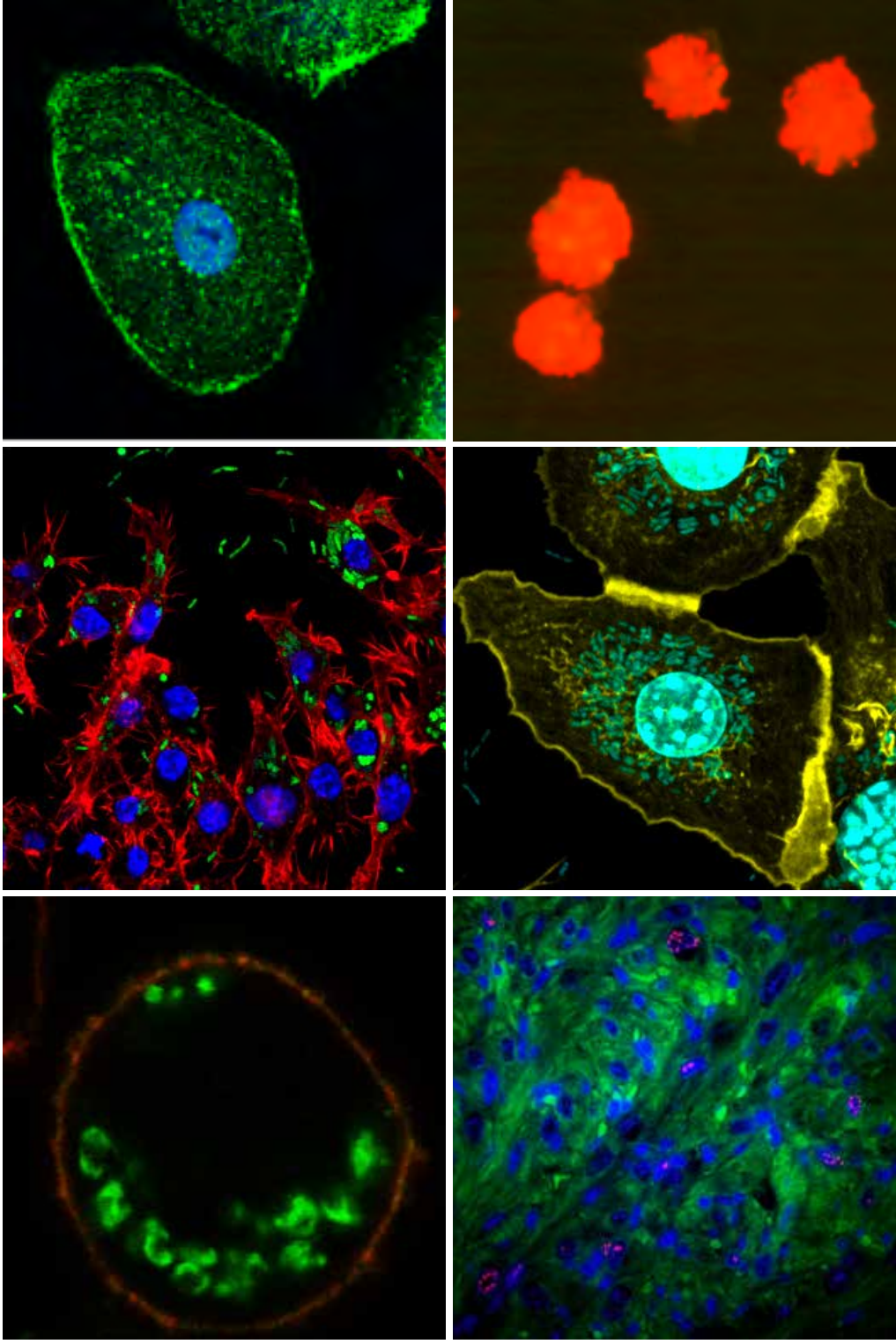

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine

Clinical Research 2021

Sections

Cover images (from bottom left, clockwise):

Image 1: Staining of a novel anti-frizzled7 monoclonal antibody directed at tumor stem Cells. Credit: Benjamin Dekel lab.

Image 2: Growing adult kidney spheroids and organoids for cell therapy. Credit: Benjamin Dekel lab.

Image 3 & 4: Vibrio proteolyticus bacteria infecting macrophages. Credit: Dor Salomon.

Image 5: K562 leukemia cells responding to complement attack (red-complement C9, green-mitochondrial stress protein mortalin) Credit: Niv Mazkereth, Zvi Fishelson.

Image 6: Cardiomyocyte proliferation in newborn mouse heart by phosphohistone 3 staining (purple). Credit: Jonathan Leor.

Editor: Prof. Karen Avraham
Graphic design: Michal Semo Kovetz, TAU Graphic Design Studio
June 2021

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 clinical 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, Prof. Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Ami Fishman, Prof. Arnon Wiznitzer, and Assistant to the Dean, Michal Gilboa.

TEL AVIV UNIVERSITY

Table of Contents

Cancer

K562 leukemia cells responding to complement attack
(red-complement C9, green- Rab11, blue- mitochondria mitotracker)
Credit: Niv Mazkereth, Zvi Fishelson

Prof. Nadir Arber, M.D., M.Sc., MHA

Integrated Cancer Prevention Center
Djerassi Oncology Center
Tel Aviv Sourasky Medical Center

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Dr. Shiran Shapira, Ph.D.

Head – Research Laboratory

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Cancer Prevention Research Laboratory

Positions

Professor of Medicine & Gastroenterology

Yechiel and Helen Leiber Professor for Cancer Research

Chair, Israeli Gastroenterological Association

Head, Integrated Cancer Prevention Center, Tel Aviv Sourasky Medical Center

Head, Promotion Center and Integrated Cancer Prevention Center Head, Djerassi Oncology Center

Former head, Cancer Research Center, Tel Aviv University

Former head, Dotan Center for Hemato-oncology, Tel Aviv University

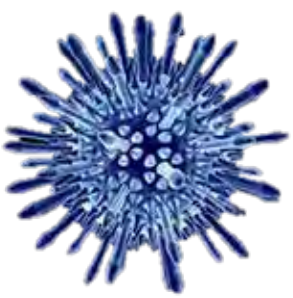
Research

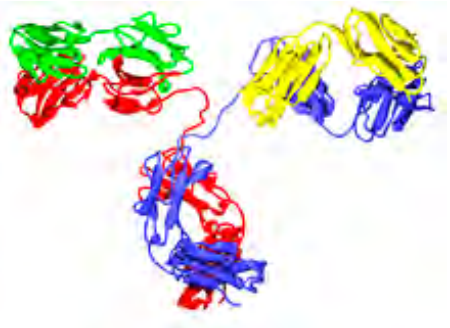
Laboratory of Molecular Biology – ICPC

The Integrated Cancer Prevention Center (ICPC) has diverse and broad experience in translational research focused on early detection, prevention and therapy of cancer, particularly in tumors of the gastrointestinal (GI) tract. The team is highly experienced in clinical studies, molecular epidemiology as well as in molecular and cell biology studies of cancer.

Currently, on-going researches at the ICPC focus on translational research, bridging between basic researches in the lab and clinicians and patients in the clinical center. The center has a long history of planning, developing, and conducting clinical trials, with a main focus on investigator-initiated and cooperative group trials investigating the activity of drugs for the prevention and treatment of colorectal cancer (CRC).

Basic research takes place at the Laboratory of Molecular Biology, headed by Dr. Shiran Shapira, a senior scientist and member of the academic staff at Tel Aviv University. Dr. Shapira devotes herself to cancer research in the fields of early detection, prevention, and cancer therapy. She possesses extensive experience in wide range of biology areas





with foucing on cancer research, biochemistry, molecular biology, signal transduction, antibody engineering, protein expression and purification and gene delivery.

Research Team

Prof. Nadir Arber, MD, MSc, MHA, Head of ICPC; Dr. Shiran Shapira, PhD, Head of Laboratory; Dina Kazanov, MSc; Dr. Eliezer Liberman, MD; Ilana Bostenai, PhD student; Ahmad Fokra, PhD student; Sally Zigdon, MSc; Lina Tiklan

Projects

1. Early detection – development of new methods for the early detection of CRC and colorectal adenomas as well as other types of solid and hematological cancers. The tested samples taken from humans, blood and urine.

2. Prevention – Serving as the PI of several international, multicenter trials in the prevention of GI tumors, and in particular sporadic and familial CRC.

3. Identifying high risk subjects through molecular epidemiology – We have identified a new polymorphism in the APC gene (E1317Q), which is more common in Sephardic Jews and Arabs and is associated with a HR of ~4. When it is combined with another polymorphisms in the CD24 gene (V248A) the OR is 7.8.

4. Detection of new oncogenes that play a role in the multistep process of CRC carcinogenesis.

The research team at the Laboratory of Molecular Biology has been exploring, for several years, the hypothesis that CD24 is a potential oncogene in GI malignancies and may serve as a biomarker and target for the treatment of cancer and cancer-related chronic inflammatory disorders such as, inflammatory bowel diseases (IBD).

5. Treatment – Development of novel therapeutic strategies for cancer treatment with a main focus on immunotherapy using humanized anti-CD24 monoclonal Abs, immunotoxin and bi-specific

6. Design of novel therapeutic agents targeting Ras and Wnt pathways that play an important role in GI carcinogenesis, based on gene therapy using adenoviruses and highly sophisticated viral vectors such as adenoviruses, lentiviruses and adeno-associated viruses.

7. Wound healing- CD24 may represent a novel clinical intervention strategy to accelerate the healing of wounds both acute and chronic injuries for patients. The proposed treatment may enable faster recovery from injuries while reducing the risk of infection, toxicity and other possible side

Publications

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Prof. Osnat Ashur-Fabian, Ph.D.

Translational Oncology; Meir Medical Center
Department of Human Molecular Genetics and Biochemstry, Sackler Faculty of Medicine

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Investigating Hormone Metabolism in Cancer

Positions

Associate Professor, Sackler Faculty of Medicine

Principle Investigator, Translational Oncology Laboratory, Sapir Medical Center, Kfar- Saba

Research

Our research deals with the role of thyroid hormones in cancer progression and on the development of a novel class of targeted cancer therapy. A set of small molecules that specifically block the thyroid-cancer axis were developed. Our research group is the first to show the potent elimination of various cancer types by these novel drugs.

Publications

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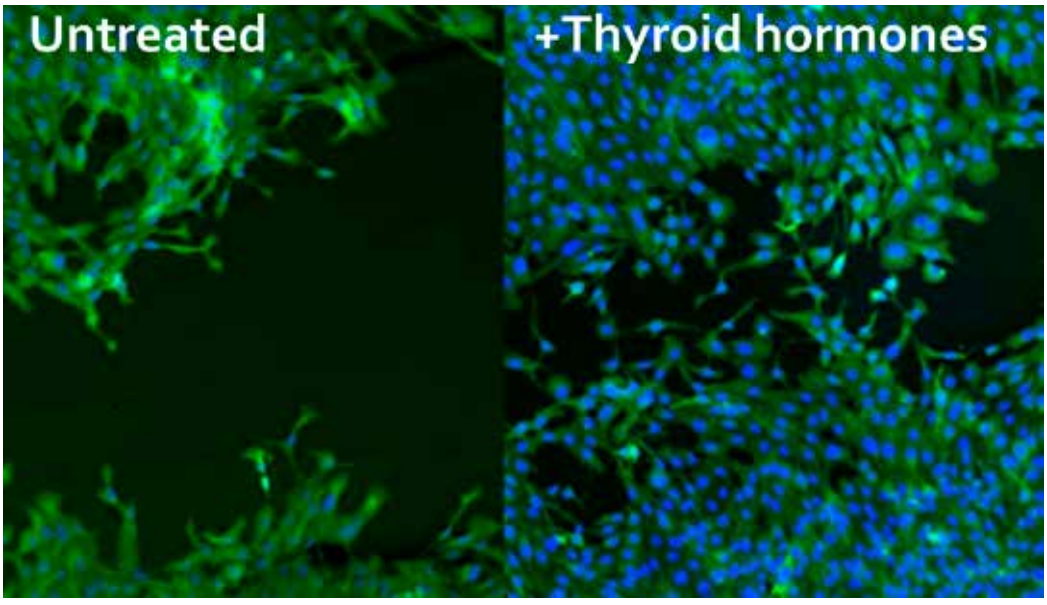

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Prof. Iris Barshack, M.D.

Department of Pathology
Sheba Medical Center, Tel-Hashomer

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Investigating Markers of Inflammation and of Neoplastic Processes for Diagnosis and Treatment

Positions

Professor of Pathology

Vice Dean, Head of School of Medicine, Sackler Faculty of Medicine, Tel Aviv University

Head, Department of Pathology

Co-director, Tumor Tissue Bank, Molecular Diagnostic Service, Precision Medicine Project (diagnostic service), Digital Pathology Project, Sheba Medical Center, Tel Hashomer

Research

The profession of Pathology encompasses three main constituents: diagnostics, teaching and research. Within the department, description, processing and examination of the macroscopic specimen is performed by the doctors of the department. The specimens undergo histochemical staining. If necessary for the sake of diagnosis, additional specialized histochemical and immunohistochemical stains are carried out. Furthermore, the department executes other techniques that enable precise diagnosis such as: FISH, PCR, In-situ hybridization and Electron Microscopy visualization. The department delves in a large array of research projects with the cooperation of other departments within and outside of the hospital, and intrinsic research of the department itself.

The department encompasses a laboratory specific for histochemical staining, a laboratory for immunohistochemical staining that performs in-situ hybridization, as well as a laboratory for PCR, Electron Microscopy, FISH and for Molecular Pathology. Moreover, we are leading the tumor tissue bank of the Sheba Medical Center, and the Molecular Diagnostic Service of the Sheba Medical Center, using an advanced NGS platform for diagnostic and research purposes. We also perform on a routine and research basis immunohistochemical stainings and molecular methods for precision medicine and immunotherapy. Furthermore, the department includes an advanced system for photographing and processing both macroscopic and microscopic constituents, and leads the Digithal Pathology Project of the Sheba medical Center.

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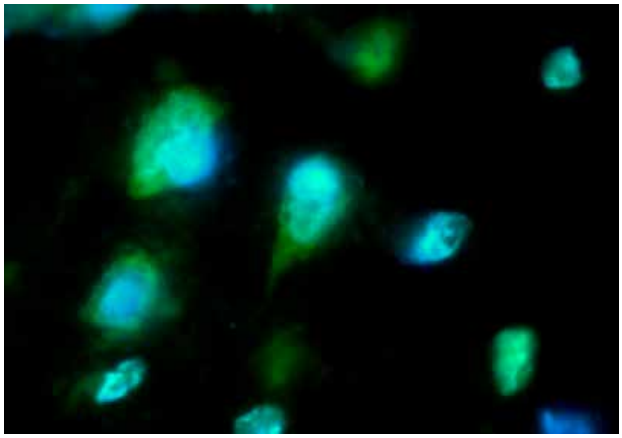

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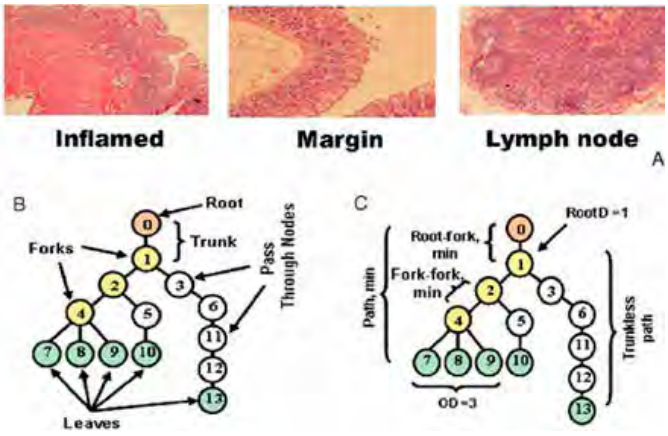

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Another branch is that of independent research. One of the great accomplishments has been the conceptual implementation of the use of microRNAs to aid in the identification of different tissues and the application of this knowledge to identify metastases of unknown origin. In situ hybridization of microRNAs is an important methodology used in our research for studing the pathogenesis of inflammatory and of neoplastic processes. Another area of research in which the department is leading is the development of the technology of tissue microarrays. The department leads the investigation of inflammatory processes and lymphoproliferative tumors according to the production and study of heavy chain B lymphocytes within the tissue. In light of this investigation, the department received a number of important research grants.

Publications

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Prof. Yair Herishanu, M.D.

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Investigating the Microenvironment Interactions and B-cell Receptor Signaling in Chronic Lymphocytic Leukemia

Positions

Associate Professor, Sackler Faculty of Medicine

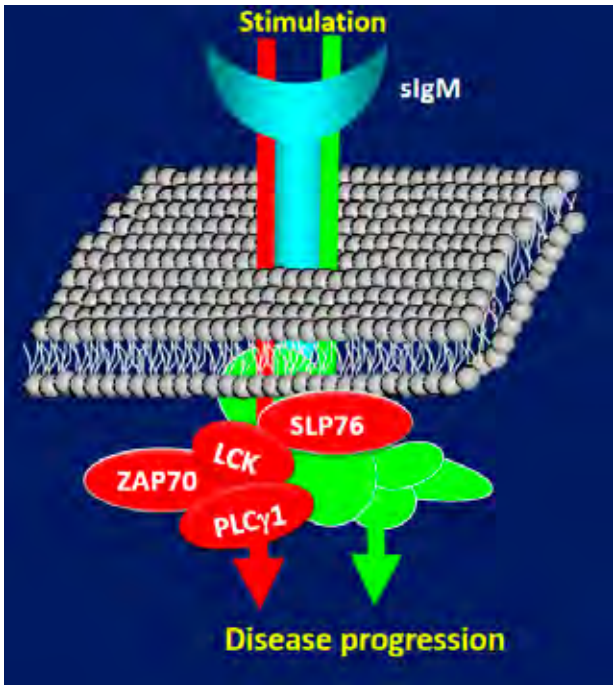
Head, CLL Service, Tel Aviv Sourasky Medical Center

Secretary, Israeli CLL Study Group

Committee Member, Israel Society of Hematology

Research

We study interactions between the CLL cells and the tissue microenvironment and explore new aspects of the B-cell receptor (BCR) signaling in CLL cells. Our previous work characterized distinct *in vivo* gene expression signatures of CLL cells derived from the different compartments of blood, bone marrow and lymph nodes. Recently, we have shown that SLP76, an adaptor protein of the T-cell receptor pathway, is ectopically expressed in CLL cells and mediates alternative signaling downstream of the BCR (Figure). Our research is aimed to discover novel targets of therapy of CLL. Our group is well experienced in performing cell biology assays, flow cytometry and image analysis, protein analysis and gene silencing in primary CLL cells, and is highly skillful in studying signaling in CLL cells.



CLL cells ectopically express T-cell receptor associated signaling molecules, which potentiates their B-cell receptor responsiveness.

Publications

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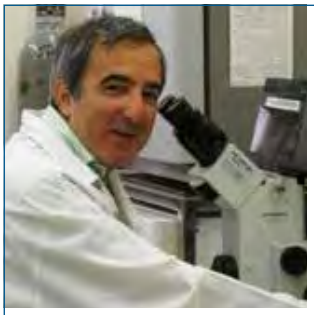
Grants

2019-2023	Israeli Science Foundation (ISF), Dissection of the mechanism governing the B-cell receptor function in chronic lymphocytic leukemia as a key regulator of disease progression
2020-2021	Israel Cancer Association, Spatial and dynamics of early B-cell receptor signaling and actin cytoskeleton in CLL cells
2020-2021	Weizmann Institute-TASMC Joint grant-novel approaches to target the B-cell receptor signaling in CLL



Prof. Shai Izraeli, M.D.

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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

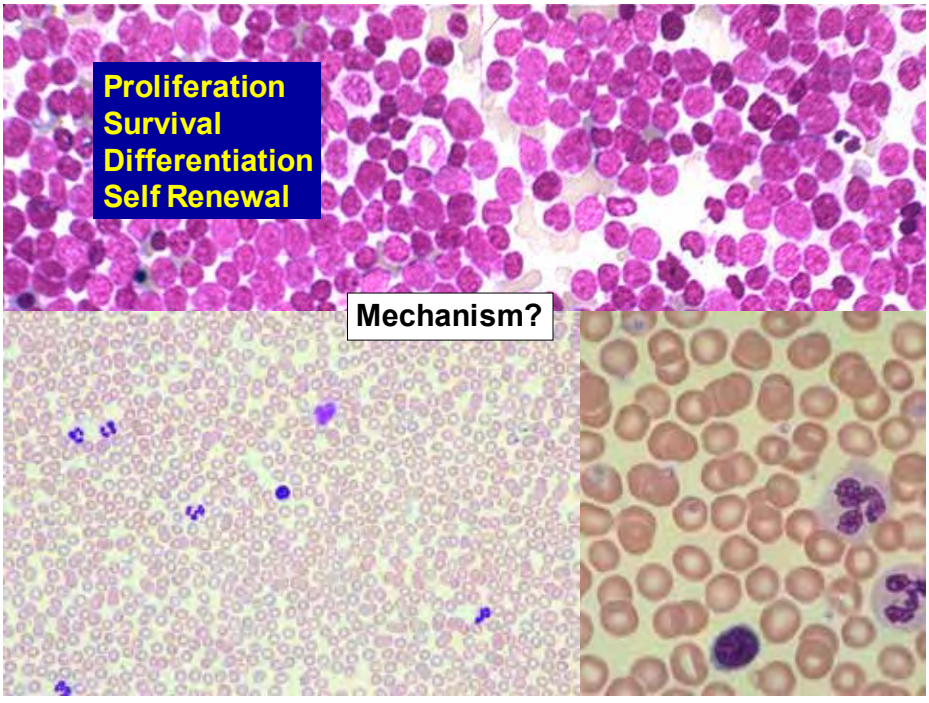
We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

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.



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

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

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

Publications

David, A., H. Amartely, N. Rabinowicz, M. Shamir, A. Friedler, and **S. Izraeli**. Molecular basis of the STIL coiled coil oligomerization explains its requirement for de-novo formation of centrosomes in mammalian cells. *Sci Rep*, 2016. **6**: 24296.

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Reviews

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Grants

2016-2019 German Israel Foundation

Dr. Ben Zion Katz, Ph.D.

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Development of B-Cell Malignancies

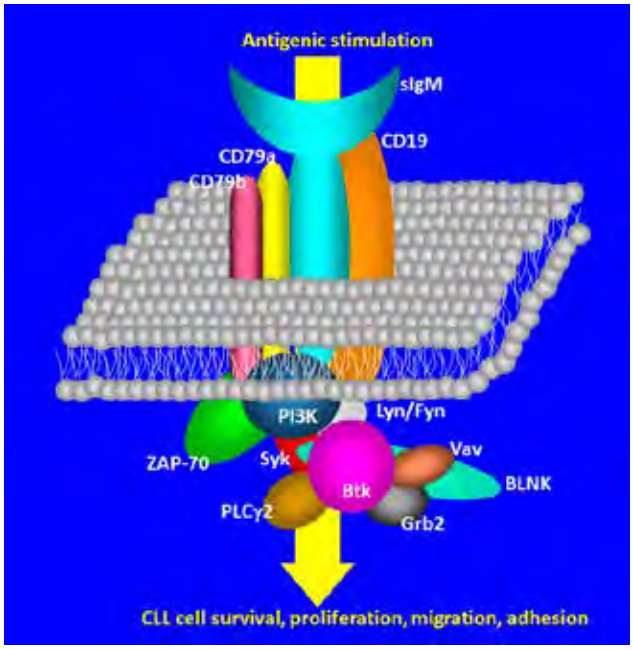
Positions

Senior Lecturer, Sackler Faculty of Medicine

Deputy Director, The Hematology Laboratory, Tel Aviv Sourasky Medical Center

Research

The focus of the research in the laboratory is on B-cell malignancies, their developmental processes, and the clinical significance of the malignant B-cells physiological and molecular phenotypes. We utilize a wide range of both clinical and basic research laboratory techniques, and study tissue culture model systems, as well as primary patient-derived samples.



Specific research programs
A) The role of microenvironmental interactions in the pathogenesis of chronic lymphocytic leukemia.
B) The function of CD19 and CD38 in the physiology of malignant B-cells.
D) Development of novel laboratory methodologies to study B-cell malignancies
The complexity of the B-cell receptor.

Publications

Dezorella, N., Kay, S., Baron, S., Shapiro, M., Porat, Z., Deutsch, V., Herishanu, Y., **Katz, B.-Z**. *Measurement of lymphocyte aggregation by flow cytometry-physiological implications in chronic lymphocytic leukemia.* (2016) Cytometry B Clin. Cytom. 90:257-266.

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Dr. Guy Lahat, M.D.

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Tumor-Microenvironment Cellular Interactions in Cancer Progression and Metastasis

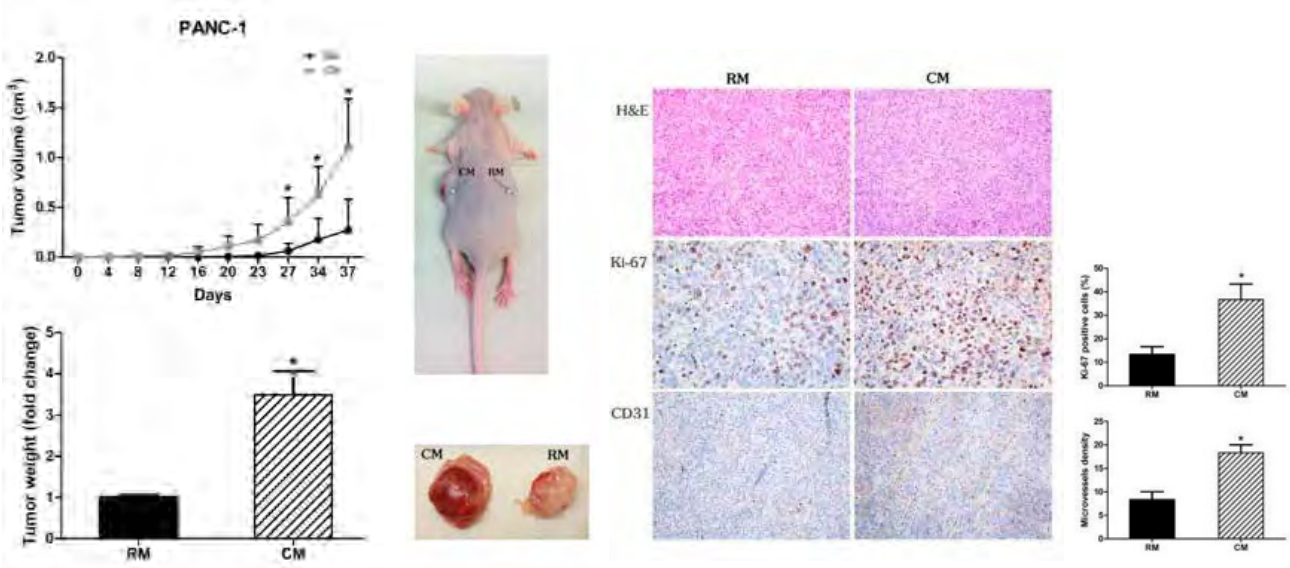
Positions

Chair, Department of Surgery A

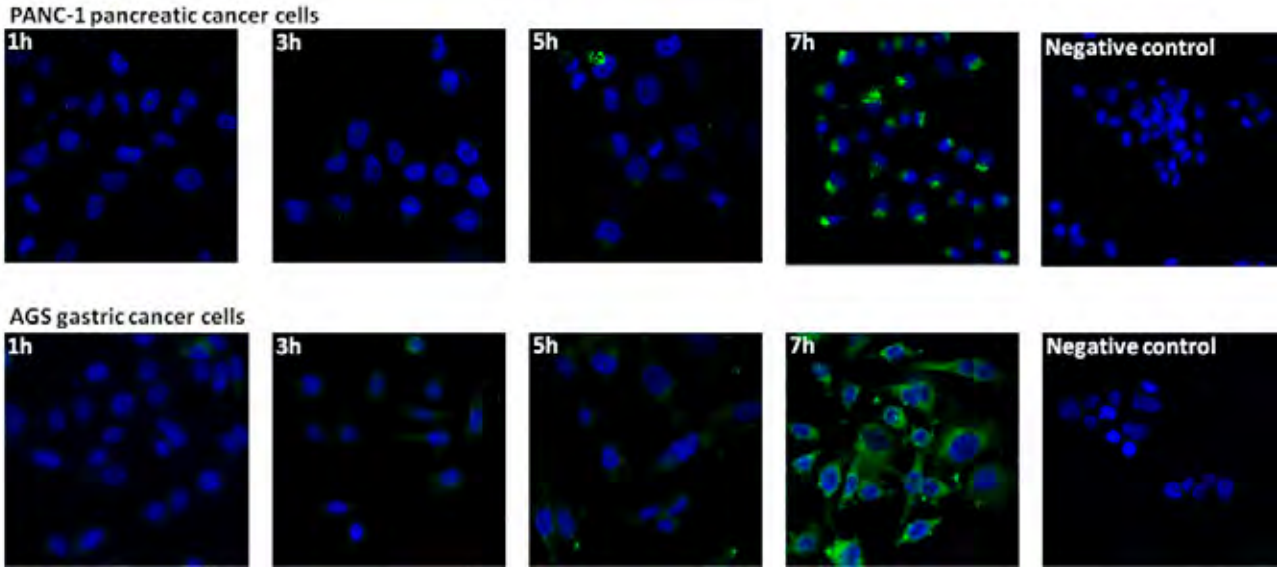
Senior Lecturer, Sackler Faculty of Medicine

Research

The surgical oncology research lab was established in order to conduct clinical and basic science research in order to further understand disease patterns and mechanisms, thus, trying to improve diagnosis and treatment outcomes of the patients we operate on. Moreover, the lab is a platform for the development of future academic surgeons, passionate about both research and the field of surgery. We focus on patient-driven translational research, studying the molecular basis of various soft tissue sarcoma (STS) tumors, and gastrointestinal malignancies. We aim to explore distinct signaling pathways and molecules that may play a role in cancer progression and metastasis. Specifically, we investigate the cross talk between metastatic GI cancer cells and the omentum. We also investigate the potential role of miRNAs as molecular biomarkers for staging, prognosis, and pattern of future spread. For these purposes we frequently utilize in-vitro and in-vivo models, human cancer specimens from our clinically annotated tissue bank, as well as various advanced molecular and bioinformatic approaches.



Tumor growth is promoted by omental fat in vivo. PANC-1 pancreatic cancer cells were initially pretreated in vitro with human omental fat conditioned medium (CM) or control regular medium (RM) for 24h. The tumor cells were then injected subcutaneously into the flank of nude mice. (A) Tumor growth and weight of PANC-1 tumors was facilitated in mice following pre-treatment with omental fat CM (n=15); (B) Representative mice and tumor images; (C) Marked increase in proliferation (Ki-67) and microvessel density (CD31) by human omental fat CM.



Uptake of omental fat exosomes by cancer cells. PKH67-labeled omental fat exosomes were incubated with PANC-1 pancreatic cancer cells (upper panel) and AGS gastric cancer cells (lower panel), reaction was stopped at different time points (1, 3, 5 and 7 hours) and cells were analyzed by confocal microscopy. The nucleus of PANC-1 and AGS cells was stained with dapi. Negative control- PANC-1 and AGS cells with no addition of labeled exosomes.

Publications

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Investigating the Immuno-Proteome in Cancer

Positions

Senior Physician, Institute of Pulmonary Medicine, Sheba Medical Center

Senior Lecturer, Sackler Faculty of Medicine

Research

We study the proteins and peptides involved in the interaction between immune cells and tumor cells. While genomics has boosted our knowledge on the molecular basis of human disease, both DNA sequencing and gene expression analysis report on indirect effects that often do not correlate with the actual expression and activity of proteins in cells and tissues. Importantly, proteins are the most prevalent drug targets. Thus, we employ advanced high-throughput immuno-proteomics, using mass-spectrometry-based methods, cell biology, biochemistry and *in vivo* models to reveal proteins with a novel immuno-regulatory function that can serve as drug targets in cancer and autoimmune diseases.

Publications

Strazza M, Azoulay-Alfaguter I, **Peled M**, Mor A. assay of adhesion under shear stress for the study of T lymphocyte-adhesion molecule interactions. J Vis Exp. 2016;(112):54203.

Azoulay-Alfaguter I, Strazza M, **Peled M**, Novak HK, Muller J, Dustin ML, Mor A. The tyrosine phosphatase SHP-1 promotes T cell adhesion by activating the adaptor protein CrkII in the immunological synapse. Sci Signal. 2017;10(491):eaal2880.

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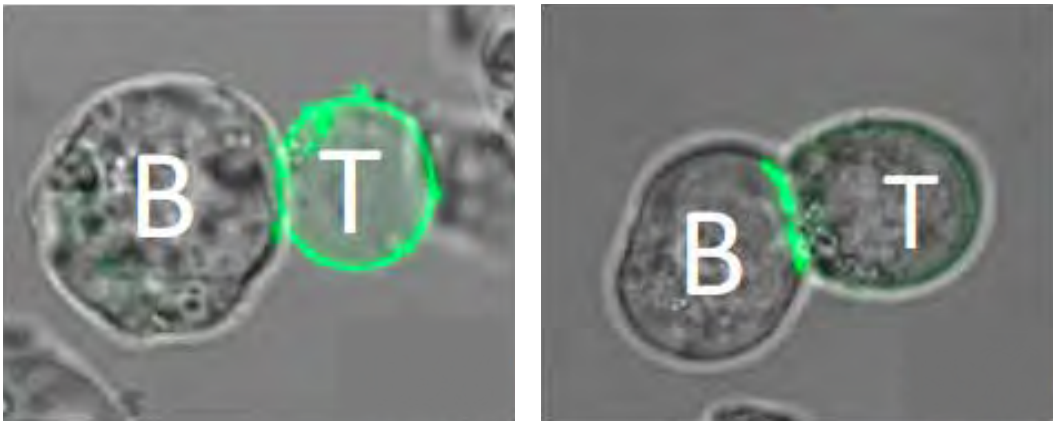
A **B**



EFHD2 is required for PD-1 clustering at the immunological synapse. Freshly isolated human T cells were transfected with non-targeting siRNA (siControl) (**A**) or siRNA targeting EFHD2 (siEFHD2) (**B**) and with GFP–PD-1 expression plasmid, followed by co-culturing with Raji B cells expressing PDL1 and loaded with SEE. Cells were subjected to real-time imaging by confocal microscopy.

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Grants

2019-2021 Israel Science Foundation

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Immunotherapy of Brain Tumors: From Basic Mechanisms to Clinical Translation

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Chairman, The Neurosurgery Section, Tel Aviv Sourasky Medical Center

Full Professor, Sackler Faculty of Medicine

Former Chairman, Tumor Section of European Association of Neurosurgical Societies

Positions – Ilan Volovitz

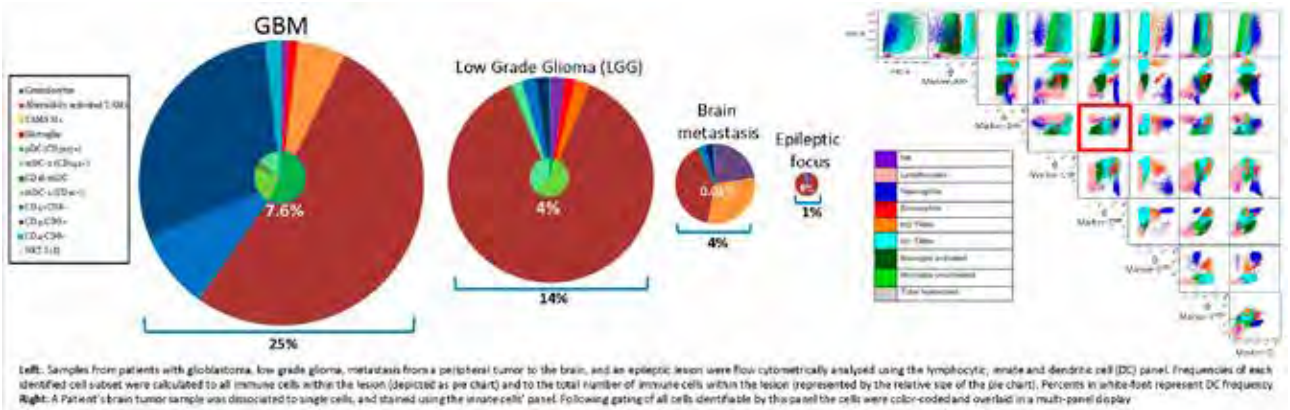
Lab Head, Cancer Immunotherapy Lab, Neurosurgery Department, Tel Aviv Sourasky Medical Center

Research

Our laboratory studies the unique immunology of brain tumors by combining basic-science with clinically-applied investigation. Utilizing the discrepancy between the relatively weak immune surveillance inside the brain and the potent one outside it, the lab has developed a novel method to treat brain tumors utilizing a concept we termed 'Split Immunity'. The concept was recently translated from rats to human glioblastoma (GBM) patients. To monitor the post-therapy changes in the anti-tumor immune response, the lab has developed a unique set of high resolution immune assays that follow the peripheral (outside the tumor) and the intratumoral immune response.

Main research interests

- Development of scientific and clinical insights into the concept of 'Split Immunity' and how it affects the treated patients.



Left: Samples from patients with glioblastoma, low grade glioma, metastasis from a peripheral tumor to the brain, and an epileptic lesion were flow cytometrically analyzed using the lymphocytic, innate and dendritic cell (DC) panel. Frequencies of each identified cell subset were calculated to all immune cells within the lesion (depicted as pie chart) and to the total number of immune cells within the lesion (represented by the relative size of the pie chart). Percents in white font represent DC frequency. Right: A Patient's brain tumor sample was dissociated to single cells, and stained using the innate cells' panel. Following gating of all cells identifiable by this panel the cells were color-coded and overlaid in a multi-panel display

- Mapping of the entire adaptive and innate cellular immune milieu found inside human brain tumors using advanced multicolor (up to 12-color) flow cytometry.
- Using a cell-centered approach called "Immune Cytomics" to study the network of interactions formed between the different intra-tumoral immune cells and between immune and tumor cells.
- Evaluating how novel, non-immune-based, treatments for brain tumors affect the anti-tumoral immune responses.

Publications

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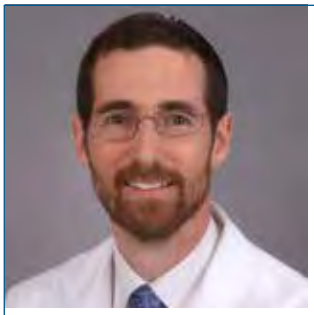
Gelerstein E, Berger A, Jonas-Kimchi T, Strauss I, Kanner AA, Blumenthal DT, Gottfried M, Margalit N, **Ram Z**, Shahar T. Regression of intracranial meningioma following treatment with nivolumab: Case report and review of the literature. J Clin Neurosci. 2017.



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Radiation Biology: Translating Biological Insights from the Lab to Impact Cancer Patient Care

Positions (Dr. Lawrence)

Director, Center for Translational Research in Radiation Oncology

Senior Lecturer (regular track), Sackler Faculty of Medicine

Assistant Professor (adjunct), Dep. Radiation Oncology, Thomas Jefferson University

Research

Radiation therapy is a cornerstone of modern cancer care. Ionizing radiation kills cancer cells by generating reactive oxygen species, damaging DNA, and inducing chromosomal damage. Yet many aspects of radiation biology remain unknown. The lab focusses on understating cells' ability to survive ionizing radiation, a phenomenon known as radioresistance. We seek to answer the question

of how some tumors are able to withstand very large doses of radiation. We hypothesize that cells withstand the intense onslaught of DNA damage by adapting their metabolic processes, diverting biosynthesis pathways to nucleotide synthesis and REDOX management. Another explanation of why cells in-vivo appear to resist radiation is the result of the interaction between tumor cells and the microenvironment. Ongoing projects in the lab are challenging and developing both these concepts.

The research center also performs clinical research, initiating and running clinical trials. Hence, a particular strength of the lab is the ability for our findings to impact patient care through the performance of clinical trials.

Publications

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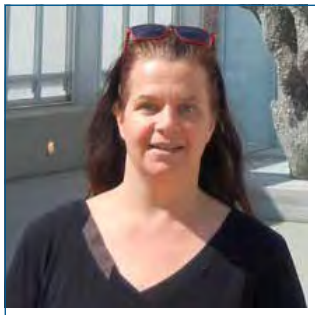

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miRNAs in Solid Malignancies / Immunotherapy Research / Clinical Cancer Research

Positions

Senior Lecturer, Sackler Faculty of Medicine

Senior Medical Oncologist, Clinician-investigator, Oncology Institute & Cancer Research Center, Sheba Medical Center, Tel Hashomer

Research

As a clinician-investigator and a practicing medical oncologist, our lab is engaged in basic, translational and clinical cancer research.

Basic research: Our lab at the Cancer Research Center at the Sheba campus studies the role of microRNAs in solid malignancies. We were the first to show that a large micr-RNA cluster on chromosome 14q32 is silenced in melanoma. This cluster was later dubbed 'the larger tumor suppressor miRNA cluster' and was shown to be down-regulated in a wide range of malignancies. We showed the involvement of three miRNAs from this cluster in melanoma progression, and continue to study the role of this cluster in the pathogenesis of this disease. In the last year, we have also studyed the involvement of miRNAs in bladder cancer; specifically, preliminary results suggest that a family of miRNAs are associated with the development of resistance to chemotherapy in bladder cancer; research is currently ongoing.

Translational research: Immunotherapy, namely the activation of the immune system against cancer, is revolutionizing cancer treatment, yet not all cancers, and not all patients within a given cancer, respond to immunotherapy. Currently, the biomarkers associated with response to immunotherapy are unknown. In collaboration with Dr. Irit Gat-Viks from the Faculty of Life Sciences at TAU, we are embarking on a clinical trial in which we will prospectively search for immune cell populations within the systemic circulation that are associated with response to immunotherapy. We will perform RNA sequencing of immune cells before and following immunotherapy treatment and analyze the cell populations using deconvolution algorithms developed at the Gat-Viks lab.

Clinical research: Whereas the list of anti-neoplastic treatments is constantly growing across the cancer spectrum, currently there are almost no proven predictive biomarkers of response to treatment with any of these agents, and clinical decisions are generally empirical and based on 'trial and error'. We are interested in finding associations between lab variables/plasma biomarkers and response to anti-neoplastic treatment in genito-urinary malignancies; specifically, we recently addressed the following clinical questions:

1. We described clinical and laboratory variables associated with response to the hormonal agent abiraterone in prostate cancer.

2. We showed that the neutrophil-lymphocyte ratio is associated with response to chemotherapy in bladder cancer, and that a high lymphocyte count is associated with pathological complete response at cystectomy following neo-adjuvant treatment.

3. We described the patterns of change of a several plasma biomarkers following treatment with the biological agent cabozantinib in prostate cancer.

4. We summarized our clinical experience with the immunotherapeutic anti-PD1 antibody pembrolizumab, showing that low lymphocyte counts are associated with lack of response.

These clinical works, taken together, show that the adaptive arm of the immune response is imperative in amounting response to both chemo and immuno-therapy.

Publications

Leibowitz-Amit R, Israel A, Gal M, Atenafu E A, Symon Z, Portnoy O, Laufer M, Dotan Z, Ramon

J, Fridman E, Berger R. Association between the Absolute Baseline Lymphocyte Count and Response to Neoadjuvant Platinum-based Chemotherapy in Muscle-invasive Bladder Cancer. Clin Oncol (R Coll Radiol). 2016;28(12):790-796.

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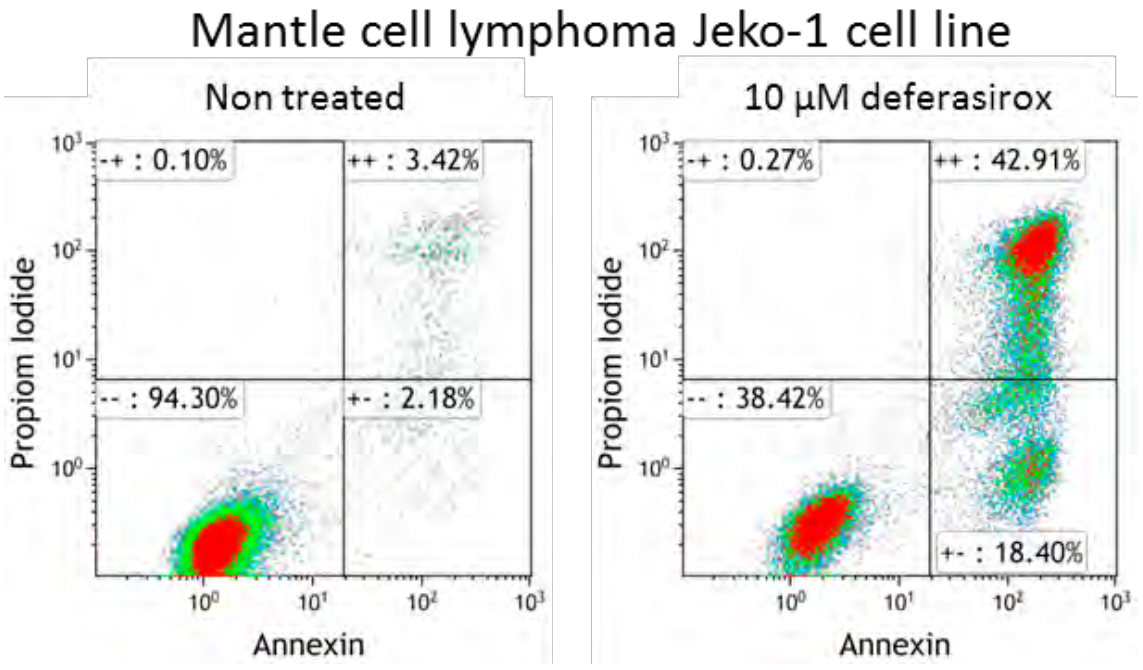
Hematological Malignancies

Positions

Prof. Raanani, Clinical Full Professor in Hematology, Sackler Faculty of Medicine

Research

Our primary field of interest is finding new therapies or better therapies for the treatment of incurable hematological malignancies. Our projects focus on exploring the effect of new agents on different leukemia and lymphoma cell lines and patient samples. We study the molecular pathways involved in the initiation and maintenance of hematological tumorigenesis and try to understand the effect of the different agents on these molecular pathways. We apply cutting-edge technologies including, molecular protein and cellular biology, microarray and NGS analysis. Understanding normal hematological development and understanding the molecular effect of different chromosomal abnormalities



Deferasirox is a rationally-designed oral iron chelator used to reduce chronic iron overload in patients who receive long-term blood transfusions. We showed that this agent can induce apoptosis in mantle cell lymphoma.

(translocations, deletion, etc.) is essential for understanding the the processes leading to the induction and maintenance of hematological malignancies and for designing targeted treatments for these malignancies.

Publications

Gover-Proaktor A*, **Granot G***, Shapira S, Raz O, Pasvolsky O, Nagler A, Lev DL, Inbal A, Lubin I, **Raanani P**, Leader A. Ponatinib reduces viability, migration, and functionality of human endothelial cells. Leuk Lymphoma. 2016;12:1-13.

Gover-Proaktor A, **Granot G**, Shapira S, Raz O, Pasvolsky O, Nagler A, Lev DL, Inbal A, Lubin I, **Raanani P**, Leader A. Ponatinib reduces viability, migration, and functionality of human endothelial cells. Leuk Lymphoma. 2017;58(6):1455-1467

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Investigating Mechanisms of Hepatitis B Virus Persistence and Its Link to Liver Cancer

Positions

Head, Department of Medicine D and the Laboratory of Liver Research

Senior Lecturer, Sackler Faculty of Medicine

Research

Current research interests focus on the role of the innate immune system in HBV infection and the role of HBV infection in liver carcinogenesis.

1. Studying the molecular mechanisms by which HBV confers resistance to sorafenib in order to get a deeper understanding of HBV oncogenicity and to gain insight into possible molecular targets for HCC interventions.
2. Characterizing the molecular signature of type I interferon induction and response following HBV infection.
3. Characterizing the interferon-response genes (ISGs) induced by HBV and their effect on HBV life cycle.
4. Investigating the mechanism(s) of HBV inhibition by the innate immune response.

Publications

Scheel, Troels K.H., Luna, Joseph M., Liniger, M., Nishiuchi, E., Rozen-Gagnon, K., **Shlomai, A.**, Auray, G., Gerber, M., Fak, J., Keller, I., et al. 2016. A Broad RNA Virus Survey Reveals Both miRNA Dependence and Functional Sequestration. *Cell Host Microbe* 19:409-423.

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Grants

	Israeli Science Foundation (ISF)/ Physician-Scientist Grant
2016-2020	US-Israel Binational Science Foundation (BSF) Grant (with CM Rice)

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Pediatric Brain Tumors, Leukemias and Lymphomas

Research

Targeted therapies aimed at new targets identified by in-house analysis of genetic panels studing pediatric cancer patients' DNA.

Immunotherapy with new bispecific antibodies.

Incorporation of checkpoint inhibitors.

T-CARs for patients with relapse/refractory ALL. This innovative treatment has been performed in only a few centers in the USA and was successfully given to 5 patients. Pediatric brain tumors and neuroblastoma studies in the lab including pathogenesis, innovative therapies, discovery of new molecular aberrations, new biomarkers, new therapeutic targets the effect of new drugs on cell lines, primary cells and xenografts, studying the influence of changes in the levels of non-coding RNA's (mirs and link-RNA) on the tumor. Improvement of the activity of cytokine induced killer cells stemming from alfa/beta depleted T cells left over after haploidentical transplantations. Studying the effects of phytocannabinoids, synthetic cannabinoids and endocannabinoid-like substances on pediatric glioblastomas and neuroblastoma.

Main research areas:

1. T-CARS therapy for relapsed/reistant CD19 expressing leukemias and lymphomas
2. The effects of cannabinoids on pediatric tumors
3. Cytokine induced killer cells against pediatric tumors
4. Pediatric brain tumors research

Publications

Zinc enhances temozolomide cytotoxicity in glioblastoma multiforme model systems. **Toren A**, Pismenyuk T, Yalon M, Freedman S, Simon AJ, Fisher T, Moshe I, Reichardt JK, Constantini S, Mardor Y, Last D, Guez D, Daniels D, Assoulin M, Mehrian-Shai R. Oncotarget. 2016.

Yalon M, Tuval-Kochen L, Castel D, Moshe I, Mazal I, Cohen O, Avivi C, Rosenblatt K, Aviel-Ronen S, Schiby G, Yahalom J, Amariglio N, Pfeffer R, Lawrence YR, **Toren A**, Rechavi G, Paglin S Correction: Overcoming Resistance of Cancer Cells to PARP-1 Inhibitors with Three Different Drug Combinations. PloS One. 2016.

Yalon M, Tuval-Kochen L, Castel D, Moshe I, Mazal I, Cohen O, Avivi C, Rosenblatt K, Aviel-Ronen S, Schiby G, Yahalom J, Amariglio N, Pfeffer R, Lawrence Y, **Toren A**, Rechavi G, Paglin S. Overcoming Resistance of Cancer Cells to PARP-1 Inhibitors with Three Different Drug Combinations. PloS One. 2016.

Fisher T, Golan H, Schiby G, PriChen S, Smoum R, Moshe I, Peshes-Yaloz N, Castiel A, Waldman D, Gallily R, Mechoulam R, **Toren A**. In vitro and in vivo efficacy of non-psychoactive cannabidiol in neuroblastoma. Curr Oncol. 2016.

Mehrian-Shai R, Yalon M, Moshe I, Barshack I, Nass D, Jacob J, Dor C, Reichardt JK, Constantini S, **Toren A**. Identification of genomic aberrations in hemangioblastoma by droplet digital PCR and SNP microarray highlights novel candidate genes and pathways for pathogenesis. BMC Genomics. 2016.

Keidan I, Ben-Menachem E, Berkenstadt H, **Toren A**. A Simple Diagnostic Test to Confirm Correct Placement of Dysfunctional Central Venous Catheters Before Chemotherapy in Children. J Pediatr Hematol Oncol. 2016.

Dr. Orit Uziel, Ph.D.

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Cell to Cell Communication in Cancer: The Role of Exosomes

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Exosomes are nanosized particles that are formed in different types of cells, travel in blood and other body fluids and carry a cargo of prtoeins and nucleic acids. This cargo is delivered to neighbouring cells. Our lab studies the role of exosomes in cell to cell communication and the potential use of exosomal cargo as biomarkers for diagnostics and followup of patients with cancer. Previously, we found that exosomes derived from various neoplastic cells contain hTERT transcript of telomerase, an enzyme that is unique to cancer cells and is only rarely found on non-neoplastic cells. Furthermore, this transcript is actively translated and mediates canonical and non-canonical functions in the recipient cells. In parallel we have found that in cancer patients, about 2/3 of the sera derived exosomes contain detectable telomerase transcript.

Currently we are focused on the potential use of exosomal hTERT as a cancer biomarker. We follow the presence of telomerase in exosomes isolated from patients with cancer in response to treatment. This followup is conducted on exosomes derived from patients with lung cancer, breast cancer and

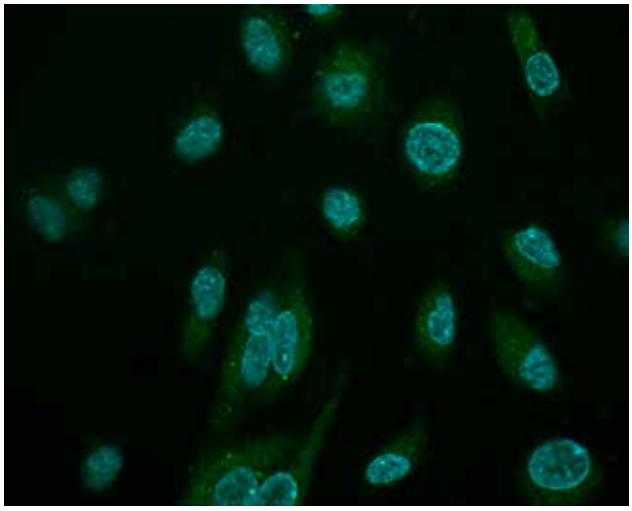

Figure 1. FITC-stained exosomes are taken up by HUVEC cells analyzed by fluoresent microscopy.

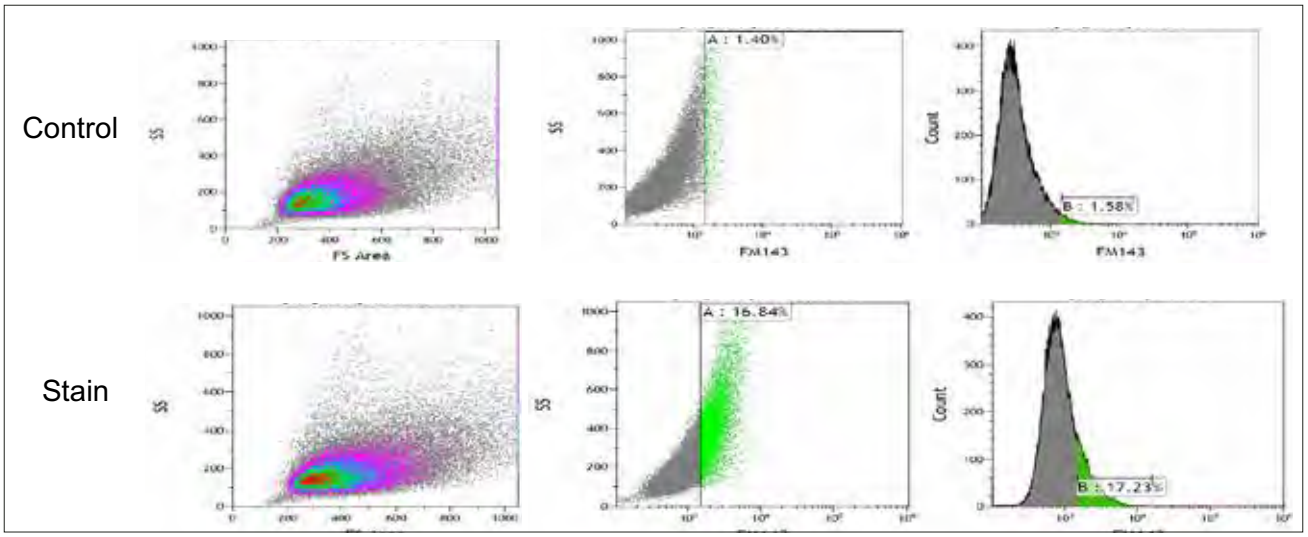

Figure 2. FM-134 stained exosomes are taken up by HUVEC cells analysed by flow cytometry.

glioblastoma multiforme in which we also correlate the disease stage with the presence of mutations present at telomerase promoter as well. We study also other types of cargos that are delivered by exosomes as well.

Additionally, we are studying the crosstalk of exosomes isolated from cancer cells and cells of their microenvironment. In figure 1, the uptake of FITC-stained cancer cell exosomes by HUVEC (Human Umbilical Vein Endothelial Cells) is shown. In figure 2, the same uptake is shown by FACS analysis.

Publications

Gutkin A, **Uziel O,** Beery E, Nordenberg J, Pinchasi M, Goldvaser H, Henick S, Goldberg M, Lahav M. Tumor cells derived exosomes contain hTERT mRNA and transform nonmalignant fibroblasts into telomerase positive cells. Oncotarget. 7, 59173-88, 2016.

Uziel O, Yerushalmi R, Zuriano L, Beery E, Nordenberg J, Lubin I, Adel Y, Shepshelovich D, Pery S, Rizel S, Pasmanik-Chor M, Frumkin D, Lahav M. The role of BRCA1 in telomere regulation: implications for genomic stability and malignant transformation. Oncotarget. 7, 2433-54, 2016.

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Goldvaser H, Gutkin A, Beery E, Edel Y, Nordenberg J, Wolach O, Rabizadeh E, **Uziel O**, Lahav M. Characterisation of blood-derived exosomal hTERT mRNA secretion in cancer patients: a potential pan-cancer marker. Br J Cancer. 2017 Jun 22.

Uziel O, Gutkin A, Beery E, Lahav M. Exosomes as mediators for cell- cell comunicastion: the relevance to cancer and to the enzyme telomerase. Harefua. 156, 710-714, 2017.

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Harpaz T, Abumock H, Beery E, Edel Y, Lahav M, Rozovski U, Uziel O. The effect of ethanol on telomere dynamics and regulation in human cells. *Cells* 7, 169, 2018.

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Stein JY, Levin Y, Uziel O, Abumock H, Solomon Z. Traumatic stress and cellular senescence: The role of war-captivity and homecoming stressors in later life telomere length. *Journal of Affective Disorders*. 238, 129-135, 2018.

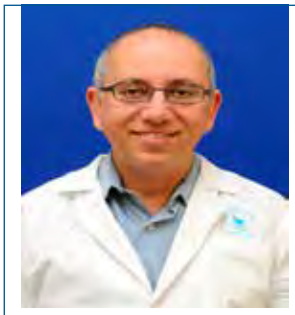
Aloni R, Levin Y, Uziel O, Solomon Z. Premature aging among trauma survivors – The longitudinal implications of sleep disruptions on telomere length and cognitive performance. J Gerontol B Psychol Sci Soc Sci. pii: gbz077. 2019.

Shalem-Cohavi N, Beery E, Nordenberg J, Rozovski U, Raanani P, Lahav M, Uziel O. The effects of proteasome inhibitors on telomerase activity and regulation in multiple myeloma cells. *Int J Mol Sci* 20, 2509-2521, 2019.

Koslow M, Shitrit D, Israeli-Shani L, Uziel O, Beery E, Osadchy A, Refaely Y, Epstein Shochet G, Amiel A. Peripheral blood telomere alterations in ground glass opacity (GGO) lesions may suggest malignancy. *Thorac Cancer*. 10, 1009-1015, 2019.

Zach L-O, Beery E, Lahav M, Uziel O. The effects of Rapamycin on telomerase activity and regulation in cancer cells. Brit J Canc Res. 2: 334 – 340, 2019.

Uziel O, Lahav M, Shragian, L, Beery E, Pasvolsky O, Rozovski U, Raanani P, Yeshurun M. Pre-mature ageing following allogeneic hematopoietic cell transplantation. *Bone Marrow Transpl*, 2020.



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Deciphering Endocrine Aspects of Cancer Development

Positions

Prof. Ido Wolf, Associate Professor, Sackler Faculty of Medicine

Head, Oncology Division, Tel Aviv Sourasky Medical Center

Dr. Tami Rubinek, Senior Lecturer, Sackler Faculty of Medicine

Head – Oncology Division Research Lab, Tel Aviv Sourasky Medical Center

Klotho: the hormone that links longevity, metabolism and cancer

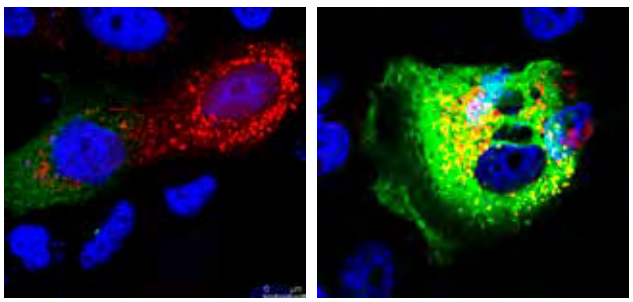
Klotho is a hormone that regulates physiologic processes, including kidney functions amd metabolism. Reduced klotho levels are associated with aging. We discovered that klotho is a potent tumor suppressor in breast, pancreatic and ovarian cancers. Current projects:

- Characterization of klotho activity in cancer by generation of transgenic mice, structure-function analyses and biochemical analyses of enzymatic activities
- Deciphring the role of klotho as a regulator of calcium fluxes, mitochondrial activity and tumor metabolism
- Discovering the role of klotho in regulator of the GH/IGF axis

The estrogen receptor (ESR1) mutations in breast cancer

Our lab was the first to discover mutations in ESR1 that confer resistance to hormonal therapies in >40% of patients with metastatic breast cancer. Current projects:

- Styding the mutations as mediators of aggressive phenotype of breast cancer



Co-localization of klotho (green) with mitochondria (red) in MCF-7 breast cancer cells.

Structural model of D538G mutated ESR1

- Studiyng the unique metabolic activity of cance cells harboring thr mutations
- Development of novel treatment strategies in breast cancer

How do cancer cells choose were to metastasize- or what regulates tropism?

We are tackling the role of specific mutations in mediating homing of cancer cells to specific organs:

- Deciphering the mechanism of homing of pancreatic tumors to different organs
- Revealing metabolic pathways enabling colon cancer cells to form brain metastasis

Publications

Aviel-Ronen S*, **Rubinek T***, Zadok O*, Vituri A, Avivi C, **Wolf I****, Barshack I**. Klotho expression in cervical cancer: differential expression in adenocarcinoma and squamous cell carcinoma. *first co-author, **equal supervisors. J Clin Pathol. 2016 ;69(1):53-7.

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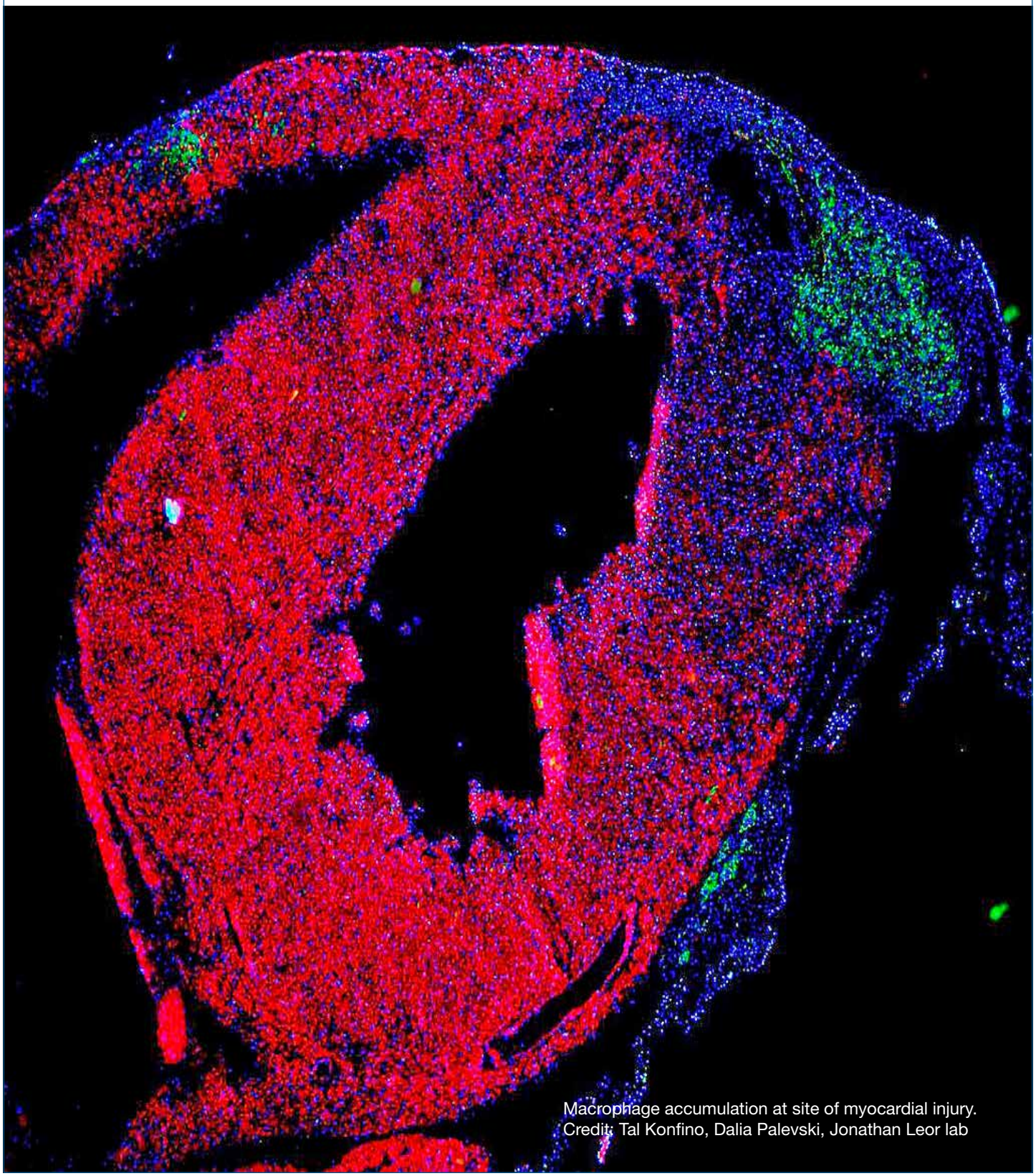
Rubinek T, Shahmoon S, Shabtay-Orbach A, Ben Ami M, Levy-Shraga Y, Mazor-Aronovitch K, Yeshayahu Y, Doolman R, Hemi R, Kanety H, **Wolf I**, Modan-Moses D. Klotho response to treatment with growth hormone and the role of IGF-I as a mediator. Metabolism, 2016;65(11):1597-1604.

Grants

2017-2022 Orion Scholarship

Cardiovascular System



Macrophage accumulation at site of myocardial injury.
Credit: Tal Konfino, Dalia Palevski, Jonathan Leor lab

Prof. Ehud Grossman, M.D.

Internal Medicine D and Hypertension Unit
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Affiliated to Sackler Faculty of Medicine

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Investigating Hypertension, Diabetes Mellitus and Metabolic Syndrome

Positions (Prof. Grossman)

Head, Internal Medicine D and Hypertension Unit, Chaim Sheba Medical Center, Tel-Hashomer

Professor of Medicine, Sackler Faculty of Medicine, Tel Aviv University

Dean, Sackler Faculty of Medicine, Tel Aviv University

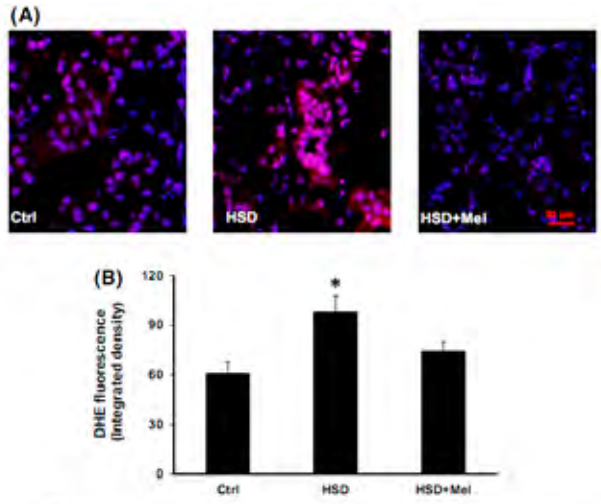

Fig. 3. Melatonin abolished high salt diet (HSD)-induced superoxide formation in the kidney. Dihydroethidium (DHE) staining demonstrating reactive oxygen species production determined in rats' kidneys. (A) Representative images of DHE-stained kidney sections and (B) quantification are presented. $*P < 0.05$ HSD versus Ctrl and HSD + Mel, n = 5, 20× magnification. Blue staining represents nuclear DAPI staining. Ctrl, control; HSD, high salt diet; Mel, melatonin.

Leibowitz A, Volkov A, Voloshin K, Shemesh C, Barshack I, **Grossman E.** J Pineal Res. 2016;60:48-54.

Research

Our research concentrates on the impact of coronary calcifications on cardiovascular morbidity and mortality in hypertensive patients. We showed that the presence of coronary calcifications is associated with increased mortality and that diabetic patients without coronary calcifications have a good prognosis. Our team also studied the effect of blood pressure control and stroke outcomes. We showed that elevated systolic blood pressure in acute stroke is associated with poor outcome and that change in BP during the first week after stroke has no effect on outcome. Our main basic research is on metabolic syndrome. How can we improve metabolic syndrome? We also studied the effect of melatonin on the cardiovascular system. Our recent paper in *J Pineal Res* showed that melatonin prevents kidney injury in a high salt diet-induced hypertension model by decreasing oxidative stress.

Publications

Shopen N, Schiff E ,Koren-Morag N, **Grossman E.** Factors That Predict the Development of Hypertension in Women With Pregnancy-Induced Hypertension. Am J Hypertens. 2016;29:141-6.

Weiss A, Beloosesky Y, Kenett RS, **Grossman E**: Change in Systolic Blood Pressure During Stroke, Functional Status, and Long-Term Mortality in an Elderly Population. Am J Hypertens. 2016;29:432-8.

Eizenberg Y, Koton S, Tanne D, **Grossman E**. Association of age and admission mean arterial blood pressure in patients with stroke-data from a national stroke registry. Hypertens Res. 2016; 39:356-61.

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Grossman C, Bornstein G, Leibowitz A, Ben-Zvi I, **Grossman E**. Effect of tumor necrosis factor-alpha inhibitors on ambulatory 24-h blood pressure. *Blood Press*. 2017:26:24-29.

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Botzer A, **Grossman E**, Moult J, Unger R. A system view and analysis of essential hypertension. J Hypertens. 2018

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Cardiovascular Regulatory Systems Focusing on the Autonomic Nervous System in Human (*Translational Science*)

Position

Associate Professor, Medicine and Physiology

Research

Recanati Autonomic Dysfunction Center

The effect of adrenoceptors activation on the coagulation system

Insight into the regulatory mechanisms of mesenteric flow

Organ-specific flow regulation, e.g. cerebral and penile blood flow

Autonomic nervous system dysregulation in CVD

Autonomic nervous system and pain regulation, including fMRI studies

Postural tachycardia Syndrome (POTS)

Collaborations: Vanderbilt University, Nashville, TN, USA, Milano University, Italy, and Eurospace Center, Germany.

Publications

Ali-Saleh M, Sarig G, Ablin JN, Brenner B and **Jacob G**. Inhalation of a Short-Acting beta2-Adrenoreceptor Agonist Induces a Hypercoagulable State in Healthy Subjects. PLoS One 11: e0158652, 2016.

Nahman-Averbuch H, Dayan L, Sprecher E, Hochberg U, Brill S, Yarnitsky D and **Jacob G**. Pain Modulation and Autonomic Function: The Effect of Clonidine. Pain Med 2016.

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Nahman-Averbuch H, Sprecher E, **Jacob G** and Yarnitsky D. The Relationships Between Parasympathetic Function and Pain Perception: The Role of Anxiety. *Pain Pract* 2016.

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Hellou R, Häuser W, Brenner I, Buskila D, **Jacob** G, Elkayam O, Aloush V, Ablin JN. Self-reported childhood maltreatment and traumatic events among israeli patients suffering from fibromyalgia and rheumatoid arthritis. Pain Res Manag. 2017;2017:3865249.

Prof. Dror Harats, M.D.

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Atherosclerosis – Research, Treatment and Prevention

Positions

Professor of Medicine, Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine

Acting Vice President of Research and Development and Academy and Chairman, IRB Committee

President, The Bert W. Strassburger Lipid Center, Sheba Medical Center

Chairman, IRB Committee of the Sheba Medical Center

CEO, Vascular Biogenics Ltd (VBL)

Research

We investigate lipid metabolism, atherosclerosis and vascular biology. In our research, we apply advanced research tools, utilizing in-vitro and in-vivo models and performing clinical trials. In our studies, we focus on basic aspects in atherosclerosis progression and developing new treatments for prevention of the disease.

The current research projects are:

The effect of carotenoids and their cleavage products on the activation of the nuclear receptor RXR and atherosclerosis in mouse models.

The effect of carotenoids on Retinitis Pigmentosa.

The effect of carotenoids on Alzheimer in transgenic mice.

The role of the coagulation Factor XI in early and advanced atherosclerosis by using apolipoproteinE/FactorXI double knock-out mice.

The role of apoA5 in atherosclerosis development by using apolipoproteinE/apoAVI transgenic mice.

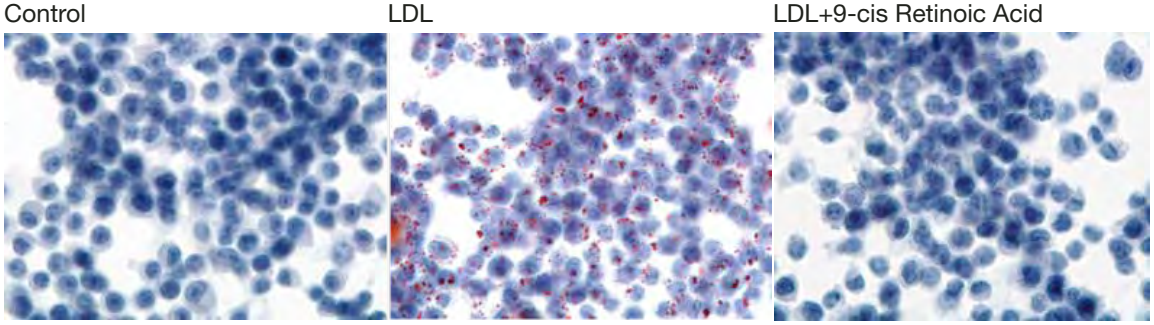
Publications

Shnerb Ganor R, **Harats D**, Schiby G, Gailani D, Levkovitz H, Avivi C, Tamarin I, Shaish A, Salomon O. Factor XI Deficiency Protects Against Atherogenesis in Apolipoprotein E/Factor XI Double Knockout Mice. Arterioscler Thromb Vasc Biol. 36(3):475-81, 2016.

Grosskopf I, Shaish A, Charach G, **Harats D**, Kamari Y. Nifedipine Treatment for Hypertension is Associated with Enhanced Lipolytic Activity and Accelerated Clearance of Postprandial Lipemia. Horm Metab Res. 2016 Feb 5. [Epub ahead of print]

Bechor S, Zolberg Relevy N, Harari A, Almog T, Kamari Y, Ben-Amotz A, **Harats D**, Shaish A. 9-cis β-Carotene Increased Cholesterol Efflux to HDL in Macrophages. Nutrients. 19;8(7), 2016.

Boehm-Cagan A, Bar R, **Harats D**, Shaish A, Levkovitz H, Bielicki JK, Johansson JO, Michaelson DM. Differential Effects of apoE4 and Activation of ABCA1 on Brain and Plasma Lipoproteins. PLoS One. 8;11(11), 2016.



Macrophage foam cell formation is inhibited by 9-cis retinoic acid

Prof. Gad Keren, M.D.

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Dr. Michal Entin-Meer, Ph.D.

Lab Manager & Senior Researcher
Cardiovascular Rrsearch Lab, Tel Aviv Sourasky Medical Center; Lecturer, Department of Cardiology, Sackler Faculty of Medicine

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Elucidating the Molecular & Pathophysiological Mechanisms Leading to the Initiation and Progression of Cardiovascular Diseases

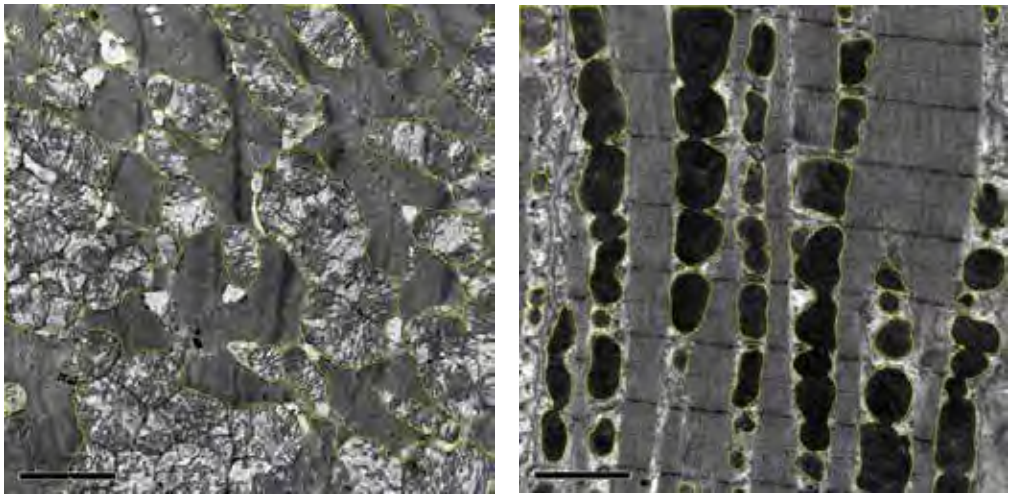
Positions (Prof. Keren)

Head, Cardiology Division, Tel Aviv Sourasky Medical Center

Professor, Department of Cardiology

Research

We study the molecular networks leading to the initiation and progression of acute versus chronic presentation of various cardiac diseases. Currently we mainly focus on studying the following cardiac pathologies: 1. Acute myocardial infarction leading to left ventricular dysfunction; 2. cardiac volume overload- a prominent pathology in valvular diseases and chronic heart failure; 3. the prevalent presentation of cardio-renal syndrome. Utilizing the appropriate in vivo models as well as various molecular and cellular techniques, we have been trying to identify novel therapeutic targets for attenuating disease progression and to improve the clinical presentation of these devastating conditions.



Captures of transmitted electron microscopy demonstrating the organized structure of cardiac mitochondria in sham-operated control rats (A) compared to the swallawed unorganized structure of the mitochondria in the heart tissue of animals with chronic kidney disease (B).

Main ongoing research topics

The potential involvement of the cation channel TRPV2, which is highly abundant on peri-infarct immune cells, in the recovery processes following an acute myocardial infarction.

Elucidating the therapeutic potential of anti-metalloproteinase antibodies as well as reagents holding anti- histone deacetylase activity for the treatment of cardiac volume overload.

Cardiac mitochondria as a promising target for attenuation of cardiac dysfunction and progression to cardiorenal syndrome in patients with chronic kidney disease.

Publications

Margolis G, Levy R, **Keren G, Entin-Meer M**. Differential effects of colchicine on cellular viability of cardiac cells in an in vitro model simulating myocardial infarction. Cardiology. 2016, 134(1):57-64.

Cohen L, Entin-Meer M, Rephaeli A, Tarasenko N, Ben Shoshan J, Hertzberg-Bigelman E, Keren G. Histone deacetylase inhibitor AN7 increases survival and may attenuate LV dilatation in mice with chronic volume overload. Suppl to Eur Heart J. 2016; 1097, P5387.

Ben Shoshan J, Steinvil A, Arbel Y, Topilsky Y, Barak L, **Entin-Meer M**, Levy R, Schwartz AL, Keren G, Finkelstein A, Banai S. Sustained Elevation of Vascular Endothelial Growth Factor and Angiopoietin 2 Levels Following Transcatheter Aortic Valve Replacement. Can J Cardiol. 2016, 32:1454-1461.

Hertzberg-Bigelman E, Barashi R, Levy R, Cohen L, Ben-Shoshan J, **Keren G, Entin-Meer M**. Down-Regulation of Cardiac Erythropoietin Receptor and its Downstream Activated Signal Transducer Phospho-STAT-5 in a Rat Model of Chronic Kidney Disease. Isr Med Assoc J. 2016, 18(6):326-30.

Entin-Meer M, Cohen L, Hertzberg-Bigelman E, Levy R, Ben-Shoshan J, Keren G. TRPV2 knockout mice demonstrate an improved cardiac performance following myocardial infarction due to attenuated activity of peri-infarct macrophages. PLoS One. 2017, 12(5): e0177132.

Ben-Shoshan J, Jubran A, Levy R, Keren G, Entin-Meer M. Increased CD11b+ cells and Interleukin-1 (IL-1) alpha levels during cardiomyopathy induced by chronic adrenergic activation. Isr Med Assoc J. 2017, 19(9):570-575.

Rozenbaum Z, Cohen L, Bigelman E, Shscham J, Keren G, Entin-Meer M. Downregulated expression of TRPV2 in peripheral blood cells following acute myocardial infarction is inversely correlated to sera levels of CRP and Troponin I. Cardiology. 2018, 139(3):169-174.

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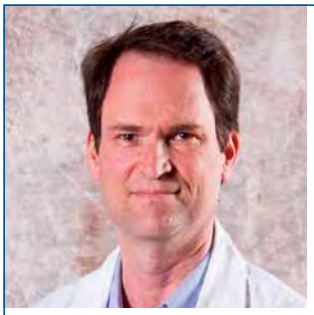
Rozenbaum Z, Topilsky Y, Aviram G, Entin Meer M, Granot Y, Pereg D, Berliner S, Steinvil A, Biner S. Prognostic implications of small left arteria on hospitalized patients. Eur Heart J- Cardiovascular Imaging, 2019; 20(9):1051-1058.

Entin-Meer M, Keren G. Potential roles in cardiac physiology and pathology of the cation channel TRPV2 expressed in cardiac cells and cardiac macrophages: a mini-review. Am J Physiol Heart Circ Physiol. 2020;318:H181-H188.

Cohen L, Sagi I, Bigelman E, Solomonov I, Aloshin A, Ben-Shoshan J, Rozenbaum Z, Keren G, Entin-Meer M. cardiac remodeling secondary to chronic volume overload is attenuated by a novel MMP9/2 blocking antibody. PloS One 2020;15(4):e0231202.

Grant

2018-2020	Ichilov-Weizmann Joint Fund
2018-2020	Ministry of Health (Chief Scientist)
2020-2022	Israel Innovation Authority-Kamin



Prof. Ran Kornowski, M.D., FESC, FACC

Division of Cardiology and Cardiac Catheterizations
Rabin Medical Center

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Positions

Full Professor, Sackler Faculty of Medicine

Rena Favaloro Chair for Heart Surgery and Interventional Cardiology

Chairman, Division of Cardiology and Cardiac Catheterizations, Rabin Medical Center

President, Israeli Society of Cardiology

Research

Prof. Kornowski has been involved in multiple technology developments and innovative treatment techniques in cardiology. The research activities include:

Development of new techniques geared towards catheter valve interventions, examining feasibility, safety and treatment outcomes.

Innovative imaging techniques of the coronary arteries and physiology.

Study of the cardiac effects of caloric restriction and neuro-hormonal pathways of weight reduction.

Translational studies of coronary thrombosis and progenitor endothelial cells.

Translational cardiovascular research of stem cells and gene therapy.

Development of new medications during and after cardiac catheterizations.

Research of novel drug-eluting stents and biodegradable scaffolds implanted within the coronary arteries.

Development of methods of “hybrid” cardiac interventions combined with minimal invasive cardiac surgery to treat structural and coronary diseases.

Mentoring and guiding students and young cardiologists in the early stage of their career.

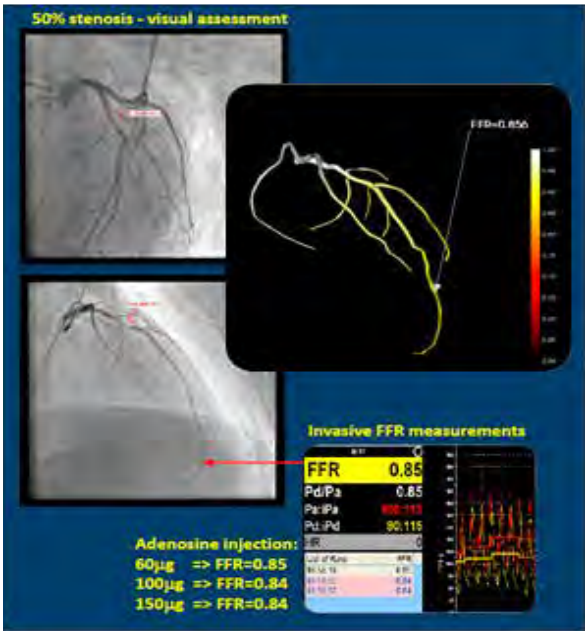

Image display of coronary angiography (Ref. Kornowski R. et al. J Am Coll Cardiol 2016;68:2235-2237)

Publications

Kornowski R, Lavi I, Pellicano M, Xaplanteris P, Vaknin-Assa H, Assali A, Valtzer O, Lotringer Y, De Bruyne B. Fractional Flow Reserve Derived From Routine Coronary Angiograms. J Am Coll Cardiol. 2016;68(20):2235-2237.

Landes U, Barsheshet A, Finkelstein A, Guetta V, Assali A, Halkin A, Vaknin-Assa H, Segev A, Bental T, Ben-Shoshan J, Barbash IM, **Kornowski R**. Temporal trends in transcatheter aortic valve implantation, 2008-2014: patient characteristics, procedural issues, and clinical outcome. Clin Cardiol. 2016.

Codner P, Levi A, Gargiulo G, Praz F, Hayashida K, Watanabe Y, Mylotte D, Debry N, Barbanti M, Lefèvre T, Modine T, Bosmans J, Windecker S, Barbash I, Sinning JM, Nickenig G, Barsheshet A, **Kornowski R**. Impact of Renal Dysfunction on Results of Transcatheter Aortic Valve Replacement Outcomes in a Large Multicenter Cohort. Am J Cardiol. 2016.

Landes U, **Kornowski R**, Bental T, Assali A, Vaknin-Assa H, Lev E, Iakobishvili Z. Long-term outcomes after percutaneous coronary interventions in cancer survivors. Coron Artery Dis. 2016.

Orvin K, Bental T, Assali A, Lev EI, Vaknin-Assa H, **Kornowski R**. Usefulness of the CHA2DS2-VASC Score to Predict Adverse Outcomes in Patients Having Percutaneous Coronary Intervention. Am J Cardiol. 2016;117(9):1433-8.

Landes U, Orvin K, Codner P, Assali A, Vaknin-Assa H, Schwartznberg S, Levi A, Shapira Y, Sagie A, **Kornowski R**. Urgent Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis and Acute Heart Failure: Procedural and 30-Day Outcomes. Can J Cardiol. 2016;32(6):726-31.

Landes U, Bental T, Orvin K, Vaknin-Assa H, Rechavia E, Iakobishvili Z, Lev E, Assali A, **Kornowski R**. Type 2 myocardial infarction: A descriptive analysis and comparison with type 1 myocardial infarction. J Cardiol. 2016;67(1):51-6.

Prof. Jonathan Leor, M.D.

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

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Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions

Professor of Cardiology, Sackler Faculty of Medicine

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

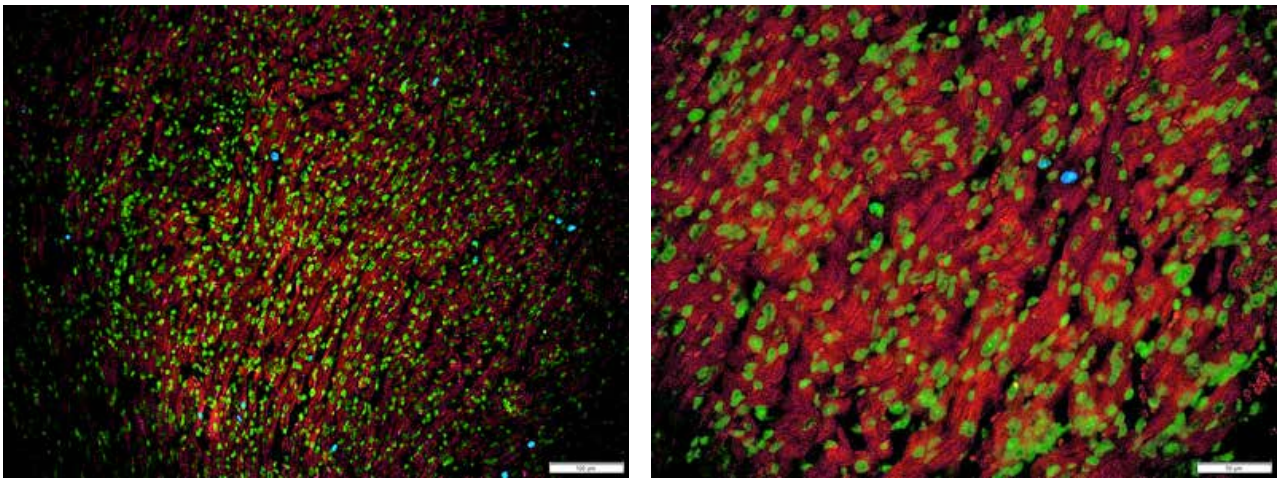
Our lab is focused on translational research. Specifically, we study cardiovascular regenerative medicine, stem cells and tissue engineering. In addition, we aim to target cardiovascular inflammation and fibrosis using novel nano-medicine and a theranostic (therapy + diagnosis) approach. We use a combination 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 (selected)

Brzezinski RY, Ovadia-Blechman Z, Lewis N, Rabin N, Zimmer Y, Levin-Kotler L, Tepper-Shaihov O, Naftali-Shani N, Tsoref O, Grossman E, Leor J and Hoffer O. Non-invasive thermal imaging of cardiac remodeling in mice. Biomed Opt Express. 2019;10:6189-6203.

Tsoref O, Tyomkin D, Amit U, Landa N, Cohen-Rosenboim O, Kain D, Golan M, Naftali-Shani N, David A and Leor J. E-selectin-targeted copolymer reduces atherosclerotic lesions, adverse cardiac remodeling, and dysfunction. J Control Release. 2018;288:136-147.

Naftali-Shani N, Molotski N, Nevo-Caspi Y, Arad M, Kuperstein R, Amit U, Huber I, Zeltzer LA, Levich A, Abbas H, Monserrat L, Paret G and Leor J. Modeling peripartum cardiomyopathy with human



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

induced pluripotent stem cells reveals distinctive abnormal function of cardiomyocytes. Circulation. 2018;138:2721-2723.

Perrino C, Barabasi AL, Condorelli G, Davidson SM, De Windt L, Dimmeler S, Engel FB, Hausenloy DJ, Hill JA, Van Laake LW, Lecour S, Leor J, Madonna R, Mayr M, Prunier F, Sluijter JPG, Schulz R, Thum T, Ytrehus K and Ferdinandy P. Epigenomic and transcriptomic approaches in the post-genomic era: path to novel targets for diagnosis and therapy of the ischaemic heart? Position Paper of the European Society of Cardiology Working Group on Cellular Biology of the Heart. Cardiovasc Res. 2017;113:725-736.

Amit U, Kain D, Wagner A, Sahu A, Nevo-Caspi Y, Gonen N, Molotski N, Konfino T, Landa N, Naftali-Shani N, Blum G, Merquiol E, Karo-Atar D, Kanfi Y, Paret G, Munitz A, Cohen HY, Ruppin E, Hannenhalli S and Leor J. New role for interleukin-13 receptor alpha 1 in myocardial homeostasis and heart failure. J Am Heart Assoc. 2017;6.

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Ben-Mordechai T, Kain D, Holbova R, Landa N, Levin LP, Elron-Gross I, Glucksam-Galnoy Y, Feinberg MS, Margalit R and Leor J. Targeting and modulating infarct macrophages with hemin formulated in designed lipid-based particles improves cardiac remodeling and function. *J Control Release*. 2017.

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.

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;58:26-33.

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.

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.

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.

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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.

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Grants

2018-2020 Ministry of Science, Polymer to treat heart failure of the 3rd age

2018-2021 Binational Science Foundation, A new method for imaging and treatment of heart failure (with Fred Epstein, Ayelet David)

2020-2022 Ministry of Science, Smart cells for heart repair

2020-2022 Ministry of Health, Targeting inflammation to treat cardiac fibrosis

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Dr. Shani Shenhar-Tsarfaty, Ph.D.

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Stress and Inflammation in the Cardiovascular System

Positions (Prof. Shapira)

Deputy Director General and Director, Rehabilitation Hospital

Associate Dean, Tel Aviv Sourasky Medical Center

Full Clinical Professor

Research

- Cholinergic regulation of stress and inflammation.
- Exercise-induced urinary protein secretion as a risk for metabolic syndrome.
- Determination of new set of control limits for the identification of patients at risk.
- The influence of work characteristics (burnout and stress) on physical health.

The Tel Aviv Medical Center Inflammation Survey (TAMCIS) is a long-term, ongoing cardiovascular cohort study evaluating stress and inflammation in 22,000 apparently healthy working adults admitting to our medical center for routine annual medical check-ups. It is designed to evaluate the association between physiological and psychological measures of stress, inflammatory profile and their additive effect on cardiovascular risk.

Our database includes more than 50,000 visits with more than 600 parameters per visit; including medical history and medication, laboratory tests (Metabolic profile, Blood chemistry, blood count and Urine tests), ophthalmologist examination, exercise test and spirometry, psychological comprehensive questionnaire consisting of socio-demographic variables, personal and family medical history, health behaviors, among them dietary and sports habits, objective as well as subjective work conditions and various psychological scales such as depression, fear of terror, burnout, perceived control and social support. Research methods include basic molecular biology as well as sophisticated statistical models. The study team includes multidisciplinary researchers and physicians, from internal medicine, cardiology and neurology departments, biology and the School of Management.

Publications

S Shenhar-Tsarfaty, **I Shapira**, S Toker, O Rogowski, S Berliner, Y Ritov, H Soreq.Weakened cholinergic blockade of inflammation associates with diabetes-related depression.Mol Med, 22, 156-161, 2016.

S Greenberg, **S Shenhar-Tsarfaty**, O Rogowski, **I Shapira**, D Zeltser, T Weinstein, D Lahav, J Vered, O Tovia-Brodie, Y Arbel, S Berliner, A Milwidsky. Exercise-induced albuminuria is related to the metabolic syndrome. Am J Physiol-Ren Physiol, 210, 1192-1196, 2016.

Shenhar-Tsarfaty S,Kliper E, Molad J, Berliner S, Shapira I, Ben-Bashat D, Shopin L, Tene O, Rosenberg GA, Bornstein NM, Ben Assayag E. Impaired renal function is associated with brain atrophy and poststroke cognitive decline. Neurology, 86, 1996-2005, 2016.

Lin T, Simchovitz A, **Shenhar-Tsarfaty S**, Vaisvaser S, Admon R, Hanin G, et al. Intensified vmPFC surveillance over PTSS under perturbed microRNA-608/AChE interaction. Translational Psychiatry. 6, e801, 2016.

Tene O, **Shenhar-Tsarfaty S**, Korczyn AD, Kliper E, Hallevi H, Shopin L, et al. Depressive symptoms following stroke and transient ischemic attack: is it time for a more intensive treatment approach? results from the TABASCO cohort study. Journal of Clinical Psychiatry. 77, 673-680, 2016.

Seyman E, Shaim H, **Shenhar-Tsarfaty S**, Jonash-Kimchi T, Bornstein NM, Hallevi H. The collateral circulation determines cortical infarct volume in anterior circulation ischemic stroke. BMC eurology. 16, 206, 2016.

Kliper E, Ben Assayag E, Korczyn AD, Auriel E, Shopin L, Hallevi H, **Shenhar-Tsarfaty S**, et al. Cognitive state following mild stroke: A matter of hippocampal mean diffusivity. Hippocampus. 26, 61-69, 2016.

Y Sofer, E Osher, R Limor, G Shefer, Y Marcus, **I Shapira**, K Tordjman, Y Greenman, S Berliner, N Stern. Gender determines serum free cortisol: higher levels in men. Endocr Pract, 22, 1415-1421, 2016.

Y Herishanu, A Polliack, **S Shenhar-Tsarfaty**, R Weinberger, R Gelman, T Ziv-Baran, D Zeltser, **I Shapira**, S Berliner, O Rogowski. Increased serum C-reactive protein levels are associated with shorter survival and development of second cancers in chronic lymphocytic leukemia. Ann Med, 2016.

Prof. Sami Viskin, M.D.

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Sackler Faculty of Medicine

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Positions

Associate Professor, Senior Lecturer, Sackler Faculty of Medicine

Chair, Israel Working Group on Cardica Pacing and Electrophysiology, Israel heart Society

Associate Editor – Circulation

Past Associate Editor – *Heart Rhythm*

Past Associate Editor – *Europace*

Research

We perform clinical studies on cardiac arrhythmias, particularly related to long QT syndrome, Brugada syndrome and early repolarization. We have several ongoing studies on long QT syndrome caused by atrioventricular block, drug induced long QT syndrome, empiric quinidine therapy for Brugada syndrome.

Publications

Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Heart Rhythm 2016;13:e50-86.

Wilkoff BL, Fauchier L, Stiles MK et al. Erratum to '2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-de fi brillator programming and testing' [Journal of Arrhythmia 32/1 (2016) 1-28]. J Arrhythm 2016;32:441-442.

Wilkoff BL, Fauchier L, Stiles MK et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace 2016;18:159-83.

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Viskin S, Havakuk O, Antzelevitch C, Rosso R. Malignant early repolarization: It's the T-wave, stupid. Heart Rhythm 2016;13:903-4.

Rosso R, Chorin E, Levi Y, Rogowski O, **Viskin S**. Radiofrequency Ablation of Atrial Fibrillation: Nonrandomized Comparison of Circular versus Point-by-Point "Smart" Ablation for Achieving Circumferential Pulmonary Vein Isolation and Curing Arrhythmic Symptoms. J Cardiovasc Electrophysiol 2016.

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Mont L, Pelliccia A, Sharma S et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Europace 2016.

Mont L, Pelliccia A, Sharma S et al. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. Eur J Prev Cardiol 2016.

Mizusawa Y, Morita H, Adler A et al. Prognostic significance of fever-induced Brugada syndrome. Heart Rhythm 2016;13:1515-20.

Michowitz Y, Viskin S, Rosso R. Exercise-induced Ventricular Tachycardia/Ventricular Fibrillation in the Normal Heart: Risk Stratification and Management. Card Electrophysiol Clin 2016;8:593-600.

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Chorin E, Rosso R, **Viskin S**. Electrocardiographic Manifestations of Calcium Abnormalities. Ann Noninvasive Electrocardiol 2016;21:7-9.

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Chorin E, Hochstadt A, **Viskin S** et al. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block. Heart Rhythm 2016.

Antzelevitch C, Yan GX, Ackerman MJ et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latinoamericana de Estimulacifin Cardiaca y Electro fi siologia [SOLAECE]). Europace 2016.

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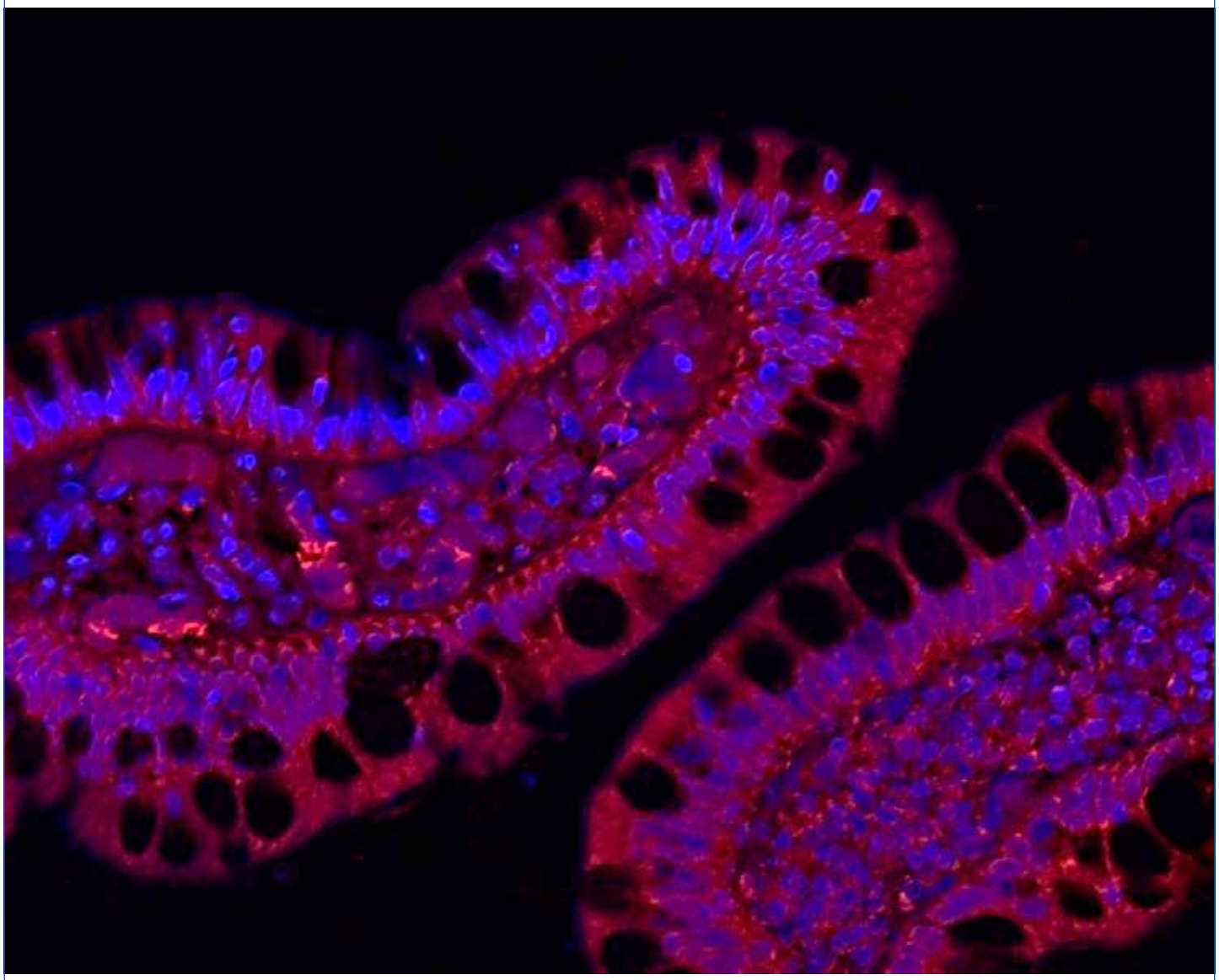
Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: Clinical characteristics, electrocardiographic parameters, and auxiliary testing. Heart Rhythm 2016;13:299-310.

Digestive System



Immunofluorescence of PAR-4 expression in human mucosal biopsy from normal pouch. Credit: Sarit Hoffman, Ilya Borovok, Iris Dotan, Nitsan Maharshak

Prof. Ziv Ben-Ari, M.D.

Sheba Medical Center, Tel Hashomer

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Basic and Translational Research of Liver Diseases

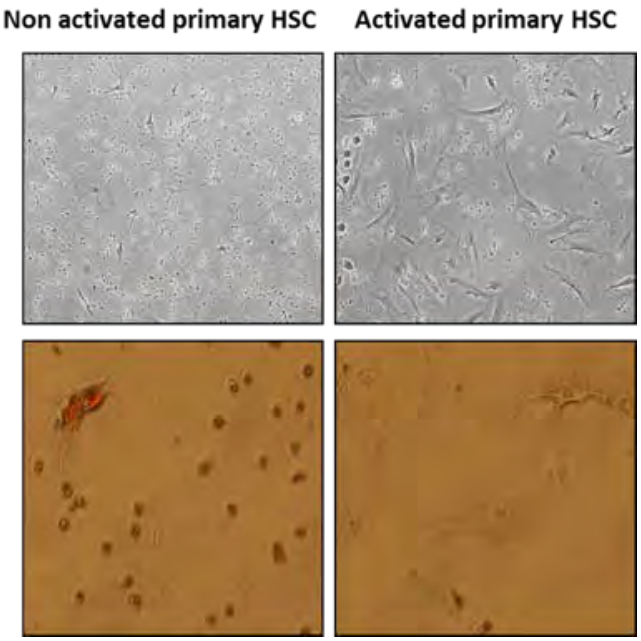
Positions

Director, Liver Disease Center

Research

Our lab is part of the Liver Disease Center at the Chaim Sheba Medical Center. We focus our studies on basic and applied liver disease research to better understand and improve the diagnosis and treatment of different liver diseases. We utilize various methods such as molecular biology, biochemistry, genetics, tissue culture and in-vitro and in-vivo models. The proximity between the Liver Disease Center and the lab creates a unique and highly successful dynamic relationship where the unsolved clinical needs are immediately translated into research for achieving better solutions.

The research in our lab is divided into two main projects:



Phenotypic alterations in HSCs after activation/differentiation to myoblast-like cells.

1. Molecular mechanisms in the development of liver fibrosis

Fibrosis is the excess accumulation of extracellular matrix (ECM), resulting from chronic, non-resolving inflammation. Multiple etiologies underlie development of liver fibrosis, such as chronic viral hepatitis B or C, autoimmune and biliary diseases, alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). Fibrosis progression toward cirrhosis is the major cause of liver-related morbidity and mortality. Patient with cirrhosis are more prone to develop liver failure, portal hypertension or infection and are at higher risk of developing hepatocellular carcinoma (HCC). In the normal liver, hepatic stellate cells (HSCs) constitute quiescent, vitamin A–storing cell. Following activation by specific stimuli released by an injured liver, HSCs undergo “activation”or transdifferentiation, yielding a myofibroblast-like cell. We are currently investigating the interactions between hepatocytes and HSCs in healthy and fibrotic livers in the different chronic liver diseases listed above. Our goal is to advance the research in this field and to establish resolution of liver fibrosis.

2. Microbiome and liver diseases

The human gastrointestinal tract hosts a large number of microbial cells, which exceeds their mammalian counterparts by approximately 3-fold. The genes expressed by these microorganisms constitute the gut microbiome and participate in diverse and essential functions, including digestion, regulation of energy metabolism and modulation of inflammation and immunity. The liver, due to its critical functional relationship with the gastrointestinal (GI) tract, is continually exposed to multiple harmful and beneficial microorganisms derived from the small and large intestines. We study the microbiota signature of patients with different liver diseases (Primary Sclerosing cholangitis (PSC), PSC-IBD, Hepatocellular carcinoma and cirrhosis) and compare

them to healthy control. Moreover, we investigate the correlation between environmental lifestyle and diet patterns, the host microbiome and disease etiologies.

Publications

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Drug Mechanisms and Immunogenicity in IBD

Positions

Director, IBD Service, Gastroenterology Dept. Sheba Medical Center

Associate Professor of Medicine, Sackler Faculty of Medicine

Member, Organization Committee, European Crohn' & colitis Organziation (ECCO)

Research

We focus on translational science, aiming to study drug mechanisms in IBD. Specifically, we study mechanisms whereby immune-modulating and biologic drugs exert their cellular effects and/or cause unwanted adverse events, as well as immunogenicity of biologic drugs, i.e. the eliciting of immune hyper-responsiveness in the recipient towards the biologic drug. We are interested also in studying novel herbal compunds for possible synergistic effects with conventional immune-modulators.

Completed projects include:

1. A study to deciper the delay in onset of action of thiopurine related to gradual depletion of antigen-specific memory T-cells
2. Development of novel and one of the first available assays to measue anti-drug antibodies against infliximab, and later adalimumab and currently vedolizumab
3. Identifying the Fab fragment as the immune-dominant fragment of infliximab, responsible for eliciting anti-drug antibodies
4. Study of cross-immunogenicity of infliximab and its bio-similar drug, CT-P13

Ongoing projects include:

1. Studying cellular mecahnisms responsible for B-cell lymphoproliferation under immune-modulating drugs
2. Studing the decay in immune-suppression following azathioprine withdrawal
3. Studying herbal Chinese compounds effects on cells propogating inflammation

Publications

Ben-Horin S, Yavzori M, Benhar I, Picard O, Fudim E, Ungar B, Lee SY, Kim SH, Eliakim R, Chowers Y. Cross-immunogenicity: Antibodies to infliximab in Remicade-treated IBD patients similarly recognize the bio-similar Remsima. Gut 2016; 65(7):1132-8.

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Engel T, Ungar B, Ben-Haim G, Levhar N, Eliakim R, **Ben-Horin S**. Re-phrasing the question: A simple tool for evaluation of adherence to therapy in patients with inflammatory bowel disease. United European Gastroenterol J. 2017;5(6):880-886.

He Y, Mao R, Chen F, Xu PP, Chen BL, Wu Y, Qiu Y, Zhang SH, Feng R, Zeng ZR, **Ben-Horin S**, Chen MH. Thalidomide induces clinical remission and mucosal healing in adults with active Crohn's disease: a prospective open-label study. Therap Adv Gastroenterol. 2017;10(5):397-406

Lahat A*, Bar-Gil Shitrit A*, Naftali N, Milgrom Y, Elyakim R, Goldin E, Levhar N, Selinger L, Zuker T, Fudim E, Picard O,Yavzori M, Ben-**Horin S**. Vedolizumab levels in breast milk of nursing mothers with inflammatory bowel disease. J Crohns Colitis 2017; 12(1):120-123.

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Orbach-Zingboim N, Mao R, Chen M, Chowers Y, Eliakim R, **Ben-Horin S**. Association of Vedolizumab level, anti-drug antibodies, and $\alpha 4\beta 7$ occupancy with response in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2017; pii: S1542-3565(17)31423-4.

Grants

2015–2020 Horizon 2020 Immungenicity of infliximab, within the SPARE trial (BioCycle consortium)

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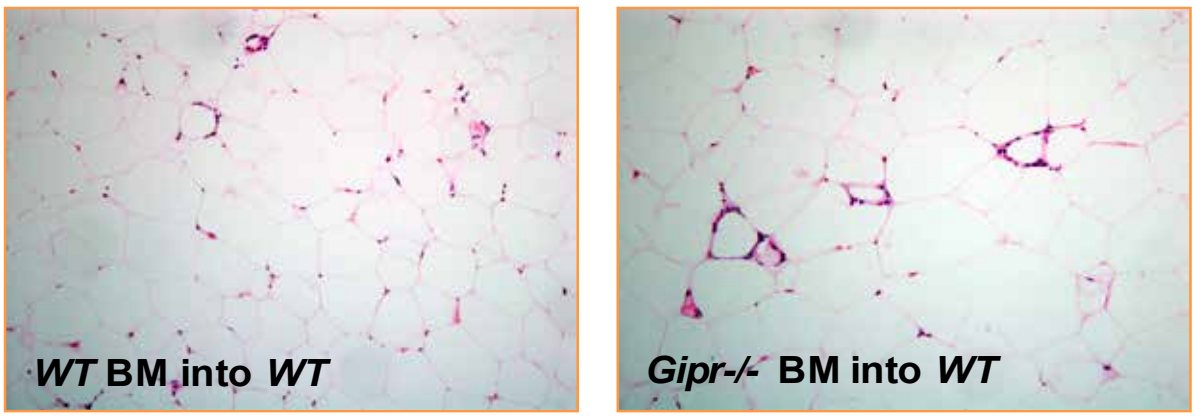
The Role of Incretin Hormones in Macrophage Regulation of Obesity, Inflammation and Insulin Resistance

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Recent studies have suggested that GIP participates in the dynamic and progressive crosstalk between the two fundamental systems of metabolism and immunity. Yet, whether GIP can directly act on immune cells and the resulting consequences on the development and progression of obesity remain elusive. We have previously demonstrated in a murine model of high fat diet (HFD) that a long-acting GIP analogue significantly reduces visceral fat infiltration of pro-inflammatory immune cells and improves insulin sensitivity, thus, highlighting a possible role for GIP as a linker between energy balance and immunologic responses. Our preliminary results clearly indicate that impairment of GIP-governed regulation of immune cells perturbs energy homeostasis, promotes insulin resistance (IR) and intensifies the inflammatory response under HFD. Therefore, we continue to investigate the direct immuno-regulatory role of GIP in immune cells and specifically in adipose tissue macrophages (ATM) and the resulting consequences on the inflammatory response and on the metabolic state in obese human and mice. Specifically, we hypothesize that GIP negatively regulates S100A8/9 in ATM and thereby affects myelopoiesis and energy homeostatasis by attenuating beiging in subcutaneous fat. In addition, we suggest that GIP positively mediates, at least in part, whole body energy homeostasis and adipose tissue metabolism through its direct effect on immune cell function. Here, we intend to utilize BM chimerism approach to target GIPR-deficiency to immune cells to explore the role of GIP in immune cells and specifically ATM. We are using chimeras reconstituted with GIP receptor (GIPR)-defficient bone marrow and determine the metabolic and immune phenotype of the mice. To specifically investigate the physiological role of GIP as regulator of ATM function, GIPR-deficiency has been targeted to ATM by using the cre-lox system and crossing the Gipr fl/fl mice with or Cx3cr1-cre mice. We are exploring the role of GIP-governed regulation of immune cell and specifically ATM function and the role of GIP-S100A8/9axis in dictating whole body energy balance, we will perform metabolic analyses that assess energy expenditure, fat versus



Visceral adipose tissue of chimeric mice reconstituted with WT or *Gipr*$^{-/-}$ bone marrow (BM) and exposed to a 14 weeks high fat diet regimen, showing increased infiltrating immune cells in the *Gipr*$^{-/-}$ BM reconstituted mice.

glucose utilization, locomotor activity as well as insulin sensitivity. Bone marrow, blood and adipose tissue myelopoiesis is assessed in the various mice exposed to a HFD regimen. We are also identifying target genes in visceral and subcutaneous fat of both chimeric mice and GIPR conditional knockout mice. Finally, we will study the ability of GIP to negatively regulate S100A8/9 in visceral fat explants and sorted ATM extracted from human obese patients.

Expected significance: Our integrative approach will allow significant progress towards revealing basic GIP governed immune-regulatory mechanisms operating at the interface between adipose tissue inflammation and metabolism and their involvement in the pathophysiology of obesity-induced IR. Insights gained in this study will uncover a yet unknown role for GIP in regulating the pathophysiological link between ATM and obesity and may lead to future identification of another class of incretin drugs, namely GIP analogs, with the potential to improve whole body insulin sensitivity via immune cell regulation.

Publications

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Host: Microbial Interactions – Translational Research in Gastrointestinal Diseases

Positions

Physician-Scientist, Sheba Medical Center

Senior Lecturer, Tel Aviv University

Adjunct Assistant Professor, Division of Pediatric Gastroenterology, Hepatology, & Nutrition, Cincinnati Children's Hospital Medical Center, OH, USA.

Research

We are interested in integrating clinical questions, "big-data" approaches, basic science, and bioinformatics with a goal to improve personalized patients' diagnostic and therapeutic decision. Our interests include host-microbial interactions in health and pathologic conditions including Crohn's disease and ulcerative colitis. We use a high-throughput approach to detect the widest range of microbial shifts and host gene expression in the actual lining of the gut and feces to characterize disease phenotype and outcome to tailor personalized therapy.

Within our research we focus on characterizing the role of non-coding elements (non-coding RNAs) and and we try to elucidate if and how these non-coding regions take part in the host:microbial interactions.

Publications

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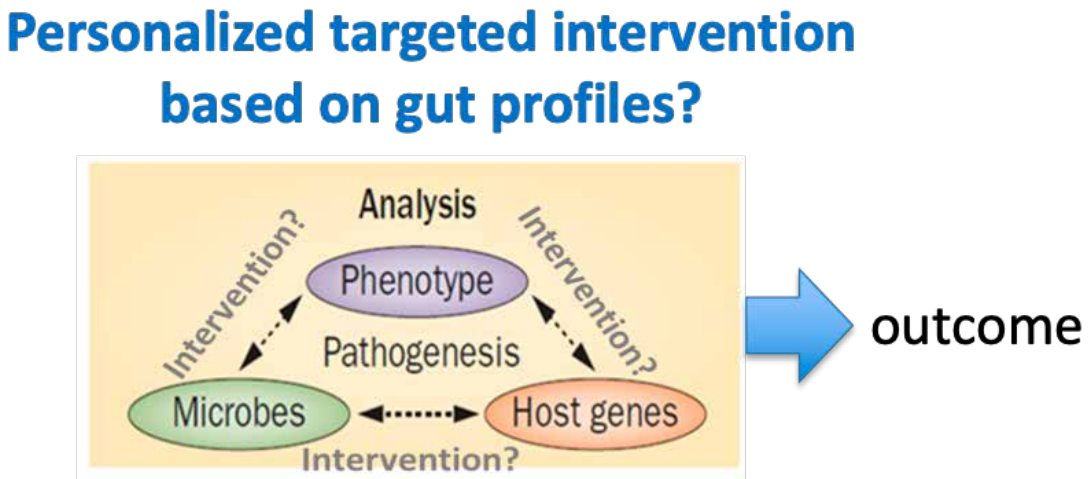

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Book chapters

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The Research Center for Digestive Tract & Liver Diseases; Department of Gastroenterology and Liver Diseases; Tel Aviv Medical Center
Sackler Faculty of Medicine

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Investigating the Microbiome-Human Interactions

Positions

Associate Professor, Sackler Faculty of Medicine

Head of Inflammatory Bowel Disease Unit and Bacteriotherapy Clinic

Deputy Chief, Department of Gastroenterology and Liver Diseases ,Tel-Aviv Sourasky Medical Center

Research

We study the role of enteric bacteria in inflammatory and metabolic related disease conditions in humans and in-vitro. Specifically, we study how bacterial proteases impact the epithelial barrier function and how enteric microbial alterations are related to diseases. Clinically, we study the implication of fecal microbial transplantation in disease conditions.

Publications

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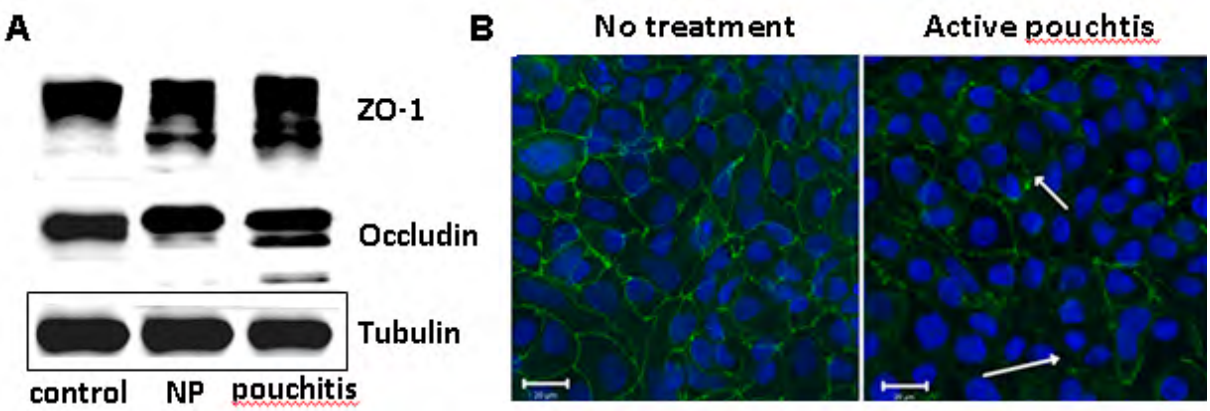

Fecal supernatants from pouchitis patients have increased proteolytic activity, disrupt epithelial tight junctions and increase epithelial permeability. Fecal supernatants isolated from pouchitis patients compared to healthy controls and normal pouch (NP) patients caused: **(A)** disruption of tight junction proteins (ZO-1, occludin) as assessed by Western blot. **(B)** Decrease ZO-1 immunofluorescence (white arrows) of Caco-2 cells mononlayters. Alexa anti mouse 488 was used as the secondary antibody (green). Nuclei were counterstained with DAPI and are shown in blue.

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Positions

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Research

Biliary atresia (BA) is a fibro-obliterative disease of the extrahepatic bile ducts affecting newborns, and is the leading indication for pediatric liver transplant. The etiology remains unknown and there is no effective treatment. We identified an isoflavonoid toxin, biliatresone, that causes BA outbreaks in Australian livestock and we showed that it causes lumen obstruction of neonatal mouse bile duct (NBD) explants. This is a novel tool for the study of BA and allows us to study the primary event in the disease, providing new potential for identifying therapeutic interventions. We found that biliatresone acts by inducing a rapid and transient decrease in reduced glutathione (GSH) and a decrease in SOX17

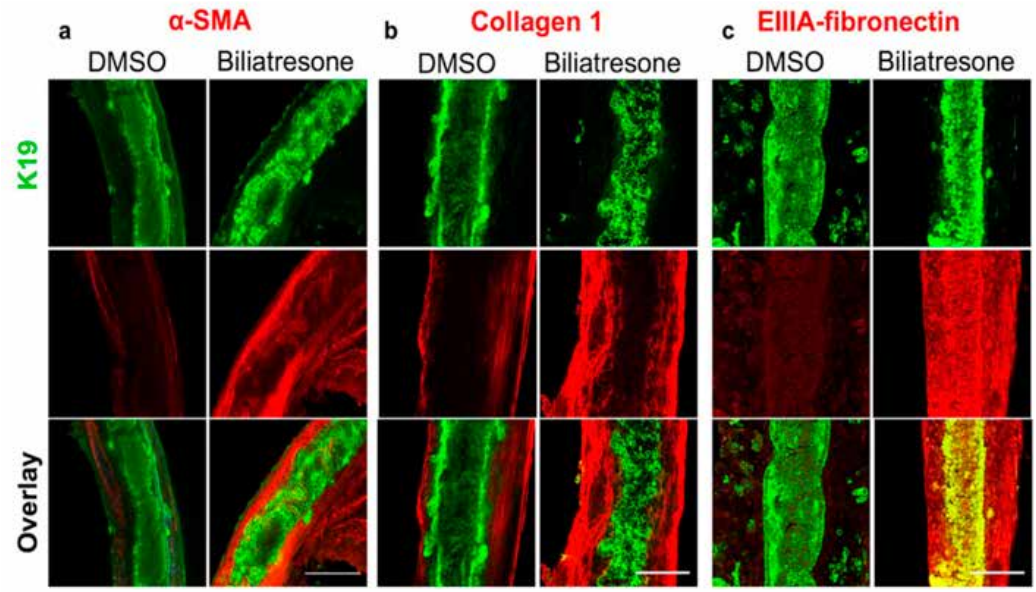

Figure: Biliatresone induces ductal fibrosis. Neonatal mouse bile duct explants were incubated with DMSO or biliatresone for 24 h and stained for the cholangiocyte marker K19 (green) or the myofibroblast marker smooth muscle actin (SMA) or collagen I or the EIIIA splice variant of fibronectin (all red). Scale bars 100 μm.

in cholangiocytes and that cholangiocyte injury can be mimicked using DL-buthionine sulfoximine (BSO) to reduce GSH or by knocking down *Sox17*. NBD cultured *ex vivo* and treated with either biliatresone or BSO showed disruption of the cholangiocyte monolayer, lumen obstruction, and subepithelial myofibroblast differentiation and fibrosis. Both obstruction and fibrosis could be prevented using GSH-protective agents, and were reversible with biliatresone wash out. In this proposal, we aim to define mechanistically the relationship between biliatresone, decreased GSH and downstream signaling molecules (Hey2, Hes1, RhoU, DAAM1 and other WNT signaling pathway genes) in the disruption of cholangiocytes and bile duct integrity. We will study the relationship between changes in cellular tubulin, loss of apical polarity, epithelial permeability and fibrosis and mechanism of repair of cholangiocyte damage and fibrosis. Understanding potential mechanisms of initial injury in BA may lead to new treatments.

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Grants

	Personalizing Mediterranean diet in Children: the Ferrero Pilot Trial (RS)
2017-2020	ISF (OWZ)

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Elucidating Mechanisms of Endoplasmatic Reticulum (ER) Stress and mTOR Cross-Talk in Drug-Induced Liver Injury

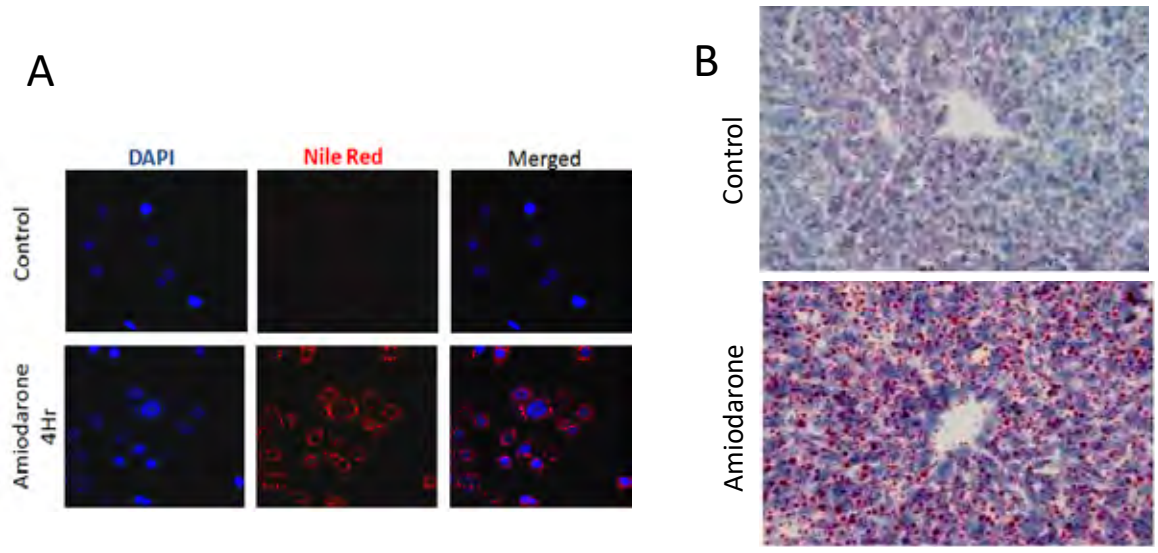
Positions

Professor, Sackler Faculty of Medicine

Head, Gastroenterology Institute, Tel Aviv Sourasky Medical Center

Research

The liver is a major site for drug metabolism and elimination, and is susceptible to drug toxicity. In fact, drug induced liver injury (DILI) has become the leading cause of acute liver failure in western countries, so DILI is a major clinical problem conferring significant health and financial burdens. The endoplasmic reticulum (ER) is the cellular site for protein folding. ER stress occurs when the amount of protein entering the ER exceeds its folding capacity. It induces a cyto-protective reaction collectively termed the unfolded protein response (UPR). We hypothesize that ER stress/UPR pathways are activated in response to hepatic drug metabolism survival-apoptosis-autophagy and together with mTOR signaling may mediate the hepatocyte damage and recovery associated with DILI. Our group is investigating the induction of ER stress/UPR by various hepatotoxic drugs, including acetaminophen (N-acetyl-p-aminophenol-APAP) and amiodarone. Our studies include DILI models in novel genetically modified mouse models with reduced ER stress. In addition, we are also exploring the therapeutic potential of chemical chaperones that relieve ER stress and may become therapies for DILI and improve liver regeneration following injury. In particular, we are focusing on the cross talk between ER stress and pathways of hepatic steatosis.



A. In vitro treatment with amiodarone induces lipid accumulation Lipid accumulation in immortalized hepatocytes assessed by Nile red staining. DAPI (blue) was used for nuclei staining. B. In vivo treatment with amiodarone leads to hepatic lipid accumulation. Oil Red O staining of liver from control or amiodarone treated mice.

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Mononuclear Phagocytes in Digestive Tract Diseases

Positions

Senior Lecturer, Sackler Faculty of Medicine, Department of Clinical Microbiology and Immunology

Director, Research Center for Digestive Tract & Liver Diseases

Research

We are studying the role of mononuclear phagocytes in the pathogenesis of IBD, liver diseases, metabolic diseases and colorectal cancer. We utilize transgenic murine systems as well as human patient tissues to mechanistically unravel the involvement of these cells in the pathophysiology of these diseases. Among our main research topics:

- The interplay between immune cells and extracellular matrix (ECM) remodeling in the pathogenesis of IBD, colorectal cancer and liver fibrosis
- Monocytes and macrophage type of immune cells as pivotal drivers of inflammation and resolution during drug-induced liver injury, liver fibrosis and IBD
- The incretin hormone GIP as key linker between metabolism and immunity in type II diabetes

Publications

Itay Moshkovitz, Hadar reichman, Danielle Karo-Atar, Perri Rozenberg, Ehud Zigmond, Yael Ziv-Haberman, Netali Ben-Baruch-Morgenstern, Maria Lampinen, Marie Carlson, Michal Itan, Lee Denson, **Chen Varol** and Ariel Munitz. A key requirement for CD300f in innate immune responses of eosinophils in colitis. 2017. *Mucosal Immunology.* 10:172-183.

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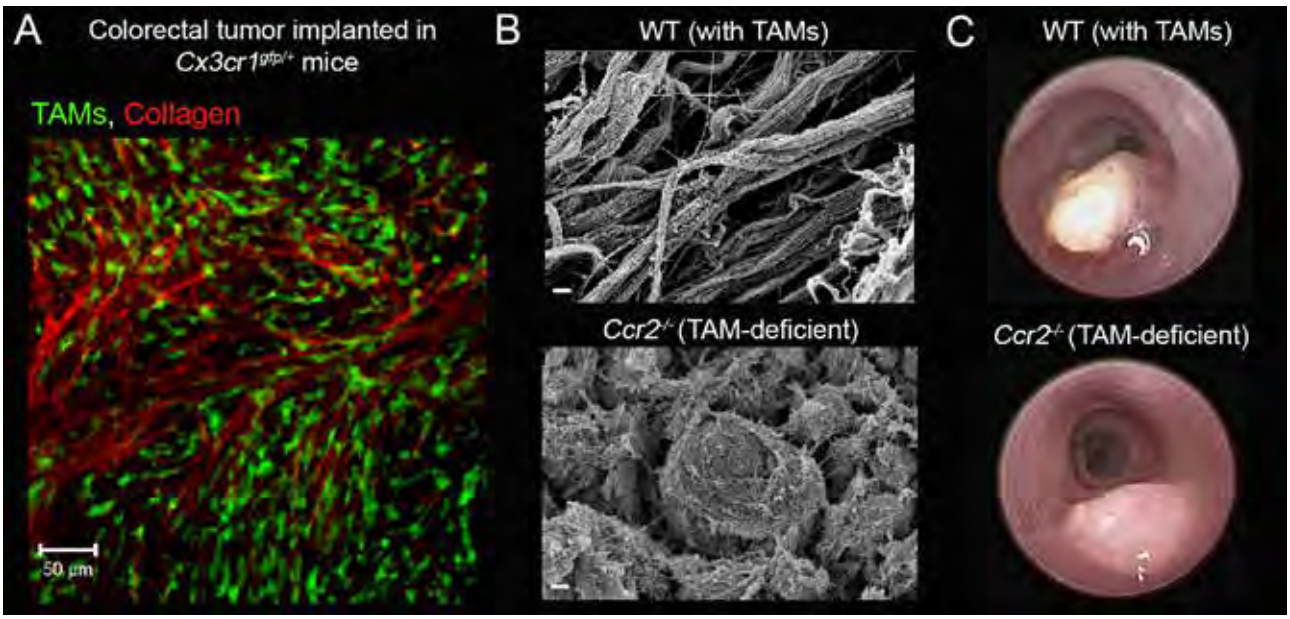

Tumor associated macrophages (TAMs) are pivotal constructors of the colorectal tumor collagenous matrix (Afik et al., JEM, 2016). (A) Confocal imaging showing the co-localization of TAMs (green) with collagen matrix (red). (B) Scanning electron microscopy (SEM) images of decellularized ECM scaffolds extracted from WT and TAM-deficient colorectal tumors. TAMs instruct collagen crosslinking and linearization processes, which are essential for tumor development, expansion and invasion. (C) Murine colonoscopy images showing the impaired colorectal tumor development in the absence of TAMs.

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Grants

2016 – present Endogenous-like inhibitors for ADAM17 and ADAM8 –novel therapeutic agents for Inflammatory bowel diseases (IBD), Azrieli Foundation

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Investigating the Mechanisms of Liver Steatosis, Obesity and Cholestatic Injury

Positions

Principal investigator, Research Center for Digestive Tract and Liver Diseases

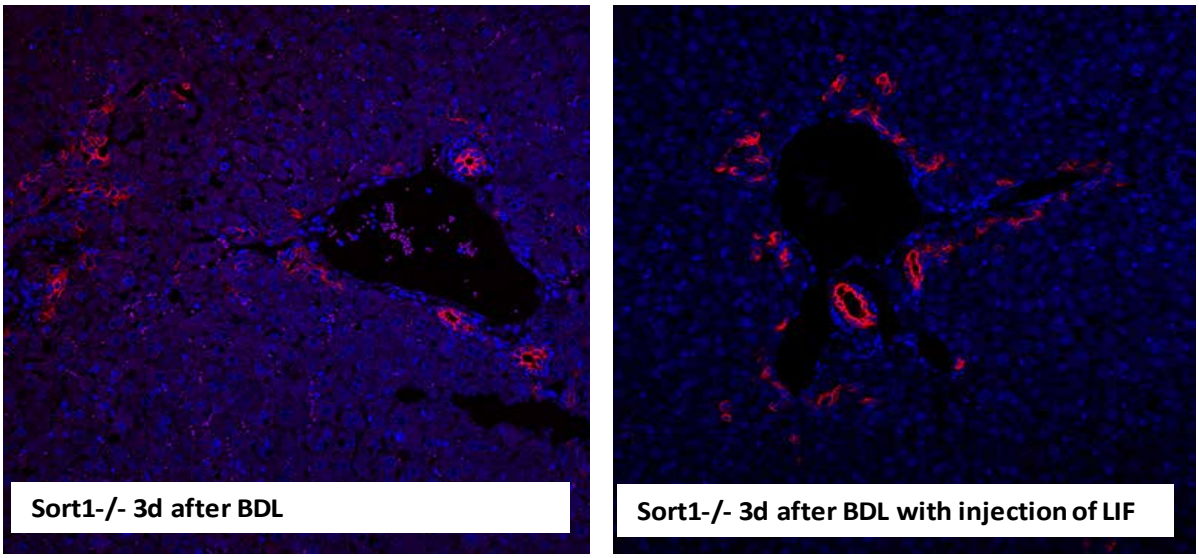
Tel Aviv Sourasky Medical Center

Senior Lecturer, Sackler Faculty of Medicine

Research

Our lab is investigating two main diseases, liver steatosis in models of diet-induced obesity and insulin resistance and cholestatic liver injury. Obesity and the metabolic syndrome accompanying it affect a large percentage of Western world population and the obesity epidemic is only expected to increase, therefore it's of the utmost importance to understand the mechanisms involved.

Cholestatic liver injury can be caused by various factors that impair bile flow and result in accumulation of bile in the liver, such as genetic defects, structural/mechanical obstruction of bile ducts impairing bile flow (e.g., common bile duct stones), toxins, and dysregulated function of the immune system. The two main cholestatic disorders in adult human patients are primary biliary cholangitis and primary sclerosing cholangitis for which liver transplantation is the only treatment as the disease progresses to liver failure. Specifically, we are investigating the roles played by sortilin, a trafficking molecule and a co-receptor, in both obesity and cholestatic liver damage, since we have found that sortilin deficiency has a protective role in diet-induced obesity and in murine models of primary sclerosing cholangitis. We are using both isolated liver cells (hepatocytes, cholangiocytes) as well as the cre-flox model where sortilin is deleted in various liver cells in order to further elucidate the mechanisms and signals regulating the protective roles of sortilin.



Staining for cytokeration 19 (red) shows formation of epithelial bile duct cells after cholestatic injury induced by bile duct ligation in *Sort1*$^{-/-}$ mice and inductionof proliferation of bile duct cells by administration of leukemia inhibitory factor (LIF).

Publications

Hubel E, Saroha A, Park WJ, Pewzner-Jung Y, Lavoie EG, Futerman AH, Rafael Bruck, Sigal Fishman S, Dranoff JA, Shibolet O*, **Zvibel I***. 2016. Sortilin deficiency reduces ductular reaction, hepatocyte apoptosis and liver fibrosis in cholestatic-induced liver injury. Am.J. Pathol. 2017; 187:122-133. *equal senior authors.

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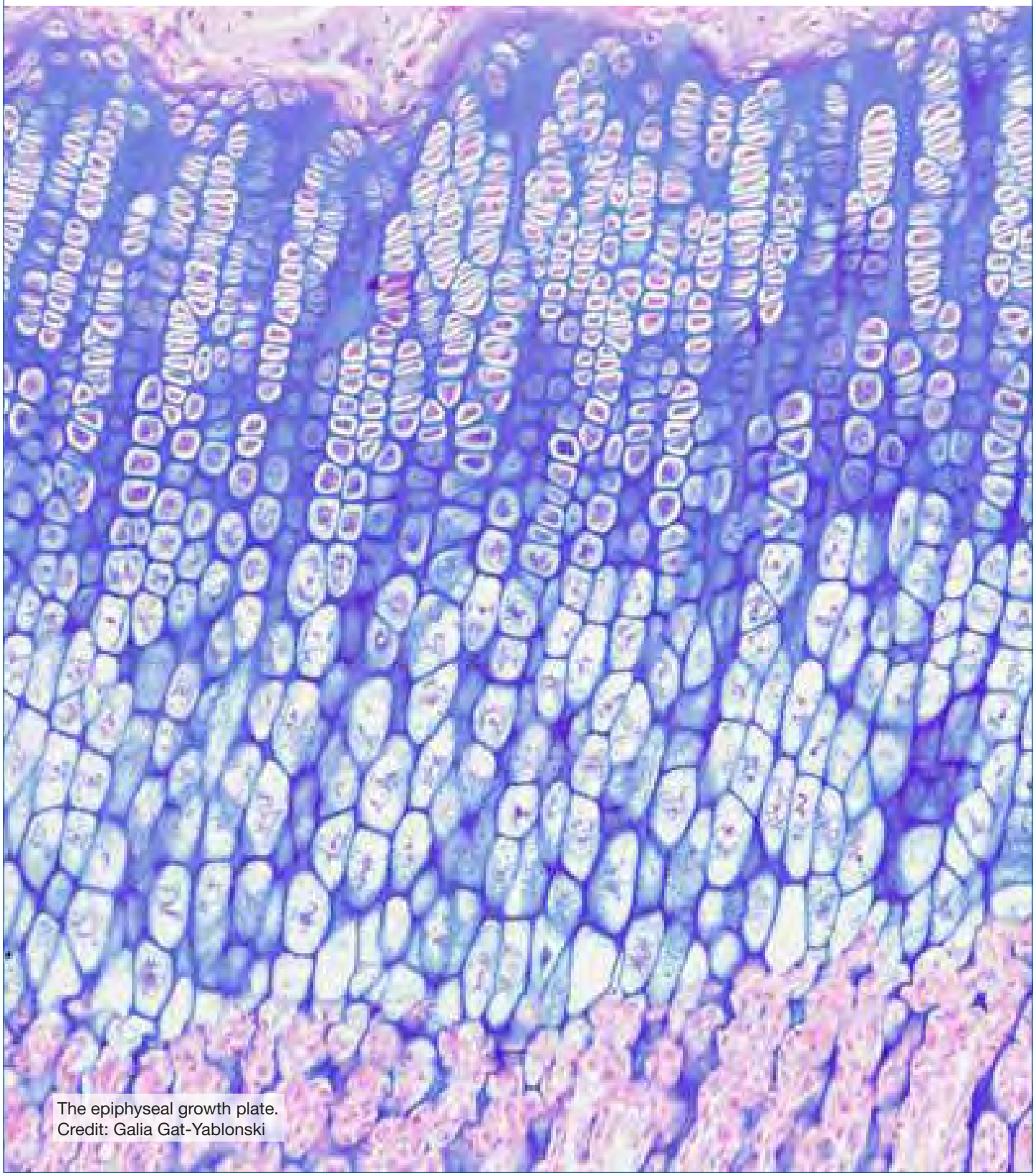
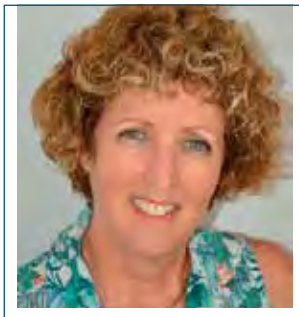
Endocrine Disease



The epiphyseal growth plate.
Credit: Galia Gat-Yablonski



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Prof. Moshe Phillip, M.D.

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Investigating the Molecular Basis of Linear Growth in Children and Animal Models

Positions – Moshe Phillip, M.D.

Professor, Sackler Faculty of Medicine

Director, Institute for Endocrinology and Diabetes

National Center for Childhood Diabetes

Schneider Children's Medical Center of Israel

Vice Dean for Research and Development, Sackler Faculty of Medicine

Positions – Galia Gat-Yablonski, Ph.D.

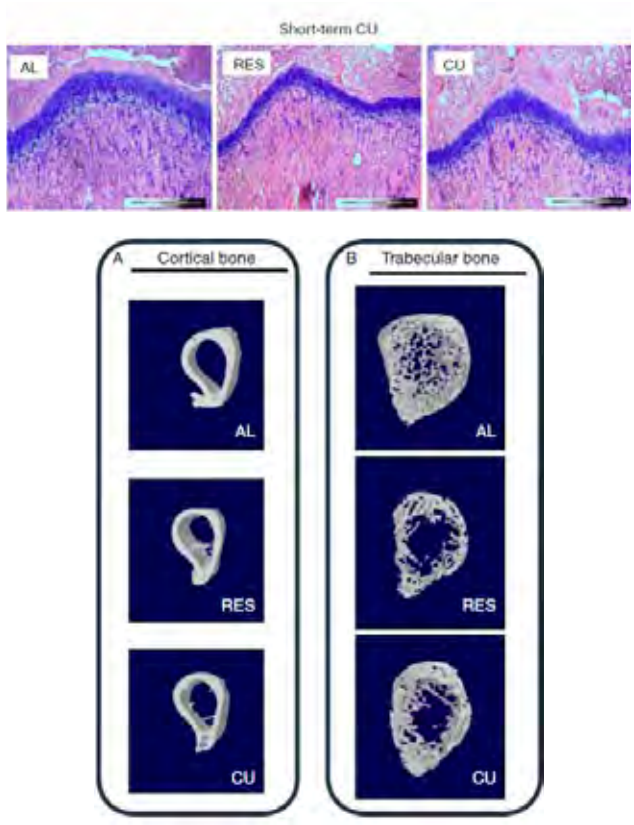
Senior Lecturer, Sackler Faculty of Medicine

Committee Member, Israel Endocrine Society

Research

Children's growth is regulated by both genetic and environmental factors. The most effective environmental factor is nutrition; however, the mechanisms connecting nutrition and longitudinal growth are still not fully understood. Deciphering theses mechanisms both in children and in animal models of rats and mice, has been the focus of our research, as currently means to improve growth in short statured children are very limited.

We have identified several novel and important factors that are involved in regulation of this process, including growth factors that are produced and secreted from adipocytes such as leptin and GDF5, transcription factors such as hypoxia inducible factor (HIF)-1, and epigenetic factors such microRNAs and histone deacetylases including SIRT1, HDAC10. We



Effect of Food restrictions (RES) and one day of re-feeding (CU) on growth plate height (above) and bone microarchitecture (below)

have also studies extensively the effect of nutritional manipulation on bone quality in young rats. We may now exploit these findings as targets of new treatment strategies for children with growth disorders as well as children with special nutritional needs like premature babies, infants and children with chronic diseases associated with nutritional problems.

Publications

Marianna Rachmiel, Pnina Strauss, Nitzan Dror, Hadassa Benzaquen, Orit Horesh, Nave Tova, Naomi Weintrob, Zohar Landau, Michal Ben-Ami, Alon Haim, **Moshe Phillip**, Tzvi Bistritzer, Eli C Lewis, Yael Lebenthal. Alpha1-Antitrypsin Therapy is Safe and Well Tolerated in Children and Adolescents with Newly Diagnosed Type 1 Diabetes Mellitus. Pediatr Diabetes. 2016;17(5):351-9.

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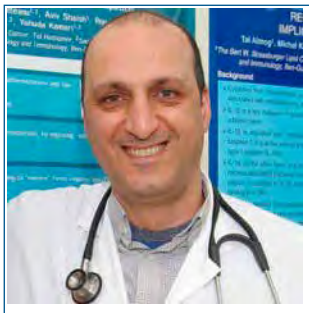

Dr. Yehuda Kamari, M.D, Ph.D.

Vascular Biology Research Unit; Bert W. Strassburger Lipid Center; Talpiot Sheba Medical Leadership Program; Sheba Medical Center, Tel Hashomer.

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Investigating Lipid Metabolism and Atherosclerosis

Positions

Senior Lecturer, Medicine, Sackler School of Medicine

Research

Our research interests are within the fields of metabolic inflammation that contributes to the derangements of fat accumulation in atherosclerosis, fatty liver disease and diabetes. Specifically, we study the role of the inflammatory cytokine IL-1α and the ubiquitin-like protein HLA-F Adjacent Transcript 10 (FAT10) in these diseases. We recently discovered that the inflammatory cytokine IL-1α has an important role in early and advanced stages of atherosclerosis and fatty liver disease. We also discovered an unexpected role of IL-1α in determining ovarian lifespan and fertility.

We apply advanced technologies including genetically modified mice (Cre/loxP), molecular and cellular biology and microarray analysis to identify and functionally characterize genes that regulate atherosclerosis with the ultimate aim to prevent and treat this deadly disease.

Publications

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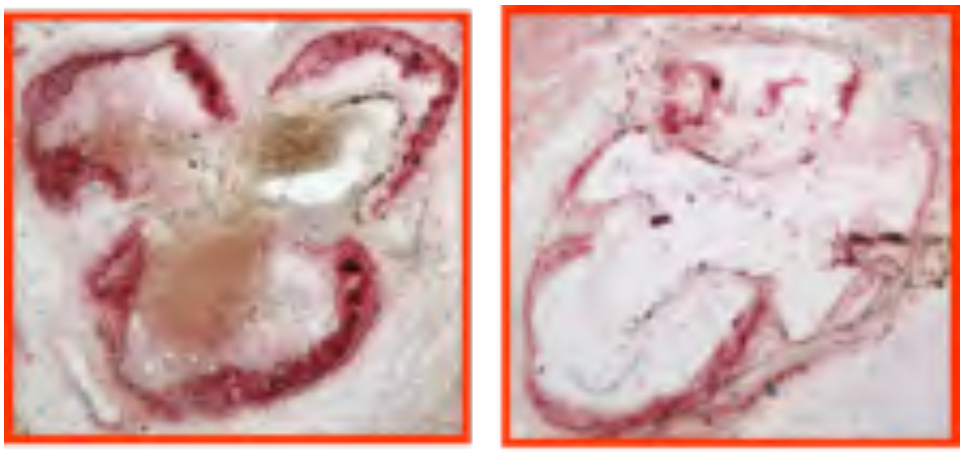

IL-1α+/+ IL-1α-/-

Bone marrow-derived IL-1α deficiency reduces atherosclerosis.

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Investigating the Impact of Maternal Fatty Acids Quality on the Fetal Gene Programming and Fingerprint of Health or Obesity Associated Disease

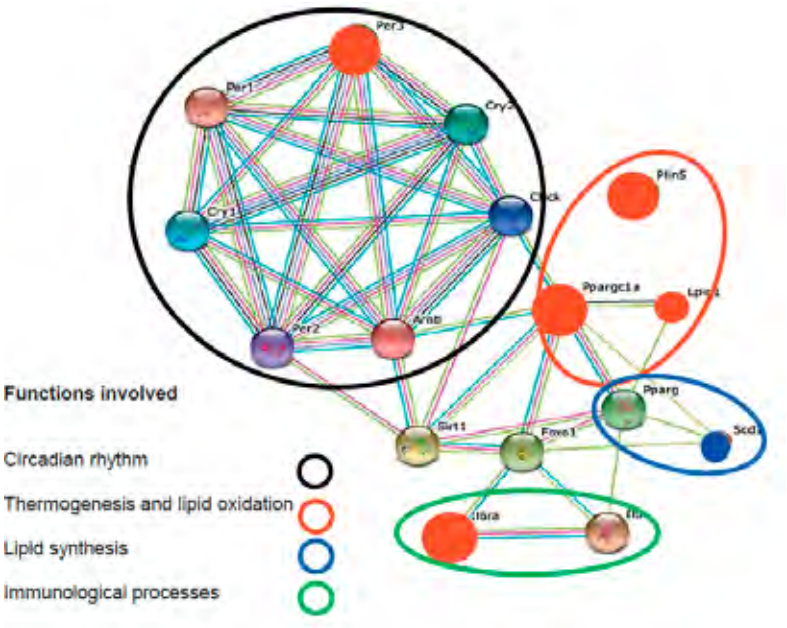
Positions

Associate Professor, CAMEA, Sackler Faculty of Medicine

Researcher at the Bert Strassburger Lipid Center, Sheba, Tel Hashomer

Research

We study the effect of maternal dietary fatty acids quality during pregnancy and lactation on the gene networks that are involved in lipogenesis and thermogenesis in the offspring. Obesity-associated chronic metabolic diseases such as Cardiovascular, Type 2 diabetes and Non-Alcoholic Steatohepatosis are purported to have an early in utero origin. The nutrigenetic impact of fatty acids quality in normcaloric diets and healthy mothers during development is almost unknown. We are exploring this question by studying the metabolic and genetic evolution of the offspring from birth to adult age in our animal nutritional model and in humans. We apply the latest methodologies including biochemistry, lipidomics, molecular biology, and microarray analysis to identify and functionally characterize genes that regulate the lipogenic and thermogenic processes that determine the energetic balance leading to obesity or its absence. Understanding the normal or obesity prone gene programming during development and characterizing the associated fingerprint in the offspring at birth is essential for the early diagnosis and design of treatments to prevent long-term metabolic obesity-associated disorders that are leading causes of disease in almost 40% of wold population and death.



Protein interaction between products of genes upregulated (red full) or downregulated (blue full) by ω3 essential fatty acid (ALA) or saturated fatty acids (SFA). Enriched functions are marked using open colored circles.

Publications

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Reproductive Endocrinology and Infertility – From Basic Science to Clinical Application

Positions

Professor, Obstetrics and Gynecology, Sackler Faculty of Medicine.

Incumbent, Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Sackler Faculty of Medicine

Director, Division of Reproductive Endocrinology and Infertility, Sheba Medical Center

Co-Editor-in-Chief, Reproductive Biology and Endocrinology

Research

Our research includes:

- Various aspects of controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).
- The role of GnRH-analogues, and specifically GnRH agonist versus antagonist in COH for IVF.
- The different modes of triggering final follicular maturation.
- Endometrial preparation for frozen-thawed embryo transfer.
- Obesity and IVF outcome.
- Fragile X Associated Premature Ovarian Insufficiency (FXPOI) in FMR1 premutation carriers.
- Pre-implantation genetic screening (PGS) and diagnosis (PGD).
- Several aspects of ovarian hyperstimulation syndrome (OHSS): pathophysiology, prediction, prevention and its relation to the inflammatory response.

Publications

Manuscripts

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Neuroendocrine Tumors

Positions

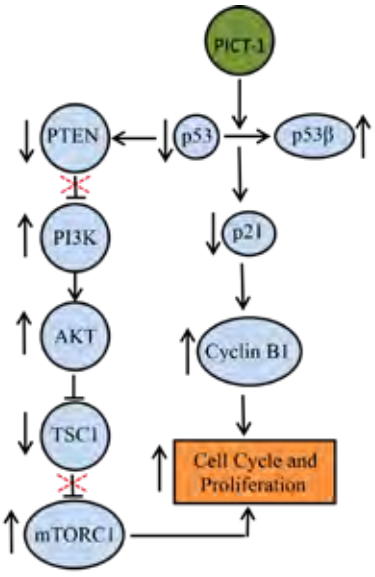
Professor of Medicine and Associate Dean, Rabin Medical Center

Sackler Faculty of Medicine, Tel Aviv University

Research

Our goal is to elucidate the molecular mechanisms that regulate the development of tumors called neuroendocrine tumors (NETs). In this heterogeneous family of tumors, we focus mainly on pituitary, medullary thyroid, lung and pancreatic NETs. We study the expression and function of genes that may affect cell proliferation and hormone secretion and we characterize the mechanisms of action of potential therapeutic compounds. In addition to various cell lines applied, cooperation with neurosurgeons and pathologists enable us access to multiple types of human tumors.

- The regulation of p53 splicing by PICT-1 and its effect on the sensitivity of neuroendocrine tumor cells to Everolimus, mTOR inhibitor
- The expression and function of Ephrins in non-functioning pituitary tumors
- Histone deacetylase inhibitors: their individual and combined effects with somatostatin analogs on PRL-secreting pituitary tumors



PICT-1 induces p53 splicing and resistance to mTOR inhibitor in Neuroendocrine Tumors

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Mechanisms for the Development of Obesity and Diabetes – Molecular and Translational Aspects

Position

Associate Professor of Medicine, Sackler Faculty of Medicine

Research

With the worldwide epidemic proportions of obesity, its related morbidities such as cardiovascular disease and diabetes have become an emerging threat for public health. While the strong genetic predisposition for these conditions is a subject of intense research, less is known about the strong influence of various environmental factors on the pathophysiology of obesity and diabetes. We have recently established the Endocrinology and Diabetes Research Center at the Institute of Endocrinology at Sheba Medical Center with the vision to promote all aspects of research in the field of obesity, insulin resistance and diabetes.

Our group has focused on the following aspects of the pathophysiology of obesity and diabetes:

a. The role of food preservatives as 'metabolic disruptors': Some environmental and nutritional factors have been demonstrated to act as 'endocrine disruptors', with the ability to act as agonists or antagonists to certain receptors in a wide variety of biological systems. We have identified a common food preservative, with distinct metabolic effects. We were able to demonstrate that this food preservative results in an increase in hepatic glucose production as well as in changes in glucagon and insulin levels leading to liver insulin resistance. Chronic exposure results in weight gain, increase adiposity and systemic insulin resistance in mouse models. We are currently working on translating our pre-clinical results to humans in a series of randomized controlled trial. In addition, we continue to work using in-vitro and in-vivo animal models to assess the effects of micronutrients in modern nutrition on the development of obesity and diabetes.

b. Cellular mechanism linking over-nutrition with inflammation, insulin resistance and diabetes: Previous studies have clearly demonstrated that chronic inflammation and cellular stress is a central feature of obesity and its associated metabolic disease cluster. This inflammatory response is distinct, appears to respond to intrinsic cues, and does not resemble the classical inflammatory paradigm. Significant data have emerged in recent years on the molecular mechanisms leading to the development of these inflammatory and stress responses and how they are linked to metabolic homeostasis. Our research is focused on the regulation and adaptation to inflammation and stress within the tissue milieu in metabolically relevant tissues such as liver and adipose tissue. More specifically, we study cell-cell communication and the propagation of inflammatory and stress signals between cells within a tissue and the potential role of such communication in mediating insulin resistance and metabolic abnormalities.

c. In addition to utilizing basic research tools to promote our understanding on the mechanisms leading to insulin resistance and diabetes, we involve in clinical studies assessing novel risk factors and potential therapeutic approaches for these conditions. We are currently involved in several studies looking at the potential role of the novel adipokine FABP4 (fatty acid binding protein 4) in the insulin counter-regulatory response to hypoglycemia and as a potential contributor to the pathophysiology of gestational diabetes.

Publications

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Grants

2017-2021 Principle Investigator

Israeli Science Foundation (ISF)

Connexin 43-mediated cell-cell communication and propagation of adipose tissue ER stress in obesity

2018-2020 Principle Investigator

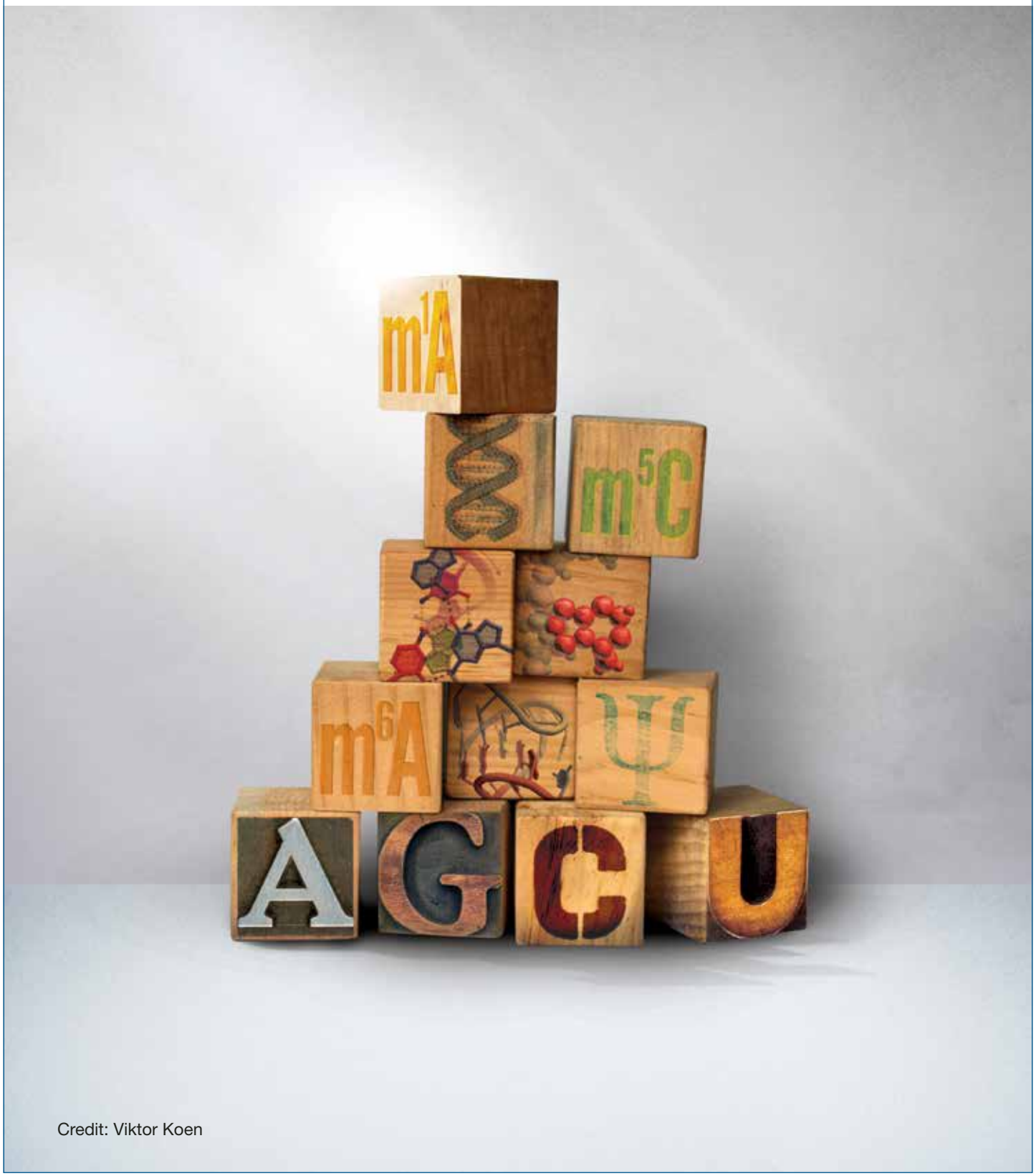
United States-Israel Binational Science Foundation (BSF)

Impact of culinary coaching telemedicine program on body weight and metabolic outcomes

2019-2021 Principle Investigator

European Foundation for the Study of Diabetes (EFSD) Patient reported outcomes and ambulatory glucose profiles in a virtual type 1 diabetes clinic

Genetic Diseases & Genomics



Credit: Viktor Koen

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Deciphering the Molecular Basis of Inborn Errors of Metabolism and Rare Genetic Disorders

Positions

Professor, Sackler Faculty of Medicine

Director, Metabolic Disease Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel-Hashomer

Chairman, Israeli Society for Metabolic Diseases (ISMD)

Research

At the Metabolic Disease Unit and the Molecular Biochemistry laboratory at the Sheba Medical Center, we strive to identify and characterize the molecular basis of an array of inborn errors of metabolism (IEM) and other rare inherited disorders. As a referral center for patients with a wide array of IEMs, we take a "bedside to bench to bedside" approach, studying the biochemical pathways and genetic basis of their disease, delineating the functional effects of the disease-causing variants, and aiming our efforts at the exciting possibilities for novel therapeutic approaches.

In the past few years, we were the first to identify a causative association between variants in several genes and a number of new neurometabolic disorders, as published in the *New England Journal of Medicine*, *American Journal of Human Genetics*, *Brain*, *Journal of Biological Chemistry*, among others. This was the case, for instance, of an autosomal recessive subtype

Clinical Features of Polyarteritis Nodosa Associated with Adenosine Deaminase 2 (ADA2) Mutations. Clinical manifestations of polyarteritis nodosa included digital necrosis of the toes in Patient B-III-3 (Panel A) and Raynaud's phenomenon and livedo reticularis in Patient B-III-6 (Panel B). Angiography of the celiac artery in Patient B-III-3 revealed an aneurysm (Panel C, arrow). Periarteritis, fibrinoid necrosis of the media, and destruction of the elastic laminae were revealed in a biopsy specimen of the superior mesenteric artery in Patient A-III-1 (Panel D, hematoxylin and eosin).

of Polyarteritis Nodosa vasculopathy, caused by variants in the *CECR1* gene, encoding Adenosine Deaminase 2 (ADA2). Since the pucblication of our results [Navon Elkan P et al. *N Engl J Med* 2014], this disorder, manifesting with early-onset cerebral infarctions (among others), has been diagnosed in numerous families worldwide.

Most recently, we identified and characterized a newly recognized inherited neurotransmitter deficiency, caused by mutations in *DNAJC12* [soon to be published in the *American Journal of Human Genetics*]. This disorder was found to manifest in hyperphenylalaninemia, dystonia and intellectual disability. Interestingly, patients with the *DNAJC12*-associated phenotype showed dramatic clinical improvement following early treatment with BH4 and/or neurotransmitter precursors, and thus this unique disorder is a new treatable and preventable cause of intellectual disability.

Publications

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Deciphering the Role of Novel Human Genes and the Pathophysiology Underlying Rare Monogenic Syndromes

Positions

Director, The Genetics Institute, Tel Aviv Sourasky Medical Center

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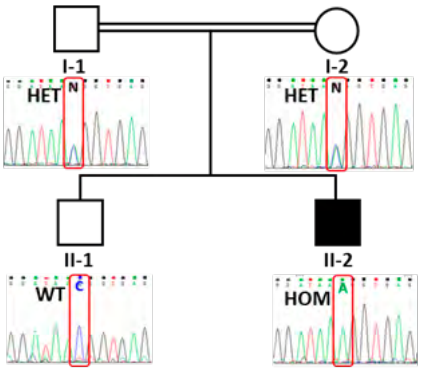
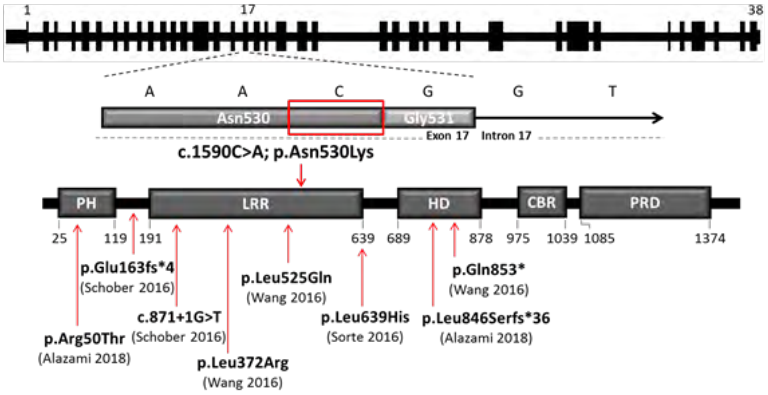
Chair, Israeli Society of Medical Geneticists

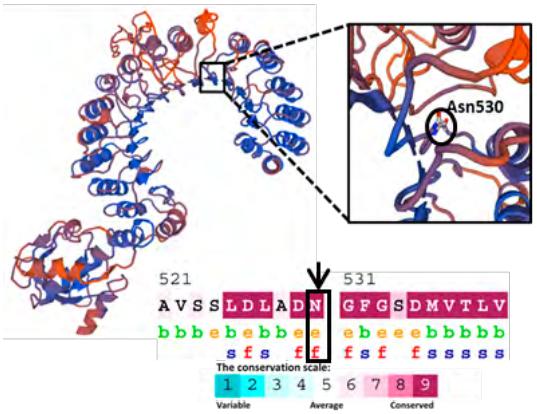
Research

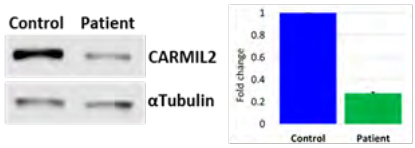
We study the the genetic basis of human Mendelian syndromes from various medical disciplines using next generation technologies, coupled with functional analyses to uncover novel disease pathways. Our laboratory combines genetic, computational and molecular biology methods to study rare diseases and investigate the pathophysiological mechanisms underlying these syndromes. In addition, we have collaborations with top experts in different medical and biological fields, both in Israel and worldwide.

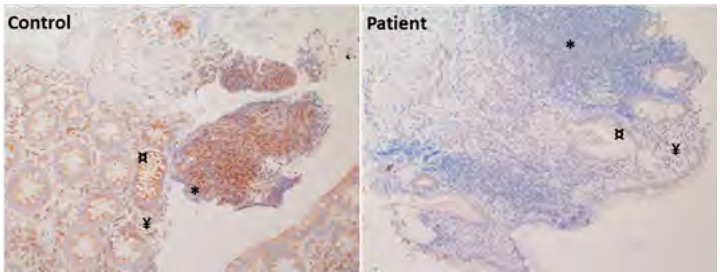
Over the last five years, we uncovered numerous novel human disease-causing genes using whole exome sequencing. These serve as a first step to better understanding human physiology in health and disease, followed by potential application of this knowledge to implement precision medicine and tailored treatments. Our discoveries provided personalized genetic counseling for families with











rare genetic disorders and promoted the birth of healthy children through prenatal and preimplantation genetic diagnoses. Moreover, our findings paved the way to tailored medical treatment for some of the patients, which became the treatment of choice for similar patients worldwide. Our research is patient-driven with the aim of continued implementation of personalized medicine and disease prevention.

Recently, we embarked on a new project aimed at identify risk and protective variants in genes involved in COVID-19 morbidity and disease severity in the hope of identifying in-risk patients and new treatment target targets. We are also taking part in an international consortium aimed at understanding the genetic predisposition to SARS-CoV-2 infection https://www.covidhge.com/

Publications

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Grants

2019-2020	Israel Innovation Authority
2020-2021	Israel Innovation Authority

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Identification of Novel Gene-Phenotype Associations in Rare Diseases

Positions

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Research

Approximately 80 percent of rare diseases are caused by altered functions of proteins encoded by single genes. Diagnostic success leading to personalized treatments and prevention of complications for individuals with rare diseases depends on progress in the discovery of genes underlying these conditions. Our goal at the Raphael Recanati Genetics Institute at the Rabin Medical Center is to decipher the etiology of rare diseases in humans. Main areas of our research include: 1) identification of new syndromes and new gene-disease associations for neurodevelopmental disorders, eye disorders, skin disorders and other phenotypes; 2) investigation of the role of artificial intelligence-based platforms in the interpretation of broad genomic sequencing results, and 3) definition of the role of clinical geneticists in connecting phenotype to genotype during genomic variant interpretation process. To date, we have identified more than 20 new gene-disease associations. As a result of these discoveries, population-based preventive carrier screening programs in at-risk populations have been established.

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Genomics and Epitranscriptomics

Positions

Professor, Sackler Faculty of Medicine

Djerassi Chair in Oncology, Tel Aviv University

Head – Cancer Research Center, Sheba Medical Center, Tel Hashomer

Head- The Wohl Institute of Translational Medicine, Sheba Medical Center, Tel Hashomer

Research

Our main interest lies in the deciphering of novel genetic and epigenetic mechanisms affecting global gene expression and their implication in cancer and neuronal disorders.

Our research interests are:

- The deciphering of the role of RNA epigenetics, including RNA editing and RNA methylation in the regulation of gene expression and cell fate.
- The study of transposable genetic elements in cancer and development
- Genetic and genomic studies relevant to cancer and genetic diseases
- Genetically non-identical tumors

Publications

Manuscripts

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Rare Diseases Diagnosis and Research

Positions

Pediatrician – Medical Geneticist, Sheba Medical Center

Director, Institute for Rare Diseases

Associate Professor, Sackler Faculty of Medicine

National Coordinator, Orphanet Israel

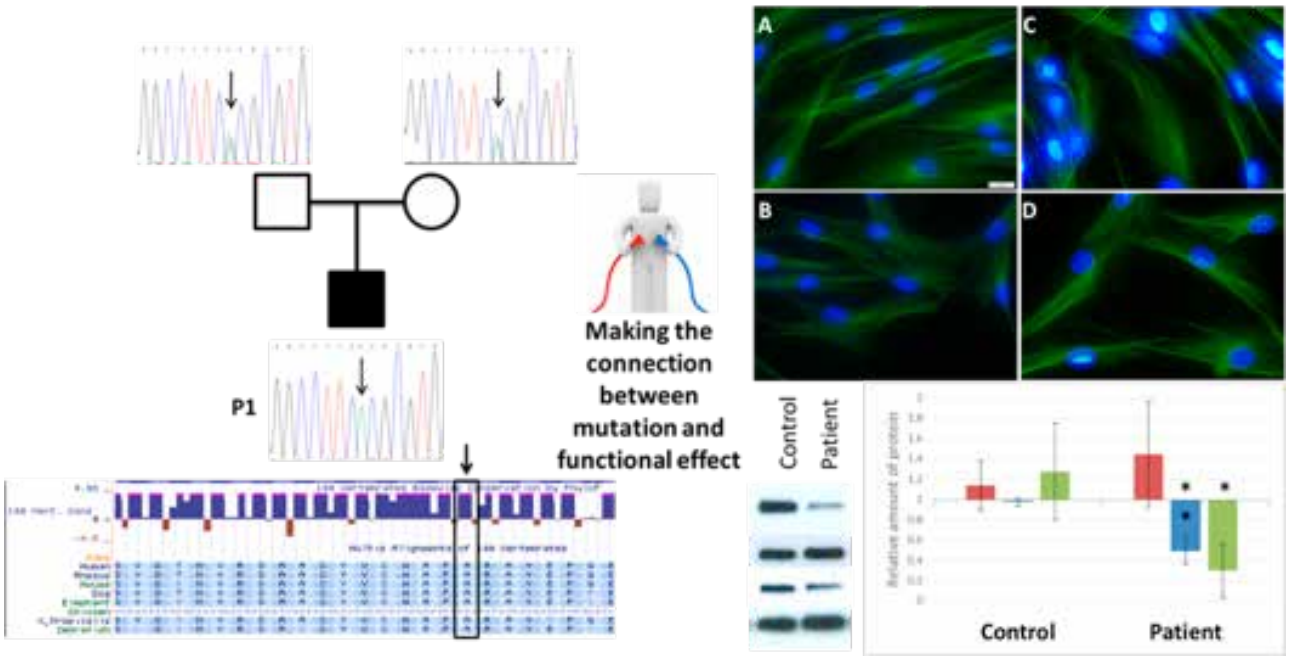
National Coordinator, Rare Diseases National Registry

Research

There are more than 6000 rare diseases affecting more than 60 million people in Europe and the US alone. Most of these diseases are affecting children , are chronic and are of genetic etiology.

Advances in rare disease research are very quickly changing the pediatric care for children affected with these non identified diseases which are very often complex. Research is one of the basics stones for building an accurate care of patients and families. Here, we wish to incorporate research to awareness, diagnosis, treatment and health policy. Our goals include identification of rare diseases causing genes, study the function of the abnormal protein , and finally deciphering new protein pathways in order to establish new therapies. Since the laboratory is in a clinical setting the results of the work is translated into genetic counseling and clinical care and sometimes treatment (MPS II-MPS IV-Fabry disease). With this in mind we are performing cellular studies and drug screens targeted to rare diseases in collaboration with other laboratories, aiming to better understand pathways such as the one linked to mucolipin 1 involved in the mucolipidosis IV clinical symptoms with the goal to provide a specific therapy.

In the field of clinical research, we focus on different subjects that include different topics such as: Natural history of MPS III (Hetz project; Understanding of the practical aspects of the medical genetics (Genet Med. 2016;18(4):372-7); Ongoing project on how the patients are dealing with the information linked to the results of the use of new technologies such as CNV and Exome sequencing.



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New Gene Identification and Genotype-Phenotype Correlation

Positions

Associate Professor of Pediatrics and Human Molecular Genetics and Biochemistry, Sackler School of Medicine

Committee Member, Israel Medical Association, Israeli Board of Medical Genetics, American Society of Human Genetics, American Board of Medical Genetics, Institutional Review Board (Helsinki) Assaf Harofeh

Member, Research and Development Committee, Tel Aviv University

Research

We study genetically undefined families using homozygosity mapping and EXOME analyses, in collaboration with other leading centers, to define disease causing genes. Once a causative mutation is defined, further functional studies are carried out. We identified at least five new genes in the last decade that enabled counseling patients and prenatal diagnosis.

We investigate the genotype-phenotype correlation of newly defined mutations to expand the disease spectrum and impact of genetic disorders.

Publications

Yablonski-Peretz T, Paluch Shimon S, Soussan Gutman L, Kaplan Y, Dvir A, Barnes-Kedar I, Kadury L, Semenysty V, Noa Efrat (Ben Baruch) N, Victoria Neiman V, Yafit Glasser Y, Michaelson-Cohen R, Katz L, Kaufman B, Talia Golan T, **Reish O**, Ayala Hubert A, Safra T, Yaron Y, Friedman E. Screening for germline mutations in breast/ovarian cancer susceptibility genes in high-risk families in Israel. Breast Cancer Res and Treat, 2016, 155(1):133-8

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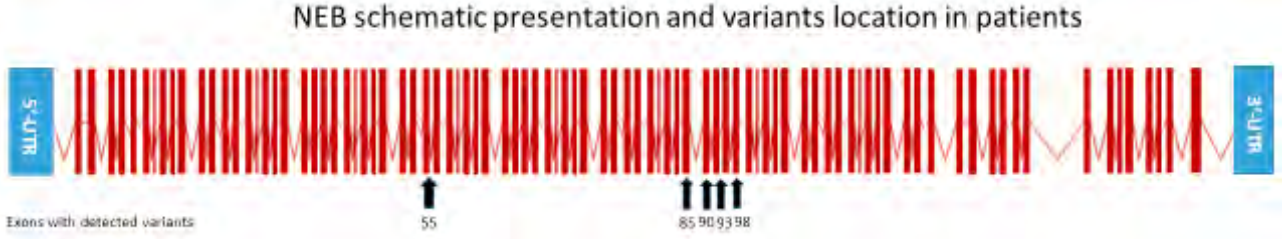

NEB gene schematic presentation. The gene contains several transcripts ranging from 149-183 exons. The arrows point at specific exons where variants were detected in patients with prenatal AMC.

Prof. Eli Sprecher, M.D., Ph.D.

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Investigating the Molecular Genetics of Skin Diseases

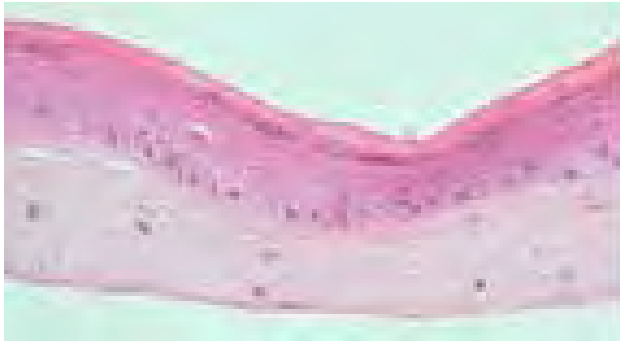
Positions

Chair, Department of Dermatology, Tel Aviv Medical Center

Professor, Sackler Faculty of Medicine, Tel Aviv university

Research

Our laboratory has been investigating the genetic basis of skin disorders for the past 15 years. Monogenic skin disorders are known to be prevalent among Middle Eastern populations, and at this regard, our laboratory is ideally situated to carry research in that field. These efforts have led to the deciphering of the molecular basis of more than 20 genetic diseases by members of our group. The deciphering of the molecular basis of a monogenic disorder invariably reveals a novel pathway whose importance is exemplified by the disease resulting from its malfunction. We systematically explore the mechanistic aspects of these new pathways using almost exclusively humanized models such as three-dimensional skin equivalents, hair organ cultures and chimeric mouse models. Once the function of a novel gene product is established, this new knowledge can be translated in the form of new treatments for rare and more common diseases alike. For example, we have found that defective expression of P-cadherin causes hair loss due to disrupted Wnt signaling. We are now developing small inhibitors for this new pathway as a new treatment for conditions associated with excessive hair growth. Based on a similar paradigm we are now also investigating the genetic basis of complex skin traits including psoriasis and pemphigus, a dreadful autoimmune disorder associated with 90% mortality if left untreated.



Artificial human skin grown in vitro

Ex vivo culture of human hair follicles

Publications

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Review

Grants

2017-2020 COST: "A European Network for Connective Tissue Calcifying Diseases". Investigators: PI Ludovic Martin (PI); Eli Sprecher et al (co-PIs)

Prof. Sidi Yechezkel, M.D.

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The Lab for microRNA Research

microRNAs in human disorders: Psoriasis

One of the main research subjects in the lab is the involvement of miRNAs in the psoriasis. We found that the miRNAs' expression differs between psoriatic and normal skin. Some of these miRNAs are involved in biochemical cycles which regulate skin development and others regulate the interplay between immunocytes and keratinocytes. We are exploring how the expression of these miRNAs is regulated and how they affect the pathogenesis of the disease.

Skin cancer squamous cell carcinoma (SCC)

Skin carcinogenesis, as in most other cancer types, is believed to be a multi-step process with several steps along its malignant evolution: Solar elastosis (SE), actinic keratosis (AK or KIN1-2), a more advanced stage of AK; (KIN3) and CSCC. Using high-throughput deep sequence analysis of five stages along the malignant evolution we clearly see that miRNAs expression is distinct in each of the predefined five stages of malignant progression, a typical signature characterizes each stage. Currently we are investigating the biochemical pathways regulated by these miRNAs and their role in the malignant transformation of keratinocytes.

Parasites exosomal miRNAs as diagnostic tool and their effect on host immune cells

Parasitic infections are responsible for considerable human suffering. Currently, diagnosis and management of parasitic infections is challenging in many settings. We hypothesize that pathogen-specific miRNA can be utilized to understand, diagnose and manage parasitic infections. We have undertaken a pilot study of schistosomiasis as preliminary proof-of-concept for need and feasibility of miRNA-based diagnosis for parasitic infections. Schistosomiasis is a parasitic disease caused by helminthes (blood-flukes) of the genus Schistosoma that affects more than 200 million people, mostly in the developing world. Infection in returning travelers

The lab researchers and students

has received increasing attention, including among Israeli travelers. We were able to detect the presence of schistosomal miRNAs in the micro-vesicles fraction harvested from the patient sera. The Schistosoma parasites have developed multiple mechanisms for modulating or suppressing host immunity. We hypothesize that the adult Schistosoma utilizes secreted exosomes as a mechanism to manipulate and escape the immune system. Currently, we have data suggesting this hypothesize.

The lab researchers and students. PhD students: Mizrahi Adi, Masalha Moamen (MD/PhD student); Postdoc fellow: Dr Layani Adi; Former lab members – PhD students: Dr Lerman Galya, Dr Zehavi Liron, Dr Bonen Hamutal; M.Sc students: Vestin Assaf, Volman Ella, Weinstein Jonathan; Scientist: Dr Elharrar Einat. Location: Sheba Medical Center.

Publications

Meningher T., Lerman G., Regev-Rudzki, N., Gold D., Ben-Dov I., Sidi., Avni D., Schwartz, E. Schistosomal miRNAs isolated from Extracellular Vesicles in sera of infected patients; a new tool for diagnosis and follow-up of human schistosomiasis. The Journal of Infectious Diseases (accepted for publication), doi:10.1093/infdis/jiw539.

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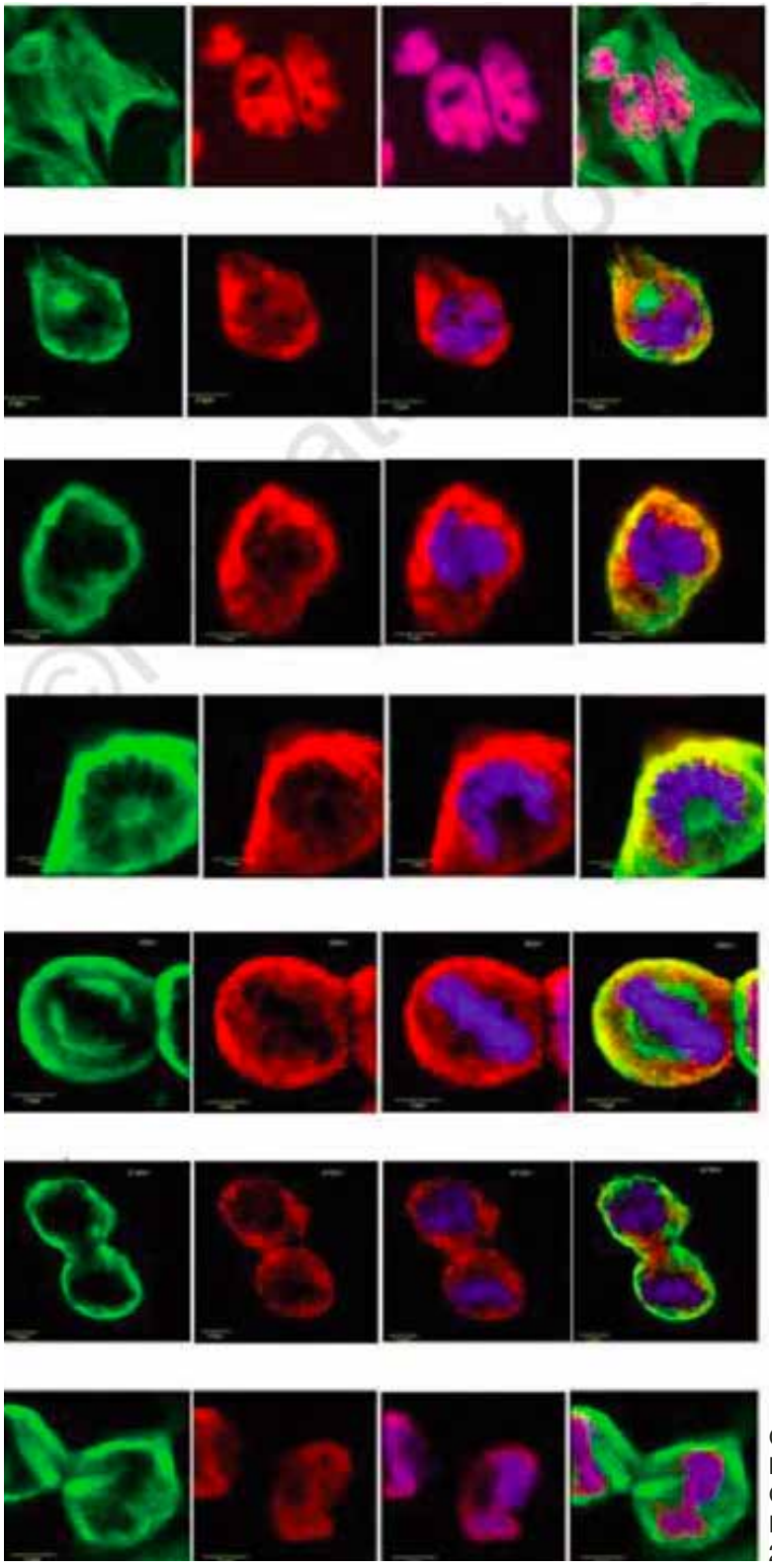
Immunology & Hematology



Cell cycle-dependent localization of codanin-1. Credit: Noy-Lotan et al. Haematologica 94:629-37, 2009

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CAR T Immunotherapy for Cancer and Beyond

Positions

Senior Scientist

Laboratory Manager and Head, Tel Aviv Sourasky Medical Center

Research

CAR (Chimeric Antigen Receptor) T cell therapy, developed by the award-winning researcher Professor Zelig Eshhar (the previous head of our lab), genetically engineers and trains T cells to specifically recognize and kill cancer cells. We recently developed a dual specific CAR for multiple myeloma, in which the activation and the co-stimulation domains are separately provided by two CARs. This split configuration allows for full and efficient stimulation of the T cells only upon engagement with tumor cells expressing both antigens and sparing cells with single antigen presentation, thus overcoming the "off tumor on target" toxicity. Furthermore, we are developing several combined therapies to overcome today's challenge of treating solid tumors as for their suppressive tumor microenvironment. Another aspect our lab is developing a better CAR T manufacturing platform.

Publications

Globerson Levin A, Rawet Slobodkin M, Waks T, Horn G, Ninio-Many L, Deshet Unger N, Ohayon Y, Suliman S, Cohen Y, Tartakovsky B, Naparstek E, Avivi I, Eshhar Z. Treatment of multiple myeloma using chimeric antigen receptor T cells with dual specificity. Cancer Immunol Res 2020.

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Zupančič E, Curato C, Kim JS, Yeini E, Porat Z, Viana AS, **Globerson-Levin A**, Waks T, Eshhar Z, Moreira JN, Satchi-Fainaro R, Eisenbach L, Jung S, Florindo HF. Nanoparticulate vaccine inhibits tumor growth via improved T cell recruitment into melanoma and huHER2 breast cancer. Nanomedicine. 2018. pii: S1549-9634(17)30589-0.

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Grants

2018-2022	Israel Science Foundation
2019-2022	Kamin
2019-2021	SPARK
2019-2022	Dotan

Dr. Gilad Halpert Ph.D.

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Improving the Management of Inflammatory/ Autoimmune and Rheumatic Diseases Using Tissue-homing Extracellular Vesicles and Medical Cannabinoids

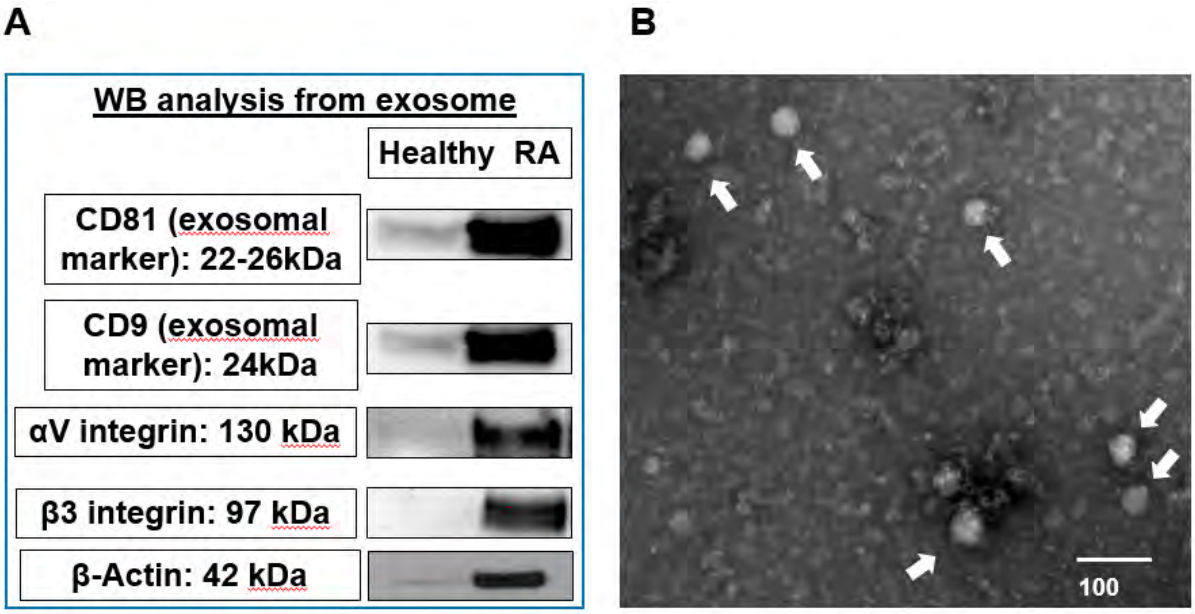
Positions

Head of research laboratory, Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center (affiliated to Tel Aviv University).

Research

Our focus and goals at the lab are to establish innovative solutions and better ways to improve the current treatment for inflammatory/autoimmune and rheumatic diseases using the following research strategies:

1. Improved drug delivery using specific tissue-homing small exctracellular vedicles ('exosomes') in inflammatory/autoimmune and rheumatic diseases: We hypothesized that isolation of tissue-specific homing exosomes derived from autologous blood sample (serum, plasma and/ or activated peripheral blood mononuclear cells) may improve the delivery of FDA-approved anti-inflammatory drugs which will be encapsulated into these exosomes and will be injected back to the patient. Tissue-specific homing receptors (such as: integrins or chemokine receptors) being expressed on the surface of exosomes will be used to enrich these tissue-specific homing exosomes using commercially available techniques (immunomagentic separation). The drug-loaded exosomes can be injected back to the diseased



The specific synovial-homing receptor αvβ3 integrin is expressed on serum-derived exosomes ($CD9^+/CD81^+$) from rheumatoid arthritis (RA) mice. A. Total exosomes were isolated from pool of serum samples of RA mice (Collagen-induced arthritis model) (n=5) and Sham (n=5) mice. Exosomes homogenates were separated using SDS-PAGE and subjected to immunoblotting with antibodies against CD9, CD81, αv, β3 (Santa Cruz Biotechnology) and β-actin (R&D system). Total 7 μgr protein were loaded into each well. B. Transmissiion Electro Microscopy (TEM) analysis shows a nano-size vesicle (~40nm) of exosomes derived from sera of RA mice.

subjects and will naturally find their way to the inflamed tissue. We believe that this approach will increase the specificity and efficiency of the current treatment, therefore it will reduce side effects as compare to the delivery of free drugs and will improve the quality of life of patients with inflammatory/autoimmune/rheumatic diseases.

2. Exploring the effect of novel therapeutic candidates: anti-inflammatory small molecules and/or natural compounds (such as plant-derived cannabinoids) in experimental inflammatory/autoimmune diseasese (Animal models of Collagen-induced arthritis, DSS-induced Coltis, Bleomycin-induced systemic sclerosis etc.). Moreover, our lab exploring the effect of these therapeutic candidates on inflammatory mediators – *in vitro* (using relevant primary cells and/or cell lines) and *ex vivo*, in patients-derived blood components (such as PBMCs) and/or in their relevant inflamed tissue biopsies.
3. Our lab has expertise also in the field of autoantibodies, through the measurement of patient-derived panel of autoantibodies, isolation of autoantibodies (total IgG/IgM or specific IgGs) from blood samples of patients and through exploring their potential pathogenic role using passive transfer of these antibodies into naïve animals following evaluation of clinical manifestations (reported by the patients) in the animals.
4. We are focusing also in exploring the potential immune-related pathomechanism of fibromyalgia sundrome – through examination of the effect of varios conventional and unconventional treatments (Neurofeedback, cannabinoids etc.) on patient-derived immune system components and neuroinflammatory mediators.
5. Our lab is also focusing on the effect of dangerous adjuvants (such as silicone, metal implants etc) on human health in general and more specifically on the immune system.

Publications

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Halpert G, Katz I, Shovman O, Tarasov S, Ganina KK, Petrova N, Tocut M, Volkov A, Barshack I, Blank M, Amital H. (2020) IVIG ameliorate inflammation in collagen induced arthritis- projection for IVIG therapy in rheumatoid arthritis, *Clin Exp Immunol*, 2020.

Reviews

Halpert, G., and Sredni, B. (2014) The effect of the novel tellurium compound AS101 on autoimmune diseases, *Autoimmunity Reviews 13*, 1230-1235.

Grants

2021-2023 Reducing networking gaps between Rīga Stradiņš University (RSU) and internationally – leading counterparts in viral infection-induced autoimmunity research, Educational Grant of EU; Role: Collaborator

2020-2021 Laboratory of Mosaic of Autoimmunity (LMA); Saint Petersburg State University; Role: Collaborator

2020-2022 Sheba Medical Center: Second chance: Improved drug delivery using gut-specific homing small extracellular vesicles for the treatment of inflammatory bowel diseases, Role: PI

Prof. Raz Somech, M.D., Ph.D.

Jeffrey Modell Foundation Center for Clinical and Research Excellence in Primary Immunodeficiencies
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Primary Immunodeficiencies (PIDs) – From Bed to Bench and Back

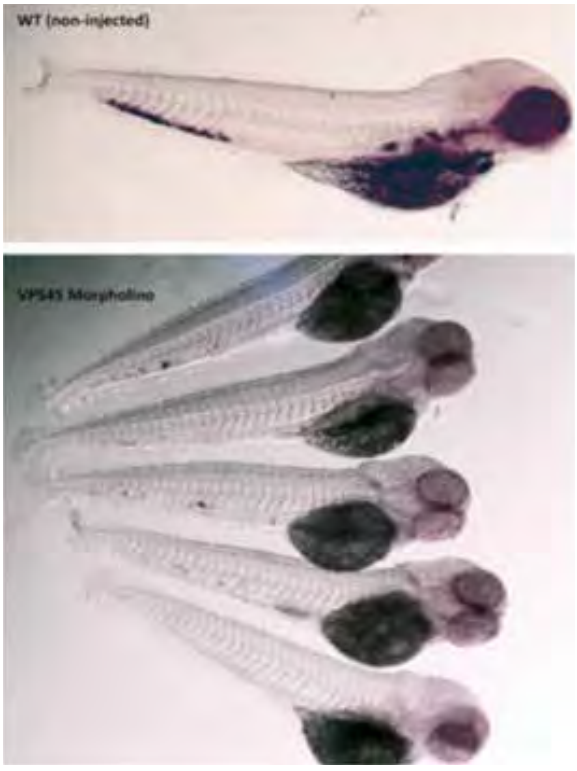
Positions

Head, Pediatric Department, Immunology Services

Research

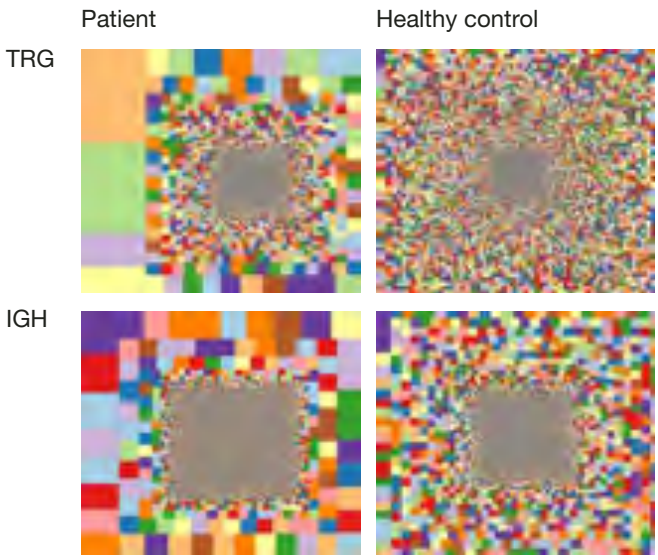
Our research focuses on:

1. Primary immunodeficiencies – finding and characterizing novel diseases
2. Newborn screening for immunodeficiency
3. Investigating fetal immunity in health and diseases
4. Next generation sequencing to illustrate and understand for T and B cell receptor repertoires



Myeloperoxidase signals in wild-type and Vps45 knockdown zebrafish embryos. In situ hybridization of WT non-injected embryo and five VPS45 deficient morpholino injected embryos 5 days after fertilization. Results of whole-mount in situ hybridization with the use of a digoxigenin-labeled RNA probe against zebrafish myeloperoxidase are shown. The myeloperoxidase detects neutrophils in the caudal hematopoietic tissue.

Our pediatric immunology clinic and laboratory are dedicated to the diagnostic evaluation, treatment, monitoring and research of patients with disorders of the immune system, including congenital immunodeficiencies and autoimmune diseases. In addition, we are leading Israel in the field of newborn screening for severe immunodeficiency and recently became the national laboratory for validating results obtained from this program. We are acknowledged as a "Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiency" (www.jmfworld.org) – which is the "gold standard" benchmark for excellence in this field. Part of our service is in-house laboratory which is well-experienced in the most advanced immunological and molecular assays that are used world-wide to assess immune function. We are interested in thymus functions in health (embryonic development and neonates) and in PIDs, as reflected by V(D)J rearrangement and thymic output of T cells, as well as B cell development, using advanced molecular methods, such as TREC and , KREC analyses and next generation sequencing (NGS). We use whole exome sequencing (WES) to discover new PIDs. This approach led us to identify to date several novel mutations that cause inherited PIDs. We found that mutations in two of these mutated novel genes, *VPS45* (*New England Journal of Medicine,* 2013) and *STN1* (*Journal of Experimental Medicine*, 2016) cause syndromic PIDs, i.e. severe congenital neutropenia (SCN5) and Coats plus, respectively. In our large PID cohort of patients some mutations were found in genes that have not been known until now to be involved in the development of the immune system. We continue to find such mutations in novel genes that cause PIDs



Immune repertoire determined by NGS for Ataxia Telangiectasia (AT) patient. Tree map representation of T cell receptor Gamma (TRG) and B cell Immunoglobulin heavy chain (IGH) repertoires in PBMCs samples from patient with AT deficiency and healthy control. Each dot represents a unique V to J joining and the size of the dot represents relative frequency within that sample. The dominant and expanded clones in TRG and IGH repertoires of a patient with AT deficiency can be noted.

with atypical clinical characteristics and study their pathophysiology mechanisms, using also a zebra fish model. Characterization of proteins encoded by the activity of these genes in immune cells of patients compared with those of healthy individuals enable us a better understanding of the development and function of the immune system, as well as designing new targeted drugs or gene therapy to the immune deficiency the patients suffer from. Another interest in our lab is to investigate T and B cell development and repertoire productions in health and disease including the development of the immune system in fetal life (*Science Translational Medicine*, 2015). We have used traditional methodologies (e.g. flow cytometry or PCR analysis) to illustrate cell repertoire in patients with immunodeficiency, autoimmunity and in developing human embryos. Yet the recent development of next generation sequencing (NGS) techniques enabled analysis of these immune repertoires to a depth that was unreached before. This was already used by us in various pathologic conditions including immunodeficiencies, autoimmune disorders and infections. One of the advantages of the NGS technology over the traditional methodologies for investigation of the expanded clones and for clinical follow-up is that it ensures finding of the clonal receptor rearrangements in every patient due to the enormous depth of sequencing. It allows for the detection of multiple sub-clones, specific preferential usage of V, D and J gene segments and complementarity determining region 3 (CDR3) characteristics and to look for clonotypic sharing in patients with a similar disease. In addition, with the use of the CRISPR-Cas9 genome editing platform, we are modeling relevant primary immunodeficiency causing genes, such as RAG1/2, DCLRE1C (artemis) and ATM in wild type human lymphocytic cell-lines, and are using this 'bed to bench and back' approach to correct these mutated genes as a strategy to develop innovative curative gene correction therapy in patients' cells.

Publications

Simon, A. J., Lev, A., Zhang, Y., Weiss, B., Rylova, A., Eyal, E., Kol, N., Barel, O., Cesarkas, K., Soudack, M., Greenberg-Kushnir, N., Rhodes, M., Wiest, D. L., Schiby, G., Barshack, I., Katz, S., Pras, E., Poran, H., Reznik-Wolf, H., Ribakovsky, E., Simon, C., Hazou, W., Sidi, Y., Lahad, A., Katzir, H., Sagie, S., Aqeilan, H. A., Glousker, G., Amariglio, N., Tzfati, Y., Selig, S., Rechavi, G. & **Somech, R.** (2016) Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects, *The Journal of Experimental Medicine*.

Rechavi, E., Levy-Mendelovich, S., Stauber, T., Shamash, J., Reinstein, S., Vernitsky, H., Adam, D., Simon, A. J., Lev, A., Raas-Rothschild, A. & **Somech, R**. (2016) Combined immunodeficiency in a patient with mosaic monosomy 21, *Immunologic Research.* 64, 841-7.

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4. Levy-Mendelovich, S., Rechavi, E., Abuzaitoun, O., Vernitsky, H., Simon, A. J., Lev, A. & **Somech, R**. (2016) Highlighting the problematic reliance on CD18 for diagnosing leukocyte adhesion deficiency type 1, *Immunologic Research.* 64, 476-82.

Dr. Orna Steinberg-Shemer, M.D., M.Sc.

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Novel Pathways Involved in Normal Hematopoiesis and Congenital Hematological Disorders

Positions

Lecturer, Sackler Faculty of Medicine

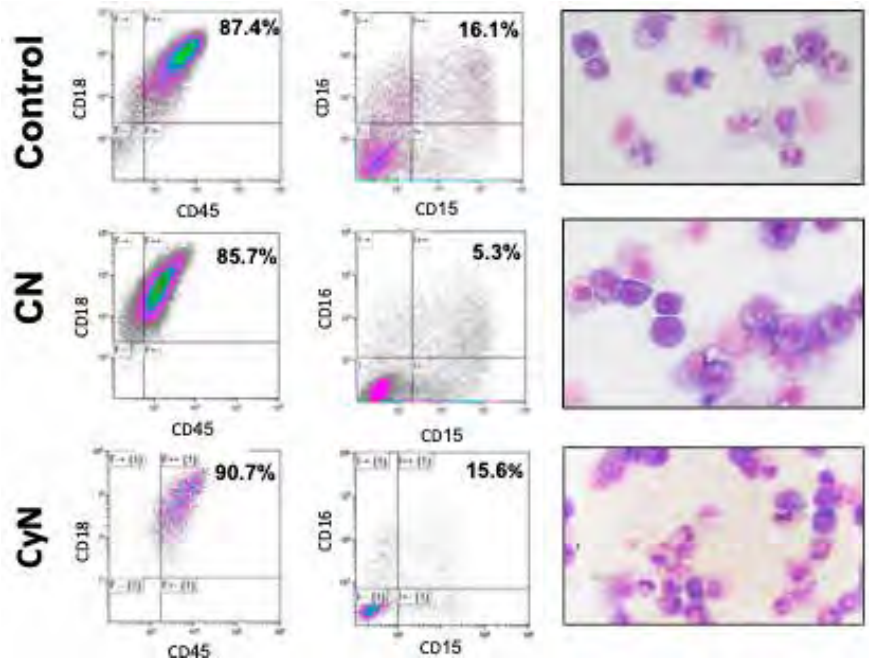
Senior Physician, Hematology Unit, Rina Zaizov Hematology-Oncology Division, Schneider Children's Medical Center of Israel

Research

We study pathways involved in normal and diseased hematopoiesis. All our research aims emerge from clinical dillemas.

Our research is divided into:

1. The study of severe congenital neutropenia and cyclic neutropenia. Severe congenital neutropenia (SCN) is a mono-lineage bone marrow failure syndrome, characterized by early onset of neutropenia accompanied by severe infections. Bone marrow examination demonstrates promyelocytic maturation arrest. Cyclic neutropenia (CyN) is a congenital syndrome characterized by oscillations of the neutrophil counts with a nadir occurring every 21 days. Mutations in the *ELANE* gene can cause both diseases. We aim to identify key signaling pathways underlying SCN and CyN and their phenotypic differences, in order to establish better diagnostic criteria and novel therapeutic approaches. We use induced pluripotent stem cells (iPSCs) generated from patients with congenital neutropenias. Our iPSC system recapitulates the myeloid differentiation arrest found in bone marrows of patients with SCN and shows a difference in the myeloid differentiation potential between SCN and CyN (Figure).
2. Elucidating the myeloid transformation processes in patients with congenital neutropenia. One severe complication of SCN is the development of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). An early event in



this process involves acquisition of truncating mutations in the receptor of the granulocyte-colony stimulating factor (G-CSF), which are unique to patients with SCN. We aim to understand the signal transduction pathways triggered by the mutated G-CSF receptor in patients with congenital neutropenia in order to improve the diagnostic, preventive and therapeutic approaches for leukemia development. This study is performed on patients-derived iPSCs using the CRISPR/Cas9 gene editing system for the introduction of somatic mutations that are similar to those found in patients.

3. Understanding the molecular processes involved in rare congenital anemia syndromes. The regulation of erythroid gene expression and erythroid differentiation is governed by the interplay between GATA1 and GATA2, that share a common DNA binding motif, and a key event in normal erythropoiesis is a "switch" in the expression of the two transcription factors. We aim to study the roles of GATA1 and GATA2 in initiating and driving red blood cell differentiation and their contribution to a rare anemia syndorme caused by mutations in GATA1. This study is preformed in immortalized human CD34+ cells in combination with gene editing methods.

Publications

Giani FC, Fiorini C, Wakabayashi A, Ludwig LS, Salem RM, Jobaliya CD, Regan SN, Ulirsch JC, Liang G, **Steinberg-Shemer O**, Guo MH, Esko T, Tong W, Brugnara C, Hirschhorn JN, Weiss MJ, Zon LI, Chou ST, French DL, Musunuru K, Sankaran VG. Targeted application of human genetic variation can improve red blood cell production from stem cells. *Cell Stem Cell*. 2016;7;18(1):73-78.

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Grants

2020-2023 Israel Innovation Authority. *The CRISPR-IL Consortium – AI technologies for improving the efficiency and accuracy of genome editing*, with Dr. Yehudit Birger and Prof. Shai Izraeli.

2020-2023 Varda and Boaz Dotan Research Center in Hemato-Oncology. *Novel method for selection of CD34+cells after editing Runx1 gene mutations*, with Prof. Dani Offen.

2019-2021 Physician-Scientist Grant. European Hematology Association. *Elucidating the pathophysiology of severe congenital neutropenia and the pathways involved in malignant transformation*.

2019-2022 Physician-Scientist Grant. Israel Science Foundation. *Elucidating the mechanisms of congenital anemia caused by germline GATA1s mutation: The roles of GATA2.*

2018-2020 Israel Cancer Association. *Elucidating the pathways involved in malignant transformation in severe congenital neutropenia patients.*

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Molecular and Cellular Studies of Rare Disorders of Hematopoiesis

Positions

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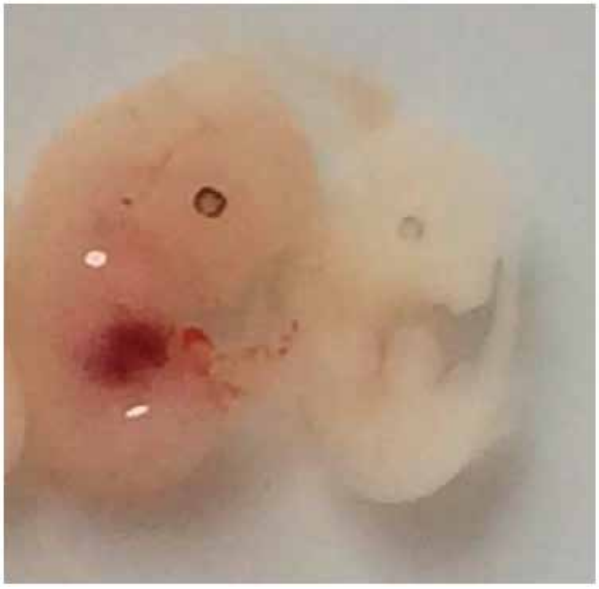
Research

We study rare hematological disorders, using different cellular model systems. The roles of codanin-1 in normal hematopoiesis and in the pathogenesis of congenital dyserythropoietic anemia type I (CDA I). CDA I is a rare disorder causing anemia and bone abnormalities. We have identified CDAN1, the gene causing CDA I, in 2002, by linkage analysis. Codanin-1, encoded by CDAN1, is ubiquitously expressed and necessary for early embryonic development. However, its roles in hematopoiesis are not known. We generated erythroid tissue specific KO mice, and identified early anemia and embryonic lethality caused by a complete lack of codanin-1. We are also utilizing other model systems for the disease, including K562 cell line, murine fetal liver erythroid differentiation system, and primary human erythroid cultures. Understanding the roles of codanin-1 in red blood cells development may shed light on specialized processes involved in erythropoiesis. Even more significant, elucidating the role of codanin-1 in CDA I may help develop novel therapeutic approaches to alleviate the anemia in these patients.



Cdan1 erythroid conditional mice embryo are small and pale, with no visible erythropoiesis in the fetal liver.

The pathomechanisms of severe congenital neutropenia and cyclic neutropenia through patients will be understandood by using derived induced pluripotent stem cells. We use the cutting edge technology of induced pluripotent stem cells generated from patients with congenital neutropenia as a model system for severe congenital neutropenia and cyclic neutropenia, caused by ELANE mutations. We aim to define the granulopoietic defects caused by these mutations, establish a genotype-phenotype correlation of iPSC lines carrying ELANE mutations causing both diseases, and study novel potential therapies by pharmacological correction of the granulopoietic defects detected.

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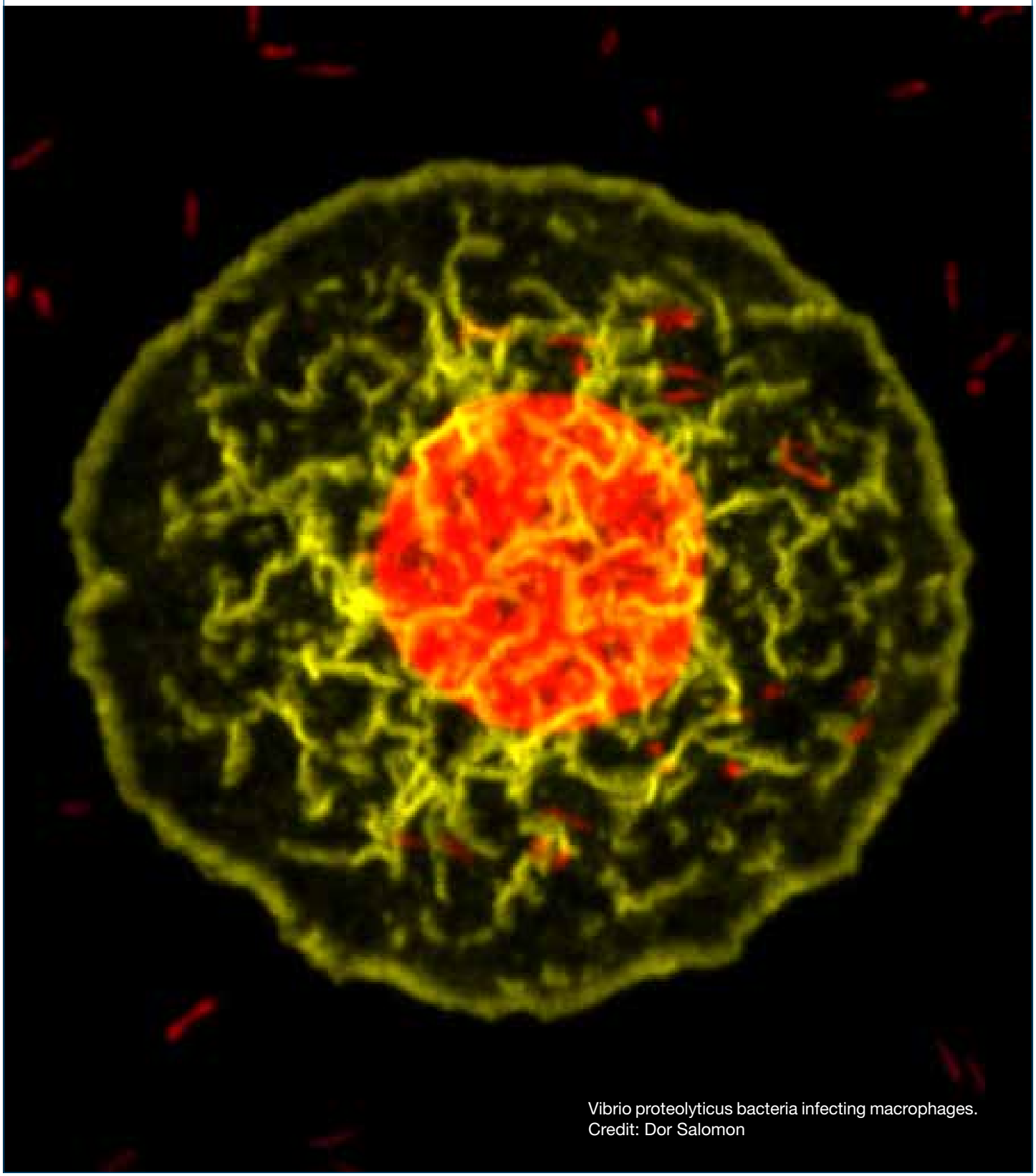
Infectious Diseases



Vibrio proteolyticus bacteria infecting macrophages.
Credit: Dor Salomon

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Mechanisms of Virulence and Drug Resistance in Pathogenic Fungi

Positions

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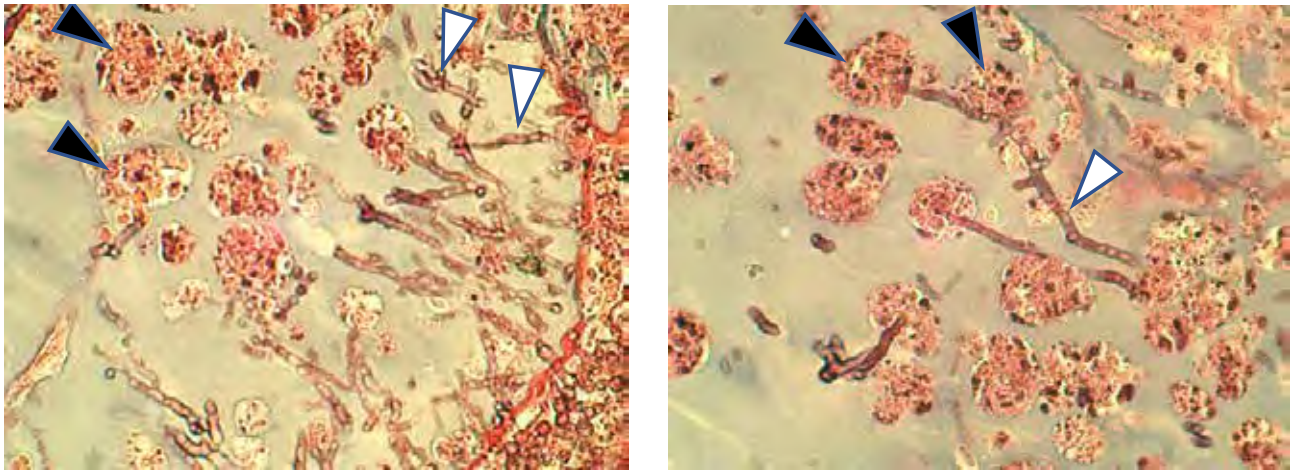
Research

We study the pathobiology and epidemiology of medically important fungi. Fungal infections are encountered with increasing frequency in advanced medical settings, and are associated with high mortality rates. Specifically, *Candida* species are frequent causes of hospital-acquired bloodstream infection, particularly in the intensive care setting, whereas *Aspergillus* species and other pathogenic filamentous fungi cause sinopulmonary and disseminated infections in immunocompromised patients.

Our work has outlined the incidence, drug resistance patterns, geographic distribution, risk factors and outcomes of *Candida* bloodstream infections in Israeli hospitals. A multicenter effort is currently underway to study the epidemiology of invasive mold infections in Israel.

We are specifically interested in *Candida glabrata*, an opportunistic pathogen notable for its limited susceptibility to antifungal agents and its tendency to rapidly evolve resistance following exposure to antifungal azole drugs. Using population analysis techniques, we showed that clinical strains of *C. glabrata* are often heterogenous at the cell-population level with respect drug resistance. This phenomenon, termed heteroresistance, facilitates the expansion of drug-resistant subpopulations during antifungal treatment. We discovered that heteroresistance is associated with over-expression of efflux transporters, and that heteroresistant strains can persist *in vivo* despite high-dose azole treatment. Heteroresistance is not captured by standard susceptibility tests performed at clinical laboratories, and may explain the mismatch between susceptibility data and treatment outcomes.



In vivo assay for angiotropism and angioinvasion: Matrigel plugs implanted subcutaneously induce the formation of endothelial cell networks (black arrowheads). *A. fumigatus* forms hyphae (white arrowheads) that invade neovessels. Genetic manipulation is used to dissect *A. fumigatus* genes responsible for angiotropism and angioinvasion.

Additional work has focused on the emerging species *Candida auris*. Unknown until recently, *C. auris* is a multidrug resistant organism that has caused simultaneous outbreaks of invasive infections in multiple countries in Europe, North and South America, Africa and Asia. We characterized the drug resistance and pathogenicity traits of *C. auris* isolates. Ongoing work at our lab aims to define optimal treatment strategies for *C. auris* infection using in vitro and animal models.

Invasion of host blood vessels is characteristic of invasive Aspergillus fumigatus infection. We have previously shown that angioinvasive *A. fumigatus* produces gliotoxin, a secondary metabolite which down-regulates host angiogenesis. We hypothesized that angioinvasion is essential for *A. fumigates* virulence. Research conducted at the Tel Aviv Medical Center Mycology laboratory and at the laboratory of Prof. Nir Osherov at the Sackler School of Medicine aims to understand the genetic underpinnings of angiotropism and angioinvasion. We predict that this line of research will uncover novel targets for the treatment and prevention of invasive aspergillosis.

Publications

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Investigating Infectious Diseases

Positions

Head of Department, Medicine E, Rabin Medical Center, Beilinson Hospital

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Research

Our research focuses on improving the treatment and management of patients with severe infections and at the same time, focusing on interventions that will reduce the rise of resistance to antibiotics in micro-organisms. Our main goal is to reduce mortality and suffering caused to patients by these infections.

Together with partners in Denmark, we have developed a computerized decision support system for antibiotic treatment in patients with moderate to severe infections. It was tested in a multi-center trial in three countries, and was shown to improve the outcome of patients, while at the same time reducing unnecessary use of antibiotics and hospital stay.

Our studies, systematic reviews and meta-analyses and clinical studies, served to change international guidelines and improve patient's management. For example:

- Study that stopped the use of single-dose antibiotics for urinary tract infection.
- A clear evidence on the benefit of appropriate empirical antibiotic treatment
- Antibiotic prophylaxis for neutropenic patients.
- Discontinuing the use of beta-lactam/aminoglycoside combinations.
- Proof that some antibiotics (tigecycline and cefipime) are less effective than others.
- Current projects
- Optimizing diagnosis, treatment and outcome definitions in elderly patients with bacterial infections (Ministry of Science, Technology and Space).
- The impact of a decision support system for antibiotic decisions on appropriateness of treatment, morbidity and mortality, consumption of antibiotics and resistance to antibiotic drugs (The Israeli national institute for health policy research).
- AIDA: Investigator-driven clinical trials of off-patent antibiotics. Preserving old antibiotics for the future (EU- FP7-HEALTH-2011-two-stage).
- Combatting Bacterial Resistance in Europe – Molecules against Gram Negative Infections (IMI – COMBACTE-MAGNET).
- Transnational Research Projects on the Transmission Dynamics of Antibacterial Resistance (ERA-NET/JPI-EC-AMR).

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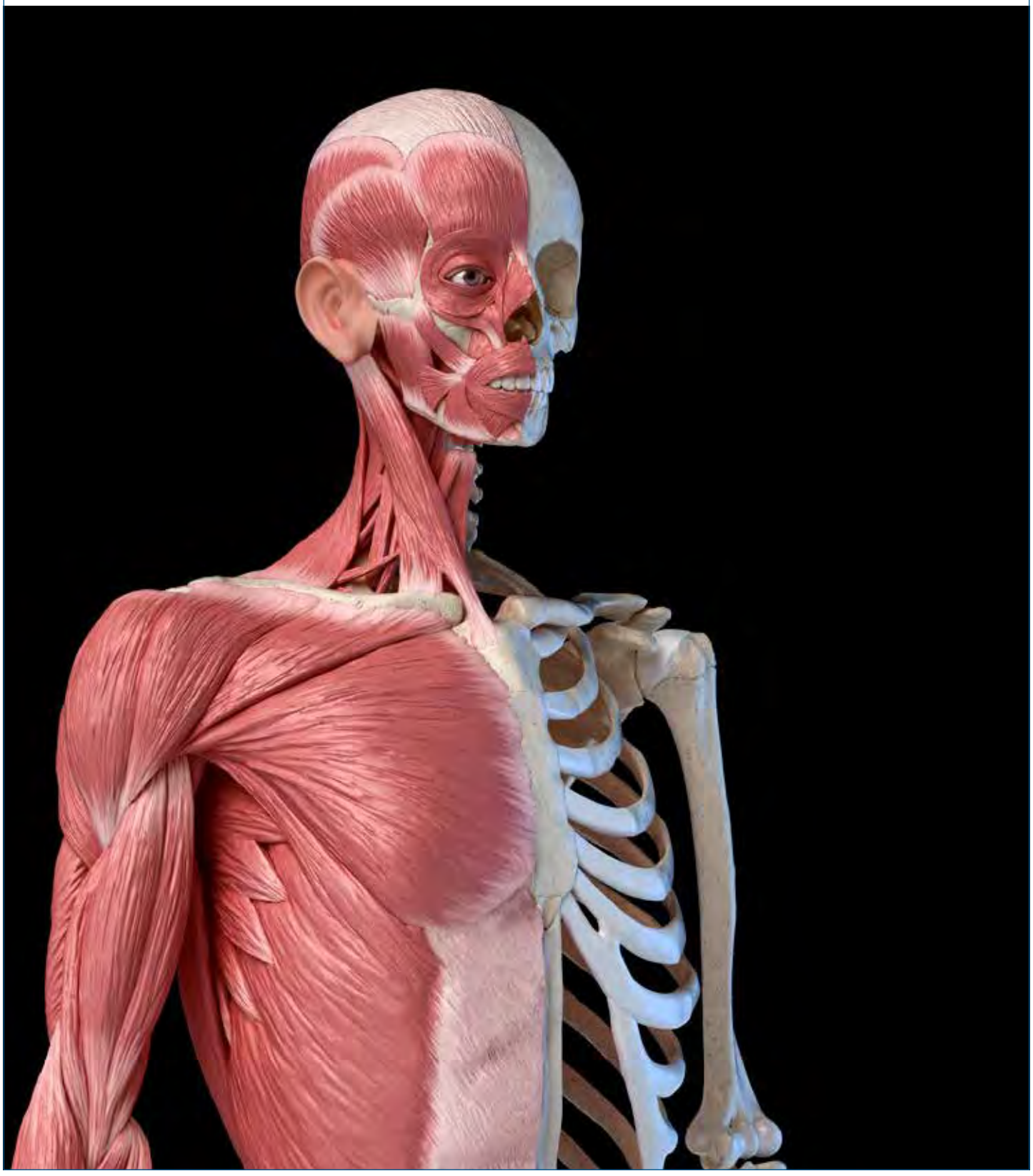
Grants

2016-2021 IMI – COMBACTE-MAGNET: Combatting Bacterial Resistance in Europe – Molecules Against Gram Negative Infections

Musculoskeletal Disorders



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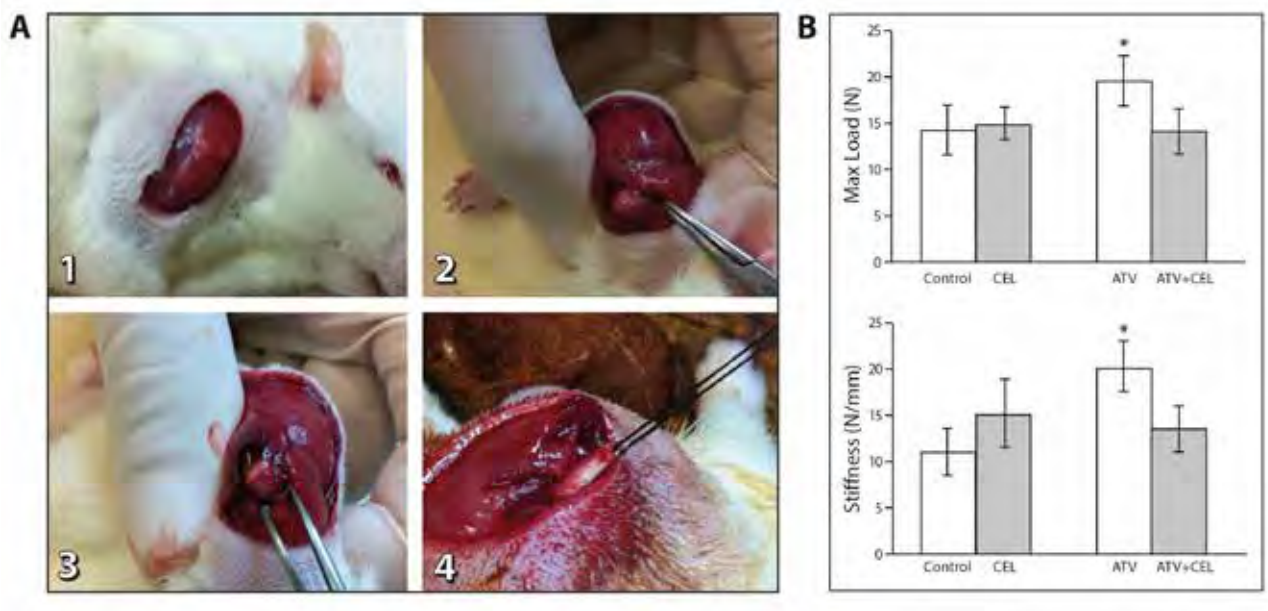
Investigating the Biomechanical Properties and Healing of Rotator Cuff Tendons



COX2-dependent stimulation of tendon healing by Atorvastatin (ATV). A. Rotator cuff repair model in rats. Under anesthesia, skin incision over the deltoid muscle (1); the deltoid is gently split (2) to uncover the supraspinatus tendon. The tendon is then cut adjacent to its footprint on the humeral head (3) and repositioned by suturing to the humerus (4). **B.** After 3 weeks, biomechanical testing in tension shows higher loads to failure and stiffness values in the ATV group compared with control, Celecoxib (CEL) and CEL+ATV groups.

Positions

Senior Lecturer, Sackler Faculty of Medicine

Committee Member, Tel Aviv Medical Center Institutional Review Board

Research

We study the biomechanical properties of rotator cuff tendons in various scenarios. Rotator cuff tears are a leading cause of shoulder pain and dysfunction in elderly as well as young population. Tendon healing is often impaired and requires surgical intervention. While technology and surgical techniques developed enormously during the last decades, biologic factors are still the limiting factor in tendon healing and re-tear. Studies are performed using a rat model imitating tendon tears and surgical repairs. Tendon healing is studied under various conditions including pharmacoligical agents and magnetic fields. The effect of pharmacologic agents on bone density and bone-tendon interface is also studied.

Publications

Maman E, Yehuda C, Pritsch T, Morag G, Brosh T, Sharfman Z, **Dolkart O**. Detrimental effect of repeated and single subacromial corticosteroids injections on intact and injured rotator cuff: biomechanical and imaging studies in rats. Am J Sports Med. 2016;44(1):177-82.

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Investigating Gait, Balance, Falls and Motor-Cognitive Interactions in Aging and Disease

Positions

Professor, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University

Director, The Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center

Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center

Movement Disorders Society Task Force on Technology

Gait Advisory Committee for the Michael J. Fox Foundation for Parkinson's Research

International Society of Posture and Gait Research Strategic Planning Committee

Board of Directors, International Society for the Measurement of Physical Behaviour

Assocaite Editor, Journal of NeuroEngineering & Rehabilitation

Associate Editor, Journals of Gerontology: Medical Sciences

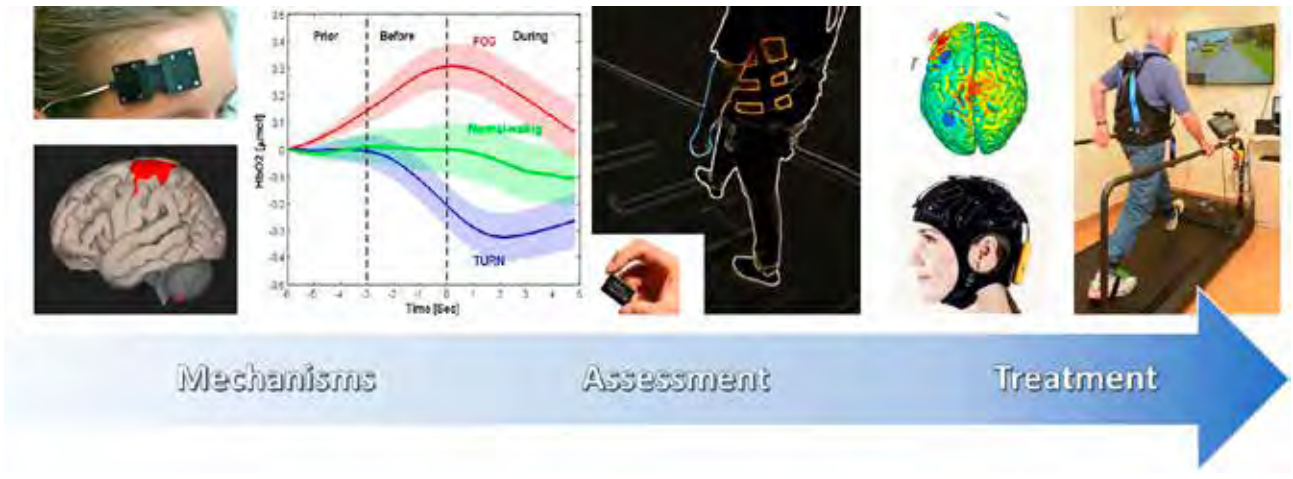
Editorial Board, Gait & Posture

Review Editor in Movement Disorders, Frontiers in Neurology

American Federation of Aging Research's National Scientific Advisory Council

Research

At the Center for the Study of Movement, Cognition, and Mobility, we investigate balance, walking, and falls as well as the prevention and restoration of loss of mobility, motor function, and cognition associated with aging and neurological disease (e.g., Parkinson's, multiple sclerosis, Alzheimer's, post-stroke, children with ADHD). Our research team leverages a combination of clinical, engineering and neuroscience expertise to achive three main objectives: 1) acquire new understandings of the *mechanisms* that contribute to cognitive and motor function and their changes with aging and disease; 2) construct and validate new methods and tools for early *detection* and *tracking* of cognitive and motor decline associated with aging and neuro-degeneration. This includes the development of new "bio-markers" that can be used for early



Examples of the modalities that we use to study, assess and treat gait, balance, falls and motor-cognitive interactions.

diagnosis, prognosis, and for quantitative tracking of disease progression, aging, and the response to therapeutic interventions (e.g., at-home monitoring using wearable devices and machine learning) and 3) develop novel methods for *prevention* and *treatment* (e.g., using virtual reality, pharmacologic therapy, motor learning, non-invasive brain stimulation).

Examples of ongoing projects in the lab include a) fMRI, EEG, and fNIRS imaging of balance and gait in Parkinson's disease and aging during usual walking and during challenging conditions such as when negotiationg obstacles; b) virtual-reality based intervention for gait and cognitive function in older adults and patients with multiple sclerosis; c) transcranial direct current stimulation to study the mechanisms and to ameliorate freezing of gait in patients with Parkinson's disease; d) Smartphone-based intervention to improve gait and cognition and to reduce fall risk in older adults; e) transcranial direct current stimulation to study the mechanisms and to reduce fall risk and the effects of dual tasking in older adults; f) investigation of genetic contributions to gait and mobility; g) 24/7 monitoring of gait and mobility using body-fixed sensors to study the effects of osteoarthritis on mobility and to identify early markers of Parkinson's disease. h) neural network studies of cognitive aging and mobility; i) effects of high intensity exercise on cognition, gait and mobility in older adults with mild cognitive impairment.

Publications

Manuscripts

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Reviews

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Grants

2016-2020 Michael J Fox Foundation for Parkinson's Research, The Effects of Multi-focal Transcranial Direct Current Stimulation on Freezing of Gait in Patients with Parkinson's Disease: A Randomized Controlled Trial (JM Hausdorff, PI)

2016-2021 National Institutes of Health, Racial Differences in Late-Life Cognitive decline and risk of Alzheimer's Disease (L Barnes, PI; JM Hausdorff Israeli PI)

2017-2022 National Institutes of Health, Impaired Gait in Older Adults: Pathologies of Alzheimer's disease and Related Disorders (A Buchman, PI; JM Hausdorff Israeli PI)

2017-2021 National Institutes of Health, Exploring Cognitive Aging Using Refernce Ability

	Neural Networks (Y Stern PI; JM Hausdorff Israeli PI)
2017-2021	National Health Medical Research Council (Australia) BRAIN Training Trial: Balance, Resistance, or INterval Training Trial: A Randomised Controlled Trial of Three Exercise Modalities in Mild Cognitive Impairment (M Fiatarone-Singh PI; JM Hausdorff Israeli PI)

Prof. Yoram Nevo

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Investigating the Pathophysiology and Therapeutic Option for Muscular Dystrophy

Positions

Director, Institute of Neurology

Scneider Children'S Medical Center of Israel

Professor, Sackler Faculty of Medicine

Chair, Israeli Child Neurologist Association

Research

The main goal of our research is to develop new therapies for Duchenne and Becker muscular dystrophy (DMD and BMD) and other neuromuscular dystrophies which currently have no cure. DMD is the most common muscular dystrophy in children. DMD patients suffer from progressive muscle atrophy and weakness**,** lose independent ambulation by the age of 13 years and often die in their third decade.

Our laboratory focuses on understanding biochemical and molecular mechanisms leading to muscle dystrophy and the significant processes contributing to its secondary effects and disease progression, such as chronic inflammation and fibrosis. We are using diverse anti-inflammatory and anti-fibrotic agents and also combination therapies, to tackle the massive inflammation and fibrosis to improve outcomes in mouse models of DMD and of congenital muscular

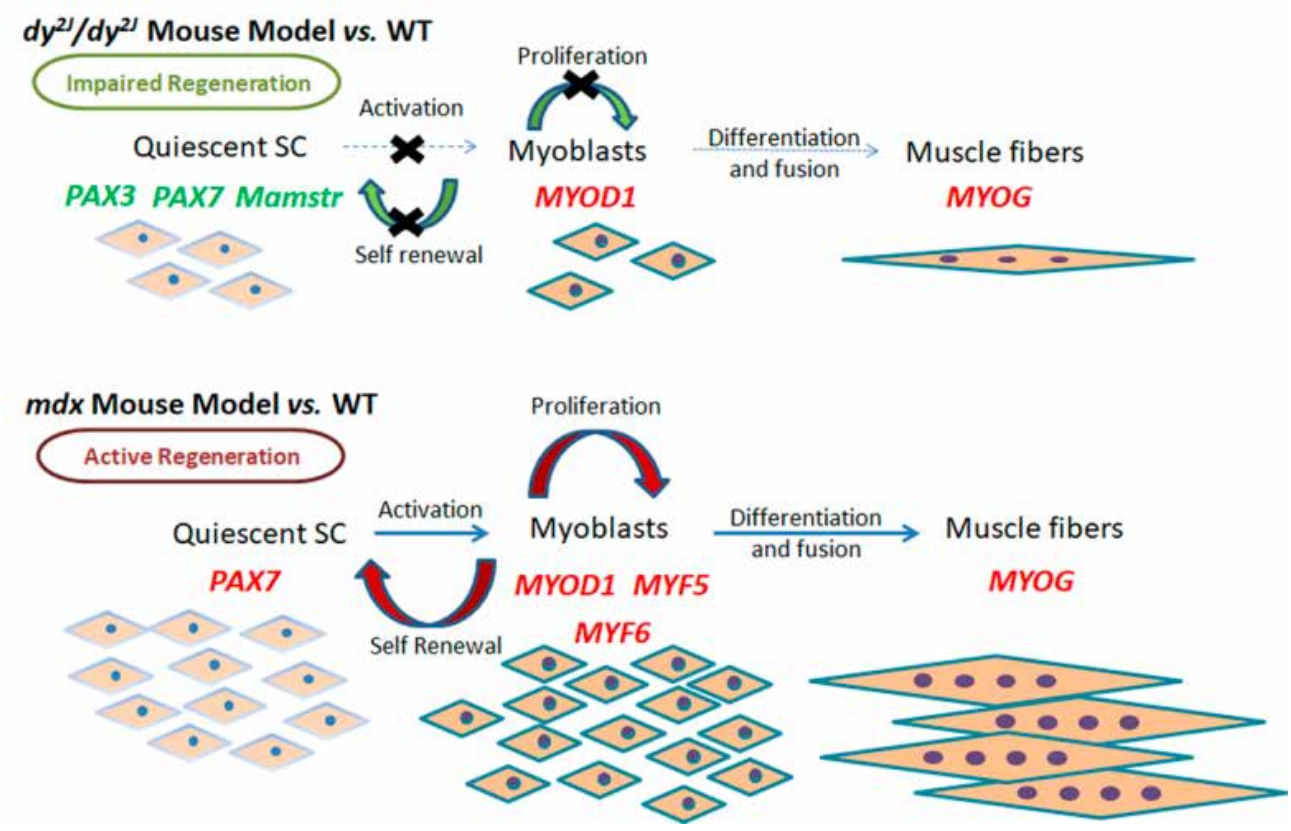

Figure 1. Model for the impaired regeneration mechanism in dy^{2J}/dy^{2J} mouse skeletal muscle (Yanay et al 2019).

dystrophy (CMD). We also combined different novel strategies of gene therapy, small molecules and nanotechnology such as liposomes, exosomes and other nanoparticles to deliver drugs specifically to muscles. Diverse methodologies, including mouse models, human muscle biopsies, primary muscle satellite cells, and bioinformatics techniques are employed. We use novel high throughput sequencing (RNA-Seq) platform enabling us to identify novel genes that promote muscle regeneration and seek to extend the animal findings to humans. In addition to pure translational studies, biomarkers in our laboratory are evaluated as an aid to study Duchenne and Becker muscular dystrophy patients' physical activity and performance.

Publications

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Neurological & Psychiatric Diseases

Functional MRI results, scanned at the Strauss Computational Neuroimaging Center, TeL Aviv University
Credit: Tom Schonberg

Dr. Felix Benninger, M.D.

Felsenstein Medical Research Center, Beilinson Hospital
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Laboratory of Clinical Neuroscience

Positions

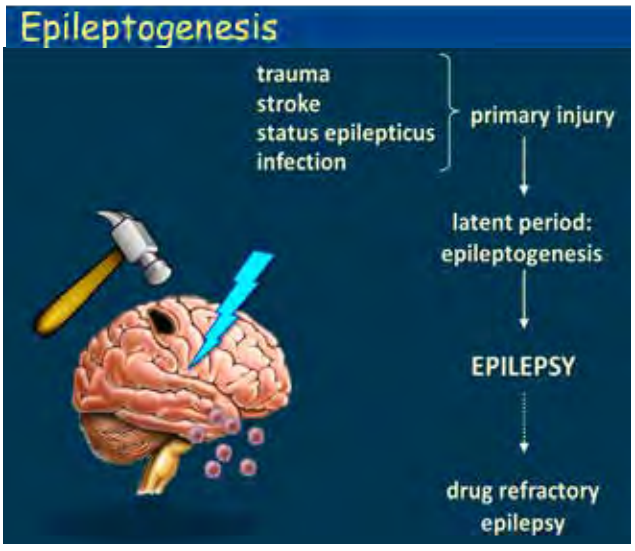
Head of Laboratory, Felsenstein Medical Research Center

Senior Lecturer, Sackler Faculty of Medicine

Research

Our laboratory is interested in the development (genesis) and the patho-physiology of neurological disorders. We are highly translational and are trying to find solutions starting with real-life clinical problems with our methodology in the laboratory. Besides general neurology, we are focusing on the development of epilepsy (epileptogenesis) and the possibility to find a preventive treatment for patients about to develop epilepsy instead of treating, as today, the symptoms: epileptic seizures.

Our methods in the laboratory include electroencephalogram EEG in living and freely moving rodents as well as video-EEG recordings. Hereby, seizures can be detected, and quantified, and possible preventive treatment assessed. Furthermore, we are using human EEG in a highly computational analysis developed by Dr. Oded Shor to separate patient groups (dementia, depression, schizophrenia and patients with epilepsy) by using a short EEG recording. Our goal here is to predict diseases using brain signature of the EEG even before symptom onset. In collaboration with the genetics department at Rabin Medical Center, we are using protein modelling and normal-mode-analysis (NMA) to re-classify possible single nucleotide mutations previously not known to have a physiological impact. This is done by a method created by our post-doc Dr. Oded Shor and includes the use of in-silico protein dynamics with entropy quantification to compare different proteins. We are a very fluid group and open for new projects and very much appreciate our close collaboration with the team of Prof. Daniel Offen at the same institute. Our strengths lies in the ability to be close to patients problems through clinics and ward rounds as well as having highly qualified mathematical and computational knowledge.



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Dr. Yuval Bloch, M.D.

Cognitive and Emotion Research Lab
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Investigating Cognitive and Emotional Difficulties that Typify Different Psychopathologies in Life Span: Therapeutic Brain Stimulation

Positions

Co-Cordinator, Course of Continuing Medical Education in Psychiatry, TAU

Head, Child and Adolescent Outpatient Clinic "Shalvata"

Head, Cognitive and Emotion Research Lab

Research

Our research work is embedded in our clinical dielemas and difficulties. Our studies have focused on: Cognitive and emotional domains in the course and development of different pathologies, especially depression and ADHD. We are interested in the interplay between anxiety and ADHD and a differential effect of Methylphenidate on state anxiety. We were able to show effects of depression on cognition in depressed adolescents with some cognitive domains related to state the depressive episode and others to the the trait. In recent years, our studies have focused on brain stimulation, especially deep transcranial magnetic stimulation (rTMS), effects of pharmaco and psychotherapy and placebo on emotions and cognition.

Publications

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Grants

The Israel National Health Policy (NIHP) grant "Collecting routine outcome measures" in the mental health system". 2014-present

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Investigating Chronic and Acute Pain Mechanisms and New Ways for Pain Modulation and Relief

Positions

Head, Institute for Pain Medicine, Sourasky Medical Center

Research

Chronic pain is a complex physiological condition affecting around 17% of the population. While acute pain, following noxious stimuli or tissue damage, is useful as a warning sign and usually disappears when the trauma is over, chronic pain persists even though the tissue has been healed. Moreover, chronic pain often triggers an array of neurologic, immunologic, physical and psychological changes that worsen the patient's situation and are not related to the original cause of the pain.

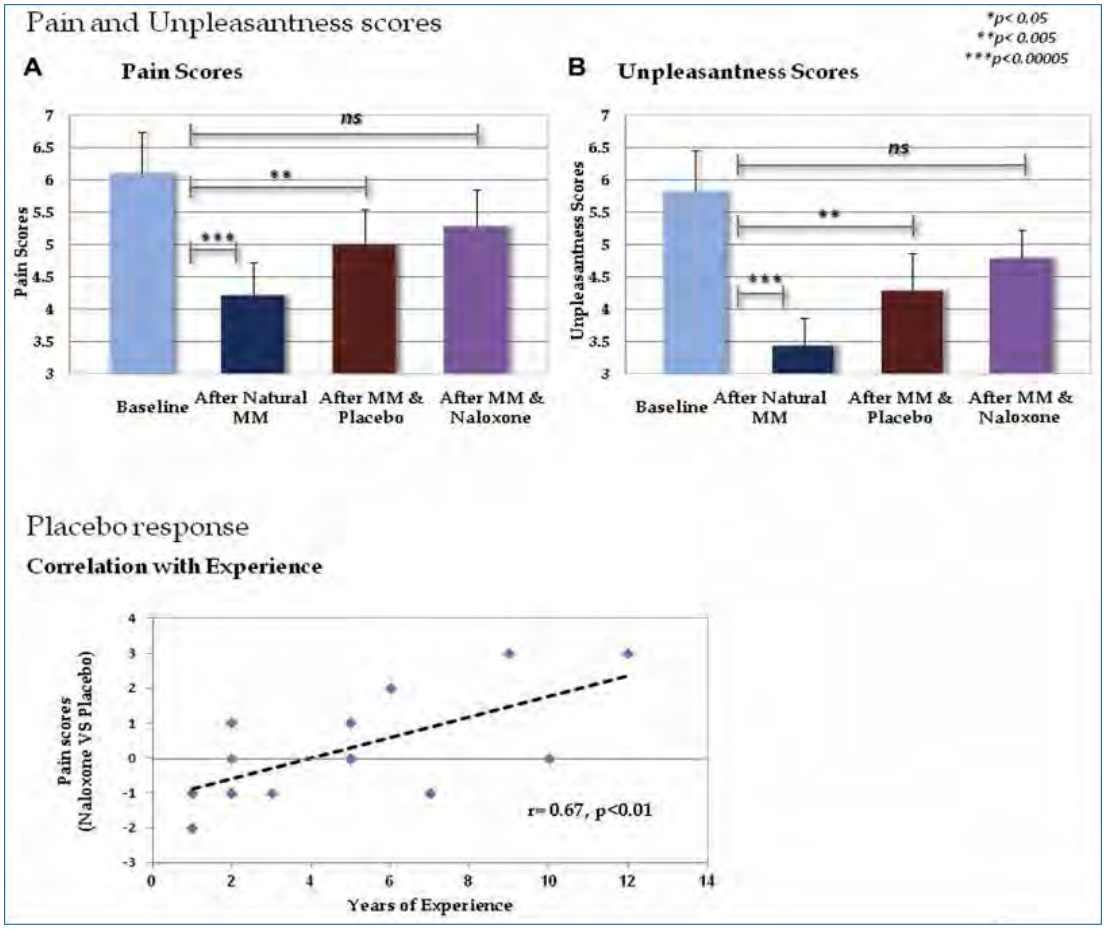

Figure: (Top panel) Mean pain and unpleasantness scores. Mean pain (A, left panel) and unpleasantness scores (B, right panel) following: a painful cold stimulus (baseline); natural meditation; meditation after placebo administration; and meditation after naloxone administration, respectively. Bars represent standard error. (Bottom panel) The differences in pain scores following naloxone vs placebo and participants' mindfulness meditation (MM) experience. The positive correlation of the response to intervention with years of experience suggests reduced response to placebo with increasing experience.

At the Institute for Pain Medicine, we focus on the biochemical basis of pain transmission and pain relieving treatments. For example, in a recent study we showed, for the first time, that meditation involves endogenous opioid pathways, mediating its analgesic effect. In another study, we investigated gender effect on the relationships between parasympathetic activity and pain modulation. We found that women demonstrated higher parasympathetic activity compared to men, which resulted in a subsequent lower pain perception. In a third study, we showed that many patients suffering from complex regional pain syndrome (CRPS), are diagnosed with alexithymia which can be regarded as an outcome of CRPS, highlighting the importance of early CRPS diagnosis and support. These and additional research findings hold promising therapeutic implications and further elucidate the fine mechanisms involved in human pain modulation.

Future research/programs: TMS TDCS Biofeedback, Pain rehabilitation programs, Cannabis database

Publications

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The Pathophysiology and Development of Movement Disorders and Specifically Parkinson's Disease

Positions

Research

We have been leading a large-scale research endeavor to clinically and epidemiologically characterize the Ashkenazi Jewish Parkinson's Disease (PD) population in Israel and to identify genes that influence the risk of developing the disease in this population. In recent years our group has conducted groundbreaking research on the influence of mutations in two major genes – LRRK2 and GBA. The research was first aimed at identifying the prevalence of mutations in these genes in patients with PD and explores differences in phenotype. Our research then evolved to include first degree relatives of these patients to explore early markers of disease in healthy asymptomatic carriers. In addition to examining the contribution of risk mutations, the existence of protective haplotypes or genes was also investigated. For example, recent work has shown that immune system B cells may contribute to protection from the disease or influence its progression. The above described research has opened new avenues of exploring disease identification, progression and even prediction and could potentially impact treatments in PD.

We are also keenly interested in understanding the relationship between cognitive functions and quality of gait, as well as the risk of falling and the neurophysiological basis of the phenomenon of Freezing of Gait (FOG) in Parkinsonism. Our early work on identifying and quantifying FOG resulted in a standardized validated and widely used questionnaire (FOGQ). In addition, our group makes use of accelerometers and gyroscopes to record gait during usual activities, in both the laboratory setting and in the home environment, to better understand changes in performance during daily activites, medication cycles, habits and behavior. Using specified indices, the importance of the variance between different steps was identified, as a measure of fall risk and as a sensitive measure of sub-clinical changes, susceptibility to cognitive loads and perhaps a marker of disease.

In recent years, we have also been involved in exploring new interventions for the patients with PD. These include exploring the effects of tDCS stimulation and virtual reality to improve motor-cognitive function and functional abilities of patients with PD. This work builds on the study of movement disorders, on the one hand, and on examining ways to ameliorate motor symptoms in patients with PD.

In parallel, our group has been heavily involved in clinical trials phase 1-4 with new technologies treating movement disorders of different kinds, as well as community-based epidemiological studies. Using the database of the second largest HMO in Israel (Macabbi Health Care), we characterized PD in Israel, as well as the risks to develop Parkinson and potential protective factors.

Publications

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Grants

2016-2021 Biogen, USA (PI), Identifying markers of disease in a population at risk for developing Parkinson's disease.

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Using Functional Imaging to Investigate Affective Neuroscience

Positions

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Research

Our group has been applying advanced brain imaging techniques, including functional magnetic resonance imaging (fMRI), Diffusion Tensor imaging (DTI) intracranial and scalp electroencephalography (EEG) and magnetic encephalography (MEG) to study mental processing in the healthy and diseased human brain. Our research theme has focused on portraying the neural underpins of individual emotional experience and expression. The accumulative work in affective neuroscience in the last two decades has paved the way for promising translations of imaging technologies for the cure to mental suffering. For example, the lab has pioneered the development of a new real-time imaging approach for the non-invasive identification of "neural finger-prints" that can reliably depict deep limbic areas through trans-modalities' learning computation (e.g. from fMRI to EEG). This new method enables accessible bed-side Brain Computer Interface procedures aimed to alleviate and/or prevent stress related psychopathologies.

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Investigating the Vestibular and Ocular Motor Systems

Positions

Professor, Department of Neurology, Sackler Faculty of Medicine.

Director, Dizziness and Balance Disorders Service, Department of Neurology, Meir Medical Center

Head, Machado-Joseph Disease (MJD) Clinic (recognized by the Israel Ministry of Health)

Research

The vestibular system stabilizes gaze during head movements, ensuring clear vision of the seen world. This is mainly accomplished by the vestibulo-ocular reflex (VOR), which produces compensatory (opposite) eye movements for head rotations. Then, eye position in space is held steady and images do not slip on the retina. During everyday life activities, the vestibular system acts with the optokinetic and visual fixation systems to hold images of the seen world steady on the retina; while saccades, smooth pursuit and vergence eye movements obtain and hold images of objects of interest on the fovea. Moreover, in everyday life activities, the vestibular, visual, ocular motor, propioceptive and motor systems work together to reach exquisite balance, equilibrium and perform accurate motor tasks. Interaction between sensory (vestibular, visual, proprioceptive) and motor (eye movement, locomotion) systems; i.e sensory-motor integration is essential to maintain balance, equilibrium and perform accurate motor tasks including locomotion. Our Vestibular and Eye Movement Laboratory is fully equipped with modern systems for measuring vestibular function, all type of eye movements and balance and gait function.

Our three major ongoing interest and research projects include:

1. Vestibulo-Ocular Reflex (VOR) and eye movement abnormalities as possible biomarkers of Spinocerebellar Ataxia Type 3.

Spinocerebellar Ataxia Type 3 (SCA-3), also known as Machado-Joseph Disease (MJD), is an autosomal dominant neurodegenerative disorder for which genetic testing can reveal those at risk for developing the disease. Quantitative measures that would identify pre-symptomatic gene carriers at the threshold of clinical diagnosis would be extremely valuable in early diagnosis, tracking disease progression, and assessing treatment. This is a crucial subject of investigation not only in SCA-3 but also in other neurodegenerative diseases. Eye movement abnormalities have been reported as reliable neurophysiologic biomarker and even proposed as “a window into disease prevention.” By using bedside vestibular tests and laboratory recording of eye movements, we have described severe VOR deficit and different saccadic abnormalities in patients with SCA-3. Our specific aim is to investigate if VOR and eye movements can be used as biomarkers to quantify the appearance and progress of SCA-3 even pre-symptomatically.

2. Dizziness, vertigo, balance: Clinical and basic research

Dizziness, vertigo and problems with balance are among the most frequent complaints at all ages. Our current research focuses on the following topics:

The contribution of VOR impairment to the perceptual and emotional experience of blurred vision, dizziness and oscillopsia (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).

The relationship between vestibular pathology and the development of anxiety, balance impairment and spatial disorientation (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).

The evaluation of a novel specs device with stabilizing marks on the peripheral visual field to alleviate dizziness.

The search for novel physical and virtual reality strategies to improve balance and alleviate dizziness.

3. Cerebellar Disorders

As our Neurology Department at the Meir Medical Center houses the only Machado-Joseph Clinic in Israel recognized by the Ministry of Health, we therefore have access to most MJD sufferers and many other cerebellar patients in the country and focusing on the following research topics:

Respiratory function in cerebellar degeneration.

Autonomic nervous system function and emotional features in cerebellar diseases.

Cognitive and behavioral changes in cerebellar degeneration.

Physical and pharmacological treatment of cerebellar disorders.

Language and reading difficulties in cerebellar diseases (in collaboration with the School of Education, Tel Aviv University).

The role of the cerebellum in the hedonic experience of music (in collaboration with the Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center).

The mutational origins of Machado-Joseph Disease in the Jew Yemenite subpopulation in Israel (in collaboration with the IBMC – Institute of Molecular and Cell Biology, and IPATIMUP – Institute of Pathology and Molecular Immunology of University of Porto, Portugal).

Publications

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Neurogenetics Syndromes

Positions

Professor, Psychiatry & Sagol School of Neuroscience

President, Israel Society of Biological Psychiatry

Director, The Behavioral Neurogenetics Center

Director, The Child Psychiatry Division, Sheba Medical Center

Research

We have been studying neurogenetics syndromes – 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome for two decades. 22q11.2DS is the most common known microdeletion syndrome. The 22q11.2DS phenotype consists of cleft and cardiovascular anomalies and immunological abnormalities. Additionally, all individuals with 22q11.2DS cope with cognitive deficits and one-third of the patients develop schizophrenia-like psychotic disorders and many manifest with autism spectrum disorder. We study the pathways leading to psychosis, autism and cognitive deficits in 22q11.2DS. Our focus is identifying cognitive, behavioral and psychiatric risk factors associated with the evolution of psychosis in 22q11.2DS. We also study molecular and immunological pathways to psychosis and to the behavioral and cognitive phenotype of the syndrome using blood samples and animal models. We collaborate with many centers from US and Europe under the umbrella of the International Brain and Behavior Consortium funded by the NIMH.

Publications

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Grants

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Investigating the Biological Basis of Severe Mental Illness and Drug-Response Mechanisms

Positions

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Senior Lecturer, Sackler Faculty of Medicine

Senior Researcher, Biological Psychiatry Lab, Felsenstein Medical Research Center

Visiting Researcher, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Research

Severe mental illness includes chronic, clinically debilitating disorders such as schizophrenia and mood disorders. Among the most important prognostic factors of people suffering from schizophrenia is the adherence and clinical response to medications, notably antipsychotic compounds. There is a portion of about third of the patients who will not have enough response to medications. The only effective drug for this population is clozapine, yet only half of these patients would response to clozapine. The rest are termed ultra-refractory patients, and currently are devoid of any evidence-based medical therapy.

Our research is focused around deciphering the biological basis of response and refractoriness to antipsychotic compounds, and especially to clozapine. We employ various research methods to study both clinical human samples and animal models of psychotic traits. The main goal of the project is to utilize the information gathered from understanding mechanisms into clinical practice as potential therapeutic targets. Current projects in our lab consist of analysis of biochemical assays of both human and animal tissues, for inflammatory markers, vitamin D, glutamate, neurotrophins, dopamine and other related neurotransmitters.

Another field of psychobiology research in our lab is the relationship between the immune system and the brain in pathological conditions. There is growing evidence that neuroinflammatory factors are involved in the pathophysiologic mechanisms leading to schizophrenia, along with genetic components. We study the 22q11.2 deletion syndrome (22q11.2DS). Individuals with this syndrome have a microdeletion of a section of the long arm of chromosome 22 and have a characteristic phenotype including immunological abnormalities and other pathologies. Individuals with 22q11.2DS have a 30% risk of developing schizophrenia. As a result, this syndrome is an optimal genetic model for studying the interaction between the immune system and schizophrenia.

Depression is another mental disorder that we are investigating in our lab in order to evaluate the relationship between abnormalities in the immune system and this mental condition.

Our lab is located at the heart of the intersection between basic science and clinical practice. It is physically located at the Belinson campus, in close

proximity to the Geha Mental Health Center. The staff is composed of senior clinical researchers, as well as senior neuroscientists, working in collaboration. We aim to bring together clinical information with animal model data to eventually take back as therapeutic interventions for a population with severe illness and urgent unmet needs.

Publications – Krivoy

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Grants

National Institute of Psychobiology in Israel

Stanley Medical Research Institute

The Israel National Institute for Health Policy Research

Publications – Taler

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Bloch K, Gil-Ad I, Vanichkin A, Hornfeld SH, Koroukhov N, **Taler M**, Vardi P, Weizman A. Intracerebroventricular Streptozotocin Induces Obesity and Dementia in Lewis Rats: Rat Model of Dementia Associated with Obesity. *J Alzheimers Dis*. 2017;60 (1):121-136Mekori–Domachevsky E, **Taler M**, Shoenfeld Y, Gurevich M, Sonis P, Weisman O, Weizman A, Gothelf D. Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome Are Associated with Psychosis and Cognitive Deficits. *Journal of Clinical Psychiatry*. 2017, 78(9)

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Grants

National Institute of Psychobiology in Israel

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Dr. Yulia Lerner, Ph.D.

Neurodegeneration Lab: Cognitive Neuroscience Research

Positions

Senior Lecturer, Sackler Faculty of Medicine

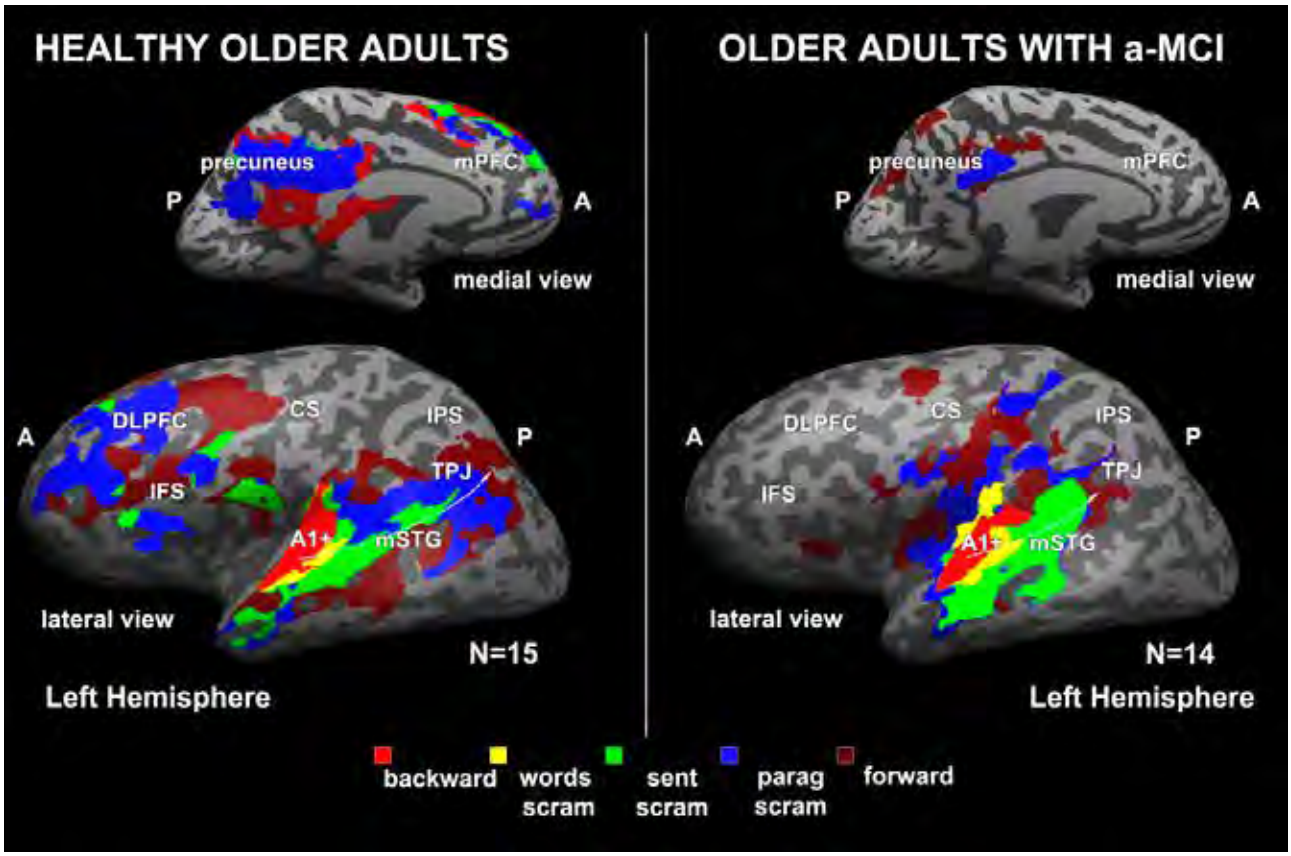
Senior Researcher, Tel Aviv Sourasky Medical Center

Research

Our lab focuses on study neural activity undergoing complex real-life events. The research involves functional and structural brain imaging, neuropsychological assessments and physiological measurements. We apply our paradigms to neuro-psychiatric disorders (e.g. mild cognitive impairment (MCI), schizophrenia, etc.), for the understanding the pathological conditions. To study factors of vulnerability in a causal manner we apply prospective imaging approach or comparing groups of affected to unaffected individuals under similar conditions (e.g. older adults and MCI, patients with schizophrenia and their unaffected siblings). While applying multi-modal paradigms, we are concentrated on developing methods for identification of "functional neuromarkers" for the disease.

Main research topics

- Investigation of human brain responses and behavior under natural conditions
- The architecture of neural circuits involving in processing of non-verbal information
- Developing functional neuromarkers for abnormal cognitive states



Hierarchical organization in healthy older adults and participants with aMCI during story processing

Publications

Golland Y., Levit-Binnun N., Hendler., **Lerner Y**. (2017) Neural dynamics underlying emotional transmissions between individuals. SCAN, May, 01-12. *doi:10.1093/scan/nsx049*

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Positions

Sackler Faculty of Medicine

Physician-in-Chief, Lev Hasharon Medical Center

Research

We study the association between drug use and psychiatric disorders. We harness epidemiological and clinical approaches aimed at improving the understanding of mental health related aspects of drug use.

Specifically, much of our current reseach focuses on psychiatric outcomes of cannabis use. In recent decades, there has been a significant increase in the prevalence of cannabis use, as well as in the potency of cannabis consumed. This holds several medical and social implications, some of which are yet unclear. We focus on exploring mental-health related outcomes of cannabis use by conducting epidemiological research using large population-based samples and analysis of “big-data” based on internet-based sources. In addition, we expolore specific neuro-biological and neurocognitive aspects of heavy cannabis use by utilizing advanced functional technologies such as Transcranial Magnetic Stimulation (TMS). Our studies regarding the effects of cannabis on depression and anxiety are commonly cited in World Heatlh Organization publications, and our reports on mental-health related aspects of medical marijuana and prescription opioids have served as a based for national policy papers.

Publications

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URL:
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Functional Neuroimaging Laboratory

Positions

Head, Functional Neuroimaging Laboratory, Department of Diagnostic Imaging, Sheba Medical Center, affiliated to Sackler Faculty of Medicine

Researcher, Sagol Neuroscience Center, Sheba Medical Center.

Research

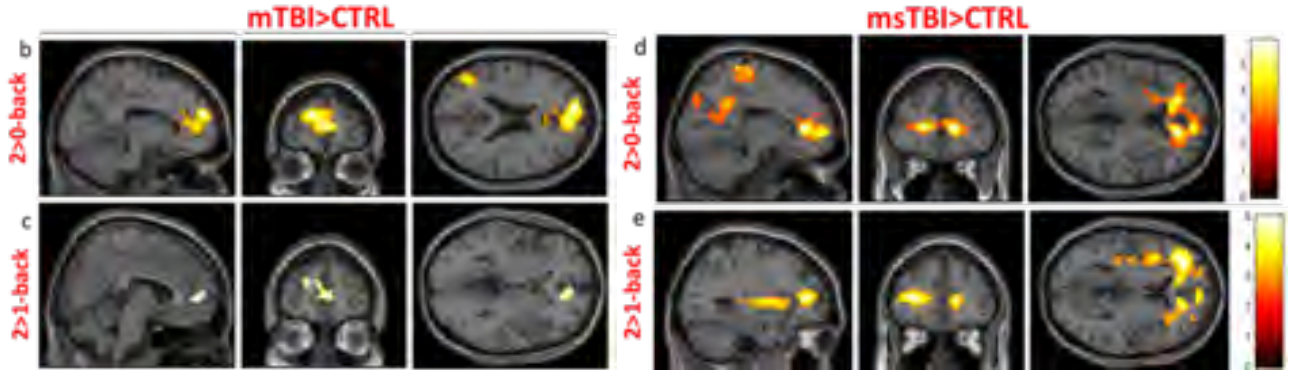
The Functional NeuroImaging Lab Studies brain pathologies, in particular the way the brain reorganizes due to brain injury (TBI). We use various tools including: advanced structural MRI and fMRI protocols using tailor-made fMRI tasks to examine the deficits after TBI. We apply also extensive neuropsychological batteries in order to investigate cognitive impairments. Furthermore, we examine symptoms and emotional status using validated questionnaires and scales. This data is integrated and analyzed to identify networks and patterns which will further our understanding of neuropathology and neuronal reorganization. Our research aims to improve the prediction of brain pathology's progression, to plan medical and rehabilitative interventions for the well-being of patients with brain diseases and head injuries.

Publications

Livny A., Biegon A., Kushnir T., Harnof S., Hoffman C., Fruchter E., Weiser M. Mild Traumatic Brain Injury Linked to Persistent Cognitive Deficits and Smaller Insular Volume. Journal of Neurotrauma. 2017; 34:1466-1472.

Weinstein A., **Livny A.,** Weizman A. Brain imaging studies on the cognitive, pharmacological and neurobiological effects of cannabis in humans: Evidence from studies of adult users. Current Pharmaceutical Design. 2016.

Livny A., Ravona Springer R., Heymann T., Priess R. Kushnir T., Tsarfaty G., Rabinov L., Moran R., Hoffman H., Cooper I., Greenbaum L., Silverman J., Sano M., Johnson S., Bendlin B., Schnaider Beeri M. Long-term variability in glycemic control is associated with white matter hyperintensities



The relation between severity of TBI and working-memory brain activation during an n-back task. Maximum intensity projections in three orthogonal views of the brain (from left to right: sagittal, coronal and axial) depict areas of significant activation ($p<0.005$, $k>100$) in a one-tailed-t statistic contrasting MR signal increases. The color scale shows t-values to the right. a, c: 2->0-back= high WM load; b,d: 2->1-back= WM load increase; CTRL= controls; mTBI= mild TBI; msTBI= moderate-severe TBI. mTBI patients further activated bilateral prefrontal and left parietal regions. msTBI patients revealed greater activation than controls in frontal, parietal and limbic regions.

in APOE4 genotype carriers with type 2 diabetes. Diabetes Care. 2016; 39(6): 1056-9.

Krasovsky, T., Landa, J., Bar, O., Ahonniska-Assa, J., **Livny, A**., Tsarfaty, G., Silberg, T. Functional plasticity in the absence of structural change: Apraxia and body scheme disorder 10 years after childhood brain injury. Journal of Child Neurology. 2017; 32:505-511.

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Greenbaum L., Heymann A., Sharvit-Ginon I., Alkelai A., **Livny A.**, Beeri M., Shelly S., Ganmore I., Ravona-Springer R. The CADM2 gene is associated with processing speed performance –evidence among elderly with Type 2 Diabetes. World Journal of Biological Psychiatry. 2017; 5:1-7.

Livny A., Ravona-Springer R., Heymann A., Priess R., Kushnir T, Tsarfaty G., Rabinov L., Moran R, Tik N., Cooper I., Greenbaum L., Silverman J., Sano M., Bendlin BB, Buchman AS, Schnaider Beeri M. The haptoglobin 1-1 genotype modulates the association of glycemic control with hippocampal volume in elderly with type 2 diabetes. Diabetes. 2017; 66:2927-2932.

Livny A., Reichenberg A, Fruchter E., Yoffe R., Goldberg S., Fenchel D., Burshtein S., Bachar E., Davidson M., Weiser M. A population-based longitudinal study of symptoms and signs before the onset of psychosis. American Journal of Psychiatry 2017 [Epub ahead of print].

Reviews

Weinstein A., **Livny A.**, Weizman A. New developments in brain research of internet gaming disorder. Neuroscience & Biobehavioral Reviews. 2017; 75:314-330.

Dr. Nicola Maggio, M.D., Ph.D.

Department of Neurology and Neurosurgery
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The Role of Neuroinflammation and Neurocoagulation in the Pathophysiology of Neurological Disorders

Positions

Senior Lecturer, Sackler Faculty of Medicine

Senior Neurologist and Neurophysiologist, Department of Neurology, Chaim Sheba Medical Center, Tel HaShomer

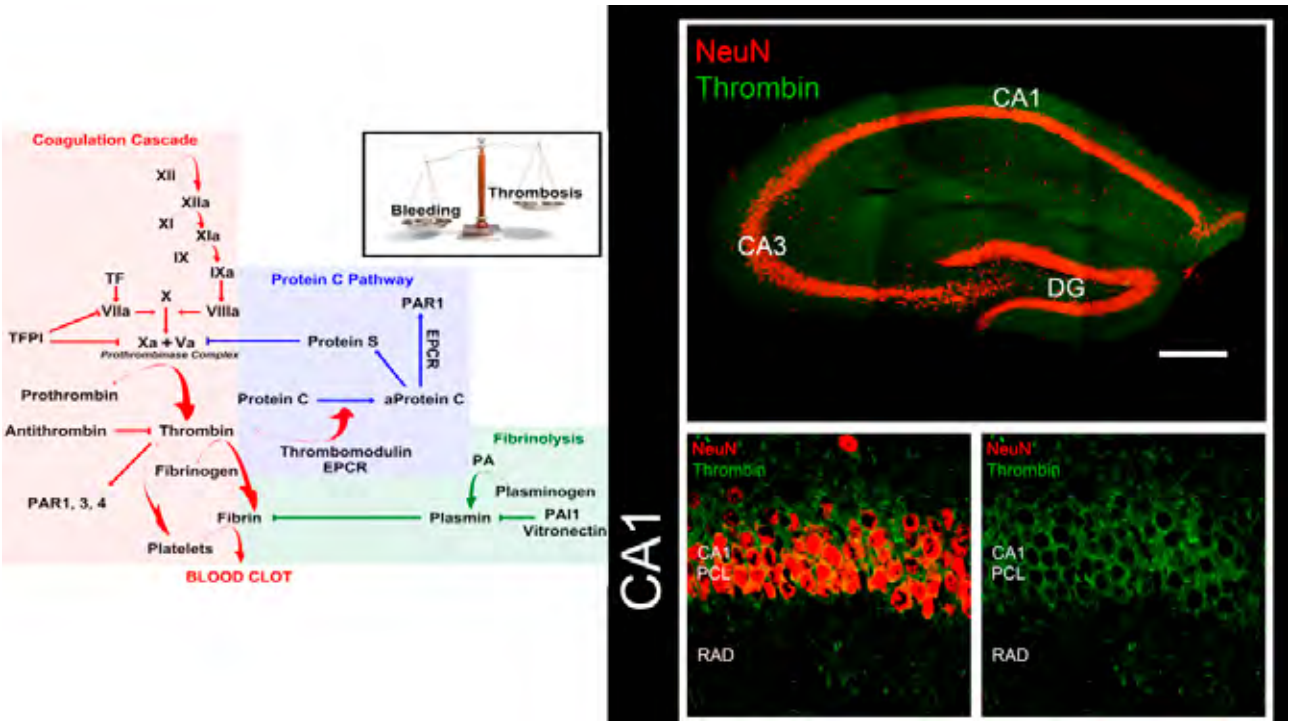
Research

Our research focuses on the understanding of the role of coagulation factors, as well as their interaction with neuroinflammation in the physiology and pathophysiology of the nervous system. We have recently discovered that thrombin, the factor that ignites the coagulation cascade, is synthesized in the brain and has a fundamental role in regulating synaptic plasticity. However, we have also shown that high concentrations of thrombin (that reach the brain upon haemorrhage) can cause seizures and epilepsy. Our research has contributed in designing novel compouds that are currently being tested in order to counteract the pathogenic actions of thrombin in the brain. We apply cutting-edge technologies including mouse genetic tools, behavioural analysis, electrophysiology and molecular and cellular biology.

Publications

Willems L.M., Zahn N., Hick M., Ferreirós N., Scholich K., **Maggio N.**, Deller T., Vlachos A. (2016) Sphingosine-1-phosphate receptor inhibition prevents denervation-induced dendritic atrophy. Acta Neuropathologica Communications. 4:28.

Givaty G, **Maggio N.**, Cohen OS, Blatt I and Chapman J (2016) Early pathology in sleep studies of patients



The coagulation pathways play fundamental roles in the physiology and pathophysiology of the nervous system. Immunofluorescence analysis reveals the expression pattern of thrombin in the hippocampus.

with familial Creutzfeldt-Jakob Disease. The Journal of Sleep Research, (5):571-575.

Schuldt G., Galanis C., Strehl A., Schiener S., Hick M., Lenz M., Deller T., **Maggio N.**, Vlachos (2016) Inhibition of Protease-Activated Receptor 1 (PAR1) does not affect dendritic homeostasis of cultured mouse dentate granule cells. (2016) Frontiers in Neuroanatomy;10:64.

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Golderman V., Shavit-Stein E., Tamarin I., Rossman Y., Shrot S., Rosenberg N., **Maggio N.***, Chapman J.*, Eisenkraft A.* (2016) The organophosphate paraoxon and its antidote obidoxime inhibit thrombin activity and affect coagulation *in vitro*.PlosOne, 2016 Sep 30;11(9):e0163787. doi: 10.1371/journal.pone.0163787. *Equal contributors and last authors.

Gera O., Shavit-Stein E., Bushi D., Harnof S., Weiss R., Golderman V., Dori A., **Maggio N.**, Ben Shimon M., Finegold K., Chapman J. (2016) Novel Expression and Localization of Protein C Pathway Components in the Peripheral Nervous System. Neuroscience;339:587-598. d

Lenz M., Ben Shimon M., Vlachos A.* and **Maggio N.*** (2016) Pilocarpine- induced status epilepticus is associated with changes in the actin-modulating protein synaptopodin and alterations in long term potentiation in the mouse hippocampus. Neural Plasticity, 2017. *Equal contributors and last authors.

Maggio N., Firer M., Zaid H., Bederovsky Y., Aboukaoud M., Gandelman-Marton R., Noyman I., Ekstein D., Blatt I., Marom E., Schwartzberg E., Israel S., Brautbar C., Ingber A., Eyal S. (2016) Causative drugs of Stevens Johnson syndrome and toxic epidermal necrolysis in Israel. Journal of Clinical Pharmacology, 2017.

Prof. Shimon Rochkind, MD., Ph.D.

Research Center for Nerve Reconstruction (RCNR)
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Investigating Reconstruction of Peripheral and Central Nervous Systems Following Injury

Positions

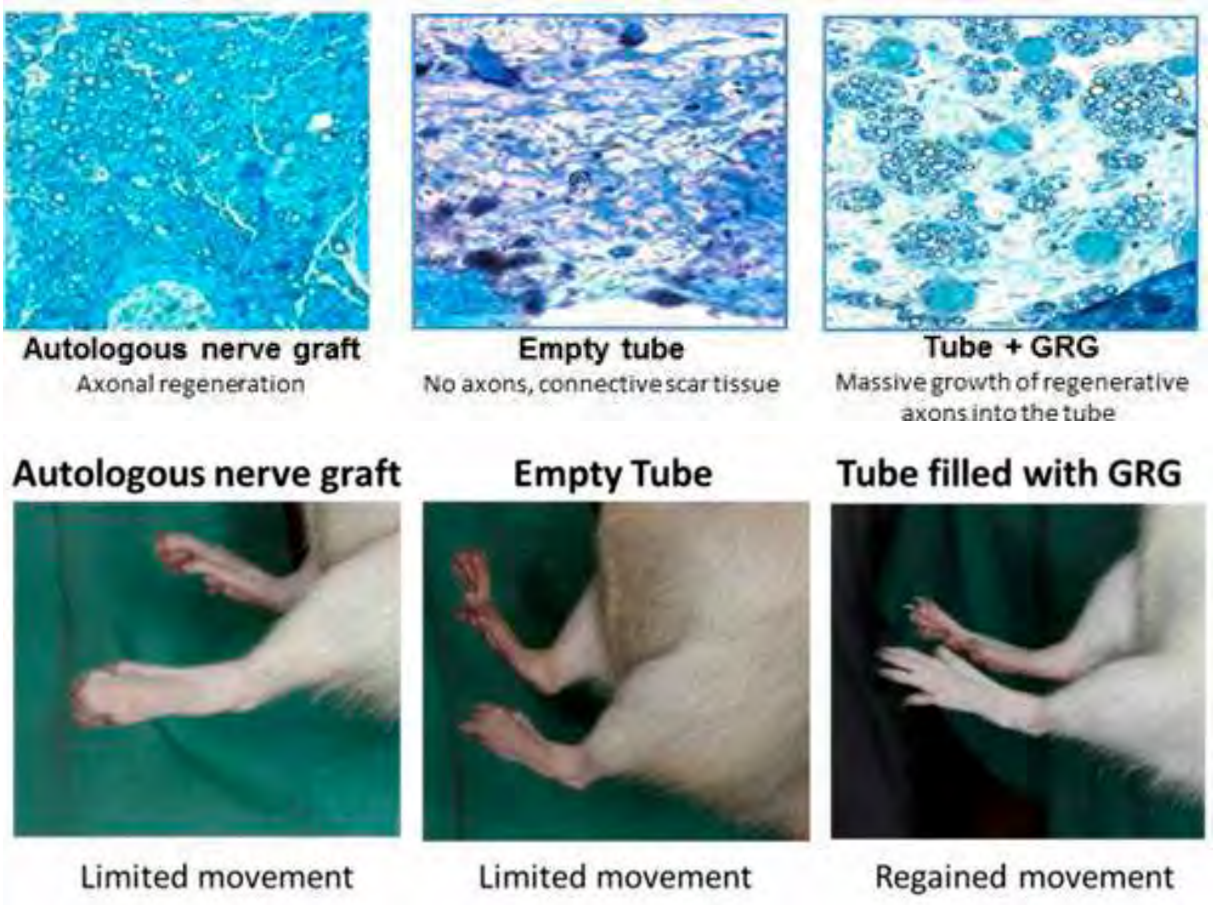
Associate Professor, Sackler Faculty of Medicine

Director, Division of Peripheral Nerve Reconstruction, Tel Aviv Sourasky Medical Center

Research

The research group is involved in projects targeting improvement in nerve reconstruction and rehabilitation from several aspects, aiming at the creation of innovative treatments to both peripheral nerve (PN) and spinal cord (SC) injuries. RCNR major projects include:

Creation of artificial nerve for nerve reconstruction using the innovative Guiding Regenerative Gel (GRG) to improve and accelerate regeneration of peripheral nerve injury (PNI) with massive defect. The GRG is a special milieu that was developed in collaboration with Prof. Zvi Nevo from Tel-Aviv University, Israel. The unique composition of GRG has recently been shown to be as efficient as autologous nerve graft, promoting axonal growth and sprouting without dependence on the addition of any external growth factors. In a short-term *in vivo* study it was shown that GRG loaded into a conduit promoted axonal sprouting of nerve cells and enabled the regeneration of a 15mm long nerve gap in rats,



which is not possible when bridging with an empty conduit (regeneration of up to 7mm). Therefore, the GRG allows a simpler procedure with less side effects, since its implantation does not involve other nerve origin, sensation loss or cosmetic defect as the "gold standard" treatment, therefore, GRG can provide a promising simple of the shelf solution for clinical use for complete PNI.

Based upon our encouraging results with the GRG, which shed light on the utilization of this innovative composite implant to bridge a gap, we postulate to improve this approach and attempt reconstruction of experimental complete SCI. Since astroglial scarring is one of the main obstacles for axonal growth and therefore spinal cord recovery, we have developed an Antigliotic Guiding Regenerative Gel (AGRG) which contains Guiding Regenerative Gel (GRG), and was proven to promote axonal sprouting and survival as well as antigliotic agents, which presented *in vitro* highly significant antigliotic activity, while reducing the amount of GAGs by more than 84%, thus inhibiting scar growth barrier formation in the site of injury.

The effect of laser phototherapy (low power laser irradiation) was explored on neuronal cells and peripheral nerve. In nerve cell cultures, laser irradiation significantly accelerated axonal sprouting (Rochkind et al., Lasers Surg Med, 2009). Animal studies in a model of incomplete peripheral nerve injury showed that laser phototherapy has an immediate protective effect, maintains functional activity of the injured nerve, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord and significantly increases axonal growth and myelinization. In a model of complete peripheral nerve injury with segmental loss, the laser-treated group showed more intensive axonal growth and morphological reconnection compared with the control group (Rochkind. Neurosurgical Focus, 2009). Recently, we found that in early stages of muscle atrophy, laser phototherapy may preserve the denervated muscle by maintaining creatine kinase activity and the amount of acetylcholine receptors. (Rochkind and Shainberg, Photomed Laser Surg, 2013). The current projects are intended to test and validate the beneficial effect of laser phototherapy on severely injured PN with a view to move forward to clinical study.

Publications

Rochkind S, Shainberg A. Muscle Response to Complete Peripheral Nerve Injury: Changes of Acetylcholine Receptor and Creatine Kinase Activity over Time. Journal of Reconstructive Microsurgery; doi: 10.1055/s-0037-1598619; 2017.

Mandelbaum-Livnat M.M, Almog M, Nissan M, Loeb E, **Rochkind S**. Photobiomodulation in Peripheral Nerve Injury with Aspect to Muscle Response. Photomedicine and Laser Surgery; 34(12):638-645; 2016.

Meyer C, Wrobel S, Raimondo S, **Rochkind S**, Heimann C, Shahar A, Ziv-Polat O, Geuna S, Grothe C, Haastert-Talini K. Peripheral Nerve Regeneration Through Hydrogel-Enriched Chitosan Conduits Containing Engineered Schwann Cells for Drug Delivery. Cell Transplantation; 25(1):159-82; 2016.

Dr. Ariel Tankus, Ph.D.

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URL: http://www.sagol.tau.ac.il/en/people/ariel-tankus/

The Neuronal Encoding of Human Speech

Positions

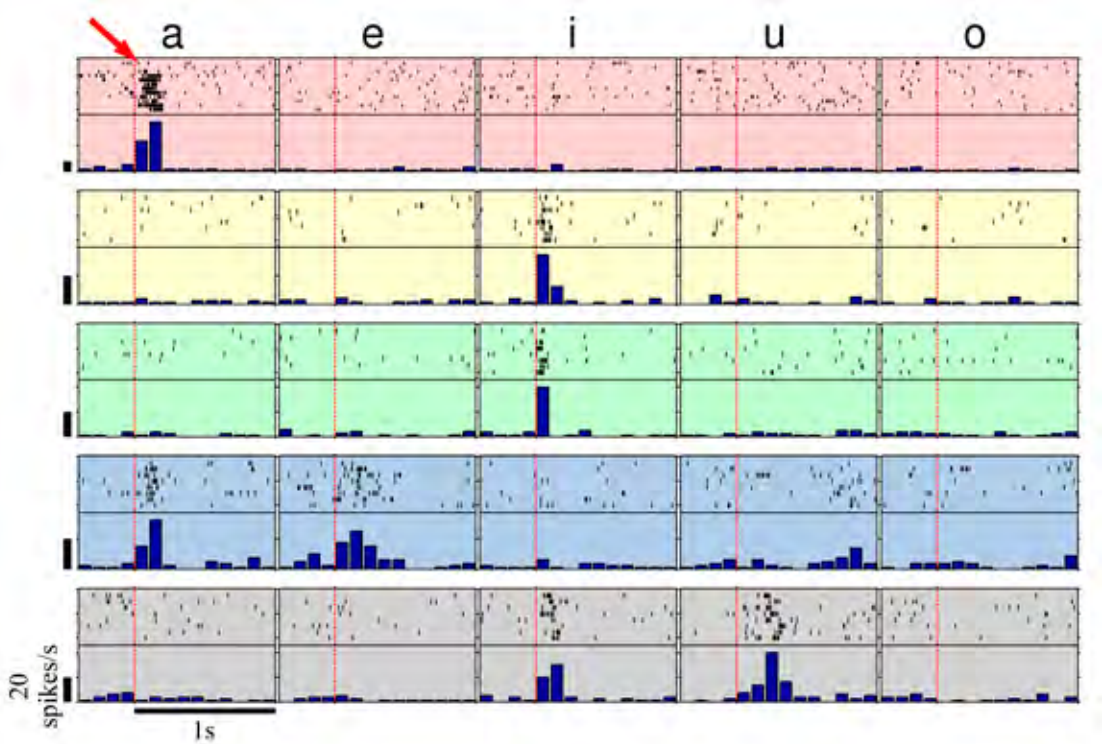
Senior Lecturer, Sackler Faculty of Medicine and Sagol School of Neuroscience

Senior Researcher and Neurophysiologist, Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center ("Ichilov")

Research

We study the neuronal representation of speech production, perception and imagery in the human brain. We explore the acoustic, phonetic and phonological levels, and the deterioration in speech due to neurological disorders, for example in Parkinson's disease. Our main focus is the encoding of speech features by single neurons (for example, see Figure 1). We also aim to develop brain-machine interfaces for restoring speech faculties in completely paralyzed persons by decoding their neuronal activity (i.e., inferring speech contents solely from spiking activity).

We take advantage of a unique clinical "opportunity" to work with neurosurgical patients undergoing implantation of electrodes for clinical reasons. Experiments are conducted intra-operatively with awake patients with movement disorders or in the ward, with epilepsy patients. Understanding the neuronal representation of human speech is essential for understanding the underlying mechanisms of speech disorders, for the development of new



Medial–frontal units that we have discovered, with high specificity to vowels. Raster plots and peri-stimulus time histograms of five units (rows) during the articulation of the five vowels a, e, i, u and o (columns). The response of each unit is specific to one or two vowels only.
Red vertical dashed lines indicate speech onset. All vertical scale bars correspond to firing rates of 20 spikes/s (from: Tankus *et al.*, Nature Communications, 2012).

therapeutic procedures, and for restoration of the ability to speak. The research thus bears enormous potential to greatly improve the quality of life of millions of people around the globe.

Publications

A. Tankus, I. Strauss, T. Gurevich, A. Mirelman, N. Giladi, I. Fried, J. M. Hausdorff. Subthalamic neurons encode both single- and multi-limb movements in Parkinson's disease patients. Scientific Reports, 7(42467), 2017.

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A. Tankus, A. Mirelman, N. Giladi, I. Fried, J. M. Hausdorff. Pace of movement: the role of single neurons in the subthalamic nucleus. Journal of Neurosurgery, 2018.

Chapter

A. Tankus and J.M. Hausdorff. Deep brain stimulation in Parkinson's disease: effects on gait and postural control. In F.A. Barbieri and R. Vitório, editors, Locomotion and Posture in Older Adults – The Role of Aging and Movement Disorders, Springer, Chapter 25, pages 385–396, 2017.

Prof. Avraham Weizman, M.D.

Laboratory of Biological Psychiatry
Felsenstein Medical Research Center (FMRC)
Sackler Faculty of Medicine
Research Unit, Mental Health Center (GMHC)

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weizmana@gmail.com

Investigating the Biological Basis of Psychiatric Disorders

Positions

Full Professor, Sackler Faculty of Medicine

Head of the Laboratory of Biological Psychiatry, FMRC

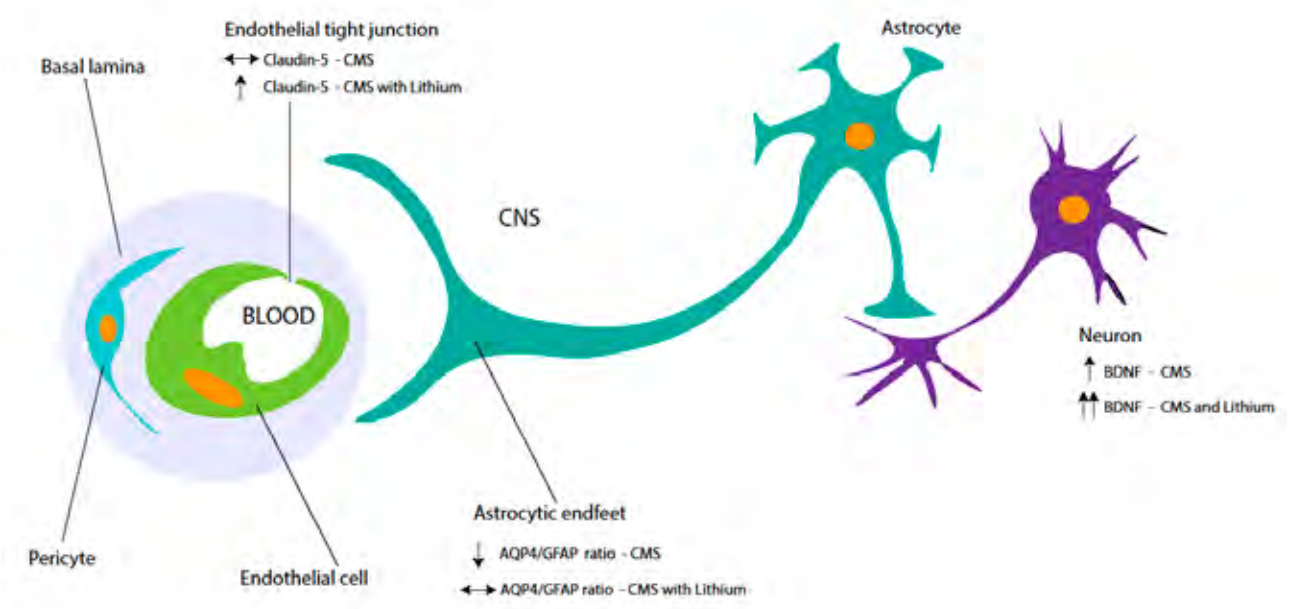
Head of the Research Unit, GMHC

Research

Our laboratory is driven by the belief that combining pre-clinical and clinical research is the key to modern translational research. We investigate brain mechanisms of mental disorders, currently focusing on neurodevelopmental disorders, development of new strategies for the treatment of psychotic disorders and psychopharmacology of mental disorders.

Our research goals are to identify genetic and environmental factors that contribute to the emergence of psychosis and depression, as well as cognitive decline. To this end we study the role of genetic variants, neuro-anatomical changes, profiles of gene expression and neuro-endocrine and neuro-immune alterations in the pathophysiology of these disorders. We attempt to identify neural, molecular pathways and brain-circuits associated with pathological behaviors. The accumulated results are used to develop new therapeutic strategies based on novel targets. We, together with Dr. Eldar Hochman from GMHC and Dr. Michal Taler and Dr. Shay Henry Hornfeld from FMRC, recently found a novel lithium mechanism of action at the BBB. In another project we developed with Dr. Konstantin Bloch, Prof. Pnina Vardi and others from FMRC, a novel strategy for the treatment of Alzheimer-like metabolic dementia that responded to transplantation of pancreatic islets.

On the clinical level, we assess the efficacy and tolerability of psychopharmacological agents in the treatment of pediatric and adult mental disorders,



Regulatory effect of lithium on hippocampal blood-brain barrier integrity in a rat model of depressive-like behavior.

especially psychotic and mood disorders. In a recent collaboration with Prof. Doron Gothelf from Sheba Medical Center and Dr. Elena Michaelovski and Dr. Miri Carmel from FMRC, we identified genetic and epi-genetic pathways that may be involved in the emergence of psychosis in patients with 22q11.2DS. In a series of pivotal studies in the field of drug addiction that was done in collaboration with Prof. Gal Yadid from Bar Ilan University, we demonstrated that the neurosteroid DHEA can attenuate drug use in subjects with addictive behaviors. With Dr. Amir Krivoy from GMHC and Dr. Michal Taler we also found that the cognitive performance of treatment resistant schizophrenia patients maintained on clozapine, may benefit from the addition of vitamin D.

Publications (out of 150)

Poyurovsky M, **Weizman A**. Treatment of Antipsychotic-Induced Akathisia: Role of Serotonin 5-HT_{2a} Receptor Antagonists. Drugs. 2020 May 8.

Gur S, Taler M, Bormant G, Blattberg D, Nitzan U, Vaknin-Dembinsky A, BrillL, Krivoy A, **Weizman A**, Hochman E. Lack of association between unipolar or bipolar depression and serum aquaporin-4 autoantibodies. Brain Behav Immun. 2020May 5:S0889-1591(20)30495-5.

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Bloch K, Hornfeld SH, Dar S, Vanichkin A, Gil-Ad I, Vardi P, **Weizman A**. Long-term effects of intracranial islet grafting on cognitive functioning in a rat metabolic model of sporadic Alzheimer's disease-like dementia. PLoS One.2020;15:e0227879.

Krivoy A, Satz J, Hornfeld SH, Bar L, Gaughran F, Shoval G, Hochman E, **Weizman A**, Taler M. Low levels of serum vitamin D in clozapine-treated schizophrenia patients are associated with high levels of the proinflammatory cytokine IL-6. Int Clin Psychopharmacol. 2020.

Amitai M, Taler M, Ben-Baruch R, Lebow M, Rotkopf R, Apter A, Fennig S, **Weizman A**, Chen A. Increased circulatory IL-6 during 8-week fluoxetine treatment is a risk factor for suicidal behaviors in youth. Brain Behav Immun. 2019 S0889-1591(19)31330-3.

Zeineh N, Nagler R, Gabay M, **Weizman A**, Gavish M. Effects of Cigarette Smokeon TSPO-related Mitochondrial Processes. Cells. 2019;8:694.

Cohen K, **Weizman A**, Weinstein A. Modulatory effects of cannabinoids on brain neurotransmission. Eur J Neurosci. 2019;50:2322-2345.

Monga S, Nagler R, Amara R, **Weizman A**, Gavish M. Inhibitory effects of the two novel TSPO ligands 2-Cl-MGV-1 and MGV-1 on LPS-induced microglial activation. Cells. 2019; 8:486. doi: 10.3390/cells8050486.

Bloch K, Dar S, Vanichkin A, Gil-Ad I, Vardi P, **Weizman A**. Trafficking of grafted pancreatic islets into the brain lateral ventricles: implications for cognition. Transplantation. 2019;103:e137-e138.

Michaelovsky E, Carmel M, Frisch A, Salmon-Divon M, Pasmanik-Chor M, **Weizman A**, Gothelf D. Risk gene-set and pathways in 22q11.2 deletion-related schizophrenia: a genealogical molecular approach. Transl Psychiatry. 2019;9:15. doi: 10.1038/s41398-018-0354-9.

Azrad M, Zeineh N, **Weizman A**, Veenman L, Gavish M. The TSPO Ligands2-Cl-MGV-1, MGV-1, and PK11195 Differentially Suppress the Inflammatory Response of BV-2 Microglial Cell to LPS. Int J Mol Sci. 2019;20:E594.

Poyurovsky M, **Weizman A**. Very Low-Dose Mirtazapine (7.5 mg) in treatment of acute antipsychotic-associated akathisia. J Clin Psychopharmacol. 2018;38:609-611.

Lax E, Warhaftig G, Ohana D, Maayan R, Delayahu Y, Roska P, Ponizovsky AM,**Weizman A**, Yadid G, Szyf M. A DNA methylation signature of addiction in T cells and Its reversal with DHEA intervention. Front Mol Neurosci. 2018;11:322.

Bloch K, Gil-Ad I, Vanichkin A, Hornfeld SH, Taler M, Dar S, Azarov D, Vardi P, **Weizman A**. Intracranial transplantation of pancreatic islets attenuates cognitive and peripheral metabolic dysfunctions

in a rat model of sporadic Alzheimer's Disease. J Alzheimers Dis. 2018;65:1445-1458.

Poleg S, Golubchik P, Offen D, **Weizman A**. Cannabidiol as a suggestedcandidate for treatment of autism spectrum disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2019;89:90-96.

Yadid G, Ahdoot-Levi H, Bareli T, Maayan R, **Weizman A**. Dehydroepiandrosterone and addiction. Vitam Horm. 2018;108:385-412.

Golubchik P, Levy T, **Weizman A**. The effect of methylphenidate treatment onpsychopathic behavior of patients having attention-deficit hyperactivity disorderwith and without oppositional defiant disorder. Int Clin Psychopharmacol. 2018;33:330-333.

Mekori-Domachevsky E, Taler M, Shoenfeld Y, Gurevich M, Sonis P, Weisman O, **Weizman A**, Gothelf D. Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome are associated with psychosis and cognitive deficits. J Clin Psychiatry. 2017 Nov/Dec;78(9):e1219-e1225.

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Krivoy A, Hochman E, Sendt KV, Hollander S, Vilner Y, Selakovic M, **Weizman A**, Taler M. Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. Schizophr Res. 2018;192:226-231.

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Weinstein A, Livny-Ezer A, **Weizman A**. Brain imaging studies on the cognitive ,pharmacological and neurobiological effects of cannabis in humans: Evidence from studies of adult users. Curr Pharm Des. 2016;22:6366-6379.

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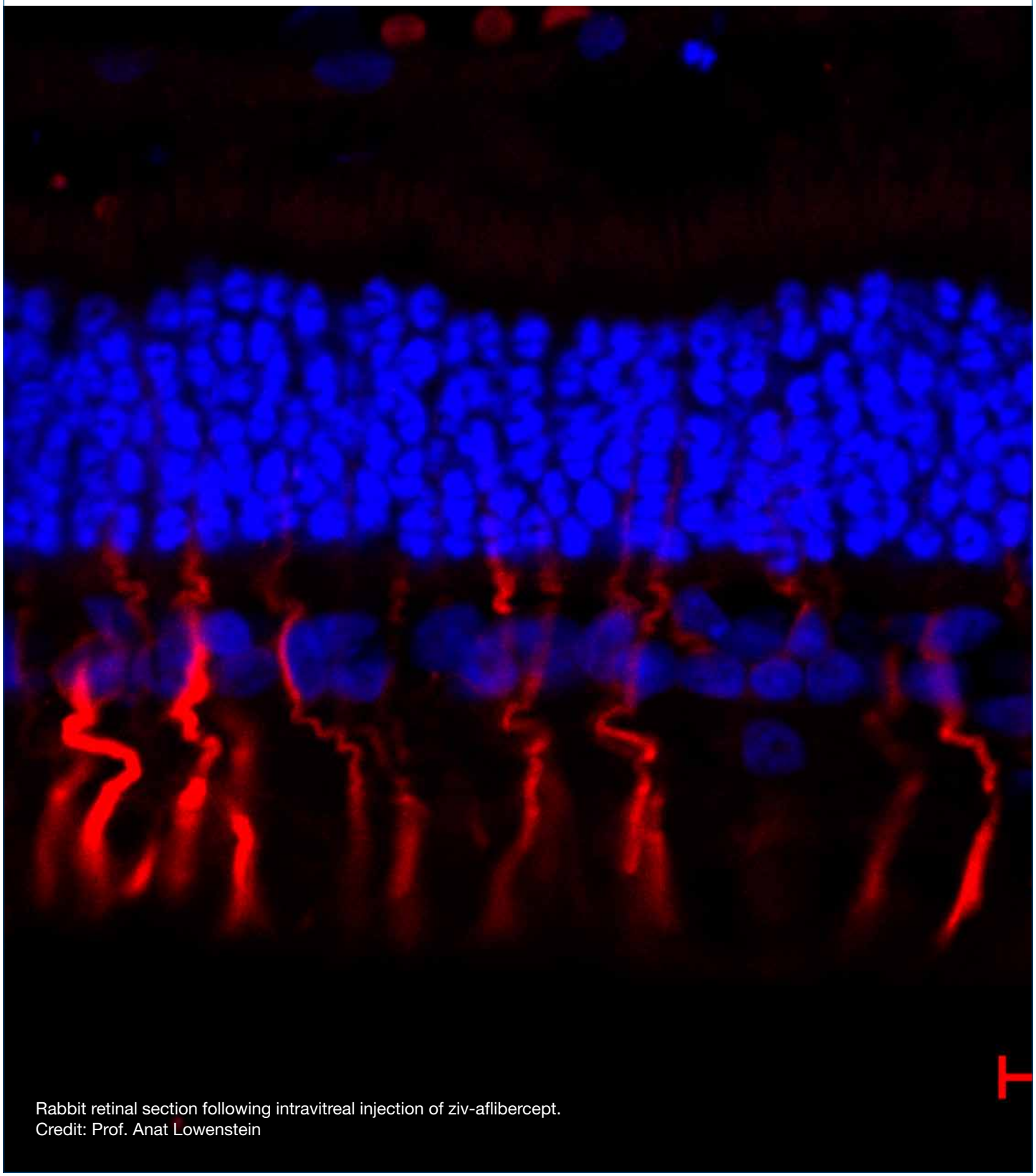
Grants

2018 – 2020 Mayer Foundation for Scientific Research

Ophthalmology



Rabbit retinal section following intravitreal injection of ziv-aflibercept.
Credit: Prof. Anat Lowenstein

Prof. Adiel Barak, M.D.

Vitro-Retinal Surgery Unit, Tel Aviv Medical Center

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Positions, Prof. Adiel Barak

Head, Vitro-Retinal Surgery Unit, Tel Aviv Medical Center

Head, Research team

Department of Ophthalmology

Stem Cells Laboratory of Ophthalmology

Positions, Dr. Aya Barzelay, M.D., Ph.D.

Head, Research team

Department of Ophthalmology

Stem Cells Laboratory of Ophthalmology

Research

Development of novel stem cells therapy for retinal degeneration diseases using mesenchymal stem cells that are isolated from subcutanoues fat of patients. Development of minimally invasive methods to isolate stem cells from the patient. Growing stem cells at the laboratory and studying their ability to develop into retinal cells. Developing methods to transplant stem cells into mice retinas in mice models of retinal degeneration.

Main research topics

-To isolate and characterize human adipose tissue derived mesenchymal stem cells from patients.

-developing minimally invasive methods for isolation and transplantation of stem cells to the patient

- Induce differentiation of ASCs into retinal cells. Designated for retinal transplantations of differentiated ASCs.

- Study the paracrine activity of ASCs in the hypoxic environment. Designated for retinal transplantations of activated ASCs.

- Evaluate the therapeutic potential of stem cells transplantations to retina in animal model of Retinal degeneration

Team

Prof. Adiel Barak, M.D.

Dr. Aya Barzelay, M.D., Ph.D.

Publications

Barzelay A, Weisthal Algor S, Katz S, Niztan A, Mezad-Koursh D, Neudorfer M, Goldstein M, Meilik B, Loewenstein A, Barak A. Adipose derived mesenchymal stem cells migrate and rescue RPE in the setting of oxidative stress". Stem Cells Int, 2018.

Antheby R, **Barzelay A**, Barak A. Vitrectomy in patients 85 years of age and older: surgical outcomes and visual prognosis. Clin Interv Aging. 2018;13:243-249.

Leshno A, **Barzelay A**, Barak A, Neudorfer M. Diagnosis of peripheral retinoschisis using ultrasound biomicroscopy, Ophth Surg Lasers Imaging Retina, 2019.

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, Gur E, Loewenstein A, Barak A. High glucose in culture media of adipose derived mesenchymal stem cells – gene expression alteration and early senescence. Stem Cell Regen Med. 2020.

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Investigating Age-Related Macular Edema and Diabetic Retinopathy

Positions

Professor of Ophthalmology, Sackler Faculty of Medicine

Assistant Dean, Sackler Faculty of Medicine

Head, Department of Ophthalmology

Incumbent, Sydney A. Fox Chair in Ophthalmology

President, Israeli Ophthalmological Society

Associate editor, *International Journal of Retina and Vitreous*

Editor in Chief, *Case Reports in Ophthalmology*

Chairperson, National Ethics Review Board Committee, State of Israel Ministry of Health

Board member, Israeli Council of Surgery and Anesthesia

Chair, Academia Ophthalmologica Internationalis

General Secretary of the Board, Euretina Society

International Committee Member, Macula Society

Research

Publications

Veritti D, Sarao V, Francescutti L, Rota N, **Loewenstein A**, Borrelli E, Sadda S, Lanzetta P. Optical coherence tomography angiography findings in diabetic retinopathy. Expert Rev Ophthalmol. 2017;12:475-484.

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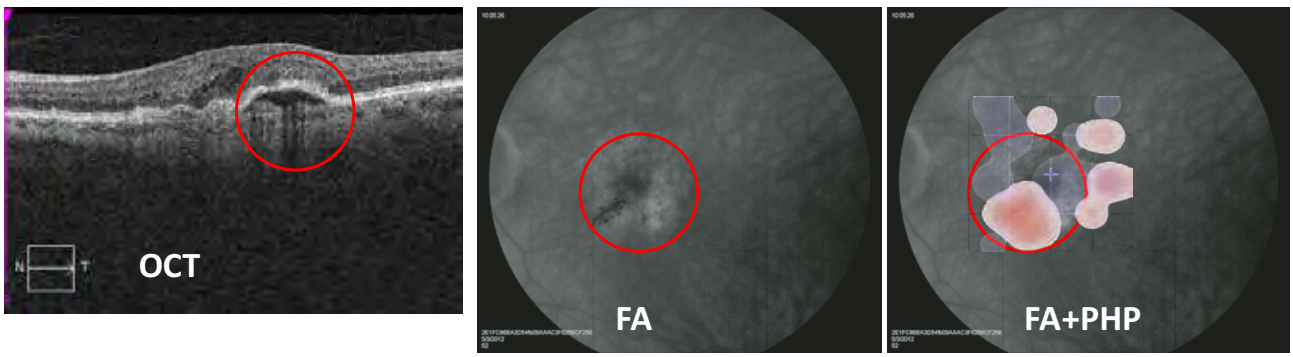

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Neurodegeneration in the Eye

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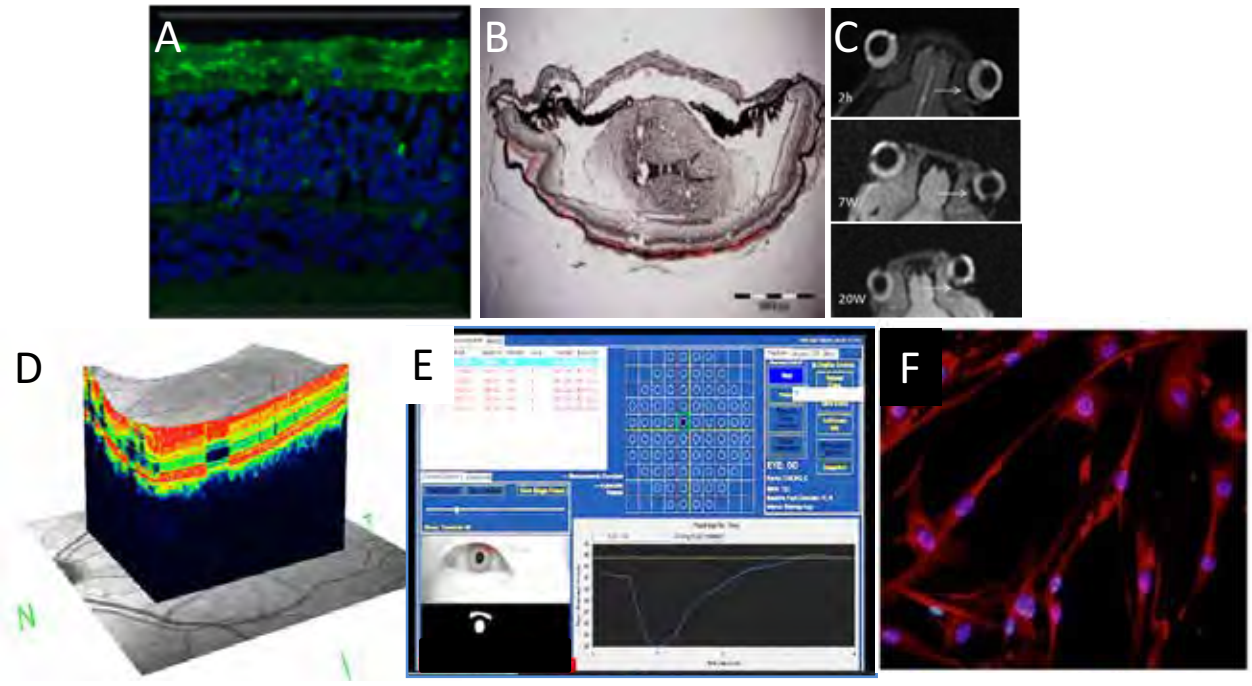

Immunofluorescence analysis (A), histopathology analysis (B) and MRI (C) for monitoring stem cell therapeutic effects in animal models. Multicolor OCT imaging (D) and chromatic multifocal pupilloperimetry (E) for objective structure & function clinical assessment. Nanotherapy for stem cell modulation (F).

Research

We lead basic science, translational medicine and clinical studies in an attempt to solve the unmet needs in neurodegenerative diseases in the eye and brain. The research focuses on clinical trials, basic science and translational medicine aimed at development of novel treatments and diagnostic tools for retinal degeneration and brain pathologies (such as Alzheimer disease and increased intracranial pressure) using a multidisciplinary approach in an attempt to discover treatments and develop drug delivery and diagnostic platforms for studying these leading incurable diseases.

Current research projects include:

- The eye as a window to the brain – using retinal structure and function measurements as novel early and objective biomarkers for brain neurodegeneration diseases (e.g. Alzheimer's disease and multiple sclerosis), brain injuries and brain tumors.

Publications

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Public Health

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Positions

Head, Epidemiology & Database Analysis Department, Maccabi Institute for Research & Innovation, Maccabi Healthcare Services

Associate Professor, Epidemiology & Preventive Medicine Division, School of Public Health, Tel Aviv University

Adjunct Investigator, Radiation Epidemiology Branch, Division of Epidemiology and Genetics, National Institute of Cancer, National Institutes of Health, Bethesda (MD), USA

Head, Academic Department of Public Health, Medical Division. Maccabi Healthcare Services

Research

Our primary research interests focuses on the use of Maccabi's large database to examine multiple dimensions of health care quality, including safety (e.g. adverse effects of IVF, renal effects of chronic medications), efficacy and effectiveness of healthcare technologies (e.g. glycemic control and outcomes in patients treated with new generation therapies for diabetes), medical and economic burden of chronic diseases and health events (e.g. congestive heart failure, hepatitis C infections) as well as pharmacoepidemiology studies such as medication adherence studies (e.g. tamoxifen in breasr cancer patients) and pleiotropic effects (e.g. statins). Our other interests include health effects of low dose ionizing radiation and specifically cancer and cataract.

Publications

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Biological Monitoring Using Micro and Nano-Sized Particles Distribution Measurement in Biological Samples to Early Detect Health Impairment in Environmental and Occupational Lung Settings

Positions

Head, Laboratory Pulmonary and Allergic Diseases

Chair Department of Environmental and Occupational Health, Tel Aviv University

Research

The "ultrafine hypothesis" suggests that smaller particles are more potent than larger particles at driving inflammation; leading to the initial proposal that respiratory ill health was associated with the number of ambient ultrafine particles. When first introduced in 1994, the "ultrafine hypothesis" met friendly skepticism, with opponents arguing that NSP (nano-sized particles) are very short-lived and disappear through heterogeneous and homogeneous aggregation within seconds or minutes and therefore are toxicologically irrelevant. This skeptical attitude has changed considerably. Research teams across the world are now working now on NSP, and there are multidisciplinary alliances among atmospheric scientists, epidemiologists, clinicians, and toxicologists, among others. Nonetheless, substantial research gaps continue to prevail. Most of the initial assessments of particulate burden and involvement

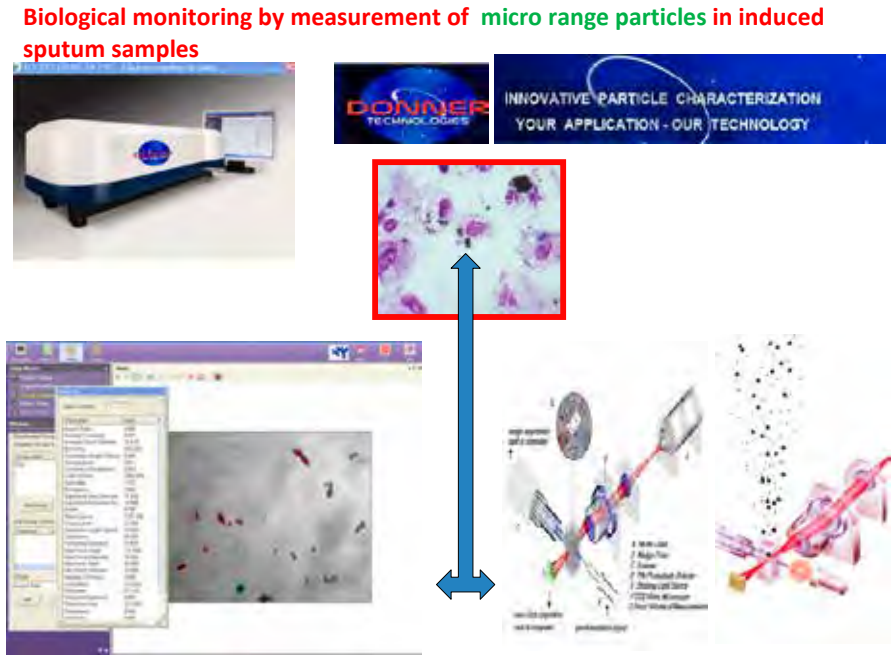

Figure 1

C: Biological monitoring by measuring ultrafine/nano ranged particles in induced sputum samples (MsC thesis of Iris Szwarcfiter)

Nanosight LM20

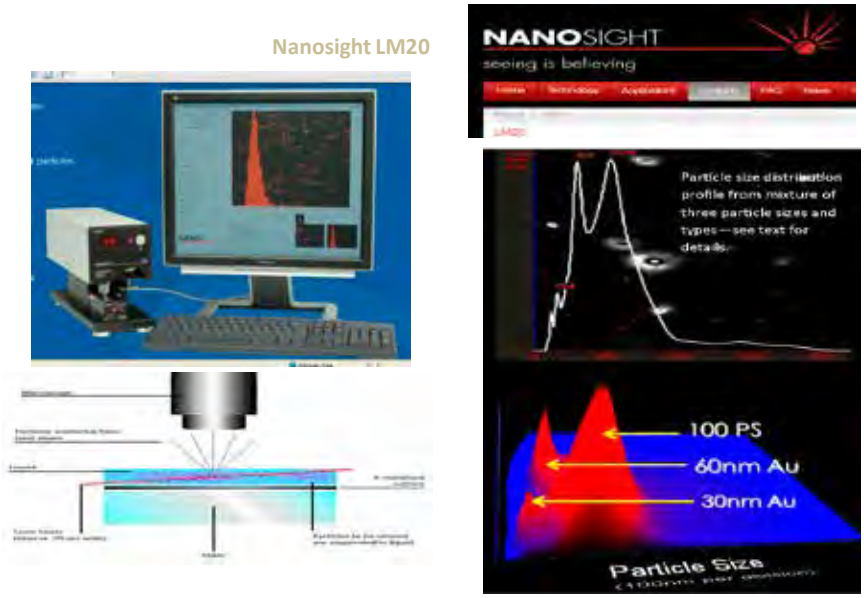

Figure 2

of inflammatory and structural cells in occupational lung diseases were made in studies using fibreoptic bronchoscopy in conjunction with bronchoalveolar lavage (BAL). The relative invasiveness of this technique, however, has restricted the use of bronchoscopy to a limited number of specialised centres, and hampered its development into a practical and suitable tool for screening programmes, exposure evaluation or repeated follow-up of workers exposed to hazardous dust in large populations.

The ongoing search for non-invasive techniques has led to a number of development approaches, such as the examination of cells, quantification of biochemical mediators, and characterization of particulate matter in samples of induced sputum (IS) as well as the quantification of biochemical mediators and characterization of particulate matter in the condensation of exhaled breath exhaled breath condensate (EBC). In the last years, we have concentrated our research on the application of these techniques in occupational and environmental exposures:

- *Particle size distribution (PSD) and dynamic shape characterization (DSC):* The size and shape of the particles will be assessed from the rich cell fraction of the processed plugs with the Eyetech Analyzer and the analyzer's video channel (Donner Technologies, Israel) using a PSD method in the range of 0.5-3,600 based on the time of transition theory where the duration of interaction between beam and particle provides a direct measurement of each particle's size (Fig 1).
- *NSP measurement.* The size and shape of the ultrafine particles ($PM_{0.1}$) are assessed from the rich cell fraction of the processed plugs in the IS sample and the EBC sample, with the NanoSight LM20 using the Nanoparticle Tracking Analysis (NTA) method of visualizing and analyzing particles in liquids that relates the rate of Brownian motion to particle size. The rate of movement is related only to the viscosity of the liquid, the temperature and the size of the particle and is not influenced by particle density or refractive index (Fig 2).

We studied several populations: Workers exposed to hazardous dust at the Israel World Trade Center (WTC), dust-exposed firefighters in the USA ten months after the WTC disaster, dental technicians exposed to beryllium (funded by the Binational Science Foundation BSF 2007-2011), workers exposed to artificial stone dust and asthmatic children in the Tel Aviv area. Our ongoing research is on the field that characterize the mineral compositions of these particles and their biological effect.

Publications

Ophir N., Bar Shai A, Alkalay Y, Israeli S, Korenstein R, Krermer M, **Fireman E.** Artificial stone dust-induced functional and inflammatory abnormalities in exposed workers monitored quantitatively by biometrics. ERJ Research. 2016 2:86.

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Prof. Varda Shalev, M.D., M.P.A.

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Director, Institute for Health Research and Innovation, Maccabi Healthcare Services

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Using Medical Databases for Personalized Medicine

Positions

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Associate Professor, Epidemiology & Preventive Medicine Division, School of Public Health, Tel Aviv University

Independent family practice partnership clinic, Rosh Haayin

Research

The emergence of precision medicine technologies has allowed medical scientists to address complex questions which necessitate very large datasets and patients' numbers. Unlike traditional methods such as randomized trials, the richness of very large sets of data enables more rapid advance toward personalized medicine. At the Maccabi Institute for Research & Innovation, we utilize large real-world databases to investigate clinical issues for better provision of care and improved outcomes. In addition to traditional and pragmatical clinical trials, we condocut multiple observational analysis using advanced data platform to enable data science studies based on Maccabi's database of 2.5M members' medical files. One example for personalized medicine is our newly developed method for identifying individuals at increased risk of harboring colorectal cancer by analyzing their complete blood counts records. We have developed a computational model using a large derivation dataset of over 450 000 Israeli individuals and validated it on 2 separate and independent datasets of primary care patients, consisting of over 139 000 Israeli and over 25 500 UK individuals. Our approach applies novel methods both in feature generation (where we use a set of linear models to handle sparse and irregular measurements along time) and in model construction (where we combined 2 tree-based models – RF and Gradient Boosting). We showed that our approach can detect 50% of CRC cases 3–6 months before diagnosis at 88% specificity in the Israeli dataset and 94% specificity in the UK dataset. The system is already successfully implemented in routine practice at Maccabi.

Publications

Giladi O, Steinberg DM, Peleg K, Tanne D, Givon A, Grossman E, Klein Y, Avigdori S, Greenberg G, Katz R, **Shalev V**, Salomon O.Head trauma is the major risk factor for cerebral sinus-vein thrombosis. Thromb Res. 2016;137:26-9.

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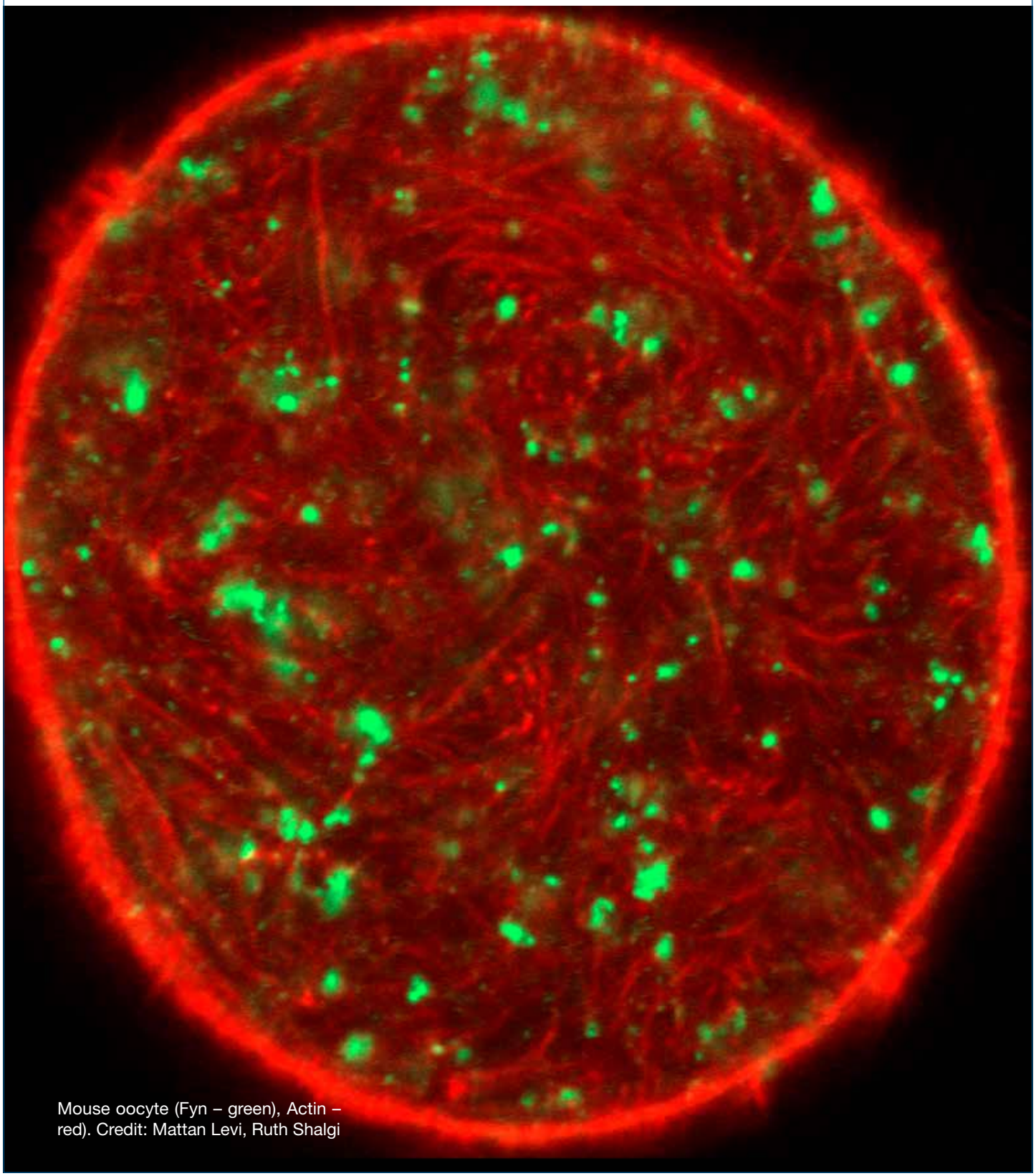
Goldshtein I, **Shalev V**, Zigman N, Chodick G, Levkovitch-Verbin H. The Maccabi Glaucoma Study: Treatment Patterns and Persistence With Glaucoma Therapy in a Large Israeli Health Maintenance Organization. J Glaucoma. 2016;25:e386-91.

Kinar Y, Kalkstein N, Akiva P, Levin B, Half EE, Goldshtein I, Chodick G, **Shalev V**. Development and validation of a predictive model for detection of colorectal cancer in primary care by analysis of complete blood counts: a binational retrospective study. J Am Med Inform Assoc. 2016;0:1–12

Goldstein D, Chodick G, **Shalev V**, Thorsted BL, Elliott L, Karasik A. Use of Healthcare Services Following Severe Hypoglycemia in Patients with Diabetes: Analysis of Real-World Data. Diabetes Therapy

Reproduction



Mouse oocyte (Fyn – green), Actin – red). Credit: Mattan Levi, Ruth Shalgi

Prof. Ariel Hourvitz, M.D., MHA

IVF Unit, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel-Hashomer, Israel; Obstetrics and Gynecology, Sackler Faculty of Medicine

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Folliculogenesis and Ovulation in the Human Ovary – Fertility Treatments and Control

Positions

Associate Professor, Obstetrics and Gynecology, Sackler Faculty of Medicine

Senior Physician, IVF Unit

Director Reproduction Laboratory, Sheba Medical Center

Lab Director

Dr. Yuval Yung, Ph.D.

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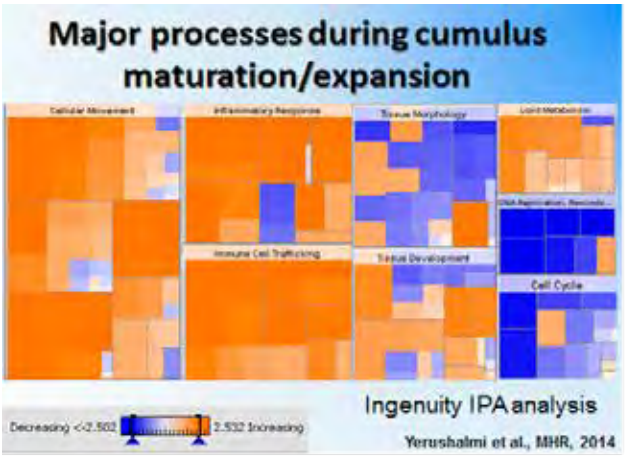
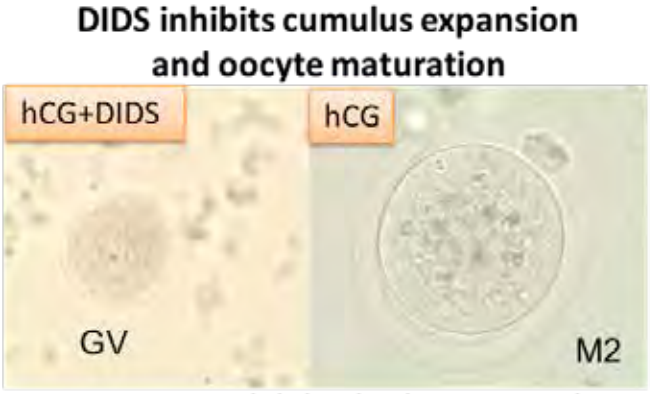
Research

Our laboratory's aim is the molecular characterization of the ovulatory cascade in the human ovary. We undertook to systematically identify novel ovulation-associated genes. Differentially expressed candidate genes (n = 1746) were identified by comparing the transcriptome of cumulus granulosa cells from compact pre-ovulatory germinal vesicle (GV) cumulus oocyte complexes with those of expanded post-ovulatory Metaphase II COCs. We assumed that differentially expressed genes likely serve as regulators of ovulation, cumulus expansion, and/or oocyte maturation. To complete the identification of factors involved in the ovulatory process, we generated a library of global miRNAs involved in this process, and by bioinformatics tools link the ovulatory miRNA library with the mRNA library. The bioinformatics analysis enables us to identify new regulatory mechanisms responsible for the oocyte maturation process and ovulation.

The resulting database provides unprecedented insight into the processes and pathways involved in follicular maturation and ovulation. This effort led us to identify and characterize several new genes involved in the human ovulatory process such as sFRP4, ADAMTS-1, Decorin and Lumican. Recently, prompted by the observation that prostaglandin transporter (PGT) constitutes a highly expressed peri-ovulatory transcript, we set out to investigate the physiological role of this key transporter protein in the ovulatory process. We were able to show that PGT is an indispensable mediator of ovulation, the inhibitors of which may constitute potential novel candidates for non-hormonal contraception (Science Translational Medicine, 2016).

These studies will contribute significantly to the understanding of the complex process of ovulation in





Yerushalmi et al., Science Trans Med, 2016

human which is central to the reproductive processes. The implications of improved understanding of this process may contribute to further development of strategies for in vitro maturation of oocytes and follicles, improve IVF success rates especially in difficult clinical conditions. Genes that their expression levels correlate with oocytes clinical outcome can be future markers for oocyte quality and selection. Elucidating new human ovulatory genes may contribute to our understanding of infertility conditions such as anovulation, and development of novel strategies for fertility control.

Publications

Sapoznik S, Bahar-Shany K, Brand H, Pinto Y, Gabay O, Glick-Saar E, Dor C, Zadok O, Barshack I, Zundelevich A, Gal-Yam EN, Yung Y, **Hourvitz A,** Korach J, Beiner M, Jacob J, Levanon EY, Barak M, Aviel-Ronen S, Levanon K. Activation-Induced Cytidine Deaminase Links Ovulation-Induced Inflammation and Serous Carcinogenesis. Neoplasia. 2016;18(2):90-9.

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Fertility Preservation Research and Clinical Center

Positions

Fertility Preservation Center, Reproduction IVF, Division of Obstetrics and Gynecology, Sheba Medical Center and Tel Aviv University.

President, International Society for Fertility Preservation (ISFP) http://www.isfp-fertility.org/

Research

Our research center is specialized in fertility preservation. We have a fully equipped basic research laboratory, together with a large clinical database with a significant number of incoming patients. This makes our research center unique for high quality basic research with clinical relevancy. Our research focuses on:

- Ovarian follicle research and the biological clock.
- Cryopreservation / transplantation of ovarian tissue and IVF.
- The effects of toxic agents and chemotherapy on reproduction and gametes.
- Modalities and agents that protect the gametes and prevent toxic damage.
- Genetic injury to the gametes.
- Methods 6to detect cancer cells in tissue.
- Endometrial receptivity.
- Interpreting cancer patients' information regarding endocrine, reproductive and psychological effects.

Publications

Meirow D, Ra'anani H, Shapira M, et al (2016). Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril. 106(2):467-74.

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Stem Cells & Regenerative Medicine

An artist's view of how single-cell clones represented by a specific color emerge during kidney development, maintenance, and regeneration. Credit: Dekel Lab, Pediatric Stem Cell Research Institute, Sheba Medical Center.

Prof. Benjamin Dekel, M.D., Ph.D.

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From Developmental Biology to Normal and Cancer Stem Cells to Novel Therapeutics

Positions

Head, Pediatric Stem Cell Research Institute, Sheba Medical Center

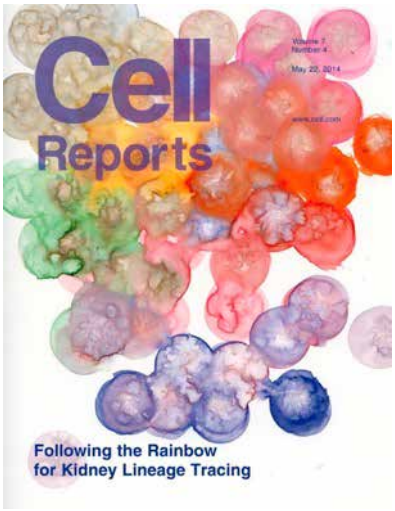
Director, Division of Pediatric Nephrology, Sheba Medical Center

Associate Professor, Dept. of Pediatrics, Sackler Faculty of Medicine

Adjunct Faculty, Dept. of Human Molecular Genetics & Biochemistry, Sackler Faculty of Medicine

Member, American Society of Clinical Investigation

President, Israel Stem Cell Society



The cover illustration shows how single-cell clones emerge during development, maintenance, and repair to generate a multicolored kidney. *Dekel and colleagues* report that continued growth of the mammalian kidney in adulthood is performed by lineage-restricted clonal progeny that continuously add new epithelial cells to each segment of the kidney and are responsive to Wnt signaling. Lineage-restricted progenitors are also observed in development after renal epithelial induction and during acute renal injury. Rainbow mice, which express one of four alternative fluorescent reporters in each cell, allow genetic lineage tracing of individual clones.

Research

Our laboratory takes a multi-disciplinary approach including genetics, genomics, molecular biology, biochemistry, and the development of preclinical human-mouse models to cast light on fundamental problems of kidney developmental biology, tissue regeneration, and cancer; while, at the same time, holding promise for novel disease therapies. Our central hypothesis is that *normal and transformed tissue stem cells* drive these processes and therefore we aim to discover such cells and study their molecular mechanisms. In the field of human kidney development and pediatric renal cancer (Wilms tumor), we have pioneered the identification and isolation of normal and malignant renal stem/progenitor cells and have shown how these novel cell types are of relevance to human disease; on one hand utilization of the normal stem cells in tissue repair and regeneration and on the other hand development of targeted therapy against cancer stem cells and tumor eradication. These bench discoveries have been fundamental to translation to bedside; our approach for tumor stem cell eradication has already sparked a multicenter clinical trial for the treatment of patients with relapsing Wilms' tumors.

Publications

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Reviews and chapters

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Laboratory for the Research of Skin Disease

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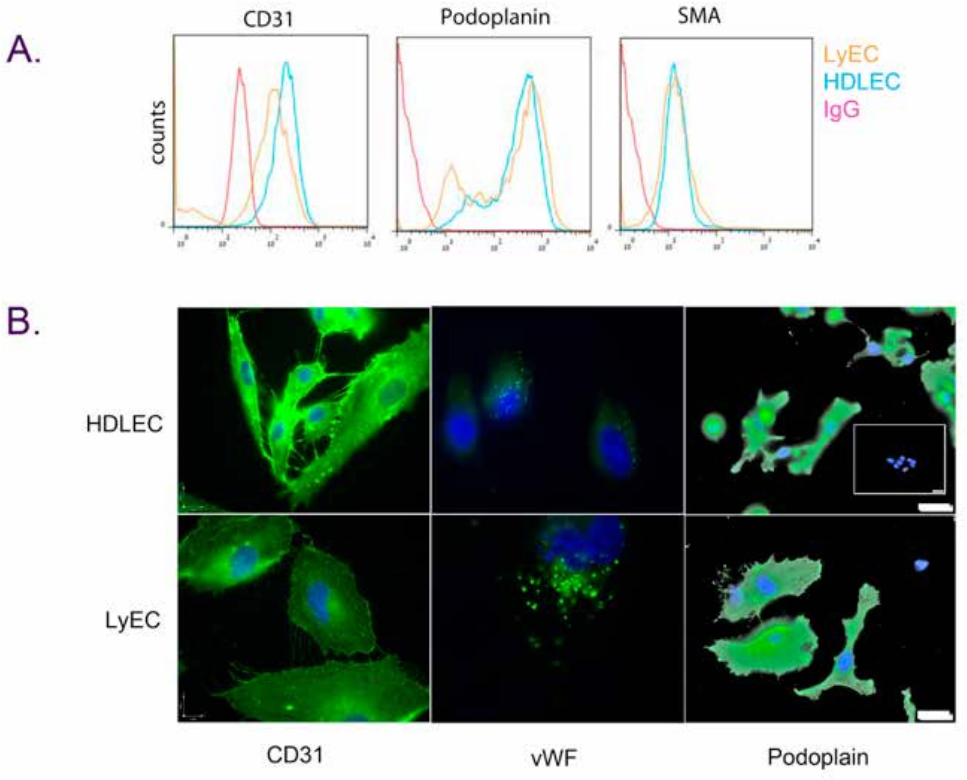
Lab Manager: Dr. Gil Leichner Ph.D.

Research

We study skin diseases with a focus on angiogenesis and lymphangiogenesis. Deficiency in development or function of the vascular or lymphatic vasculature causes various anomalies in humans, and active angiogenesis and lymphangiogenesis play a significant role in tumor metastasis. The presence of vascular anomalies can cause emotional and social problems. Moreover, some malformations are painful or even life-endangering. Current treatments for these diseases do not achieve optimal results. The goal of my research is to isolate and characterize the endothelial cells, the major cellular component of the vascular malformations in order to develop targeted therapy for these lesions. We apply cutting-edge technologies including molecular biology, and microarray analysis to characterize the molecular paths that regulate the endothelium development. Other areas studied in the lab are editing in psoriasis and Cutaneous graft versus host disease



Isolation and characterization of endothelial cells from lymphatic malformations. FACS (A) and immunofluorescence analyses shows pure lymphatic endothelium phenotype with reduced expression of the differentiation marker CD31.

Publications

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hESCs in Development, Genetic Disorders and Cell Therapy

Positions

Dalit Ben Yosef

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

Research

The Wolfe PGD-Stem Cell Lab focuses on studying issues related to early embryonic and developmental processes, genetic disorders and different aspects of cell therapy using our unique collection of PGD-derived human embryonic stem cells (hESCs).

We derive hESCs directly from affected embryos, which are obtained as a by-product of the preimplantation genetic diagnosis (PGD) procedure. PGD is performed for couples at high risk of transmitting a genetic defect and who wish to ensure the birth of a healthy child. It requires in vitro fertilization (IVF), which makes the pre-implantation embryos available for biopsy and single-cell molecular analysis. Following IVF-PGD, embryos diagnosed as being disease-free are transferred into the uterus for implantation, whereas the affected embryos that would be otherwise discarded are used to establish hESC lines that carry the naturally inherited mutations. This setup provides the benefit of efficient coordination between the generously donated affected embryos and the stem cell lab that focuses on researching these very unique samples. By means of these capabilities, we have already established >50 mutant hESC lines associated with 18 different inherited disorders.

These lines make it possible for us to study the molecular and pathophysiological mechanisms underlying the genetic disease of which they were diagnosed. In addition, since we have a large collection of hESC lines derived under the same conditions, we are able to perform different studies on the pluripotent, genetic and epigenetic properties of these cells.

Publications

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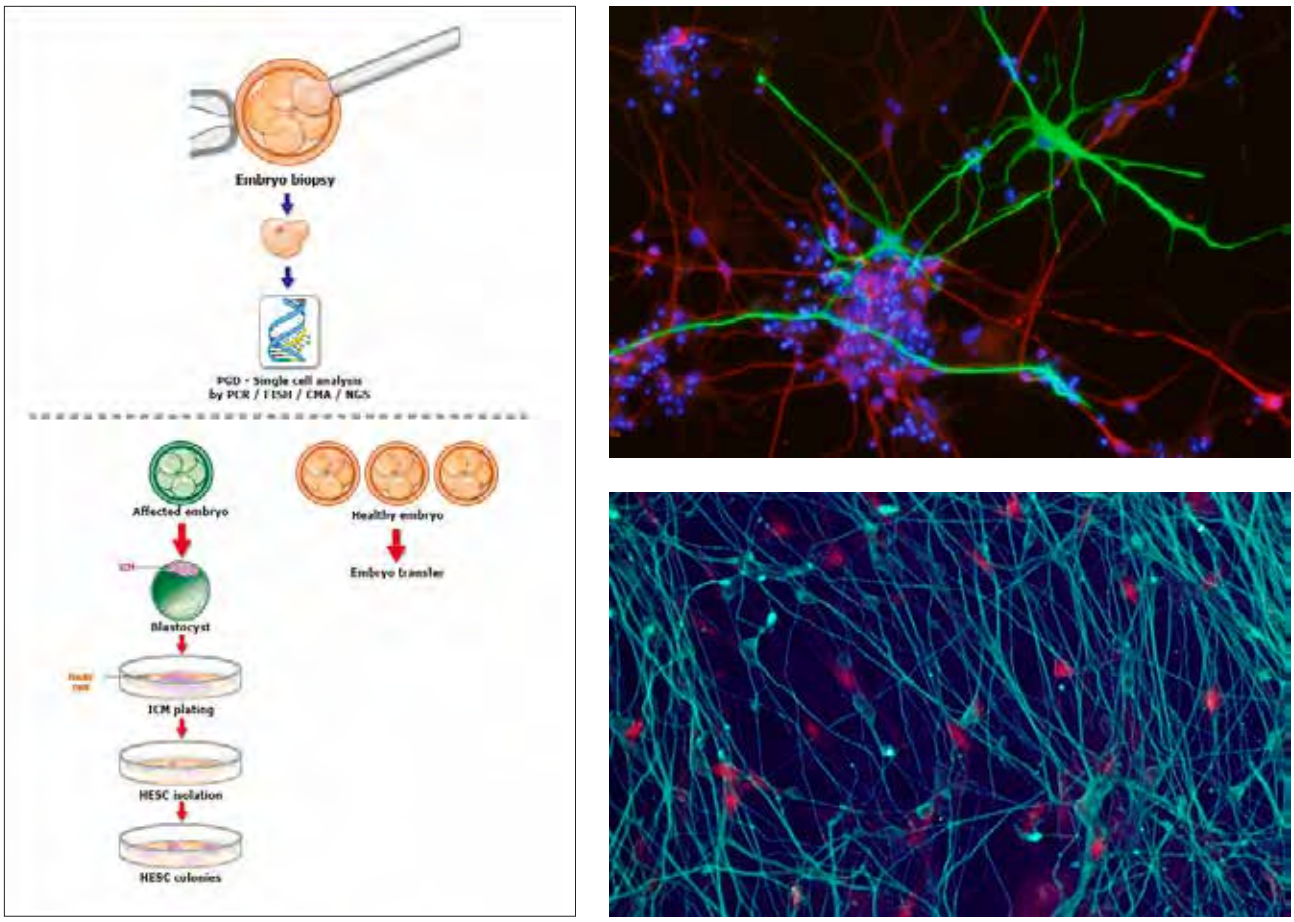

Left: HESCs are derived from PGD embryos affected by genetic disorders. Right: Neurons derived from HESCs: A. Neurons (MAP2, red) and glia (GFAP, green) from fragile X HESCs at day 128 of differentiation. B, C Neurons (Tuj1, green) from normal HESCs express FMRP (red) throughout differentiation (B, C: early and late differentiation, respectively). D. Neurons (Tuj1, green) created by transcription factor induced directed differentiation silence FMRP (red) by day 14 (Tuj1neg rat astrocyte feeder cells are labeled; whereas Tuj1pos HESC derived neurons are not).

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Deciphering Basic Kidney Biology to Improve the Lives of Those Affected by Kidney Disease

Positions

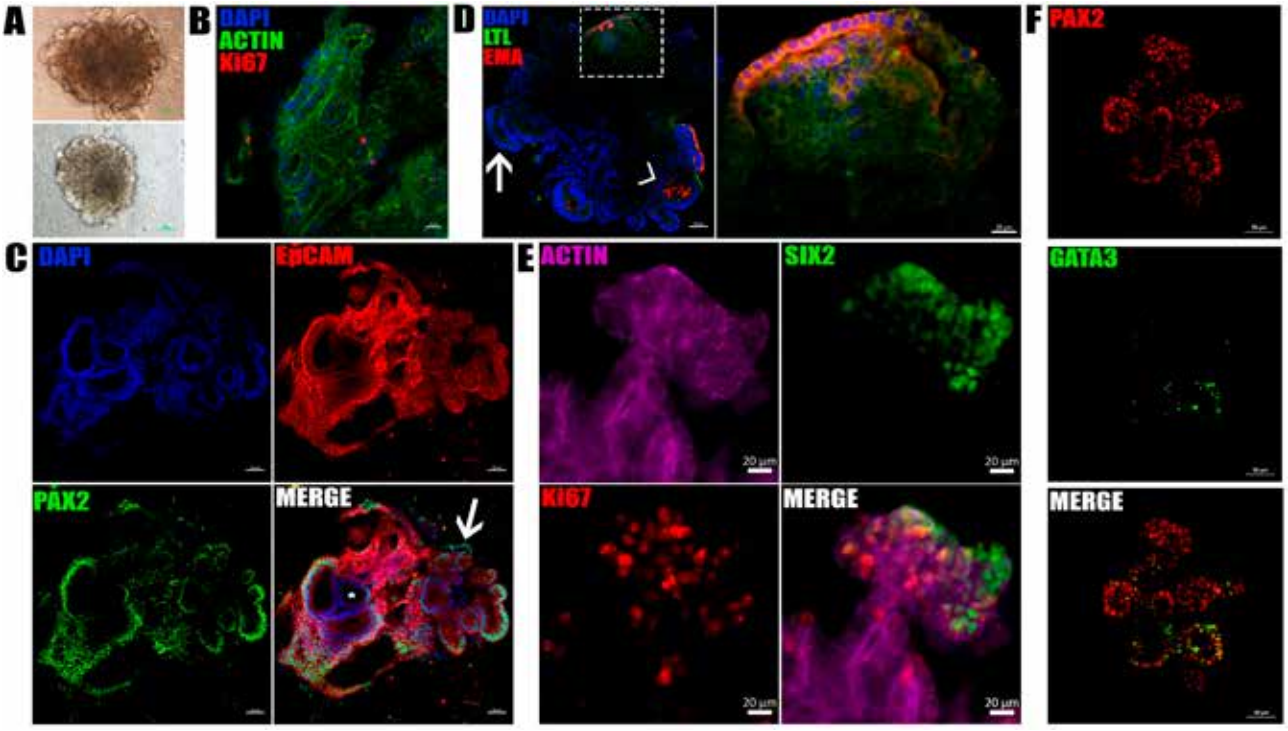
Lecturer, Sackler Faculty of Medicine

Principal investigator, Kidney Research Lab, Sheba Medical Center

Sheba Medical Center Physician-Scientist Program

Research

Kidney research is both intriguing and important. On the one hand, the kidney is highly complex and only partially understood. On the other hand, kidney diseases are very common, resulting in much morbidity and mortality. These include chronic kidney disease (CKD), which affects 15% of the population



Kidney organoids. (A) Phase-contrast microscopy showing large, convoluted organoids. (B) Staining for the apical marker F-Actin and Ki67, showing formation of convoluted tubular structures with a small subset of cells actively proliferating. (C) Staining for the epithelial marker EpCAM and renal progenitor marker PAX2, showing small clusters of PAX2+EpCAM cells (arrow) and multiple EpCAM+ tubules, some of which express PAX2, indicating an undifferentiated phenotype while some lack PAX2 expression and hence more mature (asterisk). Note nuclear PAX2 localization. (D) Left: the organoids harbor both LTL+ proximal (arrow) and EMA+ (arrowhead) distal tubules. Right: magnification of marked area. Note double positive tubules, indicating primitive phenotype prior to segment specification. (E) The organoids contain a cells population with nuclear expression of the CM marker SIX2, many of which are actively proliferating, as shown by Ki67 expression. This population lies adjacent to tubular structures. (F) The organoids harbor both PAX2+GATA3+ cells, indicative of a UB-lineage and PAX2+GATA3- cells of the CM lineage. Scale bars: A: 100μM; B&E: 20μM; C&F:50μM; D: left: 50μM, right: 20 μM.

and is cureless, and renal cell carcinoma (RCC), the most common renal cancer, which kills ~175,000 people a year worldwide.

Our main goal is to uncover new aspects in the basic biology of the kidney and new molecular mechanisms underlying kidney disease. However, we also focus on translational aspects and work hard to leverage our discoveries into new diagnostic, prognostic and therapeutic approaches. As a hospital-based lab, with a team that also includes physicians, we have the unique advantage of having all the expertise needed to truly implement a bench-to-bedside and backwards approach. To achieve these goals, we use a wide range of methodologies and research areas, including stem cell biology, large-scale 'omics' analyses (mainly at the transcriptional and epigenetic levels), 3D culture methods and animal models.

Publications

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Grants

2021-2024	Sheba Medical Center Physician-Researcher Excellence Program
2020-2021	Suzanne Eichinger-Henke Grant (Sackler Faculty of Medicine, TAU)
2021-2023	Israel Cancer Association
2021-2024	Estates Committee, Ministry of Justice

Renal System

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Optimazing Graft Survival in Patients after Kidney Transplantation

Positions

Clinical Senior Lecturer, Sackler Faculty of Medicine

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Research

Kidney transplantation is the treatment of choice for patients with end stage kidney disease (ESKD). However long-term survival of kidney allograf is suboptimal with only minimal improvement during the last years. In our research we try to find the optimal immunosuppression that will minimize immunological insult to the kidney allograft as well as the risk of infection malignancy and cardiovascular disease. We focus on the blood level of tacrolimus, the potent component of the immunosuppressant regimen. We use statistical and mathematical tools to optimize the treatment for each patient in order to get maximal graft survival with minimal complications. We also try to evaluate the risk factors for post-transplant complication in order to impliments appropriate preventive measures to minimize the risk. Our study aims are to find clinical and molecular characteristics the will able us to implement personalized Madison for each patient with maximal graft survival and minimal complications rate.

Publications

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