking" to identify sites of protein-protein interaction, and the construction of chimeric cytosolic oxidase activators. The laboratory is equipped for the performance of advanced biochemical and molecular biology techniques.

The most recent interest of our group is focused on the mapping of the hotspots of interaction between the catalytic oxidase component Nox2 and the cytosolic activator p67^{phox}. We found that the dehydrogenase region of Nox2 (residues 288-570) contains a Cys-Gly-Cys (CGC) triad (residues 369-371), which serves as a binding site for p67^{phox}. This finding is based on a novel methodology, designed by us, in which we measure the binding of recombinant p67^{phox} to an array of synthetic overlapping peptides covering



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

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

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

Publications

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

Grants

2013-2017	Assembly of the phagocyte NADPH oxidase complex, Israel Science Foundation
2011 – 2016	The David Roberts Fund

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Molecular Biology of the Insulin-Like Growth Factor System

Positions

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Head, Yoran Institute for Human Genome Research

Lady Davis Chair in Biochemistry

Chair, Department of Human Molecular Genetics and Biochemistry

Research

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

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

Publications

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Grants

2014-2016 "Intracellular βvβ3 integrin and nuclear IGF1R as chronic lymphocytic leukemia markers". Varda and Boaz Dotan Research Center in Hemato-Oncology, Tel Aviv University.

2014-2018 "Mechanistic insights into IGF1-dependent longevity genes". U.S.-Israel Binational Science Foundation.

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

2016-2017 "Nuclear IGF1R translocation adds a new layer of signaling control". Hendrik and Irene Gutwirth Fund for Diabetes Mellitus Research, Sackler School of Medicine, 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

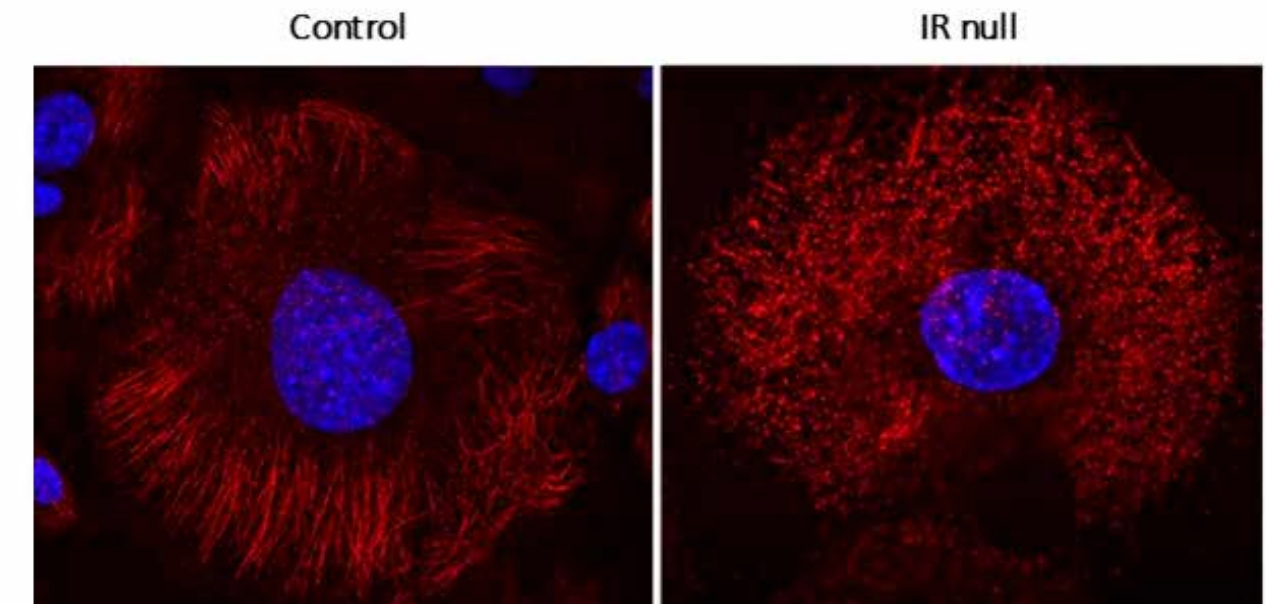
Research

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

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

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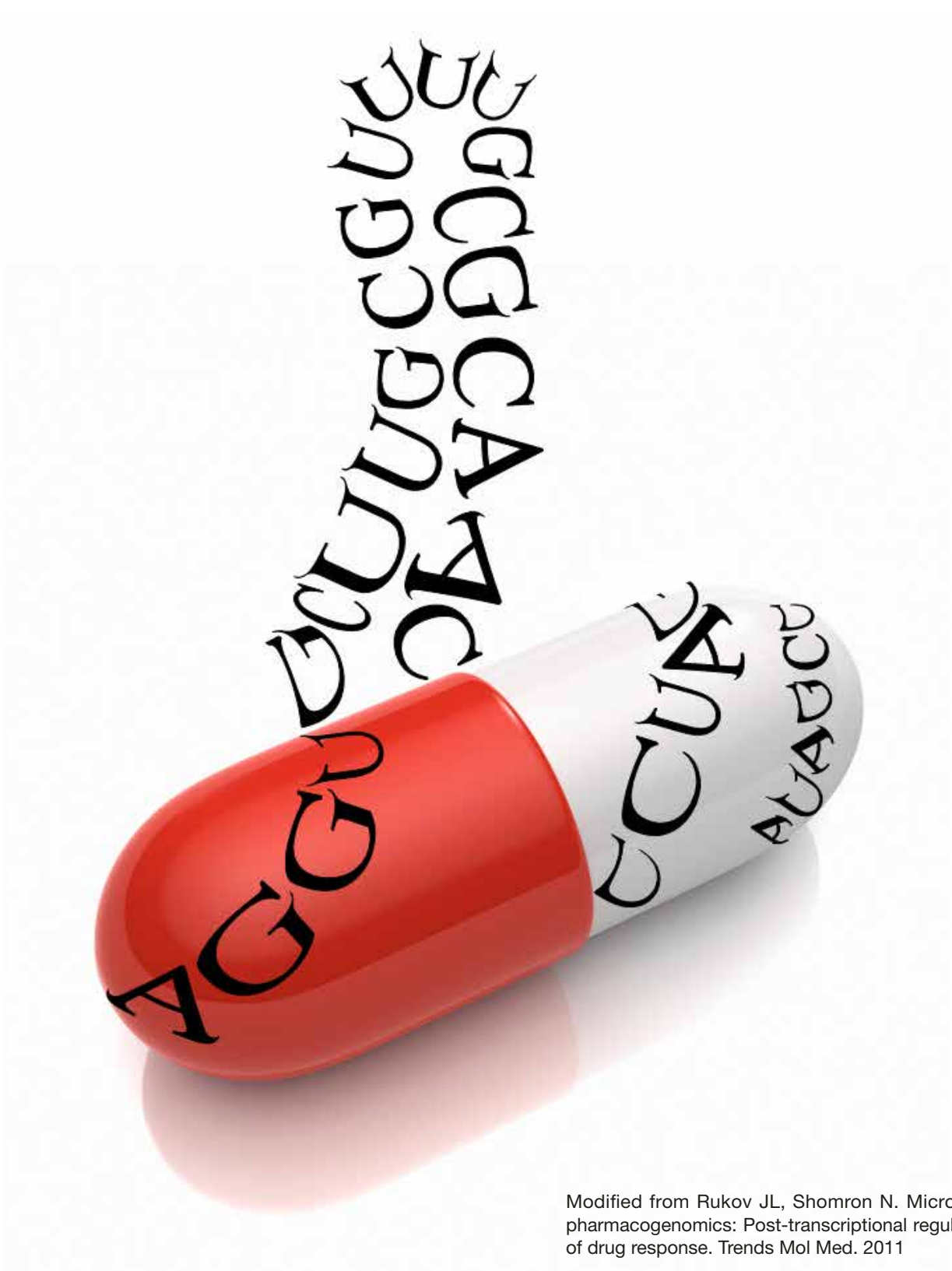
Grants

2014-2016	Industry Research Grant
2016-2017	Industry – Ramot TAU Technology Transfer Company

Patent

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

Genomics & Personalized Medicine



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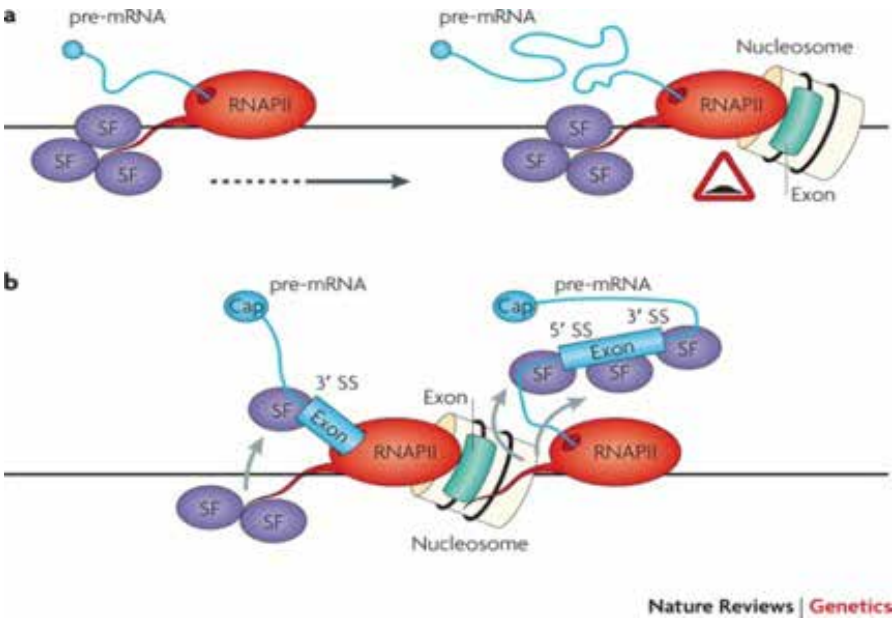
Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders & Cancer

Positions

Professor, Sackler Faculty of Medicine

Research

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



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

Publications

Hollander D, Donyo M, Atias N, Mekahel K, Melamed Z, Yannai S, Lev-Maor G, Shilo A, Schwartz S, Barshack I, Sharan R, **Ast G**. A network-based analysis of colon cancer splicing changes reveals a tumorigenesis-favoring regulatory pathway emanating from ELK1. *Genome Res*. 2016;26:541-53.

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Reviews

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

Grants

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

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Genomic Analysis of Hereditary Hearing Loss

Positions

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President, Israel Society of Auditory Research

Associate Editor, *European Journal of Human Genetics*

Research

Our primary interest is the genetic basis of hereditary hearing loss or deafness. Our group is working towards the identification, characterization and regulation of genes associated with hereditary hearing loss. For gene discovery, we focus on the Israeli Jewish and Palestinian Arab populations in the Middle East. Our studies have encompassed the prevalence of connexin 26 mutations in these populations, the most common form of deafness, to the identification of mutations in over 30 genes, since this is a genetically heterogeneous disease. We are employing deep sequencing, also known as massively parallel sequencing, to identify mutations using the latest genomic technology. Our work has provided the link between gene discovery and clinical diagnosis in genetic clinics in medical centers throughout Israel. In addition, we have studied the auditory and vestibular systems of a dozen mouse mutants, focusing on mutation identification, morphological and functional analysis of the organ of Corti and its cells, and behavioral analysis of hearing and balance disorders. This has allowed us to define the pathways leading to deafness in mouse models for human deafness. Most recently, we have demonstrated that microRNAs are essential for development and function of inner ear hair cells in vertebrates through microRNA expression, mouse mutants and target identification.

Publications

Manuscripts

Paz, A., Brownstein, Z., Ber, Y., Bialik, S., David, E., Sagir, D., Ulitsky, I., Elkon, R., Kimchi, A., **Avraham, K.B.,** Shiloh, Y. and Shamir, R. (2011) SPIKE: a database of highly curated human signaling pathways. *Nucleic Acids Res*. 39: D793-793.

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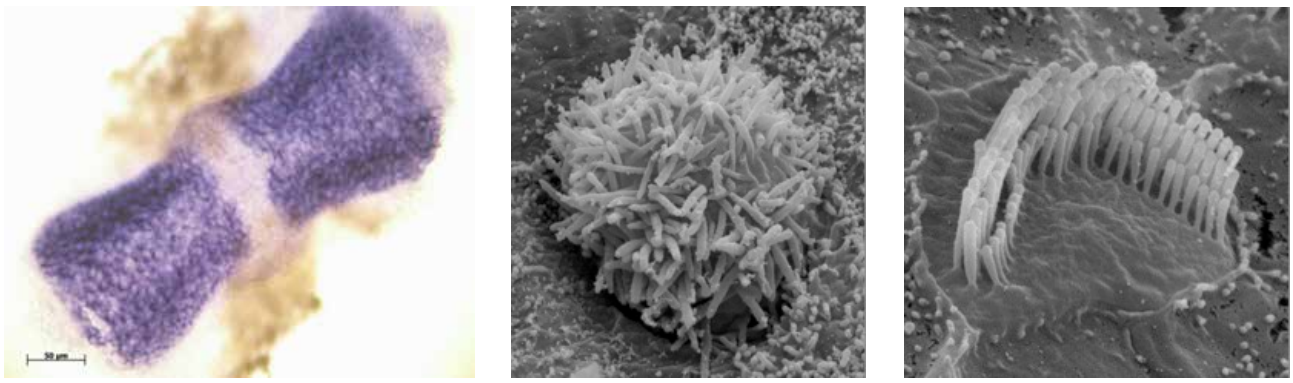

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Grants

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

2012 – 2016 Morphodynamics of Mammalian Planar Cell Polarity – a Quantitative Approach, Human Frontier Science Program, Co-PIs: Ping Chen, David Sprinzak, Fumio Matsuzaki

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

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

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Genomic-scale Bioinfomatics Exploration of Gene Regulation

Positions

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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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Reviews

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Hertzano R, **Elkon R**. High throughput gene expression analysis of the inner ear. *Hear Res. 2012, 288:77-88.*

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Genomic Biomarkers for CNS Drug Response

Positions

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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

Behar DM, Yunusbayev B, Metspalu M, Metspalu E, Rosset S, Parik J, Rootsi S, Chaubey G, Kutuev I, Yudkovsky G, Khusnutdinova EK, Balanovsky O, Semino O, Pereira L, Comas D, **Gurwitz D**, Bonne-Tamir B, Parfitt T, Hammer MF, Skorecki K, Villems R. The genome-wide structure of the Jewish people. *Nature*. 466:238-242 (2011).

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

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

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microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Publications

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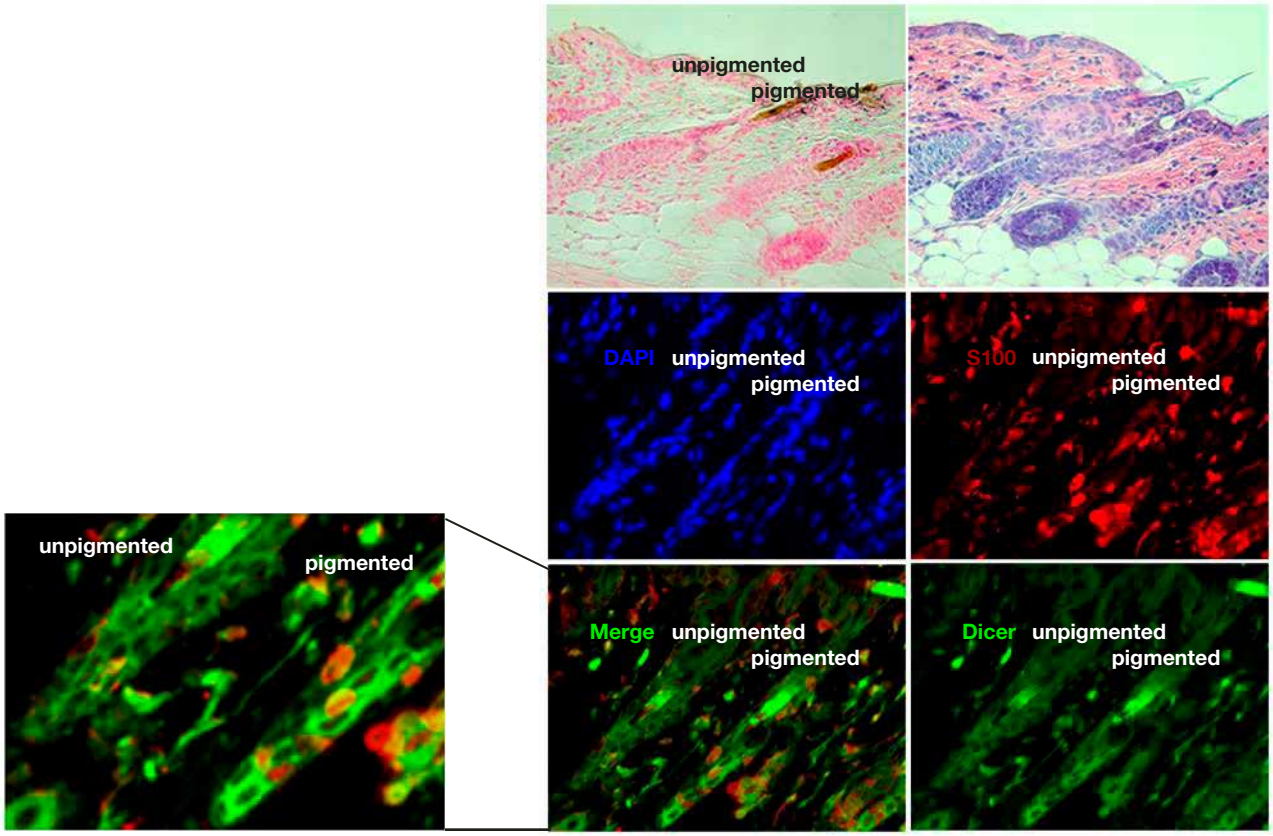

Skin section, subject to H&E (left) and Fontana-Masson staining of melanin (right), shows pigmented and unpigmented regions of (floxed/floxed); Dct(Cre/Cre); Dct-lacZ; K14-scf mouse skin. Immunofluorescent staining of the skin section indicates expression of DICER (green) and S100 (red) (400x magnification).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

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

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Genetic and Metabolic Research of Age-Dependent Chronic Degenerative Disease

Positions

Professor, Sackler Faculty of Medicine

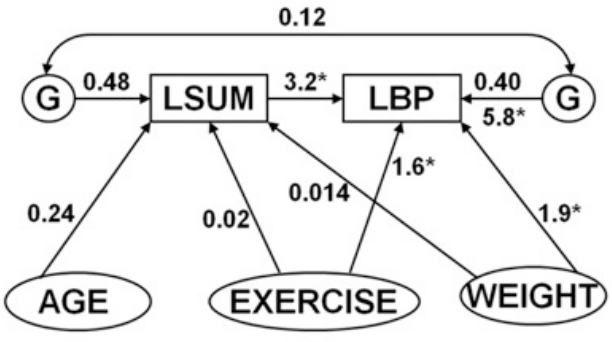
Chair, Department of Anatomy and Anthropology

Pollak Chair of Biological Anthropology

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

Research

Our research is focused on age-related chronic degenerative disease, such as osteoporosis, osteoarthritis, including disc degeneration disease and muscle mass loss – sarcopenia. The prevalence of sarcopenia is as high as 30% for those above 60 years old. In the elderly, the loss of muscle mass is correlated with profound physical impairment and disability with severe clinical consequences, including mobility loss, osteoporosis, osteoarthritis, increased fracture risk, dyslipidemia, insulin resistance, and increased mortality. However, it is also often developed at a much younger age. Despite the above clinical significance and despite the fact that a strong familial component in muscular mass variation is well established, there is almost a total lack of molecular genetic studies of this trait. This is in a great contradiction to studies concerning the other two body composition components: bone and fat mass, for each of which many dozens of studies have been published during the past two decades. It is therefore timely and imperative to invest extensive scientific research 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.



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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Grants

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

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Genomics and Gene Regulation by Small RNAs

Positions

Senior Lecturer, Sackler Faculty of Medicine

Academic Director, BioAbroad

Editor-in-Chief, *Genetics Research*

Research

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

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

Publications

Gilam A, Conde J, Weissglas-Volkov, Oliva N, Friedman E, Artzi N, **Shomron N**. Local microRNA delivery targets Palladin and prevents metastatic breast cancer. *Nat Commun*. In press.

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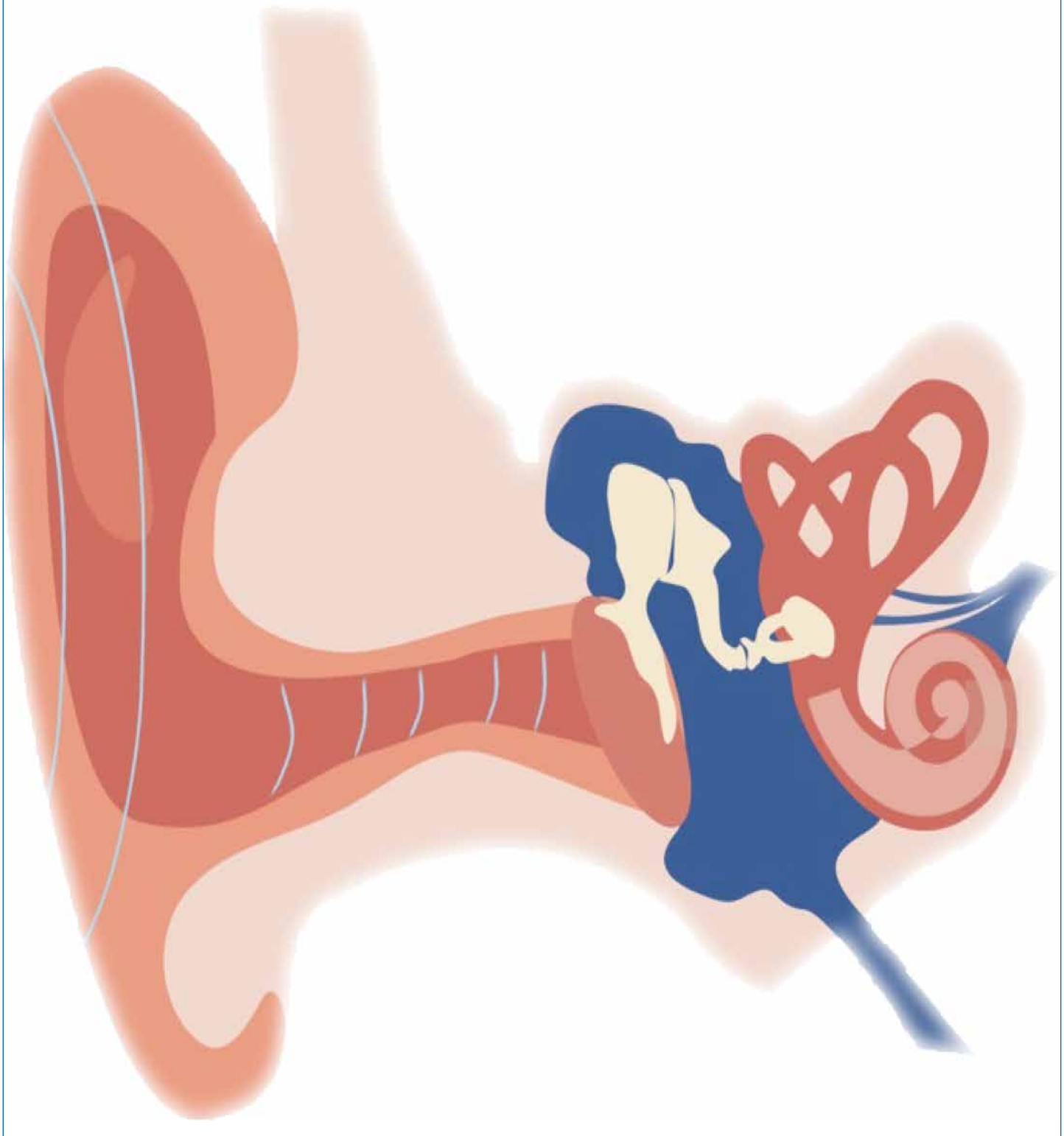
Grants

2011-2016	I-CORE Program of the Planning and Budgeting Committee, The Israel Science Foundation (grant number 41/11)
2013-2016	Israel Cancer Research Fund (ICRF), Research Career Development Award (RCDA)
2014-2016	Saban Family Foundation—Melanoma Research Alliance
2014-2016	Foundation Fighting Blindness
2014-2016	Israel Cancer Research Fund (ICRF), Acceleration Grant
2014-2016	Binational Science Foundation (BSF)
2014-2016	Israel Cancer Association

2015-2016	Check Point Institute for Information Security
2014-2015	Varda and Boaz Dotan Research Center in Hemato-Oncology, Idea Grant
2015-2018	Interdisciplinary grant of the Israeli Ministry of Science, Technology and Space on the Science, Technology and Innovation for the Third Age
2016-2018	Kamin
2016-2020	Israel Science Foundation

Hearing, Language & Speech Sciences and Disorders



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Paralinguistic Communication, Phonetics and Psychoacoustics

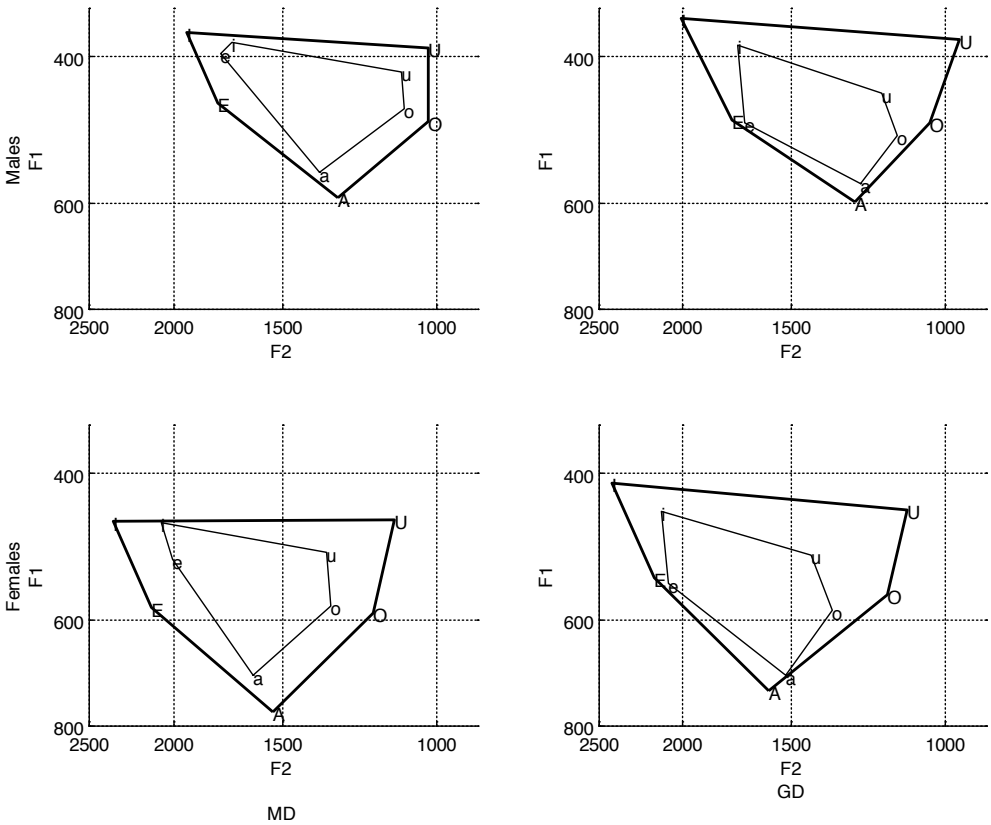
Positions

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

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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.).

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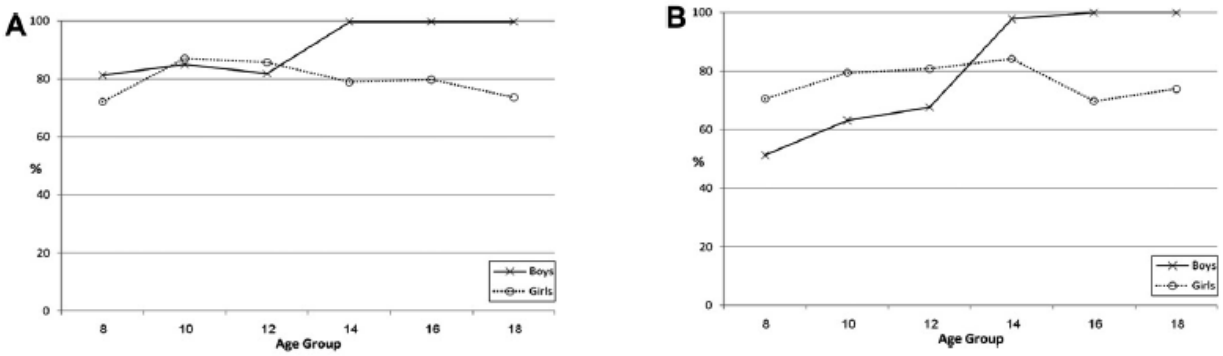

Correct gender identification rates for boys and girls in the six age groups for (A) sentences and (B) vowels.

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

Positions

Lecturer, Sackler Faculty of Medicine

Research

Our research focuses on two main fields:

(a) Learning and plasticity in the auditory system:

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

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

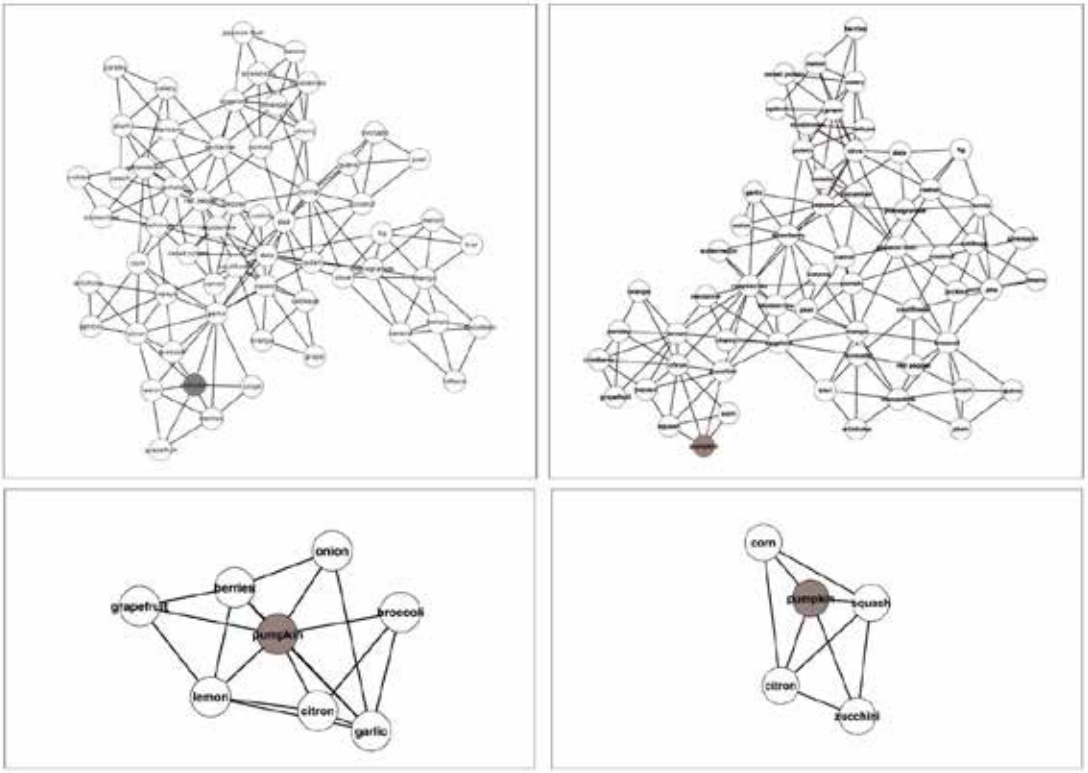
Position

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? The conditions under which second 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.

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

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

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

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Auditory Processing in the Normal and Impaired Auditory System

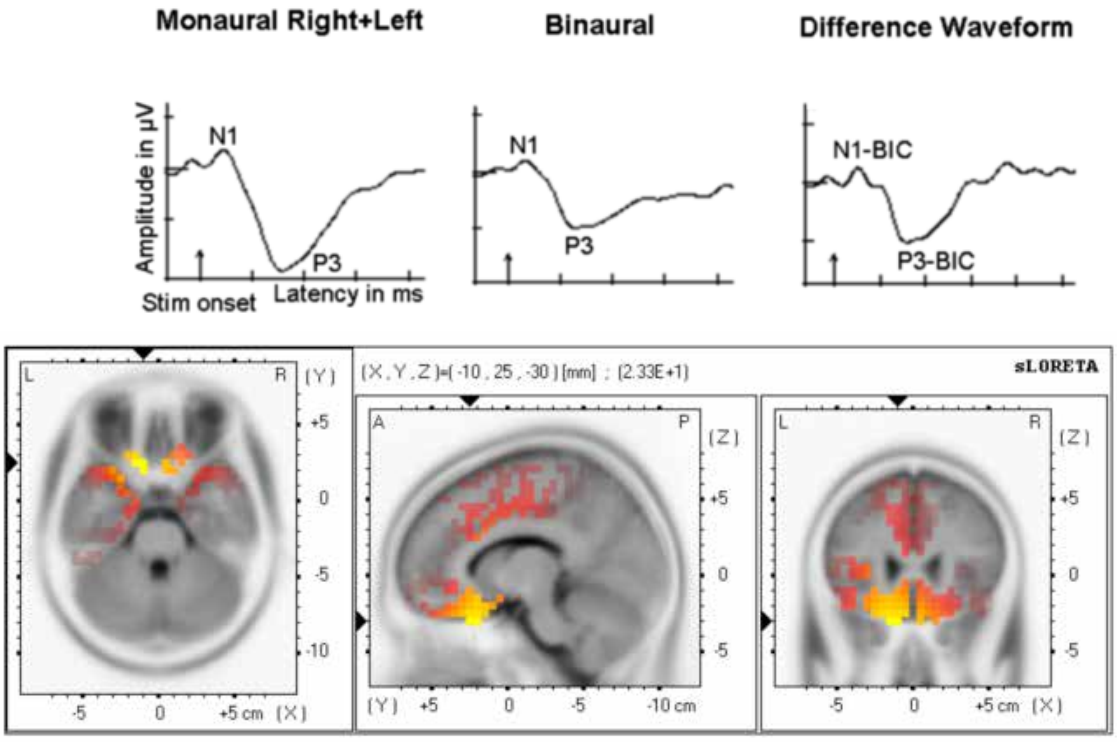
Positions

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

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

Research

Research focuses on neurophysiologic and behavioral manifestations of auditory processing, as well as the relation between the two, in the normal and impaired auditory system. By means of event-related potentials (ERPs), voltage changes recorded from the scalp that trace events in time known to reflect discrete stages of neural processing, and a functional imaging technique (sLORETA), we study the time-course and cortical activation patterns during auditory (speech) processing. Of special interest are patients that have experienced bilateral and/or unilateral auditory deprivation and are habilitated by cochlear implants (CI) and/or hearing aids (HA). Currently under study are neurophysiologic processes that underlie: (1) Binaural processing in children that were sequentially or simultaneously implanted, in those using CI and HAs (bimodal hearing), and in those with HAs; and (2) Auditory-cognitive processing in elderly patients with CI.



Grand average waveforms of normal hearing children elicited during a speech discrimination task presented monaurally and binaurally. Shown are the sum of monaural right and left waveforms, the binaural response, and the difference waveform (Binaural interaction component=Sum of right+left –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.

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

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

Publications

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

Position

Professor, Sackler Faculty of Medicine

Head, Steyer School of Health Professions

Committee Member, Israel Auditory Society of Research

Research

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

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Speech and Hearing Sciences and Rehabilitative Audiology

Position

Full 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.

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Hearing Science and Clinical Audiology

Position

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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

D. Ari-Even Roth, **C. Muchnik**, M. Hildesheimer, Y. Henkin. Auditory brainstem response in young children with autistic spectrum disorders. Dev Med Child Neurol. 54 : 23-29, 2012

C. Muchnik, N. Amir, E. Shabtai, R. Kaplan-Neeman, Preferred listening levels to personal devices in young teenagers: self reports and physical measurements. International Journal of Audiology , 51:287-293, 2012

R. Kaplan-Neeman, **C. Muchnik**, M. Hildesheimer, Y. Henkin. Hearing aid satisfaction and use in the advanced digital era. Laryngoscope, 122: 2029-2036, 2012

N. Fink, M. Furst, **C. Muchnik**. Improving word recognition in noise of hearing impaired subjects with a single – channel cochlear noise reduction algorithm. Journal of the Acoustical Society of America, 132: 1718-1731, 2012

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

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

Y. Henkin, Y. Yaar-Soffer, M. Steinberg, **C. Muchnik**. Neural correlates of auditory-cogntive processing in older adults with cochlear implants. Audiology & Neurotology 19:S21-6, 2014.

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

Berman, R.A., R. Nayditz & **D. Ravid**. 2011. Linguistic diagnostics of written texts in two school-age populations. *Written Language & Literacy,* 14, 161-187.

Schiff, R., **D. Ravid** & S. Levy-Shimon. 2011. Children's command of plural and possessive marking on Hebrew nouns: A comparison of obligatory vs. optional inflections. *Journal of Child Language*, 38, 433–454.

Bar-On, A. & **D. Ravid**. 2011. Morphological decoding in Hebrew pseudowords: a developmental study. *Applied Psycholinguistics*, 32, 553–581.

Ravid, **D.** 2012. Phono-morpho-orthographic construal: The view from spelling. Invited commentary on R. Frost's "A universal theory of reading". *Behavioral and Brain Sciences*, 35, 263–329.

Ravid, D. & R. Schiff. 2012. From dichotomy to divergence: Number/gender marking on Hebrew nouns and adjectives across schoolage. *Language Learning*, 62, 133-169.

Schiff, D. & **D. Ravid**. 2012. Linguistic processing in Hebrew-speaking children from low and high SES backgrounds. *Reading & Writing*, 25, 1427-1448.

Saiegh-Haddad, E., A. Hadieh & D. Ravid. 2012. Acquiring noun plurals in Palestinian Arabic: Morphology, familiarity, and pattern frequency. *Language Learning*, 62, 1024-1051.

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

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Abugov, N. & **Ravid, D.** 2014. The impact of Israeli Hebrew on Yiddish: noun plurals in Sanz Ultra Orthodox Yiddish. International Journal of the Sociology of Language, 226, 189–211.

Uziel-Karl, U., F. Kanaan, N. Abugov, R. Yifat, I. Meir, **& D. Ravid**. 2014. Hebrew and Palestinian Arabic in Israel: Linguistic frameworks and SLP services. Special issue on "Global issues in language disorders: Processes, frameworks and policies", *Topics in Language Disorders*, 34, 133–154.

Schiff, R. & **D. Ravid**. 2014. Morpho-syntactic load in judging adjective plural agreement: comparing adults with and without ADD. *Communication Disorders Quarterly. 36, 79-89*.

Chapters and books

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Alfi-Shabtay, I. & **Ravid**, D. 2012. Adjective inflection in Hebrew: A psycholinguistic study of speakers of Russian, English and Arabic compared with native Hebrew speakers. In M. Leikin, M. Schwarts and Y. Tobin, (eds.). *Current Issues in Bilingualism. Cognitive and Socio-linguistic Perspectives* (pp. 159-178). New York: Springer.

Ravid, D. & Schiff, R. (Eds.) 2013. Journal of Learning Disabilities Special issue on Dyslexia and Language, 46.

Abugov, N. & **Ravid**, D. 2013. Assessing Yiddish plurals in acquisition: impacts of bilingualism. In Mueller Gathercole V. C (ed.) *Bilinguals and Assessment: State of the art guide to issues and solutions from around the world.* Bristol: Multilingual Matters, 90-110.

Ravid, D. 2013. Syntactic complexity in discourse production across different text types. In Catherine Bolly & Liesbeth Degand (eds), *Across the Line of Speech and Writing Variation*. Louvain-la-Neuve: Presses universitaires de Louvain, 51-66.

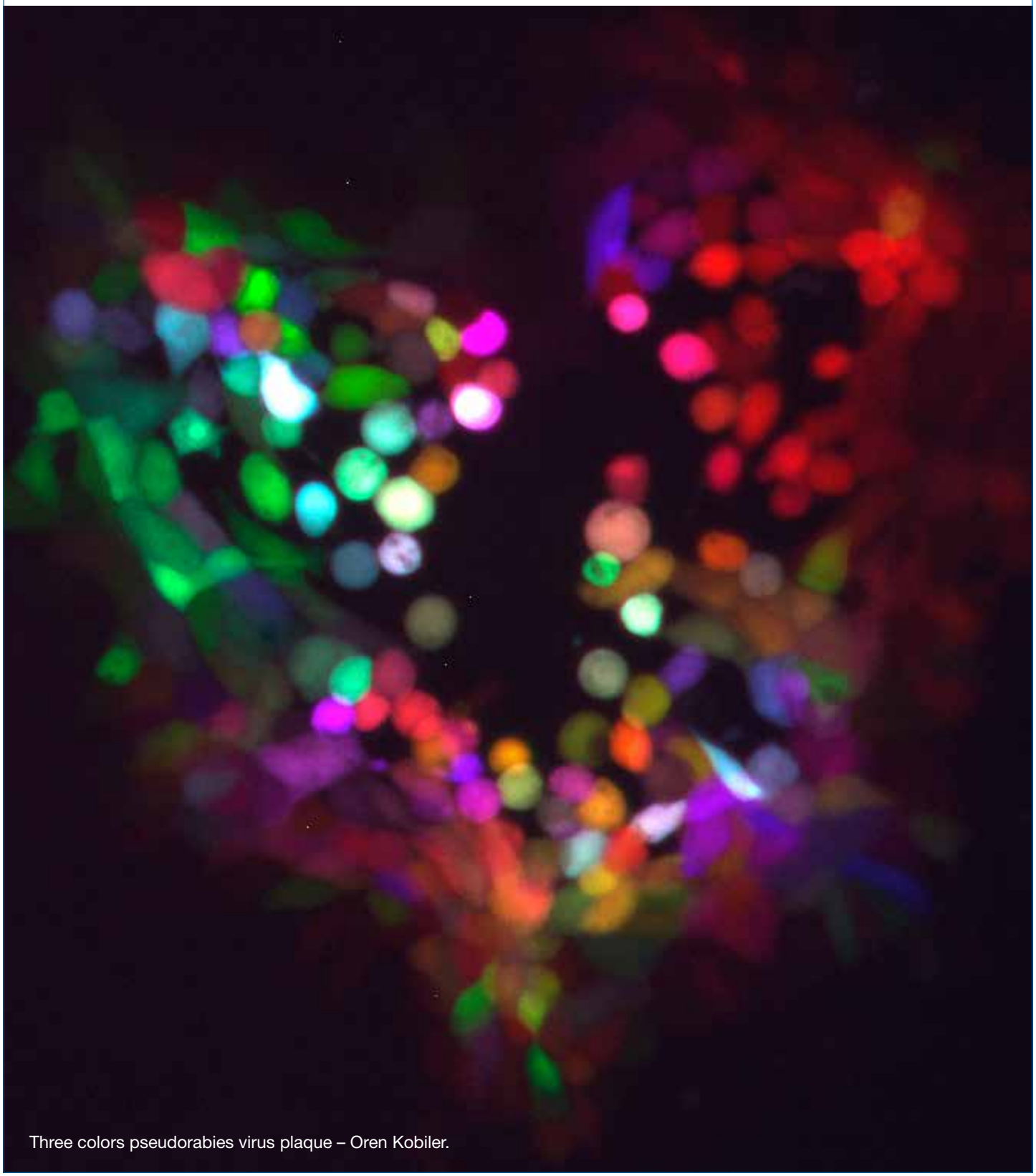
Ravid, D & G. Ginat-Heiman. 2014. L1 and L2 proficiency in Hebrew-English adolescent learners. In Adelheid Hu & Patrick Grommes (eds.), *Plurilingual Education: Policies – Practice – Language Development*. Amsterdam: Benjamins, 221-246.

Abugov, N. & **Ravid**, D. 2014. Noun plurals in Israeli Ultra-Orthodox Yiddish: a psycholinguistic perspective. In Aptroot, M. & Hansen, B. (eds.) *Yiddish Language Structures*. Berlin: Mouton De Gruyter, 9-39.

Grants

2013-2015	Discourse Syntax in Developing Text Production. Chief Scientist, Ministry of Education.
2013-2017	Verb structure and Semantics in Development. Israel Science Foundation.

Infectious Diseases



Three colors pseudorabies virus plaque – Oren Kobiler.

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Genetic Bases of Host Response to Infections and Chronic Diseases

Position

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Human Microbiology and Immunology

Research

The research in my laboratory is focused on understanding the genetic bases of host response to infections and chronic diseases, which are important for human health. My team uses mouse model for speeding up the process of identifying such genes, which may 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

Kovacs, A., Ben-Jacob, N., Tayem, H., Halperin, E., **Iraqi, F.A**. and Gophna, U. (2011) Genotype is a stronger determinant than sex of the mammalian gut microbiota. *Micro Ecol* 61:423-8.

Aylor, D.L., Valdar, W., Foulds-Mathes, W., Buus, R.J., Ricardo, A., Verdugo, R.A., Ralph, S., Baric, R.S., Ferris, M.T., Frelinger, F.A., Heise, M., Frieman, M.B., Gralinski, L.E., Bell, T.A., Didion, J.P., Hua, K., Nehrenberg, D.L., Powell, C.L., Steigerwalt, J., Xie, Y., Kelada, S.N.P., Collins, F.S., Yang, I.V., Schwartz, D.A., Branstetter, L.A., Chesler, E.J., Miller, D.R., Spence, J., Liu, E.Y., McMillan, L., Sarkar, A., Wang, J., Wang, W., Zhang, Q., Broman, K.W., Korstanje, R., Durrant, C., Mott, R., **Iraqi, F.A**., Pomp, D., Threadgill, D., Pardo-Manuel de Villena, F. and Churchill, G.A. (2011) Genetic analysis of complex traits in the emerging collaborative cross. *Gen Res* 21:1213-1222.

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

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

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

Shusterman A, Salaymeh Y, Nashef A, Soller M, Wilensky A, Mott R, Weiss EI, Houri-Haddad Y and. **Iraqi FA** (2013) Genotype is an important determinant

factor of host susceptibility to periodontitis in the Collaborative Cross and inbred mouse populations. *BMC Genet* 14: 68-79.

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Soller M and **Fuad Iraqi FA** (2014) The Collaborative Cross – a next generation mouse genetic resource population for high resolution genomic analysis of complex traits. *Livestock Sci J* 166: 19–25.

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

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

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).

Levy R, Mott RF, **Iraqi FA**, Gabet Y (2015) Collaborative cross mice in a genetic association study reveal new candidate genes for bone microarchitecture. *BMC Genomics* 16:1013: 1-14.

Abu Toamih-Atamni HJ, Mott R, Soller M and **Iraqi FA** (2016) High-fat induced development of increased fasting glucose levels and impaired response to intraperitoneal glucose challenge in collaborative cross mouse reference population. *BMC Genetics* 17:10.

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.

De Simone M, Spagnuolo L, Ivan Lorè N, Cigana C, De Fino I, Broman KW, **Iraqi FA**, Bragonzi A (2016) Mapping genetic determinants of host susceptibility to *Pseudomonas aeruginosa* lung infection in mice**.** *BMC Genomics* 17(1).

Abu Toamih-Atamni H, Botzman M, Mott R, Gat-Vicks I, **Iraqi FA** (2016) Mapping Quantitative Trait Loci associated with host susceptibility to non-alcoholic fat liver accumulations using collaborative cross mouse genetic reference population. Mamm Genome July 15 [Epub ahead of print]/

Review and editorials

Schughart K, Libert C; **SYSGENET consortium**, Kas MJ. (2013) Controlling complexity: the clinical relevance of mouse complex genetics. *Eur J Hum Genet.* 21:1191-6.

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

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.

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and Penders J. (2015) Intestinal microbiota and diet in IBS: causes, consequences or epiphenomena. *Am J Gastroent* doi: 10.1038/ajg.2014.427.

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

Grants

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

2014-2016 Italian Cystic Fibrosis Foundation (ICFF)

2014-2018 German Research Foundation (DFG-TRIO)

2015-2018 Israeli-Science Foundations (ISF)

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

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

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Investigating Viral Genetic Diversity

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Publications

***Kobiler O**., *Card J.P., McCambridge J., Ebdlahad S., Shan Z., Raizada M.K., Sved A.F., and Enquist L.W. (2011). Microdissection of neural networks by conditional reporter expression from a Brainbow Herpesvirus. *Proc Natl Acad Sci U S A.* 108:3377-82.

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

Kobiler, O., Brodersen, P., Taylor, M.P., Ludmir, E.B. and L.W. Enquist. (2011). Herpesvirus replication compartments originate with single incoming viral genomes. *mBio* 2:e00278-11.

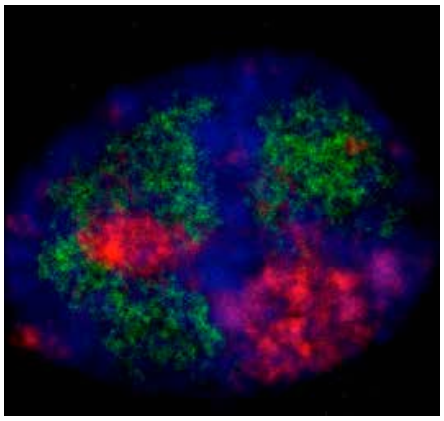
Taylor MP, **Kobiler O**, Enquist LW. (2012) Alphaherpesvirus axon-to-cell spread involves limited virion transmission. *Proc Natl Acad Sci USA*. 109:17046-51.

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

Hadas Y, Etlin A, Falk H, Avraham O, **Kobiler O**, Panet A, Lev-Tov A, Klar A. (2014) A 'tool box' for deciphering neuronal circuits in the developing chick spinal cord. Nucleic Acids Res. 42:e148

Grants

2012-2016	EU – FP7,People 7 – Marie Curie-CIG
2014-2019	Grant, Israel Science Foundation (ISF)
2014-2019	Equipment Grant, Israel Science Foundation (ISF)
2016	Marguerite Stolz Research Fellowship
2016-2020	BSF, co-PI Dr. Weitzman Matthew



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

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Human Mold Infections

Positions

Associate Professor, Sackler Faculty of Medicine

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

Director, Ella Kodesz Institute of Host Defense against Infectious Diseases

Research

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

The goals of my lab are:

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

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

Publications

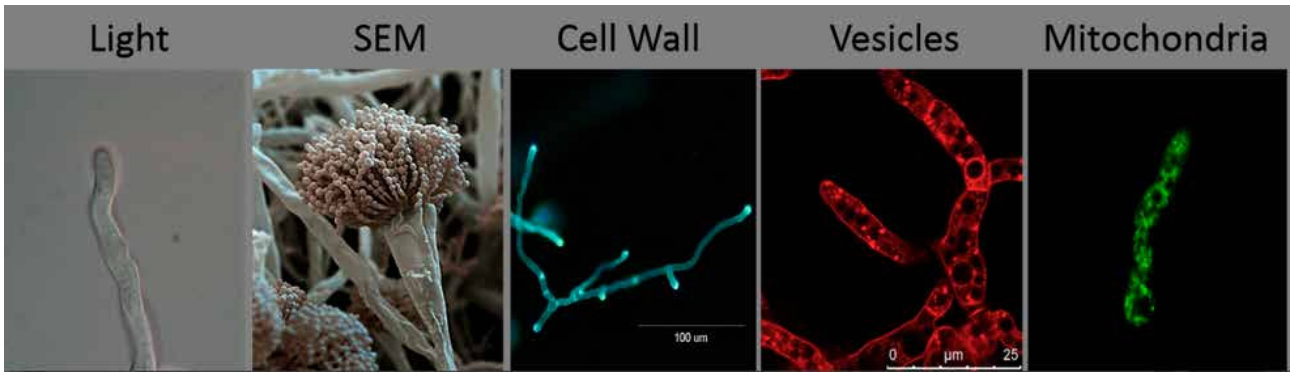
Kaltdorf M, Srivastava M, Gupta SK, Liang C, Binder J, Dietl AM, Meir Z, Haas H,**Osherov N**, Krappmann S, Dandekar T. Systematic identification of anti-fungal drug targets by a metabolic network approach. *Front Mol Biosci*. 2016;3:22.

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.



The pathogenic mold *Aspergillus fumigatus*

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.

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

Vaknin Y, Shadkchan Y, Levdansky E, Morozov M, Romano J, **Osherov N**. The three Aspergillus fumigatus CFEM-domain GPI-anchored proteins (CfmA-C) affect cell-wall stability but do not play a role in fungal virulence. *Fungal Genet Biol*. 2014;63:55-64.

Osherov N. Interaction of the pathogenic mold *Aspergillus fumigatus* with lung epithelial cells. *Front Microbiol*. 2012, 26:346.

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

Arnusch CJ, Albada HB, van Vaardegem M, Liskamp RM, Sahl HG, Shadkchan Y, **Osherov N**, Shai Y. Trivalent ultrashort lipopeptides are potent pH dependent antifungal agents. *J Med Chem*. 2012, 9:1296-302.

Arnusch CJ, Ulm H, Josten M, Shadkchan Y, **Osherov N**, Sahl HG, Shai Y. Ultrashort peptide bioconjugates are exclusively antifungal agents and synergize with cyclodextrinand amphotericin B. *Antimicrob Agents Chemother*. 2012, 56:1-9.

Sharon H, Amar D, Levdansky E, Mircus G, Shadkchan Y, Shamir R, **Osherov N**. PrtT-regulated proteins secreted by *Aspergillus fumigatus* activate MAPK signaling in exposed A549 lung cells leading to necrotic cell death. *PLoS One*. 2011, 6:e17509.

Reviews

Osherov N. The top three areas of basic research on *Aspergillus fumigatus* in 2011. *Ann N Y Acad Sci.* 2012, 1273:74-7.

Tavanti A, Naglik JR, **Osherov N**. Host-Fungal Interactions: Pathogenicity versus Immunity. *Int J Microbiol*. 2012, 562480.

Grants

2012–2016 Binational Science Foundation

2014–2016 Israel-Italy Cooperation Grant-

2014–2017 Infect-ERA Net Joint European Grant

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Host-Virus Interactions in Bacterial Systems

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

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

Publications

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

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

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

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Reviews

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

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Grants

2014-2017	Israeli Ministry of Health Grant
2013-2018	ERC Starting Grant
2014-2019	Israel Science Foundation Grant
2016-2017	Momentum Fund

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

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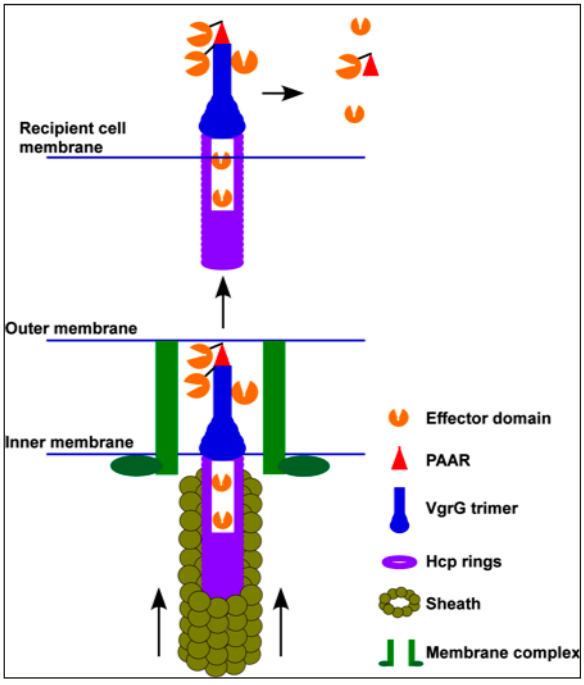
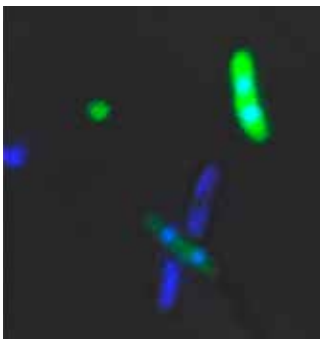
A



B



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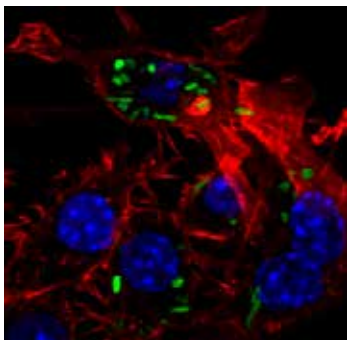

Type VI secretion systems (T6SSs) deliver effectors mediating antibacterial and virulence toxic activities. (A) A scheme of the T6SS. (B) Bacterial attackers (blue) using a T6SS with nuclease effectors to kill prey bacteria (green). (C) Bacteria (green) using a T6SS to allow survival and replication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

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Grants

2016-2019 Alon Fellowship

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.

Publications

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

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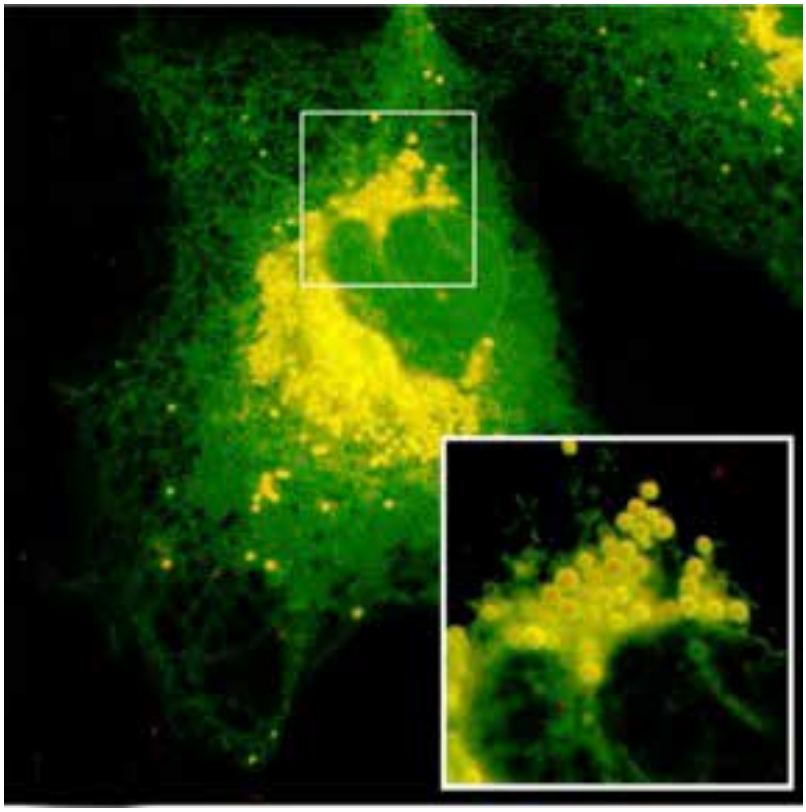

A live hepatoma cell (Huh7) expressing the viral non-structural protein 5A that localizes to the endoplasmic reticulum and lipid droplets.

localization of the NS5A non-structural viral protein. (2011). *Virology*, 414:10-8.

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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.

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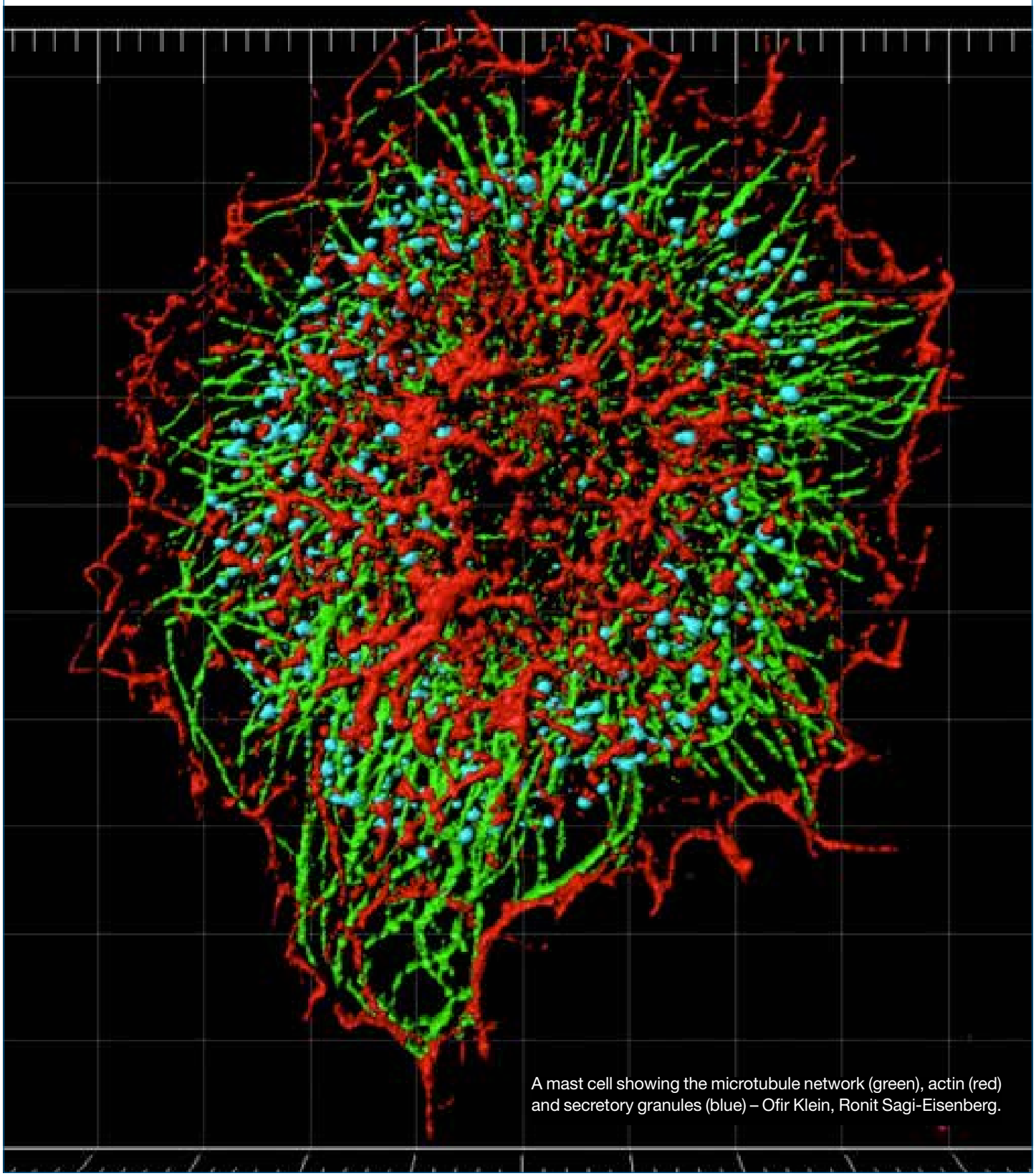
Levy G, Habib N, Guzzardi M.A, Kitsberg D, Bomze D, Ezra E, Uygun B.E, Uygun K, Trippler M, Schlaak, J.F, Shibolet O, **Sklan EH**, Cohen M, Timm J, Friedman N, Nahmias Y. (2016) Nuclear receptors control pro- and anti-viral metabolic response to HCV infection. *Nature Chem Biol*. In press.

Grants

2012-2016 Israel Science Foundation (ISF) Grant

Inflammatory and Autoimmune Diseases



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

Prof. Ariel Munitz, Ph.D.

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Regulatory Mechanisms in Mucosal Inflammation

Position

Senior Lecturer, Sackler Faculty of Medicine

Associate Editor, *Journal of Allergy and Clinical Immunology*

Research

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

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

Publications

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

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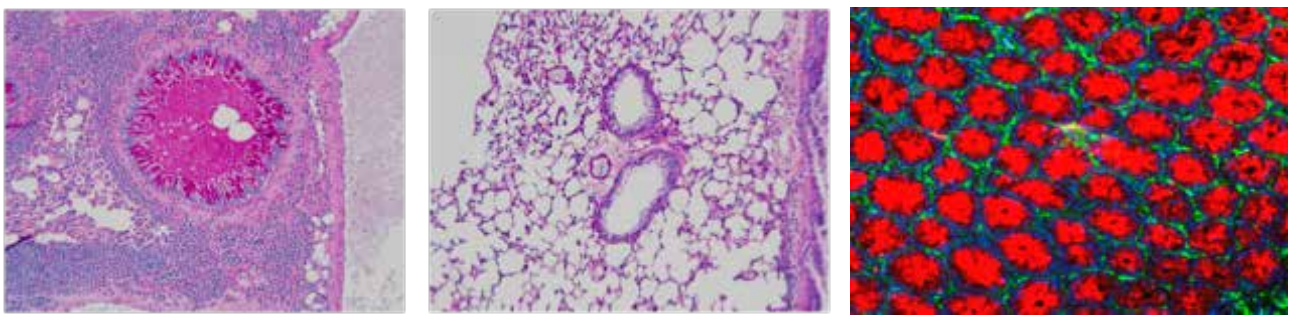

Figure legend: A photomicrograph of a normal lung displaying two large airways and a blood vessel (left). In many inflammatory conditions such as asthma and COPD, the airway is filled with mucus plugs (middle, pink stain). Right – an immunofluorescent stain of resistin-like molecule alpha (red), a proinflammatory,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

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Karo-Atar D, Bordowitz A, Wand O, Pasmanik-Chor M, Fernandez IE, Itan M, Frenkel R, Herbert DR, Eickelberg O, Munitz A. A protective role for IL-13 receptor a 1 in bleomycin-induced pulmonary fibrosis. *Mucosal Immunol*: 2014:9:240-53.

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

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

Rothenberg ME. Wen T, Shik D, Cole ET, Mingler M, **Munitz A**. IL-13Rα1 differentialy regulates aeroallergen-induced lung responses. *J Immunol,* 2011; 187:4873-4880.

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Reviews and Chapters

Munitz A, Karo-Atar D, Foster PS. Asthma Diagnosis: miRNA's to the rescue. *J Allergy Clin Immunol*. 2016. In press

Grants

2013-2016	Fritz Thyssen Stiftung, The role of IL-13Rα1 in pulmonary fibrosis
2012-2016	US-Israel Binational Scientific Foundation (BSF), The expression and function of paired immunoglobulin-like receptor B in eosinophils
2014-2017	Israel Ministry of Health
2016-2017	The Teva Research Fund for Breakthroughs in Biomedicine; Title: Role of CD300f in eosinophils
2015-2020	The Israel Science Foundation Individual Research grant #95/11; Title: Regulation of GI eosinophils by CLM-1
2015-2018	The Israel Cancer Research Fund; Title: Molecular regulation of eosinophil activation in colorectal cancer
2014-2016	The Varda and Boaz Dotan Research Center in Hemato-Oncology, TAU; Title: Role of CLM-1 in HES/CEL

Dr. Mordechay (Motti) Gerlic, Ph.D.

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

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

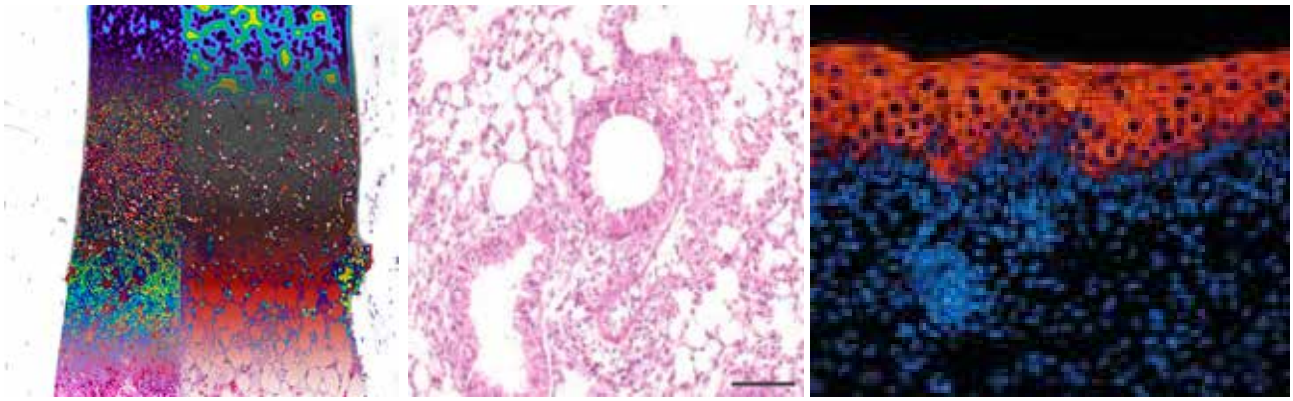
Cell death is an essential cellular process during development, but also facilitates the removal of damaged or infected cells, and is required for the resolution of innate and adaptive immune responses.

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

Recently, we discovered a physiological role for NLRP1 in driving a lethal, systemic inflammatory disease that is triggered by Caspase-1 activation and IL-1β production. Remarkably, active NLRP1 triggered a Caspase-1-dependent form of cell death, known as pyroptosis. This cell death affected hematopoietic stem and progenitor cells (HSPC), resulting in leukopenia at steady state, and cytopenia, bone marrow hypoplasia and immunosuppression, during periods of hematopoietic stress induced by chemotherapy or viral infection. Our recent research into how pathogens modulate complexes such as the NLRP1 inflammasome has defined mechanism by which *Vaccinia Virus* protein, F1L, target inflammasomes directly by binding and inhibiting the NLRP1 inflammasome formation. These findings reveal novel mechanism for viruses to evade host innate immune responses. Furthermore, we recently changed the thinking of necroptosis, which was thought to be RIPK1-dependent. We found the opposite, namely, that RIPK1 acts as a negative regulator of necroptosis, and loss of RIPK1 results in a lethal multi-organ systemic inflammatory response.

Publications

Uboldi AD, McCoy JM, Blume M, **Gerlic M**, Ferguson DJ, Dagley LF, Beahan CT, Stapleton DI, Gooley PR, Bacic A, Masters SL, Webb AI, McConville MJ, Tonkin CJ. Regulation of starch stores by a Ca(2+)-dependent protein kinase is essential for viable



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

cyst development in *Toxoplasma gondii*. Cell Host Microbe. 18:670-681. 2015.

Lawlor KE, Khan N, Mildenhall A, **Gerlic M**, Croker BA, D'Cruz AA, Hall C, Spall SK, Anderton H, Masters SL, Rashidi M, Wicks IP, Alexander WS, Mitsuuchi Y, Benetatos CA, Condon SM, Wong WWL, Silke J, Vaux DL, Vince JE. RIPK3 promotes cell death, NLRP3 inflammasome and interleukin-1 activation in the absence of MLKL. *Nature Comm*, 6, 6282, 2015.

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Correa RG, Krajewska M, Ware CF, **Gerlic M**, Reed JC. The novel NLR-related protein NWD1 is associated with prostate cancer progression and impacts androgen receptor signalling. *Oncotarget.* March 26, 2014.

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

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

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Reviews

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Grants

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

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

Prof. Ronit Sagi-Eisenberg, Ph.D.

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Molecular Basis of Allergic Diseases: Genomic and Functional Analyses

Positions

Professor, Sackler Faculty of Medicine

Chair, Scholarship Committee, Graduate School of Medicine

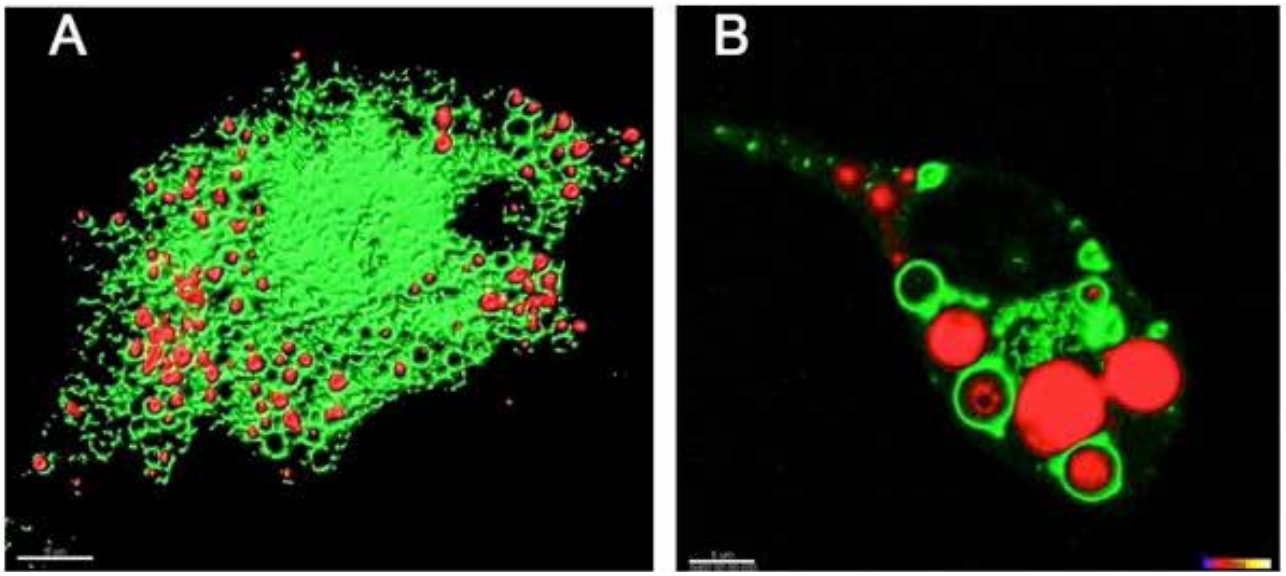
Research

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

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

Current projects in the lab include:

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



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

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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.

Azouz NP, Hammel I, **Sagi-Eisenberg R**. Characterization of mast cell secretory granules and their cell biology. *DNA Cell Biol*. 2014; 33:647-51.

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Review

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Medical Education and Ethics

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Bioethics, Biolaw and Medical Humanities

Position

Associate Professor, Sackler Faculty of Medicine

Research

The research area of our group is Medical Humanities, relying on theoretical methods with the occasional 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. Human dignity, human rights and responsibility: the new language of global bioethics ad biolaw. Cambridge (MA): MIT Press. 2012.

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

Publications

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

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

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

Barilan YM. Hope and friendship: being and Having. Philosophy, Psychiatry and Psychology. 2012; 19:191-195.

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

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

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

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Barilan YM, Brusa M. Triangular reflective equilibrium: A consciences based method for bioethical deliberation. Bioethics 2011; 25:304-319.

Barilan YM. Abortion. In: Chadwick R, Ten Have H, Meslin E. (eds.) Healthcare ethics in the era of globalization. New York, Sage, 2011; pp. 127-144.

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 doi:10.1186/s40248-015-0004-5

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.

Dr. Orit Karnieli-Miller, Ph.D.

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Studying Doctor-Patient Relationships, Communication and Medical Professionalism

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

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. DOI: 10.1080/10410236.2015.1099504*

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, DOI:10.1177/1049732314553990*

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*).

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Karnieli-Miller, O., Zisman-Ilani, Y., Meitar, D. & Mekori, Y. (2014) The role of medical schools in promoting social accountability through shared decision-making. Isra*eli Journal of Health Policy, Israel Journal of Health Policy Research* 4-1 ,3 ,2014.

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

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

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

Karnieli-Miller, O. Werner, P. Neufeld Kroszynski, G. Eidelman, S. (2012). Are you talking to me?!? An exploration of the triadic physician-patient-companion encounter in memory-clinics. *Patient Education and Counseling,* 88, 381–390.

Karnieli-Miller*, O. Werner*, P. Aharon-Perets, J. Sinoff, G. Eidelman,, S. (2012). Expectations, experiences and tensions in the memory clinic – the process of diagnosis disclosure of dementia within a triad. *International Psychogeriatrics,* 24, 1756-1770. *equal contributors

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

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

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

Karnieli-Miller, O. & Salyers, M. (2011). Clinical communications with persons who have severe mental illnesses. In Rudnick, R., & Roe, D. (Eds.) *SMI: Person-centered approaches*. Radcliffe Press, 155-167

Taylor, A. **Karnieli-Miller, O**. Inui, T.S. Ivy, S.S. & Frankel R.M. (2011). Appreciating the power of narratives in healthcare: A tool for understanding organizational complexity and values.In C. N. Candlin and S. Sarangi (Eds.) *Handbook of communication in organizations and professions*. Berlin, Germany: Mouton de Gruyter, pp. 457-479, 2011

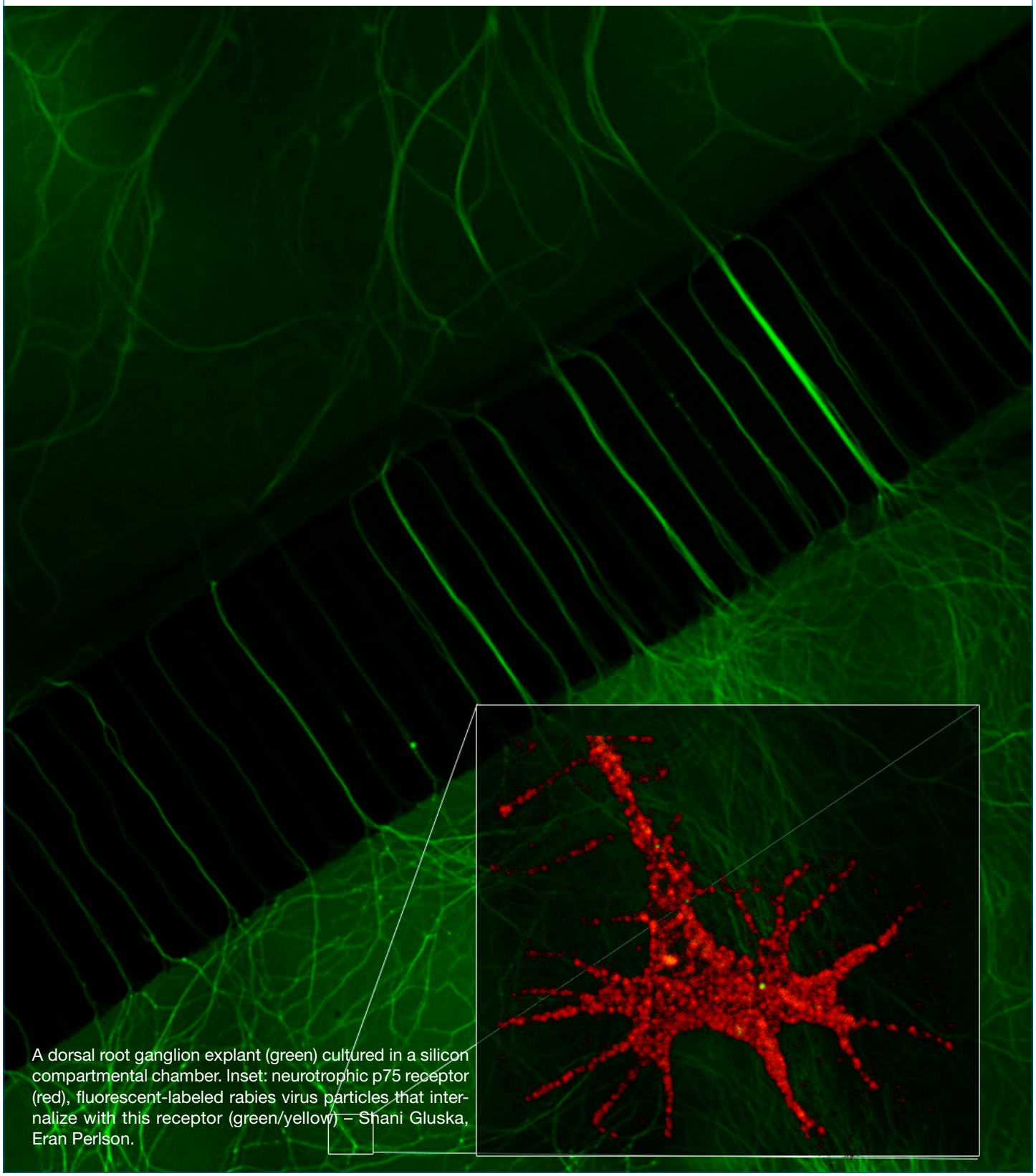
Reviews

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

Grants

2014-2016	The Magi Foundation, Identifying best practices for communication challenges of medical clowns with patients parents, adolescent patients and medical teams, PI
2015-2016	Assessing Professionalism and Communication Skills Development during Medical School: A cross sectional exploratory study
2016-2017	Preventing burnout and enhancing professionalism in the surgical unit care and medical teams

Nervous System and Behavorial 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
Sackler Faculty of Medicine

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Investigating the Molecular Basis of Visual System Development

Positions

Associate Professor, Sackler Faculty of Medicine

Committee Member, Israel Society of Developmental Biology

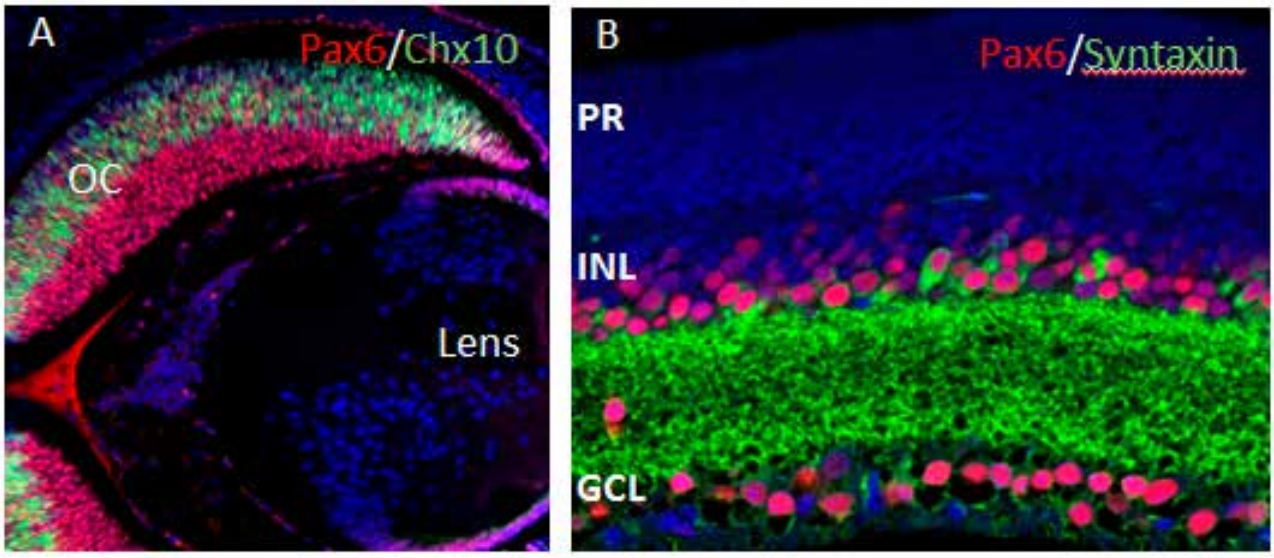
Research

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

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.

Publications

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



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

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

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Farhy, C., M. Elgart, Z. Shapira, V. Oron-Karni, O. Yaron, Y. Menuchin, G. Rechavi, and **R. Ashery-Padan**, Pax6 is required for normal cell-cycle exit and the differentiation kinetics of retinal progenitor cells. *PLoS One*, 2013. 8:e76489.

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

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

Bochner R, Ziv Y, Zeevi D, Donyo M, Abraham L, Ashery-Padan R, **Ast G**. Phosphatidylserine increases IKBKAP levels in a humanized knock-in IKBKAP mouse model. *Hum Molec Genet*. 2013, 22: 2785-2794

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

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

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Review

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

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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

Shruster, A., **Eldar-Finkelman, H**., Melamed, E., Offen, D. 2011, Wnt signaling pathway overcomes the disruption of neurogenesis induced by oligomeric amyloid β-peptide. *J Neurochem*. 116: 552-559.

Azoulay-Alfaguter, I. Yaffe, Y., Licht-Murava, A., Urbanska, M., Jaworski, J., Pietrokovski, S., Hirschberg, K. and **Eldar-Finkelman, H.** 2011, Distinct molecular regulation of GSK-3β controlled by it N-terminal region. Functional role in calcium/calpain signaling. *J Biol Chem*. 286:13470-13480

Licht-Murava, A., Plotkin, B., Eisenstein, M., **Eldar-Finkelman, H**. 2011, Elucidating substrate and Inhibitor binding sites on the surface of GSK-3 β and the refinement of a competitive inhibitor. *J Mol Biol*. 408:366-378.

Tsaadon Alon, L., Pietrokovski, S., Barkan, S., Avrahami, L. Kaidanovich-Beilin, O., Woodgett, J. Barnea, A., **Eldar-Finkelman, H**. 2011, Selective loss of GSK-3β in birds reveals distinct roles for GSK-3 Isozymes in tau phosphorylation. *FEBS Lett*. 585:1158-1162.

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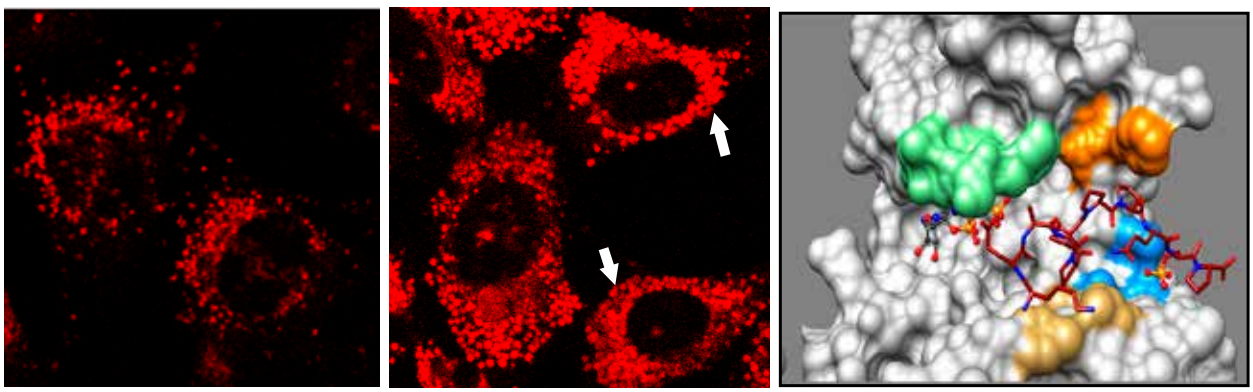

Treatment with GSK-3 inhibitor restores lysosomal activity, lysosomes shown as red dots (left). Computational model of GSK-3 inhibitor –L803-mts-binding with the substrate binding site (right).

and atom efficient access to 1-aryl-3-benzylureas. *Bioorg Med Chem Lett*. 21:5610-5615.

Monte, LM, Kramer, T., Gu, J., Anumala, R. Marinelli, L., La Pietra, V., Novellino, E., Franco, B., Demedts, D., van Leuven, F., Fuertes, A., Dominguez, JM., Plotkin, B., **Eldar-Finkelman, H**., Schmidt, B. 2012, Identification of glycogen synthase kinase-3 inhibitors with a selective sting for glycogen synthase kinase-3α. *J Med Chem*. 55:4407-4424.

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Models and Rehabilitation of Grasping

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

Member, Sagol School of Neuroscience

Research

We study human movement in typical and clinical populations, with a focus on grasping and finger movements. We are 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 stroke, dystonia or cerebral palsy. We also study the interconnection between decision making and human movements. Our approach is to construct models that describe movement and force generation by the hand and arm, taking into account the biomechanics of the hand and the neural processes leading up to making movements. This approach gives us insights into the strategies behind the complex movements and force coordination required to successfully perform grasping and manipulation, as well as a greater understanding of the causes of differences in performance in individuals with motor disorders. A goal of this research is to improve rehabilitation of hand function through improving our knowledge of these strategies.

Publications

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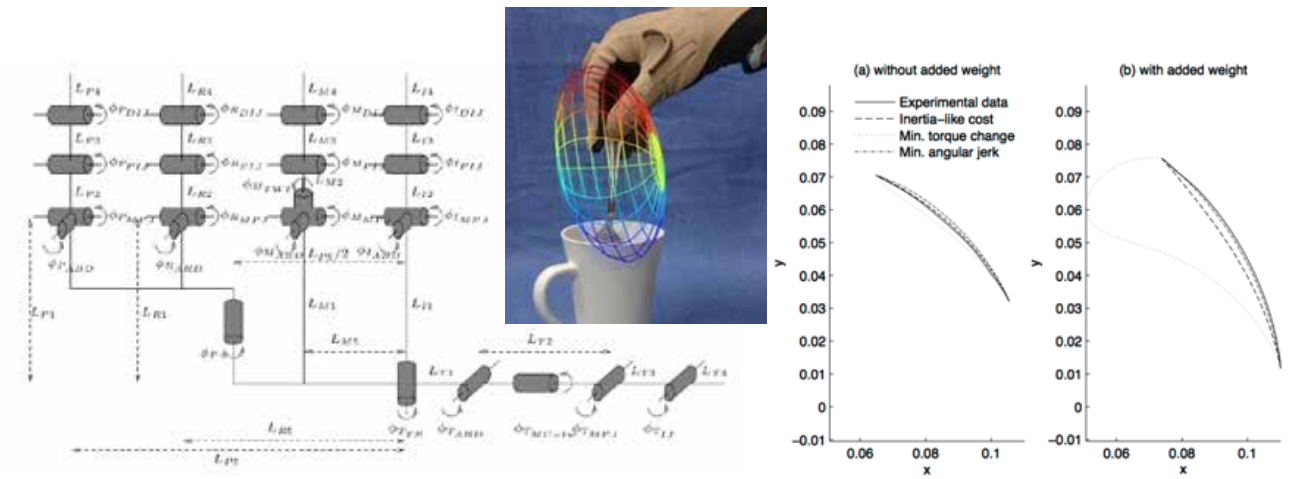

Left: We use a model of the hand with the finger joints modelled as revolute joints, with twenty degrees of freedom. **Middle:** Based on models such as these, we can determine the properties of grasps subjects select, for example, when stirring with a spoon, to determine what are the important factors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

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Neuronal Plasticity and Nerve Cell Protection in Disease

Positions

Professor of Clinical Biochemistry, Sackler Faculty of Medicine

Lily and Avraham Gildor Chair for the Investigation of Growth Factors

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

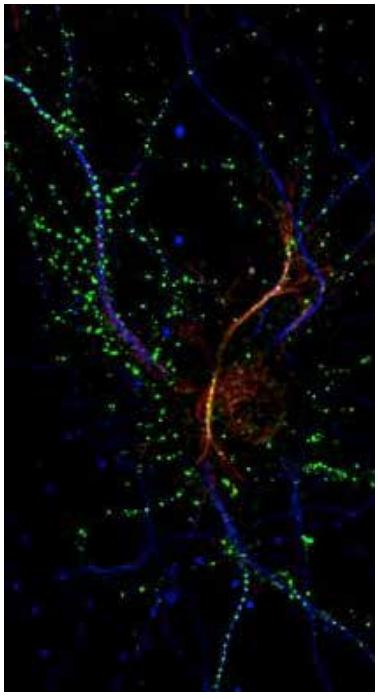
Editor-in-Chief, *Journal of Molecular Neuroscience*

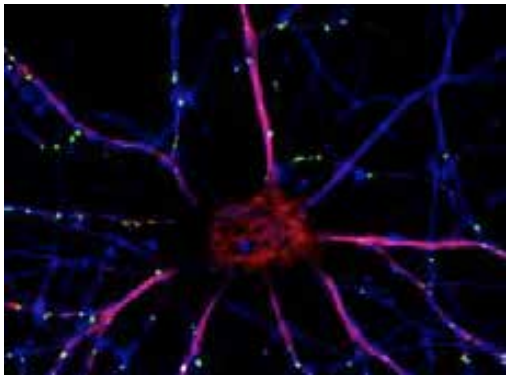
Member, MALAG (Israeli Council of Higher Education)

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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Grants

2014-2018 Israel Science Foundation – Deciphering beta-amyloid and tau neurotoxicity: Genome-wide RNA sequencing for sensitivity biomarkers- with Dr. David Gurwitz

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

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

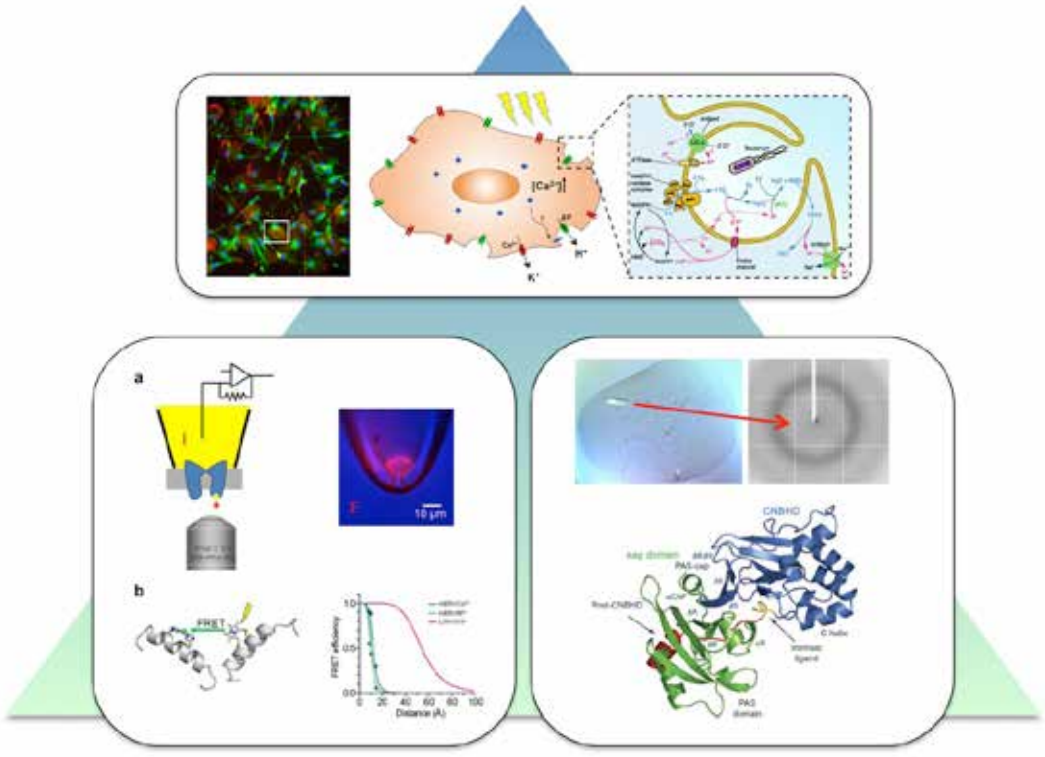
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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



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

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

Publications

Manuscripts

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Reviews

Haitin Y. (2014). A “funny” cyclic dinucleotides receptor. Nat Chem Biol 10, 413-414

Dvir M., Peretz A., **Haitin Y.** & Attali B. (2014). Recent molecular insights from mutated IKS channels in cardiac arrhythmia. *Curr Opin Pharmacol* 15C, 74–82

Grants

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

2016 – 2018 Recanati Foundation for Biomedical Research

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

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

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

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Brain Mechanisms of Human Emotion Generation & Regulation

Laboratory for Brain and Emotion Experience

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Positions

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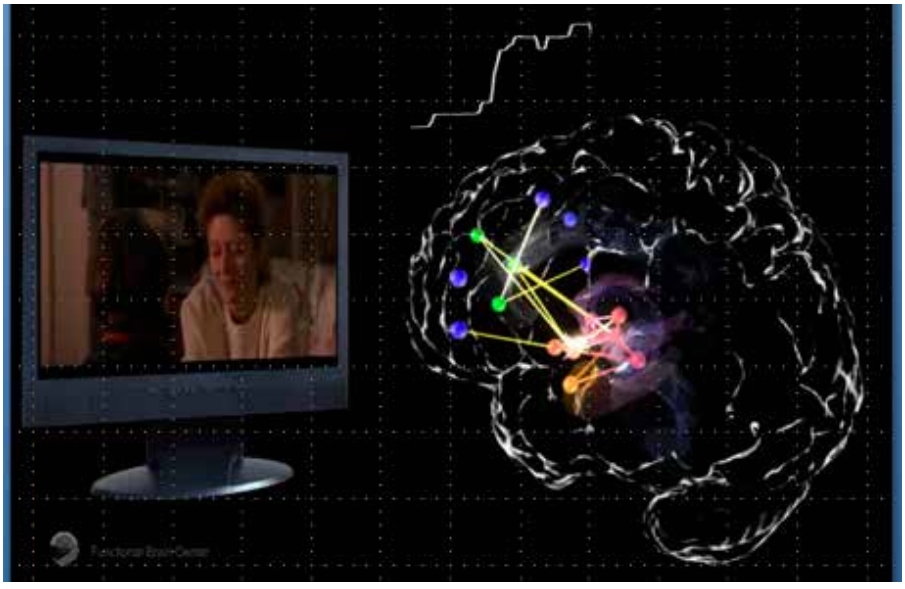
Director, The Sagol Center for Brain Functions, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center

Research

Investigating brain mechanisms underlie generation and regulation of the human emotional experience, in healthy and pathological states. The research is based on measuring indices of brain structure and functional dynamics via MRI (functional-MRI, DTI and Volumetric-MRI) and separate or simultaneous recording of electrical signals (scalp-EEG and intracranial-EEG). The characterization of individual brain response is based on correlating neural activity and connectivity with behavioral and physiological measurements of emotionality (e.g. heart rate, hormone secretion, genetic expression, skin conductance, eye movements and verbal output). Induction of emotional states is achieved via film and music media, inter-personal interactions, and interactive social games. Regulation of emotions is modulated via on-line feedback protocols from brain signals in a closed loop set-up (i.e. *NeuroFeedback*). The lab is also involved in studies aim to advance translation while focusing on neural markers of vulnerability and recovery with regard to post traumatic disorders (e.g. anxiety and depression), developmental disorders (e.g. schizophrenia and personality) and neurodegenerative disorders (e.g. parkinson disease). An essential part of this aspect of our work is the development of advanced new tools for acquiring and analyzing whole brain neural measurements; including applying multi-scale mapping for capturing dynamics of brain networks.



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).

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Department of Physical Therapy
Stanley Steyer School of Health Professions
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Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

Position

Professor, Sackler Faculty of Medicine

Movement Science Lab., Department of Physical Therapy

Associate Editor, Journal of Electromyography & Kinesiology

Research

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

Publications

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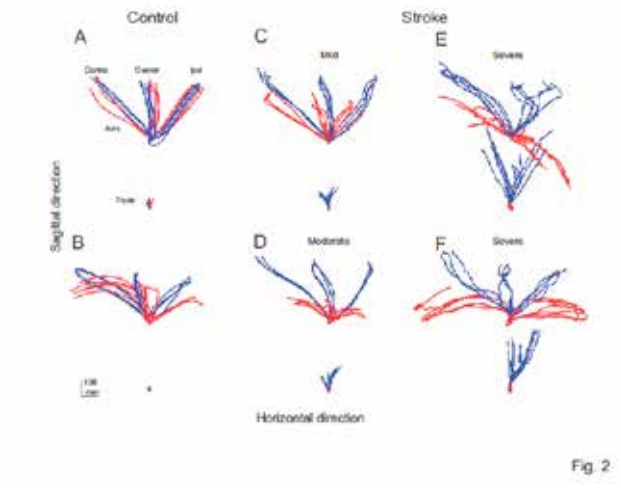

Top: Schematic view of arm and trunk rotation used in modeling arm-trunk coordination based on a geometric algebra approach**. Right**: Arm endpoint and trunk paths (horizontal plane view; i.e., from the above) during reaching movements to contra-, center and ipsilateral visual targets for two healthy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

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Grants

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

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Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

Position

Professor, Sackler Faculty of Medicine

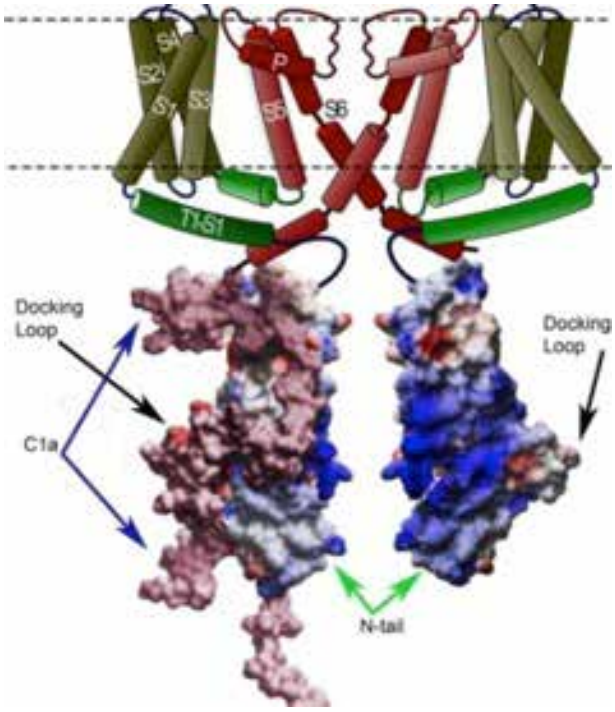
Research

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

Main research projects currently in the lab:

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

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



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

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

Research methods:

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

Biochemical: co-immunoprecipitation, 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

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

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Grants

2014-2018 Israel Science Foundation

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Sleep and Its Relation to Cognition

Position

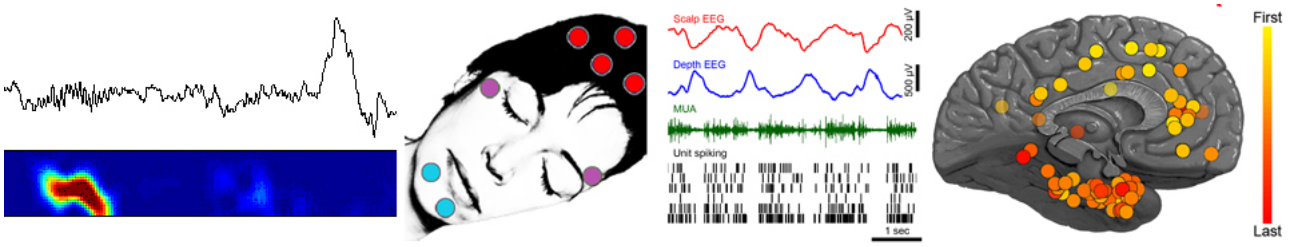
Senior Lecturer, Sackler Faculty of Medicine

Research

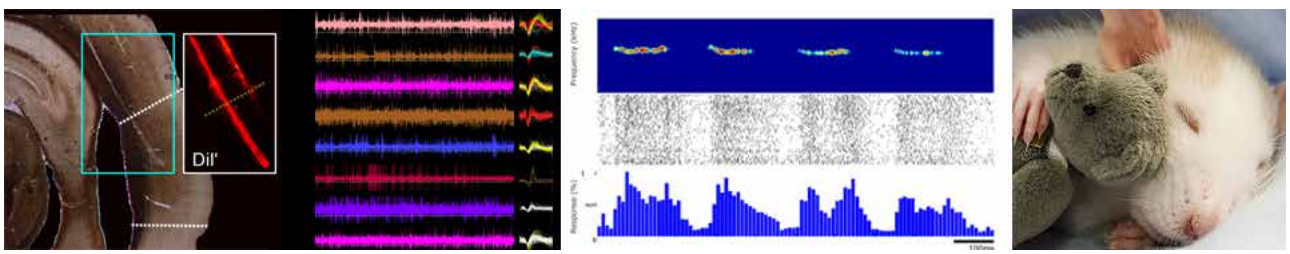
Sleep is a universal behavior that is present across the animal kingdom. We spend a third of our lives sleeping, disconnected from the world around us. Our sleep is closely regulated so that when we are sleep deprived, we ultimately compensate with longer, deeper sleep. Sleep helps our cognitive performance,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

Sleep also involves dramatic changes to our perceptual awareness. Sometimes our consciousness fades altogether while at other times we experience vivid dreams. Although our brain continues to be active, we are mostly disconnected from sensory signals such as sounds, which would otherwise be perceived, trigger plasticity and result in behavior. How does the internal state of brain activity during sleep affect brain responsiveness and perceptual awareness?

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



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



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

Publications

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Grants

2014 – 2018	EU Marie Curie Career Integration Grant (CIG)
2013 – 2018	I-CORE Cognitive Neuroscience
2015-2020	Israel Science Foundation grant
2016	Adelis Prize in Neuroscience

Dr. Moshe Parnas, Ph.D.

Department of Physiology and Pharmacology
Sackler Faculty of Medicine
Sagol School of Neuroscience

TEL AVIV UNIVERSITY

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Neural Circuits and Olfactory Perception in Drosophila

Position

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

Research

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

Projects in the lab include:

1. Intensity and identity coding in a multidimensional sensory system – the *Drosophila* olfactory system.
2. Neuropeptidergic modulation of olfaction and its effect on odour perception.
3. The role of deregulated channel proteins and altered neuronal function in Frontotemporal Dementia.
4. A novel multifaceted approach to study the mechanisms underlying the effects of human genes associated with schizophrenia using *Drosophila*.

Publications

Manuscripts

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

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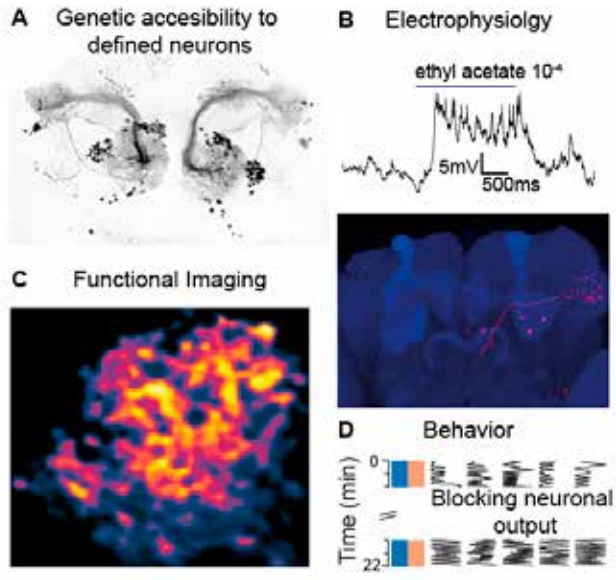

Drosophila as a model system for systems neuroscience. **A.** Using the genetic tools available for *Drosphila* there is accessibility for defined neurons. **B.** *In vivo* whole cell patch recording in awake behaving animals. **C.** *In vivo* functional imaging using genetically encoded sensors in awake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

Review

Parnas, M., Peters, M., and Minke, B. (2012). Biophysics of TRP Channels. Editor: Edward H. Egelman, In: Comprehensive Biophysics, Vol 6, Channels Proteins, Mauricio Montal. Oxford: Academic Press, pp. 68-107.

Grants

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

Dr. Eran Perlson, Ph.D.

Department of Physiology and Pharmacology
Sackler Faculty of Medicine

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Molecular Mechanisms of Neurodegeneration

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

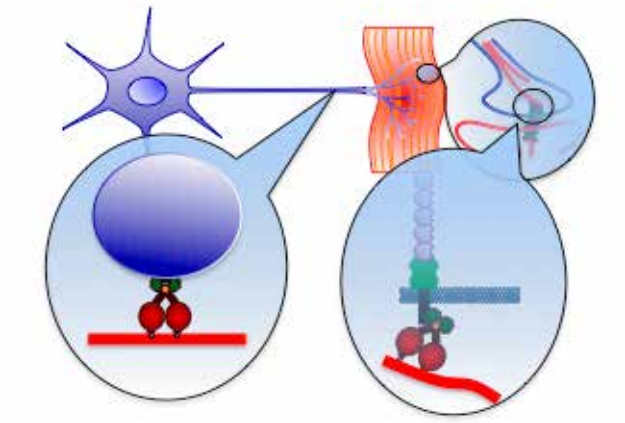
Neuronal survival and proper function depends on cell-cell communication mediated by ligand-receptor mechanisms. During neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), there is considerable synapse/neuromuscular junction (NMJ) disruption and neuronal cell death. It is non-autonomous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

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

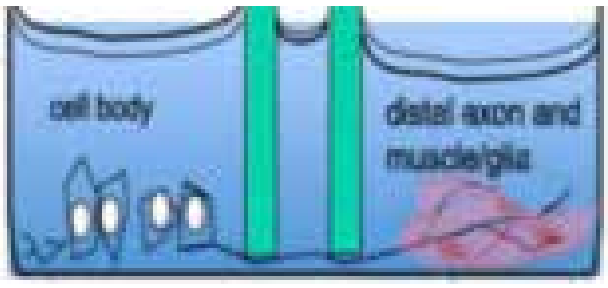
We believe that our research will generate novel insights into neurodegenerative mechanisms and ultimately, provide a molecular basis for new drugs as well as delivery methods to treat a range of neurodegenerative diseases.

Publications

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



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



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

RNA-binding protein Staufen1 in Amyotrophic Lateral Sclerosis. *Mol Cell Proteomics*. 15:506-22.

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

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

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

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Lilo E, Wald S, Solmesky L, Ben Yaakov K, Gershoni-Emek N, Gotkine M, Karosis D, Bulvik S, **Perlson E** and Weil M. (2013). Characterization of human sporadic ALS biomarkers in the familial transgenic mSOD1G93A mouse model. *Hum Mol Genet*. 22:4750-5.

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Grants

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

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

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

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

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Sackler Faculty of Medicine

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Brain Injuries: Cognitive, Behavioral and Cellular Outcome

Position

Professor, Sackler Faculty of Medicine

Research

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

Publications

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Greg, N.H, Tweedie, D. Rachmany, L., Yu, Q., Rubovitch, V, Schreiber,S., Chiang, Y-H. Hoffer, B.J., Lahiri, D., Kumar Sambamurti, K., Becker,R.E., **Pick, C.G.** Incretin mimetics as pharmacological tools to elucidate and as a new drug strategy to treat traumatic brain injury. *Alzheimer's & Dementia* 10: S62-S75 (2014).

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Katzav, A., Ben-Ziv, T., Blank M. **Pick, C. G.,** Shoenfeld Y and Chapman, J. Antibody-specific behavioral effects: Intracerebroventricular injection of antiphospholipid antibodies induces hyperactive behavior while anti-ribosomal-P antibodies induces depression and smell deficits in mice. *J Neuroimmunol*, 272:10-15(2014).

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Prof. Moshe Rehavi, Ph.D.

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Molecular Mechanisms of Drugs for Neuropsychiatric Disorders

Positions

Professor, Sackler Faculty of Medicine

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

Head, Varda and Shalom Yoram Institute for Human Genome Research

Research

Main projects in the lab include:

1. Presynaptic monoamine 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

Morag A, Pasmanik-Chor M, Oron-Karni V, **Rehavi M**, Stingl JC, Gurwitz D. (2011). Genome-wide expression profiling of human lymphoblastoid cell lines identifies CHL1 as a putative SSRI antidepressant response biomarker. *Pharmacogenomics*. 12:171-84.

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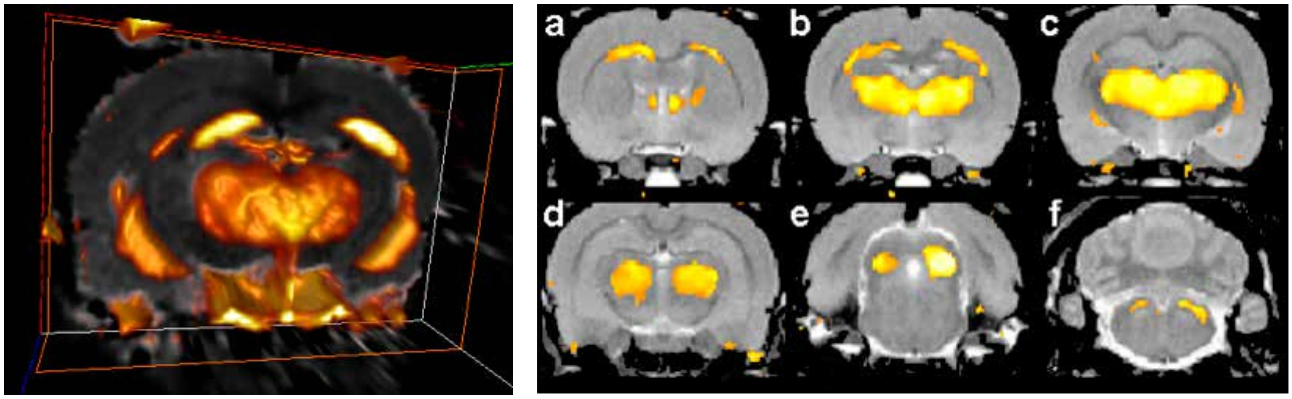
Bismuth-Evenzal Y, Gonopolsky Y, Gurwitz D, Iancu I, Weizman A, **Rehavi M**. (2012). Decreased serotonin content and reduced agonist-induced aggregation in platelets of patients chronically medicated with SSRI drugs. *J Affect Disord*. 136:99-103

Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, Shomron N, **Rehavi M**, Stingl JC, Gurwitz D. (2012) Genome-wide miRNA expression profiling of human lymphoblastoid cell lines identifies tentative SSRI antidepressant response biomarkers. *Pharmacogenomics*. 13:1129-39.



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

Doron R, Lotan D, Versano Z, Benatav L, Franko M, Armoza S, Kately N, **Rehavi M** (2014) Escitalopram or novel herbal mixture treatments during or following exposure to stress reduce anxiety-like behavior through corticosterone and BDNF modifications. *PLoS One* 9:e91455

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

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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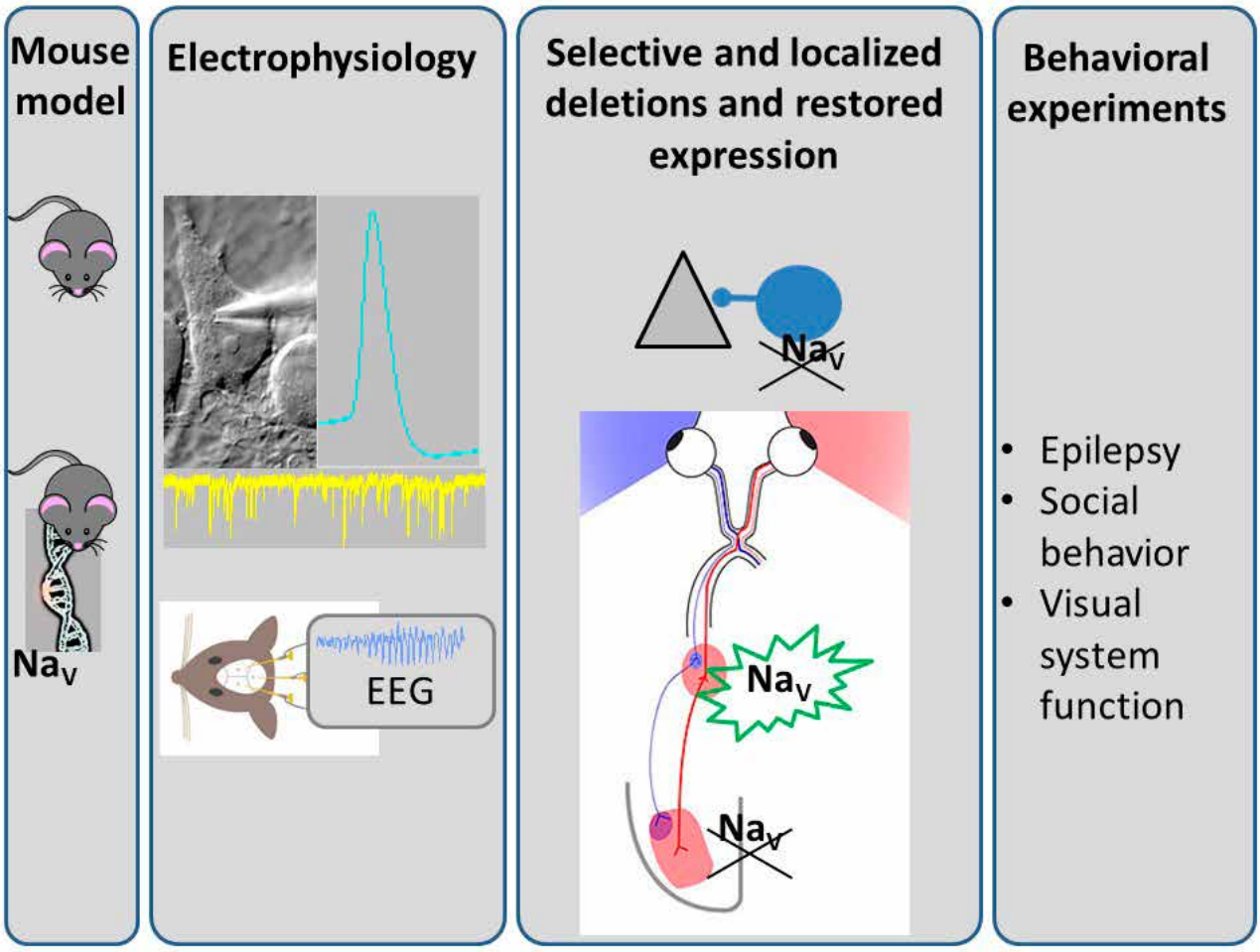
The Molecular Basis of Epileptic Encephalopathies and Autism

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

Publications

Yakubovich, D., Berlin, S., Kahanovitch, U., **Rubinstein, M.**, Farhy-Tselnicker, I., Styr, B., Keren-Raifman, T., Dessauer, C.W., and Dascal, N. (2015). A quantitative model of the GIRK1/2 channel reveals that its basal and evoked activities are controlled by unequal stoichiometry of Gα and Gβγ. *PLoS Comp Biol* 11, e1004598.

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Rubinstein, M., Westenbroek, R.E., Yu, F.H., Jones, C.J., Scheuer, T., and Catterall, W.A. (2015). Genetic background modulates impaired excitability of inhibitory neurons in a mouse model of Dravet syndrome. *Neurobiol Dis* 73, 106-117.

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Novel Antioxidant and Stem Cells for Treatment of Degenerative Diseases

Positions

Professor, Sackler Faculty of Medicine

Director, Goldschleger Eye Research Institute

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

Research

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

The following specific subjects are studied:

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

Publications

R. Beigel, H. Hod, P. Fefer, E. Asher, I. Novikov, B. Shenkman, **N. Savion**, D. Varon and S. Matetzky. Relation of aspirin failure to clinical outcome and to platelet response to aspirin in patients with acute myocardial infarction. Am. J. Cardiol. 107: 339–342, 2011.

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

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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.

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D. Ben-Zvi, **N. Savion**, F. Kolodgie, A. Simon, S. Fisch, K. Schäfer, N. Bachner-Hinenzon, X. Cao, A. Gertler, G. Solomon, E. Kachel, E. Raanani, J. Lavee, S. Kotev Emeth, R. Virmani, F.J. Schoen, J. Schneiderman. Local application of leptin antagonist attenuates Angiotensin II-induced ascending aortic aneurysm and cardiac remodeling. J. Am. Heart Assoc. 5:e003474; 2016.

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

Positions

Associate Professor, Sackler Faculty of Medicine

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

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

Member, Minerva grant committee;

Member, Azrieli PhD fellowship committee;

Member, PhD program committee, Sagol School of Neuroscience

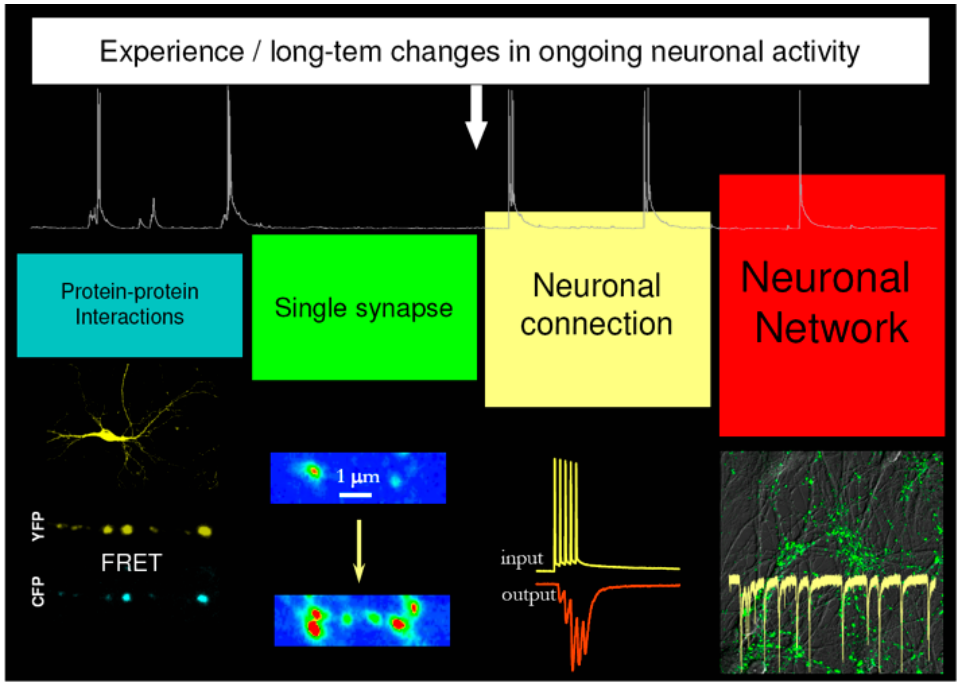
Member, Scientific Committee, Center of Nanoscience and Nanotechnology

Research

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

Publications

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



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Grants

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

2013 – 2018 Israel Science Foundation

2014 – 2017 Heritage Legacy Fund and Israel Science Foundation

2014 – 2018 Binational US-Israel Science Foundation

2013 – 2018 Rosetrees Trust, UK

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Basic and Applicative Research of Eye Physiology, Diseases and Function

Positions

Associate Professor, Sackler Faculty of Medicine

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

International Committee Member, ARVO

Research

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

The following specific subjects are studied:

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

Publications

Cohen Y, Belkin M, Yehezkel O, Solomon AS, Polat U. Dependency between light intensity and refractive development under light-dark cycles. Exp Eye Res 2011;92:40-6.

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

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Tzameret A., Sher I., Belkin M, Treves AJ., Meir A., **Nagler A, Levkovicitch-Verbin H., Rotenstreich Y., Solomon AS.** Epiretinal transplantation of human bone marrow mesenchymal stem cells rescues retinal and vision function in a rat model of retinal degeneration. Stem Cell Res, 15:387-94.

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Maharshak I, Salomon- Zimri S., Antes R,Liraz O., Nisgav Y., Livnat T., Weinberger D., Colton C., **Solomon AS,** Michaelson DM. The effect of the ApoE4 Genotype on the developing mouse retina. Exp Eye Res, 2015, 145:17-25.

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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, **Stark E**, Seymour J, Na K, Winful HF, Buzsáki G, Wise KD, Yoon E (2016) Fiberless multicolor neural optoelectrode for in vivo circuit analysis. *Scientific Reports*, in press

Wu F*, **Stark E***, Ku P, Wise K, Buzsáki G, Yoon E (2015) Monolithically integrated µLEDs on silicon neural probes for high-resolution optogenetic studies in behaving animals. *Neuron*, 88:1136-1148.

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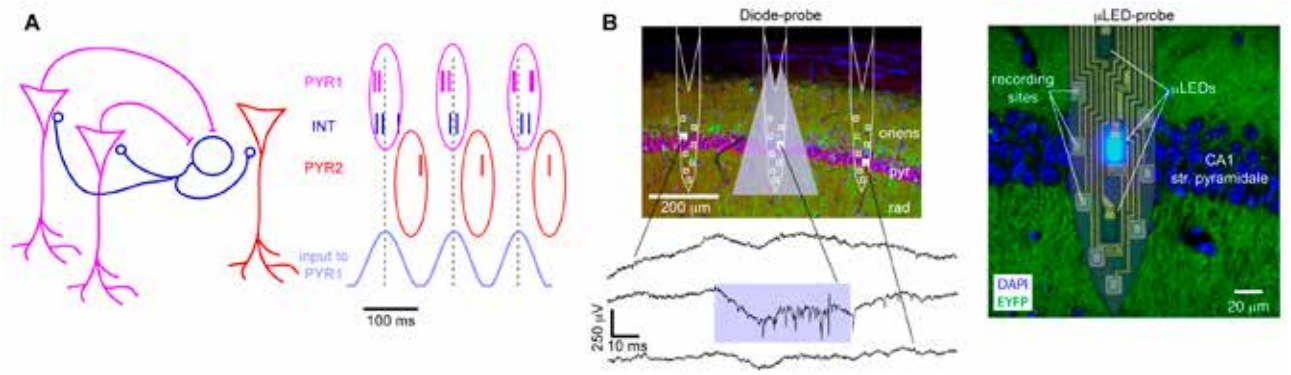
Stark E*, Roux L*, Eichler R*, Senzai Y, Royer S, Buzsáki G (2014) Pyramidal cell-interneuron



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.

interactions underlie hippocampal ripple oscillations. *Neuron* 83:467-80.

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

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

Reviews

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

Grants

2016-2021 ERC Starting Grant

2016-2020 CRCNS (NSF-BSF) Grant

2016-2020 ISF Grant

Nursing, Occupational and Physical Therapy

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School of Health Professions
Sackler Faculty of Medicine

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Investigating Sensory Modulation Disorder (SMD) Over Life Span

Positions

Lecturer, Sackler Faculty of Medicine

Research

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

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

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

Publications

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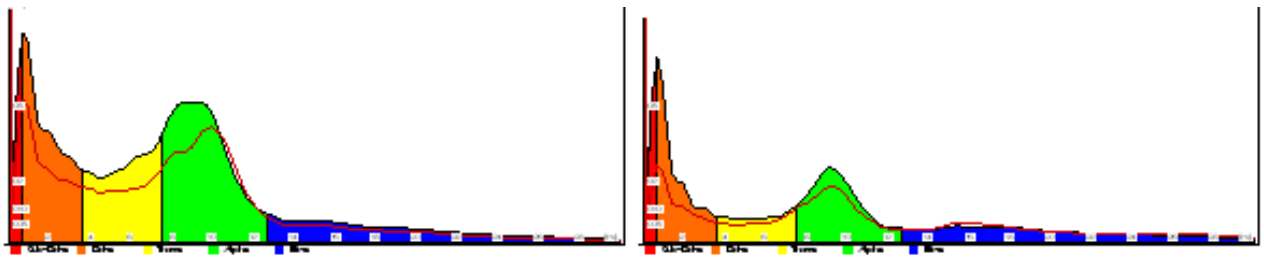
Bar-Shalita, T., Vatine, J.J., Yarnitsky, D., Parush, S., Weissman-Fogel, I. Atypical central pain processing in sensory modulation disorder: absence of temporal summation and higher after-sensation. Exp Brain Res. 2014, 232: 587-595.



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

Manuscripts

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

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

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

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

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

Barnoy, S., Pruss*, D.,* Ehrenfeld, M. and Kushnir. T. *(*2011). Epistemic authority and nurses' reactions to medical information retrieved from internet sites of different sites of different credibility. *Nursing and Health Sciences*, 13, 366-370*.*

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

Itzhaki, M., Bluvstein, I., Raz, S. and **Barnoy, S**. (2013). Factors affecting the actions and emotional reactions of nursing teachers following encounters with students who present them with Internet Information. *Nursing Education Today*, 33, 8842–846.

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

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

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

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

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

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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*, In press.

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*, In press.

Bar-Tal, Y. and **Barnoy, S**. Factors Influencing Participants' Decision to Comply with Nurse Recommendations. *Nursing Inquiry*. In press.

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, In press.

Dr. Orit Bart, Ph.D., OTR

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

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Occupational Therapy

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

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

Research

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

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

Publications

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

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

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

O. Bart, T. Agam, P. L. Weiss, R. Kizony. Using video capture virtual reality for children with acquired brain injury. *Disability and Rehabilitation*. 33, 1579-86, 2011.

T. Jarus, Y. Lourie-Gelberg, B. Engel-Yeger, **O. Bart.** Participation patterns of school-aged children with and without DCD. *Research in Developmental Disabilities.* 32, 1323-1331, 2011.

O. Bart, S. Shayevits, L. V. Gabis, I. Morag. Prediction of Participation and Sensory Modulation of Late Preterm Infants at 12 months: A Prospective Study. *Research in Developmental Disabilities, 32,* 2732-8, 2011.

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

L. Rosenberg, N. Z. Ratzon, T. Jarus, **O. Bart.** Perceived environmental restrictions for the participation of children with mild developmental disabilities. *Child: Care, Health & Development*, 38, 836-43, 2012

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

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

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

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

L. Rosenberg, **O. Bart**, NZ. Ratzon, T. Jarus. Complementary contribution of parents and therapists to child's assessment process. *Australian Occupational Therapy Journal*, 60, 410-415, 2013.

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

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

L. Gabis, K. Hacham- Pilosof, O.Bar Yosef, G. Rabinovitz, G. Leshem, A. Shilon- Hadassa, Y. Biran, B. 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.

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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.

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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.

Prof. Ruth Defrin, Ph.D.

Department of Physical Therapy
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Investigating Pain Perception and Mechanisms of Chronic Pain

Position

Associate Professor, Sackler Faculty of Medicine

Director, Biomed@TAU Pain Research Hub

Research

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

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

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

Publications

Gruener H, Zeilig G, Laufer Y, Blumen N, **Defrin R.** Differential pain modulation properties in central neuropathic pain after spinal cord injury. Pain. 2016;157:1415-24.

Zeilig G, Rivel M, Doron D, **Defrin R**. Does hemiplegic shoulder pain share clinical and sensory characteristics with central neuropathic pain? A comparative study. Eur J Phys Rehab Med. 2016 [epub ahead of print].

Weissman-Fogel I, Dror A, **Defrin R**. Temporal and spatial aspects of experimental tonic pain: understanding pain adaptation and intensification Eur J Pain. 2015;19:408-18.

Defrin R, Riabinin M, Feingold Y, Schreiber S, Pick CG. Deficient pain modulatory systems in patients with mild traumatic brain and chronic post-traumatic headache: implications on its mechanism. J Neurotrauma. 2015;32:28-37.

Benromano T, **Defrin R**, Ahn AH, Zhao J, Pick CG, Levy D. Mild closed head injury promotes a selective trigeminal hyper-nociception: implications for the acute emergence of posttraumatic headache. Eur J Pain. 2015;19:621-8.

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Defrin R, Schreiber S, Ginzburg K. Paradoxical pain perception in PTSD: The unique role of anxiety and dissociation. J Pain. 2015;16:961-970.

Levitan Y, Zeilig G, Bondi M, Ringler E, **Defrin R**. Predicting the risk for central pain using the sensory components of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). J Neurotrauma. 2015; 32:1684-92

Kucyi A, Sheinman A, **Defrin R**. Distinguishing feigned from genuine performance in psychophysical pain testing. J Pain. 2015;16:1044-1053

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Levy D, Edut S, Baraz-Goldstein R, Rubovitch V, **Defrin R**, Bree D, Gariepy H, Zhao J, Pick CG. Responses of dural mast cells in concussive and blast models of mild traumatic brain injury in mice: Potential implications for post-traumatic headache. Cephalalgia. 2015 [epub ahead of print]

Andersen TE, Lahav Y, **Defrin R**, Mikulincer M, Solomon Z. Attachment security and pain--The disrupting effect of captivity and PTSS. J Psychosom Res. 2015;79:471-6.

Defrin R, Devor M, Brill S. Tactile allodynia in patients with lumbar radicular pain (sciatica). Pain. 2014;155:2551-9.

Geva N, Pruessner J, **Defrin R**. Acute psychosocial stress reduces pain modulation capabilities in healthy men. Pain. 2014;155:2418-2520.

Defrin R, Ginzburg K, Mikulincer M, Solomon Z. The long-term impact of tissue injury on pain processing and modulation: a study on ex-prisoners of war who underwent torture. Eur J Pain. 2014;18:548-58.

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Ginzburg K, Tsur N, Barak-Nahum A, **Defrin** R. Body awareness: differentiating between sensitivity to and monitoring of bodily signals. J Behav Med. 2014;37:564-75.

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Defrin R, Lurie R. Indications for peripheral and central sensitization in patients with chronic scalp pain (trichodynia). Clin J Pain. 2013;29:417-24.

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Ratmansky M, **Defrin** R, Soroker N. A randomized controlled study of segmental neuromyotherapy for post-stroke hemiplegic shoulder pain. J Rehabil Med. 2012;44:830-6.

Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, **Defrin** R, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede RD, Waxman SG, Widerström-Noga E, Yezierski RP, Dijkers M. International spinal cord injury pain classification: part I. Background and description. Spinal Cord. 2012;50:413-7.

Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, **Defrin R**, Ivan E, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede RD, Waxman SG, Widerström-Noga E, Yezierski RP, Dijkers M. International Spinal Cord Injury Pain (ISCIP) Classification: Part 2. Initial validation using vignettes. Spinal Cord. 2012;50:404-12.

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

Weisman-Fogel, N. Zwi, **R. Defrin**. The resolution of the pain system as evaluated with psychophysical testing reveals a proximal to distal gradient of improvement. Exp Brain Res. 2012;216:181-90.

R. Defrin, A. Sheraizin, L. Malichi, O. Shachen. Spatial summation and spatial discrimination of cold-pain: effect of spatial configuration and skin type. Pain. 2011;152:2739-45.

R. Defrin, I. Eli, D. Pud. The interaction among sex, ethnicity and gender role expectations of pain. Gender Medicine 2011;8(3):172-83.

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Reviews and Chapters

R. Defrin, Chronic central pain after spinal cord injury. In: Principles of Rehabilitation Medicine, A Ohry Editor, Tel-Aviv: probook, 2011; 99-113.

de Tommaso M, Arendt-Nielsen L, **Defrin R,** Kunz M, Pickering G, Valeriani M. Pain in Neurodegenerative Disease: Current Knowledge and Future Perspectives. Behav Neurol. 2016.

Defrin R, Amanzio M, de Tommaso M, Dimova V, Filipovic S, Finn DP, Gimenez-Llort L, Invitto S, Jensen-Dahm C, Lautenbacher S, Oosterman J, Petrini L, Pick CG, Pickering G, Vase L, Kunz M. Experimental pain processing in individuals with

cognitive impairment: Current state of the science. Pain. 2015;156:1396-1408.

Grants

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

Prof. Minka Hildesheimer, Ph.D.

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Hearing Science and Clinical Audiology

Position

Professor, Sackler Faculty of Medicine

Research

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

Our research has been conducted in two areas:

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

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

B. Research on auditory plasticity in human subjects

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

Hearing in neonates and Auditory Processing Disorders: The Transient Evoked Oto-Acoustic Emission (TEOAE) is applied in hearing screening in neonates. Research was conducted to examine the reliability and validity of the test. We also investigated the development and activity of the efferent inhibitory system in newborns and premature babies using the suppression of the TEOAE test. We suggested the use of the test as a clinical tool for evaluation of auditory 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

Henkin, Y., GIVON, L., Yaar-Soffer, Y. & **Hildesheimer, M**. (2011). Cortical binaural interaction during speech processing in children with bilateral cochlear implant. *Cochlear Implant International,* 12:61-65.

Potter-Katz, H., Feldman, I. & **Hildesheimer, M**. (2011). Binaural masking level difference in skilled reading children and children With dyslexia. *Journal of Basic and Clinical Physiology & Pharmacology,* 22:59-63.

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Ari-Even Roth, D., Muchnik, C., Shabtai, E., **Hildesheimer, M**. & Henkin, Y. (2012). Evidence for atypical auditory brainstem response in young children with suspected autism spectrum disorders. *Developmental Medicine & Child Neurology*, 54:23-29.

Van Den Abbeele, T., **Hildesheimer, M**., Kronenberg, J. & Arnold, A. (2012). Multicentre investigation on electrically evoked compound action potential and stapedius Reflex. *Cochlear Implants International*, 13:26-34.

Muchnik, C., Ari-Even Roth, D., **Hildesheimer, M**., Arie, M., Bar-Haim, Y. & Henkin, Y. (2013). Abnormalities in auditory efferent activities in children with selective mutism. *Audiology & Neurology*. 18:353–361

Henkin Y, Swead RT, Roth DA, Kishon-Rabin L, Shapira Y, Migirov L, **Hildesheimer M**, Kaplan-Neeman R. (2014) Evidence for a right cochlear implant advantage in simultaneous bilateral cochlear implantation. Laryngoscope. 124:1937-41

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.

D. Ari-Even Roth, L. Kishon-Rabin, **M. Hildesheimer**, A. Karni. Asymmetric interaural generalization of learning gains in a speech-in-noise identification task. Journal of the Acoustical Society of America, 138, 2627-2634, 2015.

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Emotional Management, Cultural Competence and Decision-Making

Positions

Lecturer, Sackler Faculty of Medicine

Head, Generic BA Nursing Program

Research

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

Publications

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

Itzhaki M & Koton S. Knowledge, perceptions and thoughts of stroke among Arab-Muslim Israelis. *European Journal of Cardiovascular Nursing* 2013, 13, 78-85

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

Itzhaki M, Bluvstein I, Raz S, Barnoy S. Factors affecting the actions and emotional reactions of nursing teachers following encounters with students who present them with internet information. *Nurse Education Today* 2013, 33:842-6.

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Chapter

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Grants

2016 The Israel National Institute for Health Policy Research Grant

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Quality of Care and Patient Safety

Positions

Lecturer, Sackler Faculty of Medicine

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

Research

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

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

Publications

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Epidemiology of Cardiovascular Diseases & Risk Factors

Position

Associate Professor, Sackler Faculty of Medicine

Chair, Department of Nursing

Research

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

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

Publications

Schwammenthal Y, Bornstein NM, Goldbourt U, **Koton S**, Schwartz R, Koren-Morag N, Grossman E, Tanne D. Anticoagulation remains underused in prevention of stroke associated with atrial fibrillation: Insights from two consecutive national surveys. *Int J Cardiol.* 2011;152:356-61.

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Dombe S, Barzilai B, **Koton S**, Tabak N. Variables influencing the attitudes of nurses toward euthanasia of severely damaged newborns and premature babies. *Refuah Ve-mishpat* 2012; 45:77-89 (Hebrew).

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

Department of Occupational Therapy
Sackler Faculty of Medicine

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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

Lipskaya, L., Jarus, T., & Kotler, M. (2011). Influence of cognitive abilities and symptoms of schizophrenia on performance of Instrumental Activities of Daily Living. *Scandinavian Journal of Occupational Therapy*, *18*, 180-187.

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

Dr. Alon Kalron, Ph.D., P.T.

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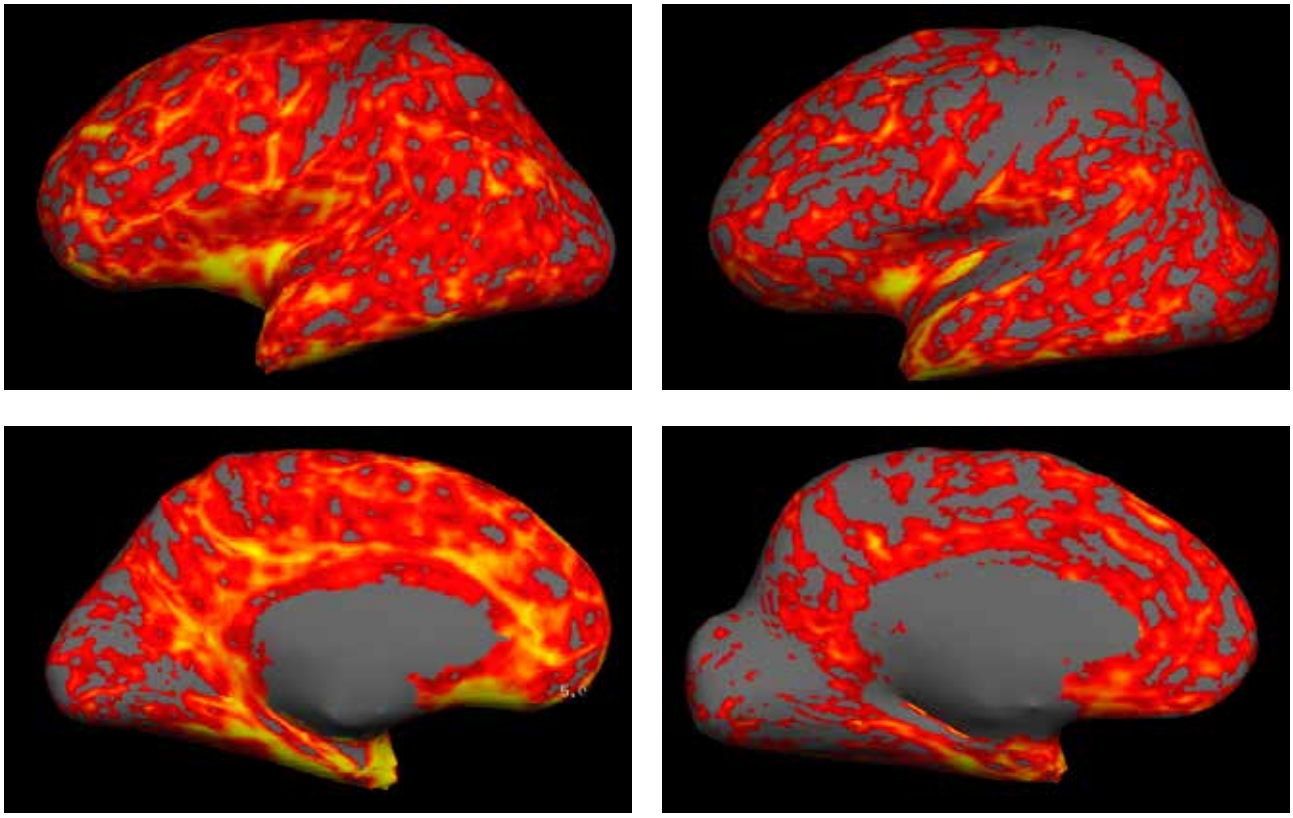
Physical activity, gait and posture in people with neurological diseases

Position

Lecturer, Sackler Faculty of Medicine

Research

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



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

Publications

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Kalron A, Achiron A, Dvir Z. Effect of a cognitive task on postural control in patients with a clinically isolated syndrome suggestive of multiple sclerosis. *Eur J Phys Rehabil Med*, 47:579-586; 2011.

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Kalron A, Givon U. Gait characteristics according to pyramidal, sensory and cerebellar EDSS subcategories in people with multiple sclerosis. *J Neurol* 2016 [Epub].

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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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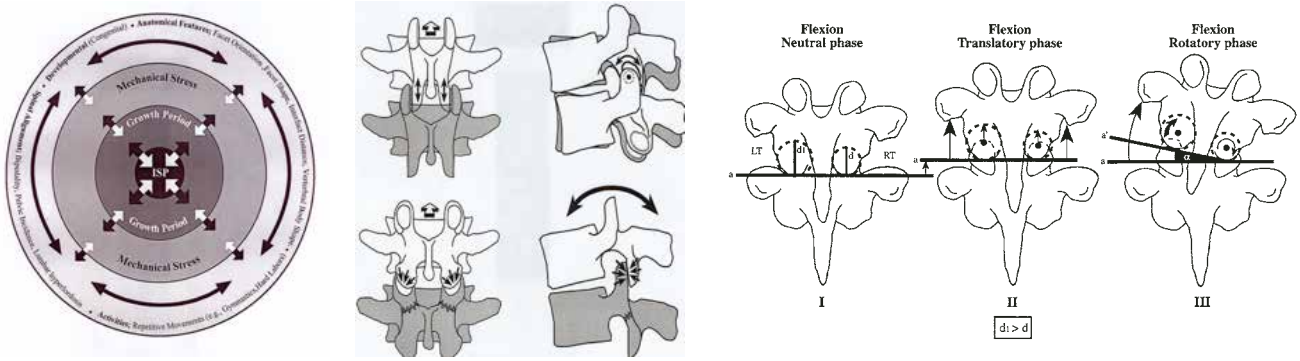

A B C

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Reviews

Blum N, Halperin D, **Masharawi Y**. Ambulatory and hospital-based quality improvement methods in Israel. Health Serv Insights. 2014;7:25-30.

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Determinants of the Adherence to Immunosuppressive Medications

Position

Head, Short-day studies BA Nursing Program

Lecturer, Sackler Faculty of Medicine

Research

Non-adherence is described as general behaviors that deviate from a prescribed health regimen. Non-adherence (NA) to immunosuppressive (IS) medications after organ transplant is a major risk factor for transplant failure, morbidity and overall treatment costs. NA rates ranging from 2%-67% during follow-up periods of 2 weeks to 20 years were reported among kidney, heart and liver transplant recipients. Objective risk factors shown to be associated with NA to IS medications were younger age, male gender, non-white ethnicity, longer time elapsed since transplantation and higher number of immunosuppressive medications prescribed. Non-objective risk factors for NA to IS medications included social isolation, low self-efficacy, lower ability of self-care, patients' beliefs about IS medications, perceived barriers, lower life satisfaction, receiving the organ from live donors and others. Our research tries to characterize cultural and social factors affecting adherence to IS treatments among transplant patients in Israel.

Publications

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Computational Biomechanics in Motor Rehabilitation

Position

Lecturer, Sackler Faculty of Medicine

Research

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

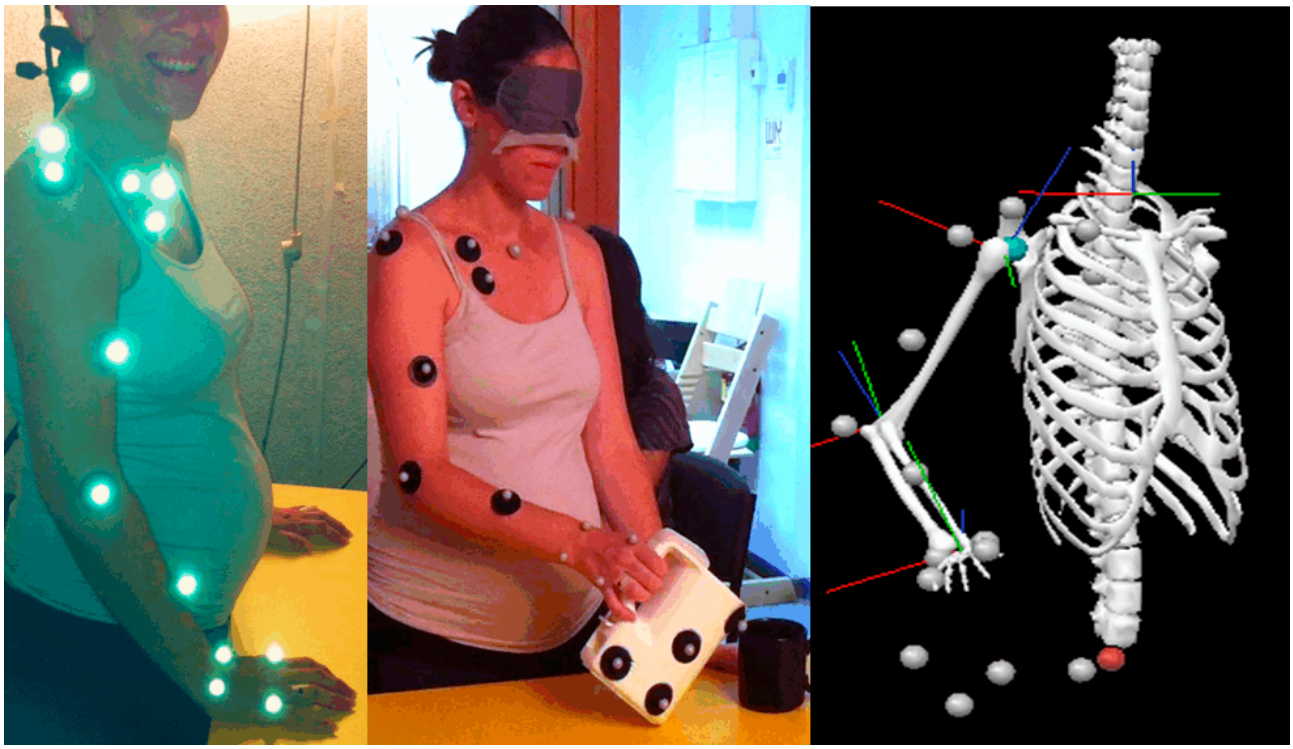
1. Design of new evaluation and treatment tools for clinicians, based on state-of-the-art technologies.
2. Quantification, evaluation and feedback, provided to the motor-impaired patient by utilizing real-time data of the kinematics, kinetics and muscular activity patterns.
3. Development of innovative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

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

Publications

Portnoy S, Siev-Ner I, Shabshin N, Gefen A. Effects of sitting postures on risks for deep tissue injury in the residuum of a transtibial prosthetic-user: a biomechanical case study. *Computer Methods in Biomechanics and Biomedical Engineering,* 14:1009-19, 2011.

Portnoy S, Vuillerme N, Payan Y, Gefen A. Clinically-oriented real-time monitoring of the individual's risk for deep tissue injury. *Medical & Biological Engineering & Computing*, 49: 473-483, 2011. *Winner of the Nightingale Prize for best paper published in*



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Levanon Y, Gefen A, Lerman Y, **Portnoy S,** Ratzon NZ. Key Strike forces and high level of musculoskeletal symptoms, *Safety and Health at Work*, 2016.

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Chapter

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Gaming for Rehabilitation of Neurological and Geriatric Populations

Position

Senior Lecturer, Sackler Faculty of Medicine

Chair, Department of Occupational Therapy

Research

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

Publications

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Book Chapters

Weiss PL, Kizony R, Feintuch U, **Rand D**, Katz N. Textbook of Neural Repair and Rehabilitation Section: Technology of Rehabilitation. Chapter # 47: Virtual Reality Applications in, iNeurorehabilitation. In press.

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Investigating the Ergonomics of Occupational Tasks and Driving Rehabilitation

Position

Associate Professor, Sackler Faculty of Medicine

Research

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

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

Publications

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Gat, S., & **Ratzon, N. Z**. (2014). Comparison of occupational therapy students' perceived skills after traditional and nontraditional fieldwork. *The American Journal of Occupational Therapy*, *68* , e47-e54.

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Karni, S., Bentur, N., & **Ratzon, N.** (2014) Participation and Quality of Life of Cognitively Impaired Older Women in Israel Following Hip Fractures. *Occupational Therapy International.* 21, 91-97.

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Golebowicz, M., Levanon, Y., Palti, R., **Ratzon, N.Z**. (2015). Efficacy of a telerehabilitation intervention program using biofeedback among computer operators. *Ergonomics,* 58*,* 791-802.

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Ratzon, N.Z., Kadury Lunievsky, E., Ashkenasi, A., Laks, J., Cohen, H.A. (2016). Simulated driving skills evaluation with pre-driving lesson ADHD teenagers. *American Journal of Occupational Therapy*. In press.

Shefer Eini, D., Ratzon, N.Z., Rizzo, A. A., Yeh, S.C., Lange, B.,, Yaffe, B., Daich, A., Weiss. P. L., Kizony, R. (2016). Camera-tracking gaming control device for evaluation of wrist range of motion. Journal of Hand Therapy. In press.

Grants

2015-2016	Israel Association of Family Physicians
2016-2019	Insurance Research Fund, The Israeli Association of Insurance Company

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The Role of Glutamate Excitotoxicity in Neurodegenerative and Malignant Diseases

Position

Lecturer, Sackler Faculty of Medicine

Research

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

Publications

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Pérez-Mato M, Ramos-Cabrer P, Sobrino T, Blanco M, **Ruban A**, Mirelman D, Menendez P, Castillo J, Campos F.: Human recombinant glutamate oxaloacetate transaminase 1 (GOT1) supplemented with oxaloacetate induces a protective effect after cerebral ischemia. *Cell Death Dis.* Vol. 9; 5:e992, 2014.

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Grants

2016 – 2019 Israel Science Foundation (ISF)

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

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

Positions

Lecturer, Sackler Faculty of Medicine

Research

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

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

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

Publications

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

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

Anbar R, Beloosesky Y, Cohen J, Madar Z, Weiss A, **Theilla M**, Koren Hakim T, Frishman S, Singer P. Tight Calorie Control in geriatric patients following hip fracture decreases complications: a randomized, controlled study. Clinical Nutrition 33:23-8, 2014

Frishman, S, **Theilla M**, Singer P, Avraham Z, Libman C, Kagan I. JCI Accreditation and its multiprofessional impact on nutrition care at Rabin Medical Center, Israel. Invited (peer-reviewed) paper, published 01 April 2014 on official site of Joint Commission International (JCI): http://www.jointcommissioninternational.org/new-study-jci-accreditation-and-nutrition-care-at-rabin-medical-center/

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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]

Kagan I, Cohen J, Stein M, Bendavid I, Pinsker D, Silva V, **Theilla M**, Anbar R, Lev S, Grinev M, Singer P. Preemptive enteral nutrition enriched with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in severe multiple trauma: a prospective, randomized, double-blind study. Intensive Care Med. 2015;41:460-9.

Lupinsky L, Singer P, **Theilla M**, Grinev M, Hirsh R, Lev S, Kagan I, Attal-Singer J. Comparison between two metabolic monitors in the measurement of resting energy expenditure and oxygen consumption in diabetic and non-diabetic ambulatory and hospitalized patients. Nutrition. 2015;31:176-9.

Chapters and Reviews

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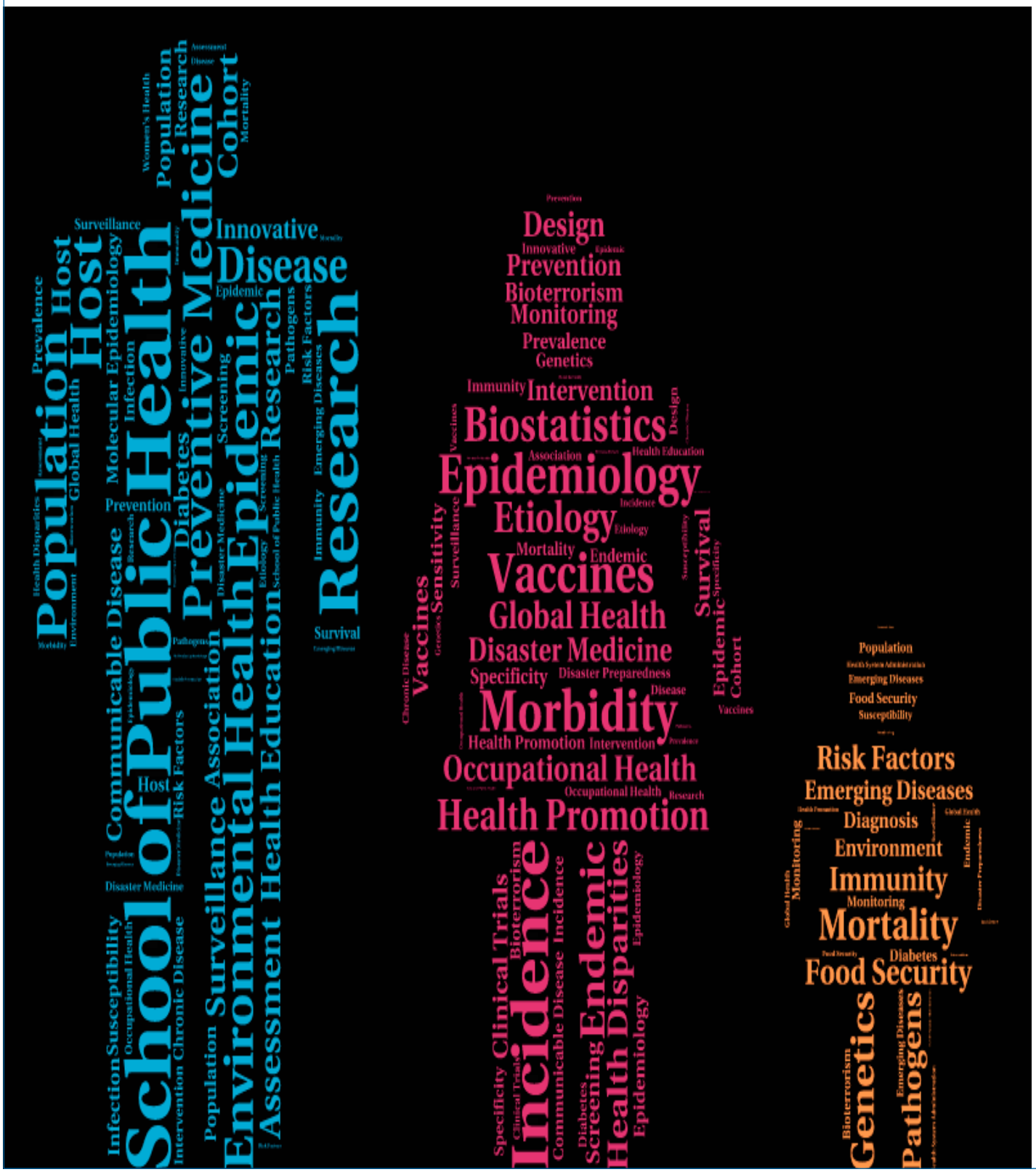
Public Health



Prof. Daniel I. Cohen, Ph.D.

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Epidemiology of Infectious Diseases

Positions

Professor of Epidemiology and Preventive Medicine

Head, School of Public Health, Sackler Faculty of Medicine

Incumbent of Diana & Stanley Steyer Chair of Cancer Prevention and Control

Director, Stanley Steyer Institute for Cancer Epidemiology and Research

Director, Tel Aviv University Center for the Study of Bioterrorism

Research

Emerging Infectious Diseases, Vaccinology

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

Publications

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and other diarrheal diseases. *Clin Infect Dis*. 2012, 54:e35-e42.

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Reviews

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Grants

2013-2016	Israel National Institute for Health Policy and Health Services Research "Evaluation of the impact of the introduction of universal immunization with the rotavirus vaccine on the burden of severe childhood diarrhea associated with rotavirus in Israel"
2011-2017	European Union: "Development of vaccines against Shigella and enterotoxigenc E. coli enteric diseases" (Leader 2 WPs)
2015-2016	Connecting Organizations for Regional Disease Surveillance (CORDS). A Middle East Sub-Regional Laboratory-Based Surveillance Network on MERS-CoV" (Co-PI)

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Aging and End of Life

Positions

Professor, Department of Health Promotion, Sackler Faculty of Medicine

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

Research

Health and Mental Health Promotion in older persons:

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

End of Life

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

Publications

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Cohen-Mansfield, J., 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* Published online before print June 2016 DOI: 10.1177/0020872816651702

Chapters

Poon, L., W. & Cohen-Mansfield, J. (Eds.) (2011) Understanding Well-Being in the Oldest-Old. Cambridge University Press.

Poon, L., W. & Cohen-Mansfield, J. (2011) Toward New Directions in the Study of Well-Being among the Oldest-Old. In: L.W. Poon & J. Cohen-Mansfield, (Eds.) Understanding Well-Being in the Oldest-Old. (pp. 3-10) Cambridge University Press.

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Grants

2016-2019	Israel Ministry of Science. Enhancing quality of care at the end of life.
2016	Minerva Foundation, Research and Dissemination Funds.
2014-2016	Israel Science Foundation. Reducing Loneliness and Social Isolation in Older Persons via a Theory-Based Intervention: A Randomized Controlled Trial.

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Cardiovascular Disease Epidemiology

Positions

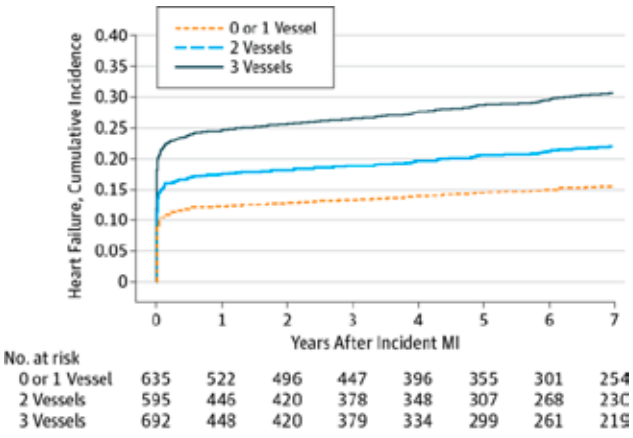
Associate Professor, Sackler Faculty of Medicine

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

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, and clinical details obtained through medical records and examinations. We are also interested in methodological aspects involved in conducting and interpreting observational studies.



Cumulative Incidence Rates of Heart Failure According to Coronary Artery Disease Categories. Death and recurrent myocardial infarction (MI) were treated as competing events. Follow-up began at the time of the index MI and was truncated at 6.7 years (the mean follow-up duration in this analysis). (Gerber et al. *JAMA Cardiol* 2016).

Publications

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Grants

2014-2016 The Environment and Health Fund, Mortality Related to Traffic Air Pollution in a Vulnerable Population: A Contemporary Experience with a Novel Exposure Model.

2016-2017 The Israel Cancer Association (ICA), Chronic residential exposure to outdoor air pollution and cancer incidence in a high-risk population: A cohort study.

Dr. Khitam Muhsen, Ph.D.

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School of Public Health
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

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

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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

Publications

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

Muhsen K, Nir A, Spungin-Bialik A, Bassal R, Goren S, Cohen D. Interaction between ethnicity, socioeconomic factors and *Helicobacter pylori* sero-prevalence among Israeli children and adolescents. J Pediatr Gastroenterol Nutr. 2011; 53:524-7

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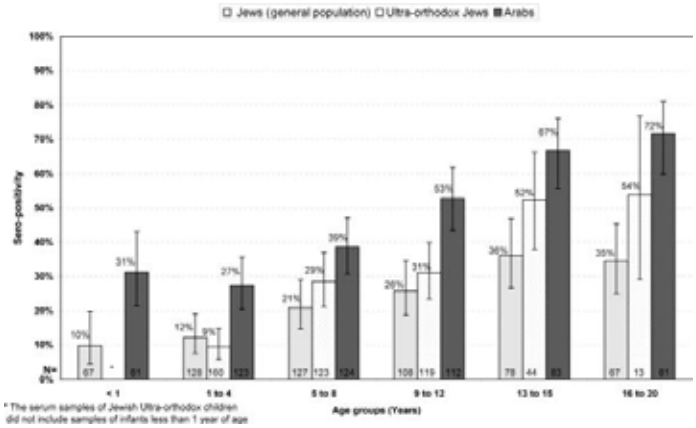

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Levine MM, Kotloff KL, Nataro JP, **Muhsen K**. The Global Enteric Multicenter Study (GEMS); Impetus, Rationale and Genesis. Clin Infect Dis. 2012; 55 Suppl 4:S215-24.

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

Chapter

Tennant SM, **Muhsen K**, Pasetti MF. Gut immunology and oral vaccination. In "Molecular Vaccines- From

Prophylaxis to Therapy". 2013. Editor Matthias Giese M. Springer Vienna. ISBN: 978-3-7091-1418-6 (Print) 978-3-7091-1419-3 (Online)

Grants

2013-2016	MAOF award, Higher Council for Education- Israel
2013-2016	Israel National Institute for Health Policy and Health Services Research (Co-PI with Prof. D. Cohen)
2014-2016	Israel National Health Policy Research Institute
2015-2017	Israel National Institute for Health Policy and Health Services Research (PI)
2016-2018	Israel Ministry of Health (PI)
2016-2018	BSF (PI with Prof. MM Levine, USA)

Dr. Chava Peretz, Ph.D.

Department of Epidemiology
School of Public Health
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

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Epidemiology of Parkinson's Disease and Environmental Epidemiology

Positions

Senior Lecturer, Sackler Faculty of Medicine

Chair, School of Public Health Seminars

Research

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

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

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

Publications

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

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

Leone M, D'Ippoliti D, De Sario M, Analitis A, Menne B, Katsouyanni K, De'donato FK, Basagana X, Salah AB, Casimiro E, Dörtbudak Z, Iñiguez C, **Peretz C,** Wolf T, Michelozzi P. A time series study on the effects of heat on mortality and evaluation of heterogeneity into European and Eastern-Southern Mediterranean cities: results of EU CIRCE project. *Environ Health*. 2013; 12:55.

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Campylobacter spp. infection and high rates among children, Israel. *Emerg Infect Dis J* 2013. 2013.

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

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

Department of Health Promotion
School of Public Health
Sackler Faculty of Medicine

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Email: rosenl@post.tau.ac.il

Improving Public Health, and Control Tobacco Use and Exposure

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

Affiliated Faculty, Harvard Global Center for Tobacco Control

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

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

External Steering Committee Member, World Health Organization EvipNet

Research

Our primary goal is to contribute to public health, at the national and global levels, through conducting research, advancing public health research methods and evidence-based health policy, and teaching and mentoring students. We focus on methodological issues of public health and health promotion research, including understanding and improving the evidence base for public health policy, systematic reviews, and rigorous evaluation of health promotion interventions.

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

Publications

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

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

Rosen LJ, Guttman N, Hovell M, Ben Noach M, Winickoff J, Tchernokovski S, Rosenblum J, Rubenstein U, Seidmann V, Vardavas CI, Klepeis NE, Zucker D. Development, design, and conceptual issues of Project Zero Exposure: A program to protect young children from tobacco smoke exposure. BMC Public Health 2011, 11:508.

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

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

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

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

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

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

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Rosen LJ, Myers V, Winickoff JP, Kott J. Effectiveness of interventions to reduce tobacco smoke pollution in homes: a systematic review and meta-analysis. Int J Environ Res Public Health. 2015;12:16043-59.

Rosen L, Kostjukovsky I. Parental risk perceptions of child exposure to tobacco smoke. BMC Public Health 2015;15:90.

Rosen L, Zucker D, Hovell M, Brown N, Ram A, Myers V. Feasibility of measuring tobacco smoke air pollution in homes: report from a pilot study. Int. J. Environ. Res. Public Health 2015; 12:15129-15142.

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

Levy D, Abrams D, Levy J, **Rosen L**. Complying with the framework convention for tobacco control: an application of the abridged SimSmoke model to Israel. Israel J Health Policy Res. In press.

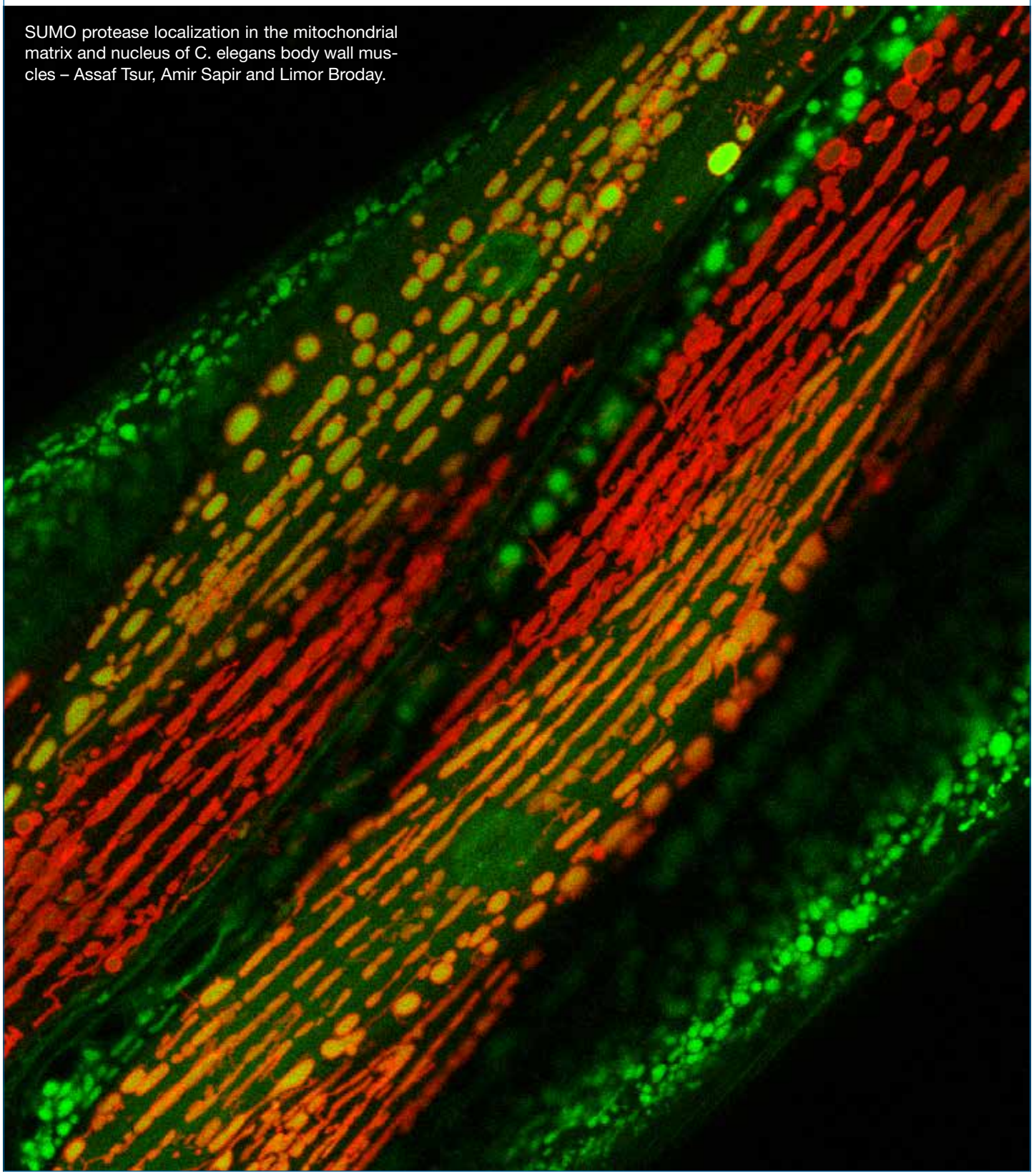
Reviews and Chapters

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

Grants

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

Reproduction, Development and Evolution



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

Dr. Limor Broday, Ph.D.

Department of Cell and Developmental Biology
Sackler Faculty of Medicine

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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

Pichinuk E, **Broday L**, Wreschner DH. 2011. Endogenous RNA cleavages at the ribosomal SRL site likely reflect miRNA (miR) mediated translational suppression. *Biochem Biophys Res Commun*. 414:706-711.

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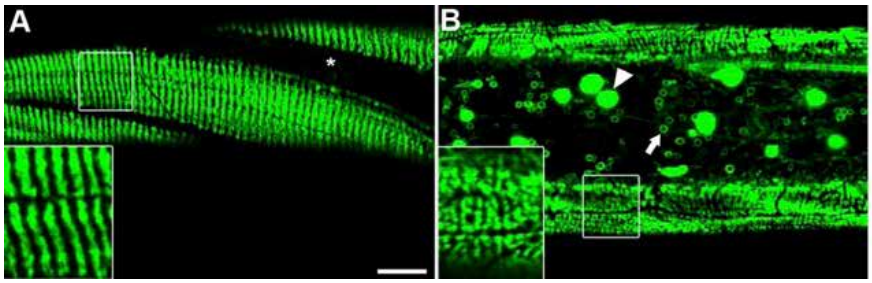
Grants

2014–2016 ICRF Project Grant



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

Dr. Yankel Gabet, D.M.D., Ph.D.

Department of Anatomy & Anthropology
Sackler Faculty of Medicine

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Genetic and Hormonal Regulation of Bone Metabolism

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

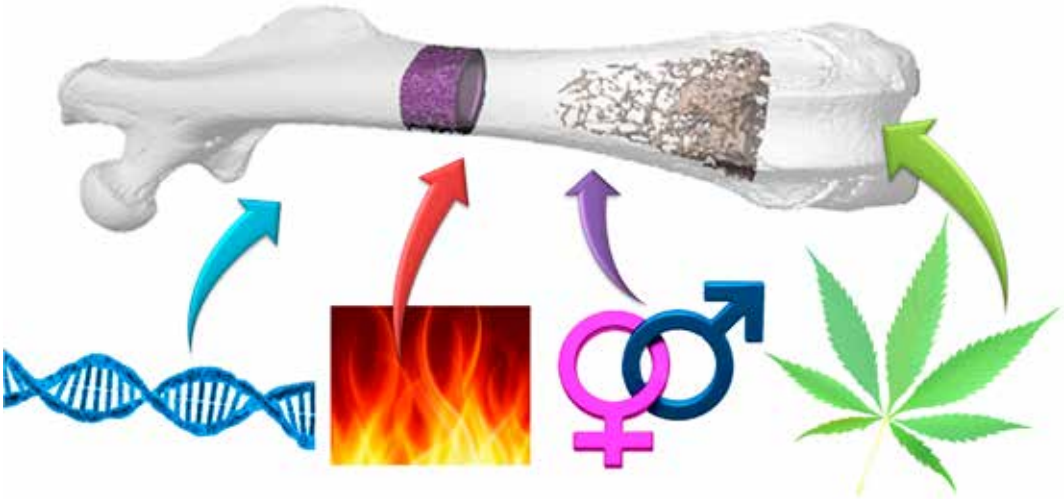
Genetics: Our laboratory focuses on the genetic and hormonal regulation of bone remodeling, microarchitecture and strength. These traits have a high degree of heritability, and one aspect of our research is to characterize new genetic determinants of bone remodeling as well as elucidate the mechanism of action of selected genes. Our GWAS confirmed the role of AVP (vasopressin) and OXT (precursor of oxytocin) in bone and identified for the first time Rhbdf2 as a significant determinant of bone structure.

Sex hormones: We investigate the actions of sex hormones with an emphasis on the skeletal dimorphism between males and females, and their interaction with other genes and transcription factors.

Erythropoietin: Epo is the main hormone that regulates blood cells production. We are investigating the role of Epo in bone remodeling in general and on the bone cells in particular.

Inflammation-induced osteolysis: Today, most dental implants undergo surface roughening to enhance osseointegration. However, ultrasonic scaling performed routinely for oral hygiene releases particles from titanium implants. We found that these particles stimulate the secretion of inflammatory cytokines and induce osteoclastogenesis in vitro and in vivo.

Cannabinoids: Cannabis-derived and endogenous cannabinoids are important regulators of bone cells. We investigate the beneficial actions of cannabinoids in bone fracture healing, osteoporosis, Osteogenesis Imperfecta, and inflammation-induced bone destruction.



Regulation of bone turnover and microstructure by genetic determinants, inflammation, sex hormones and cannabis/endocannabinoids.

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Chapter

Smith P, Avishai G, Müller R, and **Gabet Y**. Computerized Reconstruction of Prenatal Growth Trajectories in the Dentition: Implications for the Taxonomic Status of Neanderthals. In S. Condemi and G.-C. Weniger (eds.), Continuity and Discontinuity in the Peopling of Europe: One Hundred Fifty Years of Neanderthal Study, Vertebrate Paleobiology and Paleoanthropology, Springer Science+Business Media B.V. 2011.

Grants

2012-2017	Israel Science Foundation (ISF) Grant
2015-2016	American Society for Bone and Mineral Research GAP Award
2015-2017	American Society for Bone and Mineral Research GAP Award
2015-2016	Y.D. Investments Ltd
2015-2017	Kalytera Therapeutics Ltd
2016-2017	Israel Cancer Association (co-PI)

Prof. Israel Hershkovitz, Ph.D.

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Evolutionary Medicine, Paleopathology and Bio-history

Position

Professor, Sackler Faculty of Medicine

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

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

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.

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137. N. Steinberg, I. Siev-Ner, S. Peleg, G. Dar, Y. Masharawi, A. Zeev and **I. Hershkovitz**. Injury patterns in young, non-professional dancers. *J Sports Sci* 2011, 29:47-54.

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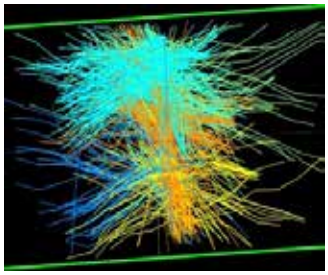
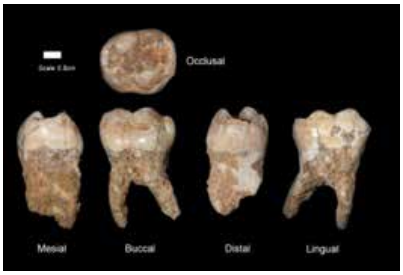


3D reconstruction of the annulus fibrosus, MRI study. Disc herniation project.



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

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

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Prof. Michael M. Kozlov, Ph.D.

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Theoretical Biophysics of Membranes and Cytoskeleton

Position

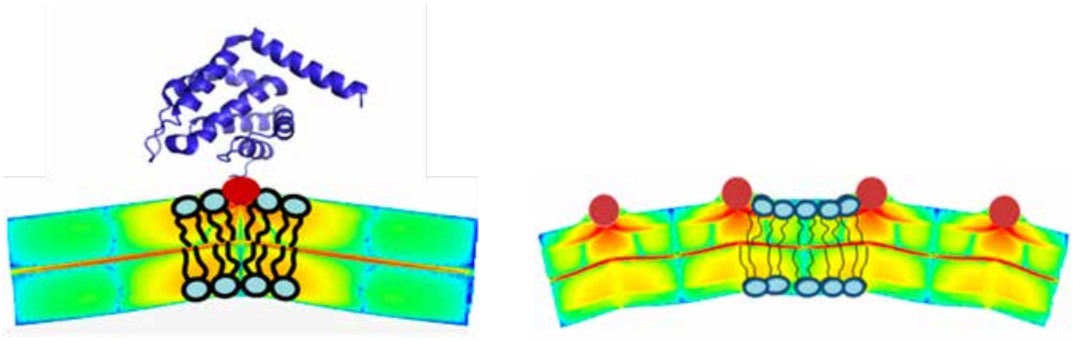
Professor, Sackler Faculty of Medicine

Joseph Klafter Chair in Biophysics

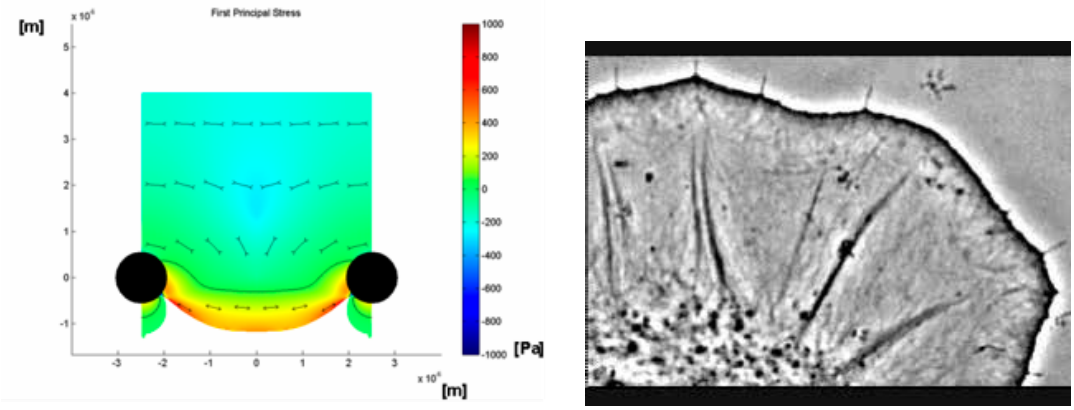
Research

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).

Publications

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G. Fabrikant, S. Gupta, G.V. Shivashankar, **M.M. Kozlov**. Model of T-cell nuclear deformation by the cortical actin layer. *Biophys J*. 105:1316-23, 2013

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A.D. Lieber, Y. Schweitzer, **M.M. Kozlov,** K. Keren. Front-to-rear membrane tension gradient in rapidly moving cells. *Biophys. J*. 108:1599-1603, 2015.

Y.H. Tee, T. Shemesh, V. Thiagarajan, R.F. Hariadi, K.L. Anderson, C. Page, N. Volkmann, D. Hanein, S. Sivaramakrishnan, **M.M. Kozlov**, A.D. Bershadsky. Cellular chirality arising from the self-organization of the actin cytoskeleton. *Nature Cell Biol*. 17:445-457, 2015.

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Reviews

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L.V. Chernomordik, **M.M. Kozlov**. Myoblast fusion: playing hard to get. *Dev. Cell*. 32(5): 529-530, 2015.

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Dr. Hila May, Ph.D.

Department of Anatomy and Anthropology
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

mayhila@post.tau.ac.il

Laboratory for Bio-History and Evolutionary Medicine

Position

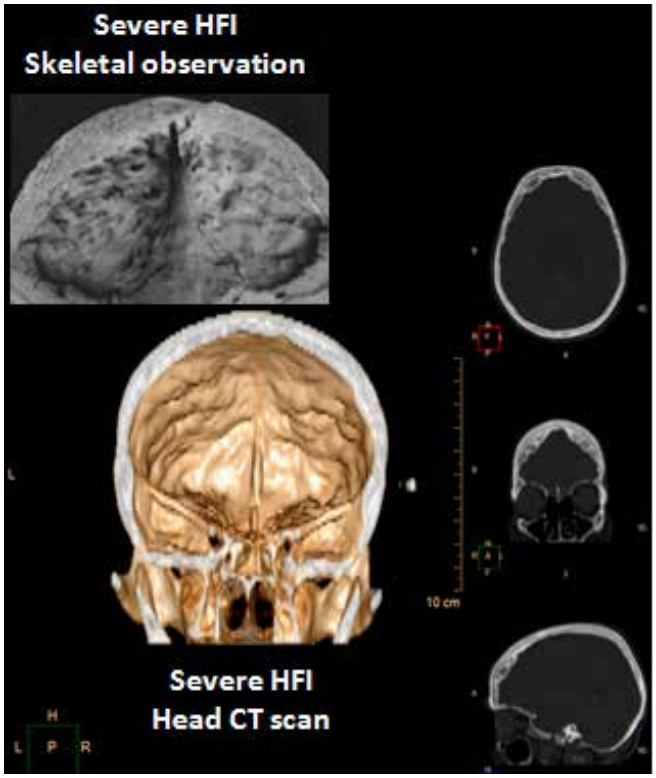
Lecturer

Research

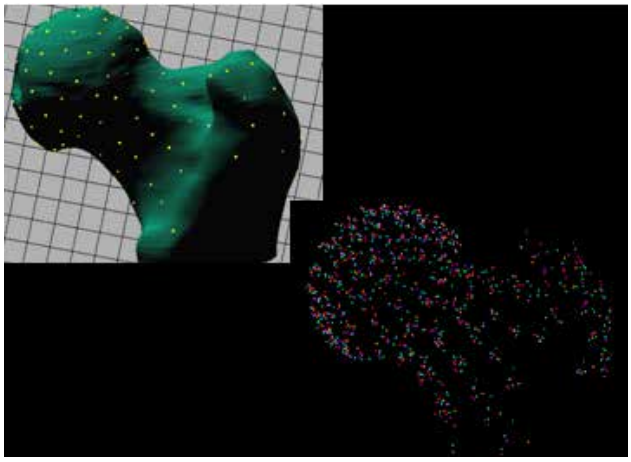
Inter-disciplinary laboratory focusing on two major topics: evolutionary history of anatomical systems and their impact on current population health, and reconstruction of ancient populations' daily life, based on their skeletal remains, with emphasis on the interaction between genetic and socio-cultural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

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

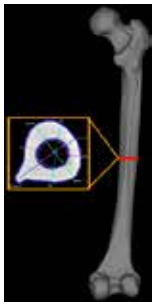
Reconstructing past population daily life: revealing daily activities of prehistoric and historic populations is a challenging task considering the evidence at hand (bones). Nevertheless, bones may furnish us with information otherwise not available, e.g., division of labor, social stratification, intensity 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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Prof. Ruth Shalgi, Ph.D.

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Reproduction in Animal Models and in Humans

Positions

Professor, Sackler Faculty of Medicine

Gabriel Pinkas Chair for the Prevention and Diagnosis of Congenital Anomalies

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

Haberman, Y., Tsaadon, L., Eliyahu, E., and **Shalgi, R.** Receptor for activated C kinase (RACK) facilitates protein kinase C (PKC) mediated cortical granules exocytosis (CGE). *Theriogenology*, 75: 80-9, 2011.

Levi, M., Maro, B. and **Shalgi R.** The conformation and activation of Fyn kinase in the oocyte determine its localization to the spindle poles and cleavage furrow. *Reprod Fertil Dev*. 23: 846-857, 2011.

Bar-Joseph, H., Ben-Aharon, I., Stemmer, S.M., Tzabari, M. and **Shalgi, R.** Novel *in vivo* imaging of acute chemotherapy-induced vascular toxicity. *PLoS One*, 9: e23492, 2011.

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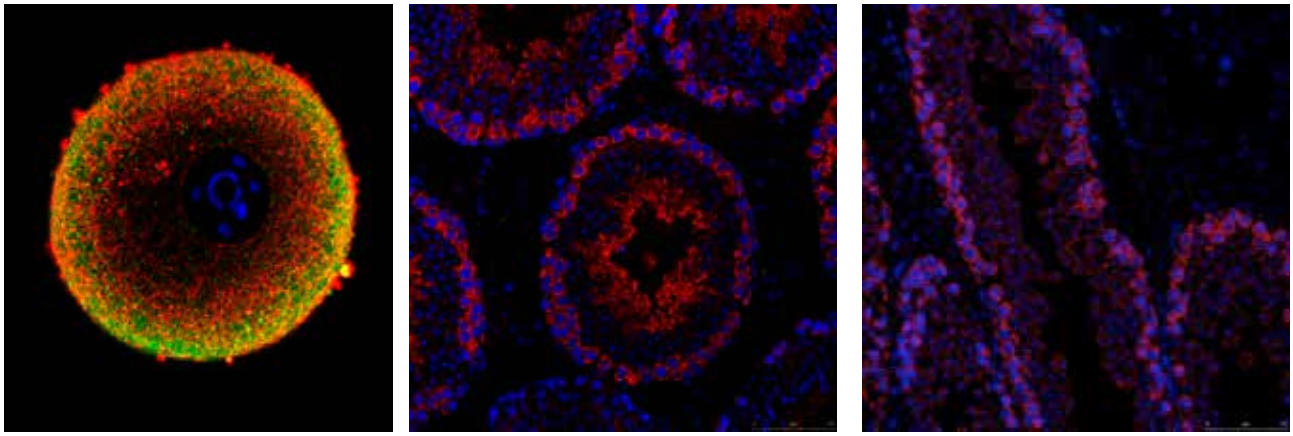

Left panel- Human oocyte stained for DNA (blue); cytoskeleton (tubulin; red); protein (Fyn kinase; green). Arrow – Germinal vesicle (genetic material); C- Cytoplasm. Confocal microscopy. Right panels -Section of sperm producing tubules in mouse testis before (left) and after treatment with chemotherapy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

Eliyahu, E., Shtraizent, N., **Shalgi, R**. and Schuchman, E. H. cation of cystatin SA as a novel inhibitor of acid ceramidase. *J Biol Chem*. 286:35624-33, 2011.

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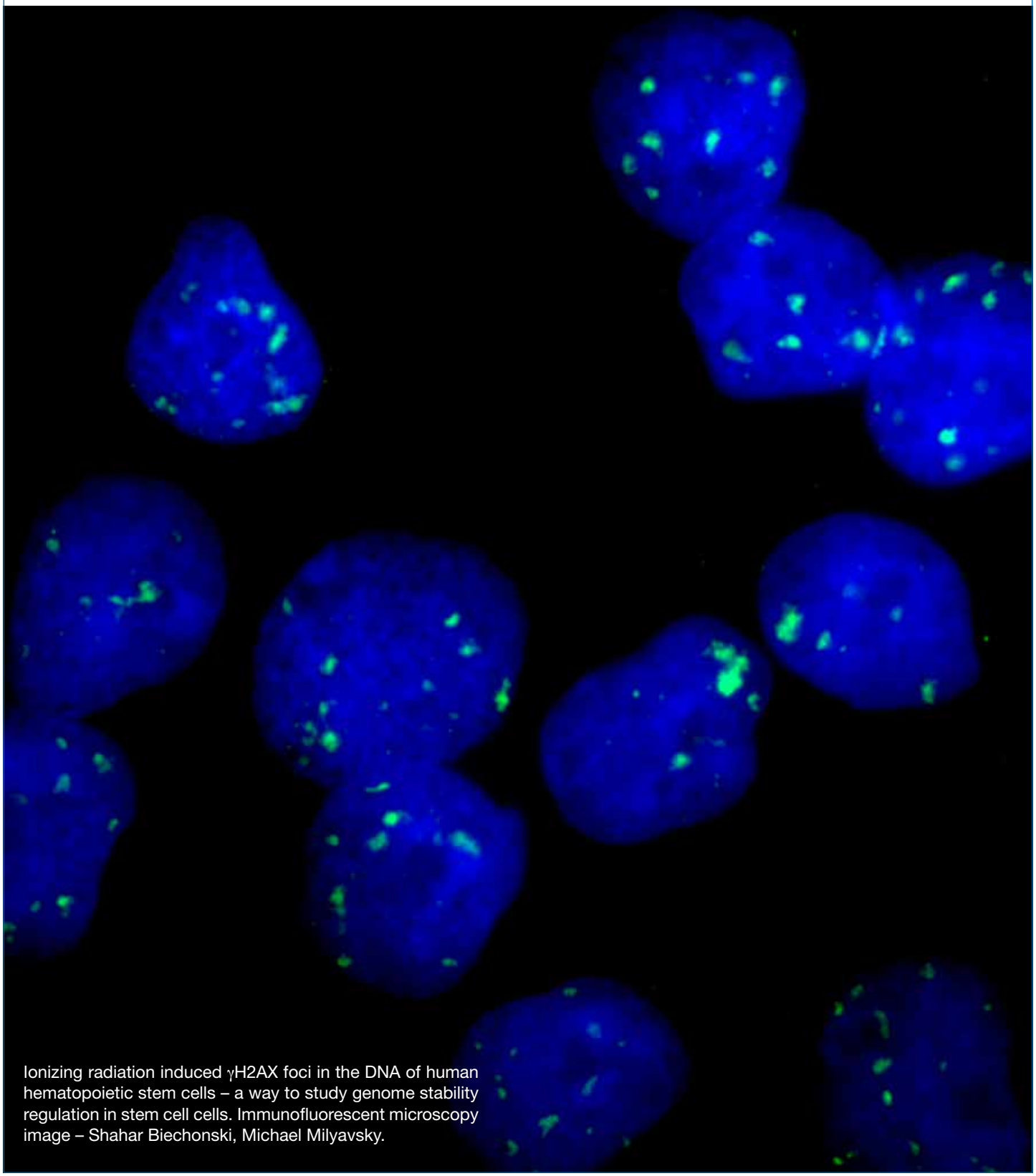
Grants

2014-2018	Israel Science Foundation (ISF) – Post transcription regulation of Fyn kinase by miR-125a-3p in the ovary – potential relevance to ovarian function
2015-2016	Lau Mintz Foundation, Sackler School of Medicine, TAU – The role of miR-125a-3p and Fyn in oocytes' meiosis
2016-2017	Israel Cancer Association – miR-125a-induced cellular switch elicits a response to anti-HER2 targeted therapy in cancer cells
2016-2017	The Colton Foundation. PEDF for the treatment for uterine fibroids.

Stem Cells and Regenerative Medicine



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.

Prof. Dafna Benayahu, Ph.D.

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Sackler Faculty of Medicine

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Musculoskeletal – Stem cells and Nanotechnology

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Cell and Developmental Biology

Research

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

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

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Mandelberg Y, **Benayahu D**, Benayahu Y. Octocoral Sarcophyton auritum Verseveldt & Benayahu, 1978: Microanatomy and Presence of Collagen Fibers. Biol Bull. 2016;230(1):68-77.

Grants

2012 -2016	Israel Science Foundation Jointly with A. Gefen
2015-2017	Ministry of Science Cooperation , Israel-china
2016-2019	Ministry of Science Cooperation, Jointly with Prof. R. Haj-Ali
2016-2020	Israel Science Foundation, Jointly with Prof. A. Gefen

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Modeling the Nervous System in Development and Disease Using Pluripotent Stem Cells

Position

Lecturer, Sackler Faculty of Medicine

Research

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

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

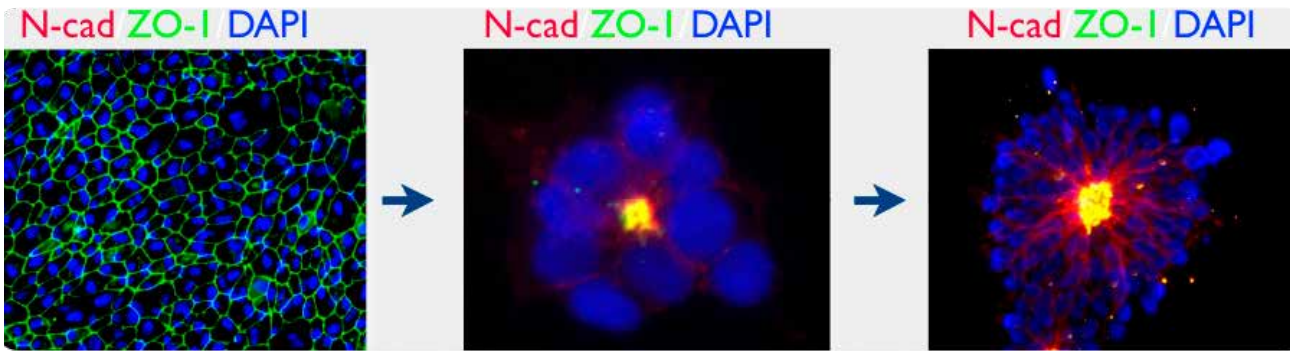
Our main goal is to learn the biology of early neural stem cells in the lab in order to develop strategies for standardizing their growth in culture without loss of differentiation potential. Such continuously self renewing cells will serve as a *gold standard NSCs* for studying nervous system development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

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

Publications

Lipchina I, **Elkabetz Y**, Hafner M, Sheridan R, Mihailovic A, Tuschl T, Sander C, Studer L, Betel D. Genome-wide identification of microRNA targets in human ES cells reveals a role for miR-302 in modulating BMP response. *Genes Dev.* 2011; 25:2173-86.

Lafaille FG, Pessach IM, Zhang SY, Ciancanelli MJ, Herman M, Abhyankar A, Ying SW, Keros S, Goldstein PA, Mostoslavsky G, Ordovas-Montanes J, Jouanguy E, Plancoulaine S, Tu E, **Elkabetz Y**, Al-Muhsen S, Tardieu M, Schlaeger TM, Daley GQ, Abel L, Casanova JL, Studer L, Notarangelo LD. Impaired intrinsic immunity to HSV-1 in human iPSC-



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

derived TLR3-deficient CNS cells. 2012. *Nature* 2012; 491:769-73.

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

Ziller MJ*, Edri R*, Yaffe Y, Donaghey J, Pop R, Mallard W, Issner R, Gifford CA, Goren A, Xing J, Gu H, Cacchiarelli D, Tsankov AM, Epstein C, Rinn JL, Mikkelsen TS, Kohlbacher O, Gnirke A, Bernstein BE, Elkabetz Y.**, Meissner A.** Dissecting neural differentiation regulatory networks through epigenetic footprinting. Nature 518, 355-9 (2014). **Equal corresponding author

Grants

2013-2016 Morasha, Modeling pathogenesis of cerebral disorders

Dr. Chen Luxenburg, Ph.D.

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The Mechanobiology of Tissue Development Homeostasis and Disease

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

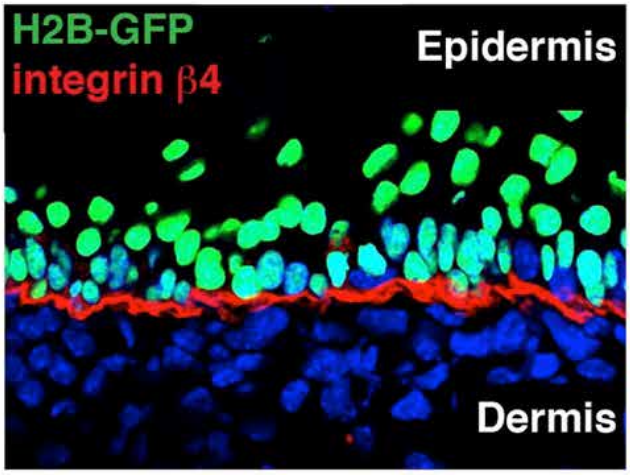
Our lab uses the mouse skin epidermis as a model system to study how mechanical and geometrical cues regulate morphogenesis, affect gene expression and contribute to cell fate determination during development, homeostasis and disease. The skin is an ideal model system for these studies for the following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

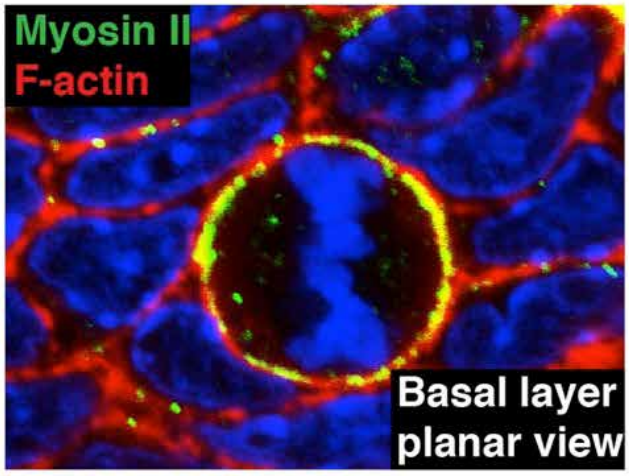
Publications

Luxenburg C, Pasolli HA, Williams SE, and Fuchs E. (2011) Developmental roles for Srf, cortical cytoskeleton and cell shape in epidermal spindle orientation. *Nat. Cell Biol*. 13:203-14

Luxenburg C, Winograd-Katz S, Addadi L, and Geiger B (2012) Involvement of actin polymerization in podosome dynamics. *J. Cell Sci*, 125, 1666-1672

Luxenburg C, Heller E, Pasolli HA, Chai S, Nikolova M, Stokes N, Fuchs E. Wdr1-mediated cell shape dynamics and cortical tension are essential





Left hand side**:** On top of classic mouse genetic tools we use state of the art *in utero* injections of lentivirus (H2B-GFP+ cells in the epidermis) to manipulate gene expression in epidermal stem cells/progenitors early in embryonic development, before cell fate specification.
Right hand side**:** Whole mount image of embryonic epidermis showing an early mitotic cell and its interphase neighbors in planar view. Note the dramatic differences in cell shape. We demonstrated that mitotic rounding is important for cells ability to orient their spindle and undergo asymmetric cell division.

for epidermal planar cell polarity. *Nat Cell Biol*. 2015;17:592-604.

Zaidel-Bar R, Zhenhuan G, **Luxenburg C**. The contractome--a systems view of actomyosin contractility in non-muscle cells. *J Cell Sci.* 2015;128:2209-17.

Grants

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

2015-2020 Israel Science Foundation (ISF) Grant

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DNA Damage Response in Normal and Leukemia Hematopoietic Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

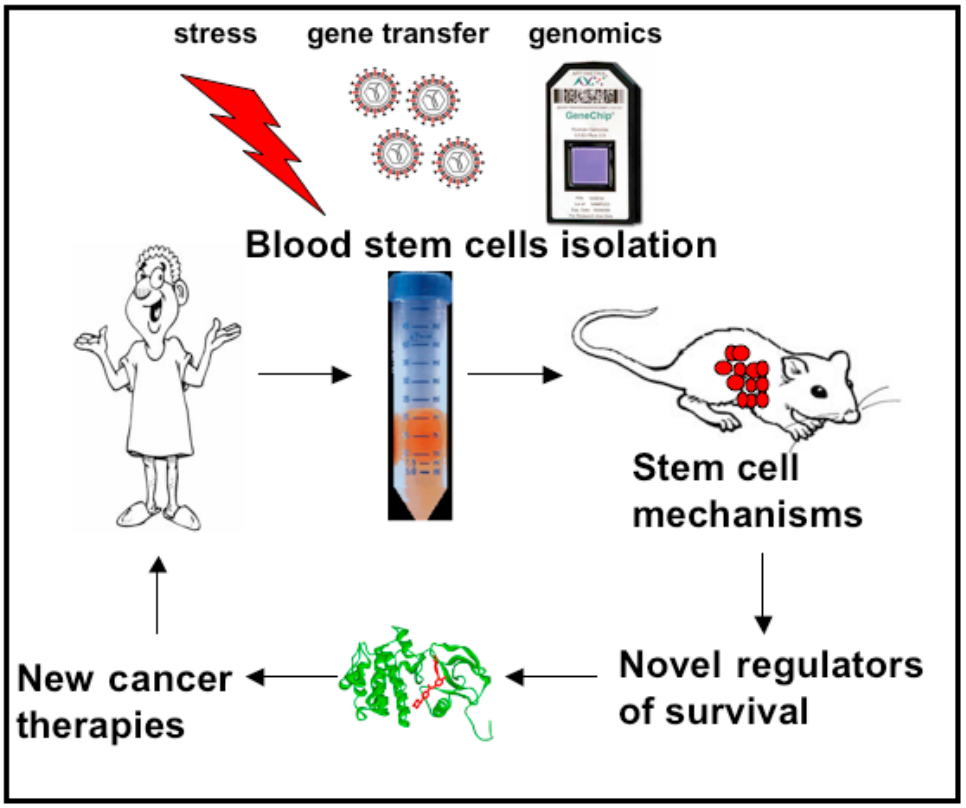
Research

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

Chan G, Cheung LS, Yang W, **M. Milyavsky**, Sanders AD, Gu S, Hong WX, Liu AX, Wang X, Barbara M, Sharma T, Gavin J, Kutok JL, Iscove NN, Shannon KM, Dick JE, Neel BG, Braun BS. 2011. Essential role for Ptpn11 in survival of hematopoietic stem and progenitor cells. *Blood* 117:4253-61.

Louria-Hayon I., Ruston J.C.F., , Gish G, Jin J, Kofler M. M., Lambert J-P., Adissu H. A., **Milyavsky M**,



Herrington R., Minden M. D., Dick J. E., Gingras A-C., Iscove N. N., and T. Pawson. 2013. The Lnk adaptor suppresses radiation resistance and radiation-induced B-cell malignancies by inhibiting IL-11 signaling. *Proc Natl Acad Sci USA* 110: 20599-604.

Milyavsky M, Gole B, Wiesmüller L. Replication stress in MLL-rearrangements.*Oncoscience*. 2015;2:938-9.

Review

Biechonski, S., and M. Milyavsky. 2013. Differences between human and rodent dna-damage response in hematopoietic stem cells: at the crossroads of self-renewal, aging and leukemogenesis. *Transl Cancer Res* 2:372-383.

Grants

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

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