

Faculty of Medicine

**Hospital-Based
PhD Research 2023**

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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.

The Faculty of Medicine

The Tel Aviv University Faculty of Medicine is Israel's largest medical research and training complex. The Faculty of Medicine of Tel Aviv University (TAU) was founded in 1964. Research at the 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 by preclinical faculty members, and in the hospitals affiliated to the Faculty by PhD and MD clinical faculty members. The Faculty of Medicine includes the 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 and 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 PhD clinical faculty members 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 multi-nationally with schools, hospitals and research centers throughout the world. The faculty is known for research in the following areas: cancer biology, stem cells, diabetes, neurodegenerative diseases, infectious diseases and genetic diseases, including but not limited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians and PhD researchers in 181 affiliated departments and institutes in 18 hospitals hold academic appointments at TAU. The Gitter-Smolatz 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. The 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 Faculty of Medicine is led by the Dean, Prof. Prof. Karen Avraham, Associate Deans Prof. Rina Rosin-Arbesfeld, Prof. Eli Sprecher, Prof. Neta Erez, Prof. Anat Gafter-Gvilli, Prof. Ronen Zaidel-Bar, Prof. Benjamin Dekel, and Assistant to the Dean, Michal Gilboa.

This brochure reflects the research being performed by the PhD Clinical faculty members at the Faculty of Medicine-affiliated hospitals.

Prof. Karen B. Avraham, PhD,
Dean

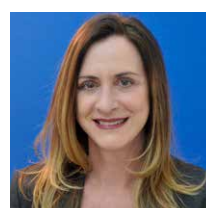
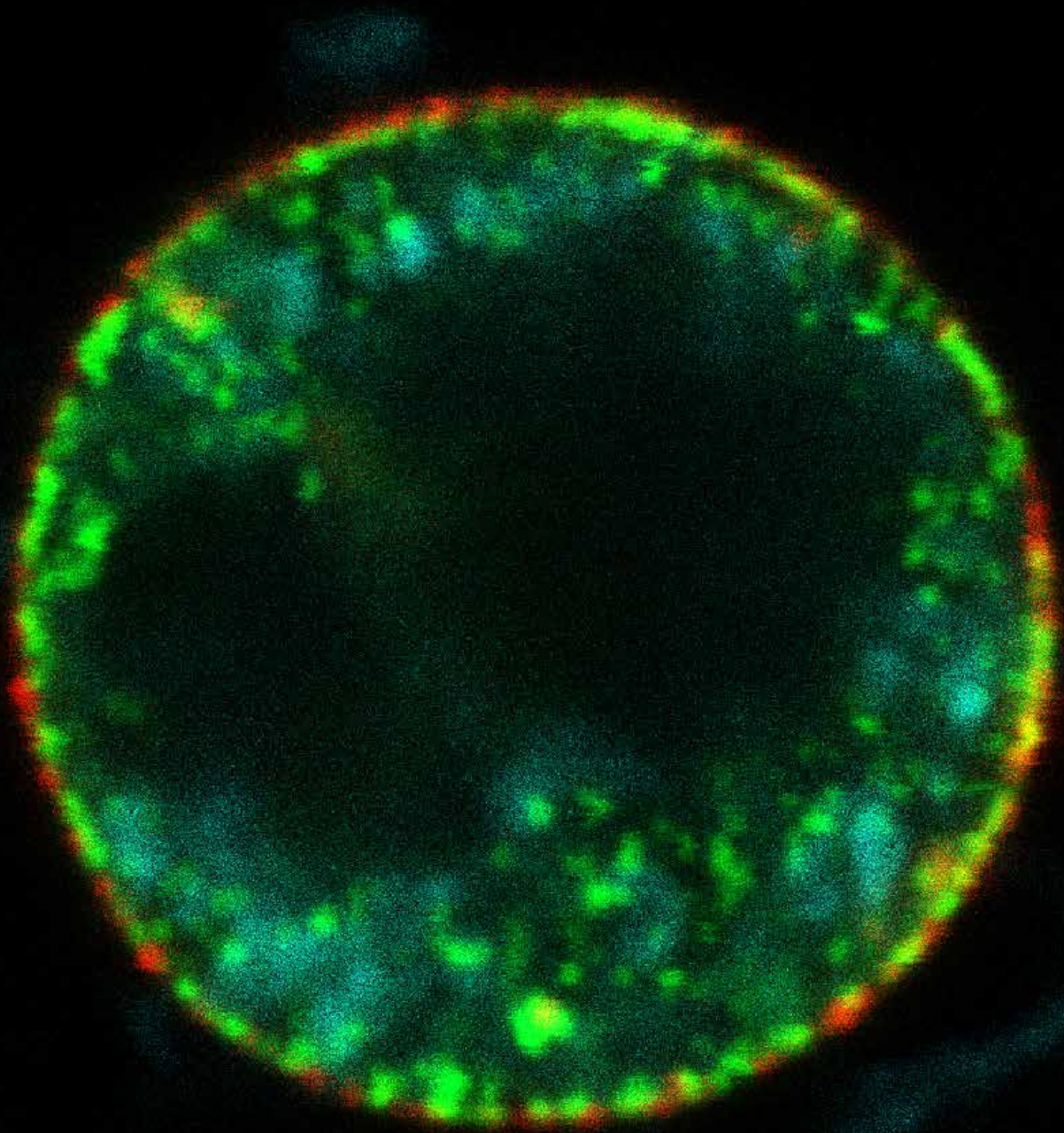


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Cancer

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





Prof. Osnat Ashur-Fabian, Ph.D.

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



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Investigating Hormone Metabolism in Cancer

Positions

Associate Professor, Faculty of Medicine

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

Founder & CSO, DioTree LTD.

Research

Our research deals with the role of thyroid hormones (T4 and T3) 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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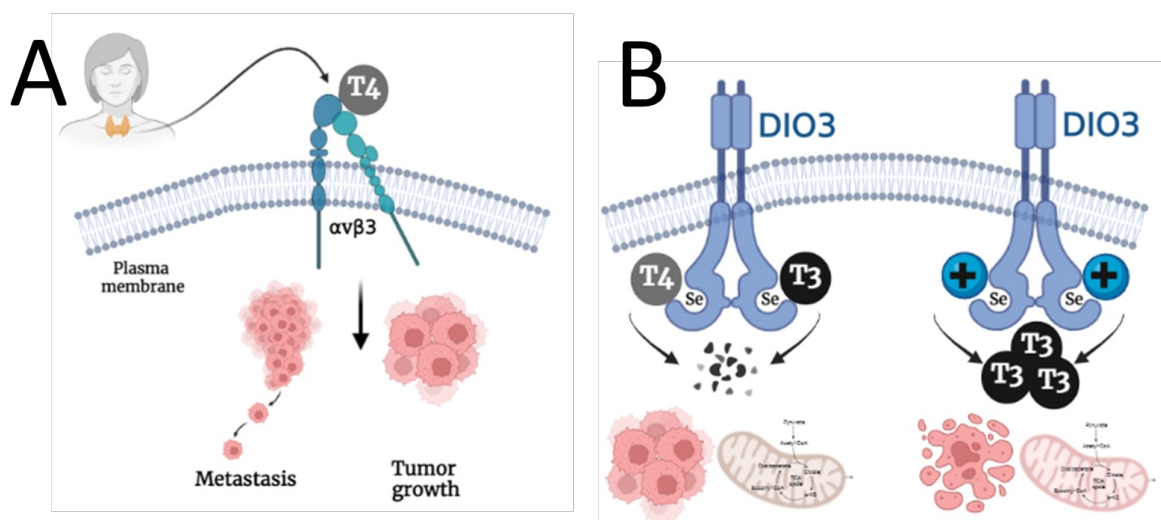
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Grants

2022-2025	Israel Cancer Research Fund (ICRF)
2022-2024	Clalit Research Grant



Dr. Liat Drucker, Ph.D.

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Multiple Myeloma in its Bone Marrow Niche

Positions

Senior Lecturer, Faculty of Medicine

Research

We study multiple myeloma (MM) within its bone marrow (BM) microenvironment. Our group has uncovered intricate signals underlying the dynamic crosstalk between the MM and BM resident Mesenchymal Stem Cells (MSCs) that design the malignant cells' phenotype and niche and drive the malignant process from pre-malignant states to treatment refractory disease. One such mechanism is manipulation of translation-initiation in niche BM-MSCs and MM cells by direct contact and secreted components such as extra cellular matrix and microvesicles. Another strategy is using the Cannabis compound CBD to modulate the dialogue.

Ongoing studies using cutting edge cellular/molecular and high throughput techniques has led to the identification of signals unique to the malignant dialogue that may be selectively targeted to improve MM treatment. Further discoveries have shown that MM-conditioned BM-MSCs disperse unique cargoes via microvesicles thereby promoting MM progression. Indeed, much of our interest is now focused at delineating the conversion of BM-MSCs into cancer supporting entities.

Throughout our studies we maintain tight collaboration with expert clinicians at the Meir Medical Center that

gives us direct access to primary tissue samples and maintain relevance to state of the art treatments and clinical approaches. The research is expected to yield markers for disease progression and new therapeutic targets central to MM-BM niche collaboration, which is perceived as the major obstacle to MM cure.

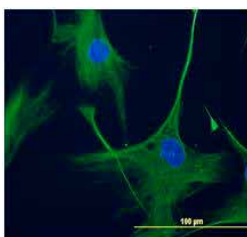
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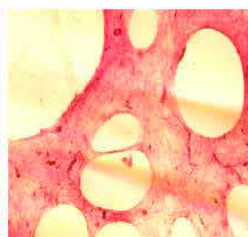
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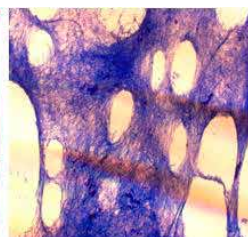
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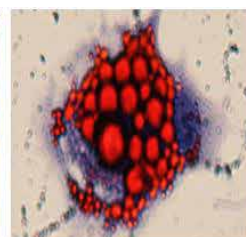
Primary human mesenchymal stem cells (MSCs)



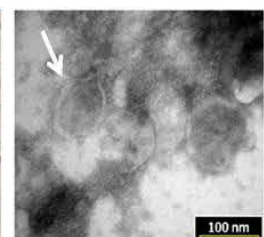
MSCs' extracellular matrix (elastin)



MSCs' extracellular matrix (collagen)



MCS differentiated into adipocyte



MSCs' microvesicles

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Attar Schneider O, Dabbah M, ***Drucker L**, *Gottfried M. Niche origin of mesenchymal stem cells derived microvesicles determines opposing effects on NSCLC: primary versus metastatic. *Cell Signal*, doi: 10.1016/j.cellsig.2019.109456, 2020

Reviews

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Grants

2018-2020	Takeda Israel LTD. CD49d expression on bone marrow mesenchymal stem cells' microvesicles as a therapeutic target in multiple myeloma
2019-2020	CannaMore. CBD as anti-myeloma treatment: is restoration of translation initiation homeostasis involved?



Dr. Ben Zion Katz, Ph.D.

The Hematology Laboratory
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Development of B-Cell Malignancies

Positions

Senior Lecturer, 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.

Publications

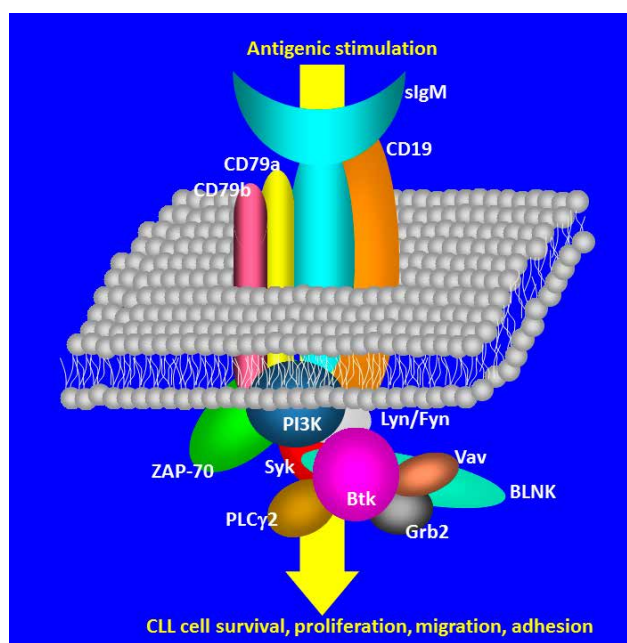
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Specific research programs

- 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.

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Grants

2018-2021

Israel Science Foundation, Novel treatment strategies for ovarian cancer based on double CAR-T cells, Co-Investigator

2019

Israel Innovation Authority, Together with Scpio Labs, Digital Analysis of Bone Marrow aspiration, Co-Investigator

2020

Dotan Hemato Oncology Fund, Cancer Biology Research Center, Tel Aviv University, Principle Investigator



Prof. Yael Mardor, Ph.D.

Advanced Technology Center
Sheba Medical Center
Faculty of Medicine



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Drug Delivery into the Brain, Brain Tumors and Brain MRI

Positions

Associate Professor, Faculty of Medicine, TAU

Chief Scientist, The Advanced Technology Center,
Sheba Medical Center

Patent committee member, Sheba Medical Center

Research

The MR Research Group at the Advanced Technology Center of the Sheba Medical Center focuses on pre-clinical and clinical research, with an emphasis on brain, brain tumors, drug delivery and MRI. The hospital setup, enabling pre-clinical/clinical research, close access to physicians and patients, and close collaboration with the industry, forms an optimal environment for translational medical research, which is the nature of most of our research projects. One of the MRI methodologies, developed by the group for differentiating active tumor from treatment-induced effects in patients with brain tumors, has been licensed to an international company and is being used for clinical decision making in various hospitals around

the world. Research performed in an attempt to extend this methodology to breast cancer and lung cancer is ongoing.

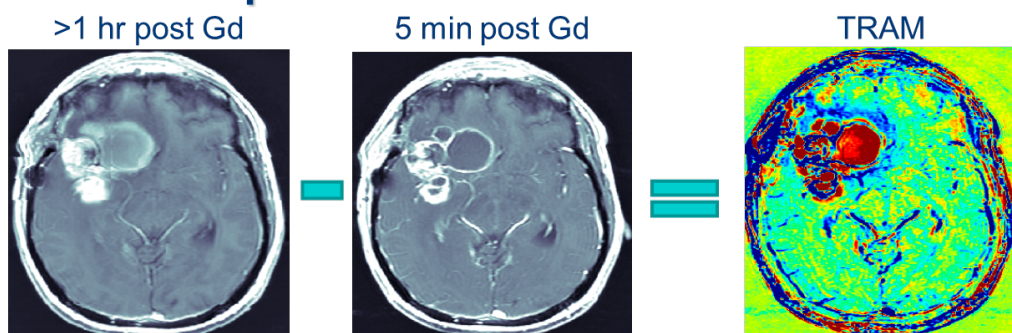
Publications

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MRI-based treatment response assessment maps (TRAMs) for differentiating tumor from treatment effects in patients with brain tumors:



Blue = tumor tissue , efficient Gd clearance at 75 min
Red = non tumor tissue, Gd accumulation at 75 min

3

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Grants

2018-2021	Israel Science Foundation, PI with Dr Itzik Cooper
2019-2023	Israel Science Foundation, Development and application of advanced analysis platform for MRI-based blood vessel characterization in tumor/benign breast tissues for personalized patient management, PI with Prof Miri Sklair
2020-2022	Point source electroporation for the treatment of brain tumors, Sheba Medical Center internal grant, PI with Dr Shirley Sharabi
2021-2023	BBB disruption by low pulsed electric fields for antibodies delivery to brain metastases, ICRF, PI with Dr Sharabi



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Immunotherapy of Brain Tumors: From Basic Mechanisms to Clinical Translation

Positions – Ilan Volovitz

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

Positions – Zvi Ram

Chairman, The Neurosurgery Section, Tel Aviv Sourasky Medical Center

Full Professor, Faculty of Medicine

Former Chairman, Tumor Section of European Association of Neurosurgical Societies

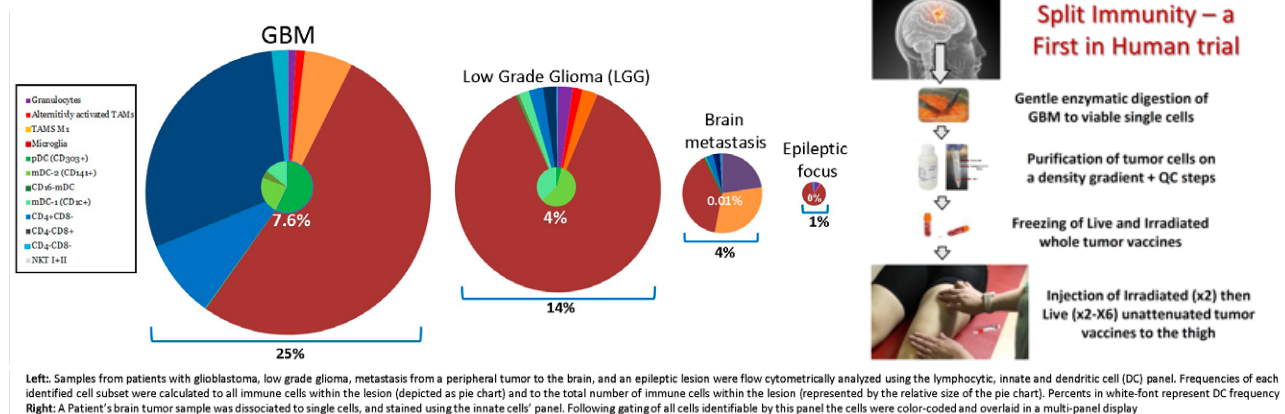
Research

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. The technology was recently translated into a company focused on identification of predictive biomarkers for cancer immunotherapy.

Main research interests

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

Simchony H, Diamant D, Ram Z, **Volovitz I**. Evaluation of the compatibility of electric tumor treating fields with key anti-tumoral T-cell functions. Simchony H, Diamant D, Ram Z, Volovitz I. *Isr Med Assoc J*. 2019;21(7):503

Solodeev I, Orgil M, Bordeynik-Cohen M, Meilik B, Manheim S, **Volovitz I**, Sela M, Inbal A, Gur E, Shani N. Cryopreservation of stromal vascular fraction cells reduces their counts but not their stem cell potency. *Plast Reconstr Surg Glob Open*. 2019;7(7):e2321

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Volovitz I, Shapira N, Ezer H, Gafni A, Lustgarten M, Alter T, Ben-Horin I, Barzilai O, Shahar T, Kanner A, Fried I, Veshchev I, Grossman R, Ram Z. A non-aggressive, highly efficient, enzymatic method for dissociation of human brain-tumors and brain-tissues to viable single-cells. *BMC Neurosci*. 2016

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Grants

2019-2020 Alrov Biomedical Fund – Treatment of Glioblastoma using the Split Immunity approach (Ilan Volovitz, Rachel Grossman and Zvi Ram)

2019-2021 Israel Innovation Authority - Identification of predictive diagnostics monitoring immune networks within human solid tumors (Ilan Volovitz, Ravit Geva)

2018-2020 Novocure - Evaluating the effects of tumor treating fields (TTFields) on dendritic cell within brain tumor (Ilan Volovitz, Rachel Grossman and Zvi Ram)



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Hematological Malignancies

Research

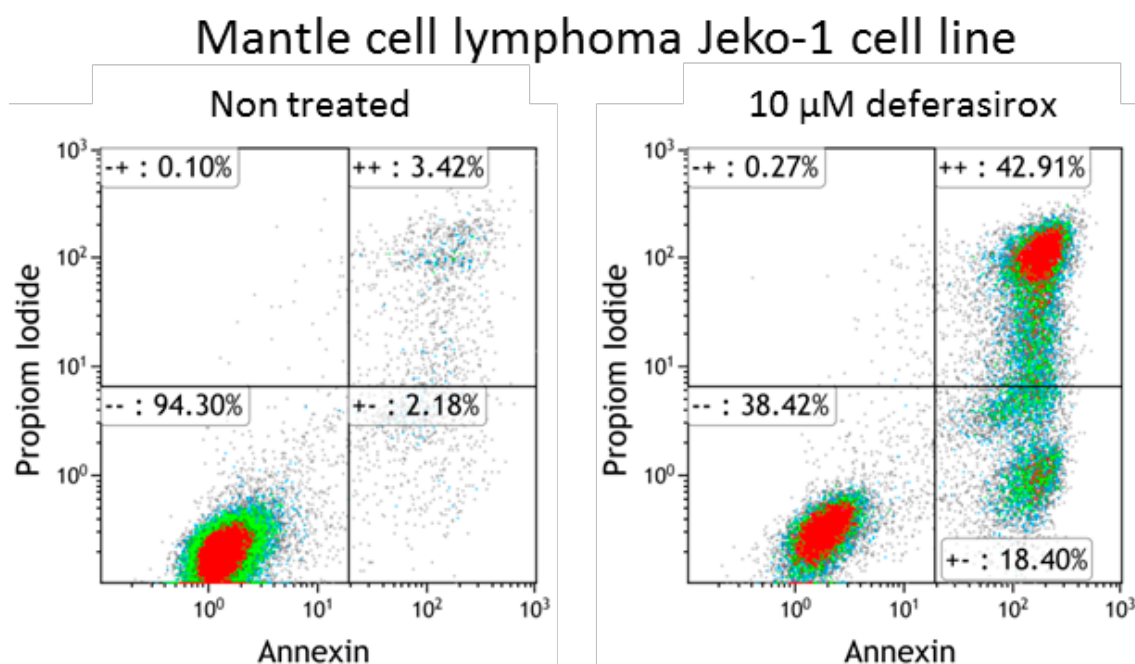
Our primary field of interest is finding new therapies or better therapies for the treatment of incurable hematological malignancies. Our projects focus on exploring the effect of new agents on different leukemia and lymphoma cell lines and patient samples. We study the molecular pathways involved in 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 (translocations, deletion, etc.) is essential for understanding the processes leading to the induction and maintenance

of hematological malignancies and for designing targeted treatments for these malignancies.

Publications

Shapira S, Raanani P, Samara A, Nagler A, Lubin I, Arber N, **Granot G**. Deferasirox selectively induces cell death in the clinically relevant population of leukemic CD34+CD38- cells through iron chelation, induction of ROS, and inhibition of HIF1 α expression. *Exp Hematol*. 2019;70:55-69.

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Hershkovitz-Rokah O, Modai S, Pasmanik-Chor M, Toren A, Shomron N, Raanani P, Shpilberg O, **Granot G**. MiR-30e induces apoptosis and sensitizes K562 cells to imatinib treatment via regulation of the BCR-ABL protein. *Cancer Lett*. 2015;356(2 Pt B):597-605.

Reviews

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Grants

2019 Dotan Research Center in Hemato-Oncology, The role of NETs in the thrombotic tendency of patients with CML treated with TKIs, Dr. Ofir Wallach

2019 Israel Cancer Association, The role of circRNA in the pathogenesis of CLL, Dr. Uri Rozovski

2019 Chief Scientist Office, The role of circRNA in the pathogenesis of CLL, Dr. Uri Rozovski

2019 Pfizer Pharmaceuticals Israel Ltd, Pathogenesis of TKIs associated vascular disease in CML: an in-vivo model, Prof. Pia Raanani

2019 Djerassi-Elias Institute of Oncology, The oncogenic role of polypeptides derived from circularRNAs in the pathobiology of chronic lymphocytic leukemia, Dr. Saar Shapira, Dr. Uri Rozovski

2020 Recanati Research Grant, Uncovering the mechanisms of TKI associated endothelial toxicity in CML, Dr. Avi Leader

2020 Israel Cancer Association, The role of circRNA in the pathogenesis of CLL, Dr. Uri Rozovski



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The Janus Faces of CD24 and its Possible Applications in Medicine

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 research at the ICPC focuses on translational research, bridging between basic research 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). Dr. Shiran Shapira heads the laboratory, where basic research takes place. We devote our cancer research in the fields of early detection, prevention, and cancer therapy. The focus is on a wide range of biological areas covering cancer research, biochemistry, molecular biology, signal transduction, antibody engineering, protein expression and purification and gene delivery. The laboratory facilities occupy more than 300 square meters and is well equipped for research in biochemistry, molecular biology, tissue culture, cell biology etc.

CD24 for early detection and surveillance of cancer using a universal simple blood test. There are many attempts to develop a blood test for early detection, but none is in clinical use. CD24 is overexpressed in numerous human cancers. We have shown that a simple non-invasive blood test evaluating CD24 levels had good sensitivity and specificity for detecting colorectal adenomas and cancer, in patients undergoing screening colonoscopy in a tertiary medical center, independentantly on subject's age, gender, size of adenoma and stage of CRC. Recently, we have significantly improved our technology, which based on measuring the levels of CD24, which could reliably identify individuals with different common types of cancer and may serve even as a novel predictive

marker in cancer therapy and can identify family members that are at an increased risk for cancer.

HuCAMTech: The "Humanized" Chicken Embryo Chorioallantoic Membrane (CAM) as a personalized platform for screening drugs. The proposed technology suggests an attractive and promising strategy for a rapid assessment of the efficacy of chemotherapy, hormone therapy, biological tools, immunotherapies, small molecules, cell therapy and other new drugs, as well as the measurement of the extent of sensitivity, responsiveness and inhibiting the proliferation of specific tumors, in one consistent model. Therefore, can significantly advance clinical behavior in cases of cancer. Currently there is no good prediction for response to therapy. Whereas rodents are the most widely used preclinical model for studying tumor development and metastasis, the chick embryo is a versatile 3R compliant model that is available as in or ex ovo, nutritionally self-sufficient, cost-efficient, reproducible and phylogenetically more similar to mammals than several other models of replacement. Its chorioallantoic membrane (CAM), a highly vascularized extraembryonic membrane that is located directly beneath the eggshell, provides the main advantage when considering models for 3D tumor formation and screening drugs in a personalized setting.

Prevention. Heading several international, multicenter trials in the prevention of GI tumors, and in particular sporadic and familial CRC.

Identifying high risk subjects through molecular epidemiology. Our team has 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.

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).

The development of a novel Anti-CD24 antibody derivatives as a hope for the future. Antibody-based drugs are revolutionizing cancer, inflammatory and autoimmune therapy. Success depends on two important factors that are inseparable; lead molecule and promising target. CD24 and its antibodies meet these criteria. Targeting CD24 may be a promising treatment for various malignancies and for other applications as well. CD24 appears to be a promising target for many cancers that currently have limited treatment options. The uniqueness of the suggested antibody is its ability to recognize a specific and unique epitope in the matured core of the protein. The humanized mAbs (unarmed, bi-specific, toxin-conjugated, BiTE and other derivatives) against CD24 are very effective. The antibody was well characterized by means of PK, toxicity, stability, efficacy (xenograft, PDXT and CAM-PDX) etc. Its mechanisms of action include ADCC, ADCP and TGI. The scFv derivative of the mAb was fused to lentiviral particles, in a specific therapeutic setting, and was given as a compensation therapy to five terminal ill patients.

Thinking "Outside of the box" using the Trojan Horse Strategy. This new therapeutic system aims to use exosomes, natural nanosized vesicles secreted by a variety of cells. The exosomes will be used as a delivery tool of specific cassette, carrying biological information, leading to the eradication of tumor cells. This cassette is based on the concept of utilizing specific hyperactive signaling pathway, which will activate lethal agents that will efficiently kill the tumor cells. It encodes a unique bacterial toxin-antitoxin system utilizes the frequency of mutations in certain oncogenes, such as Ras, leading to the transformation of normal cells into cancerous cells. In this way, the system will enable selective eradication of cancer cells without harming normal cells as previously validated in our published works. The protection of the healthy tissue is carried out by an active use of an antidote that specifically neutralizes the basal expression of the killing agent. By using the genetic status of tumor suppressor genes, such as P53, the expression of the neutralizing agent in the normal tissue increases. This treatment approach holds great promise for cancer treatment and will advance the management of human cancer due to the ability to modulate the vector depending on the genetic profile and type of cancer, and specifically overcome cellular resistance that is the major drawback of targeted therapy.

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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Kraus S, **Shapira S**, Naumov I, Kazanov D, Moshkowitz M, Santo E, Galazan L, Geva R, Shmueli E, Hallack A, Arber N. Predictive levels of CD24 in peripheral blood leukocytes for the early detection of colorectal adenomas and adenocarcinomas. *Dis Markers*. 2015;2015:916098.

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Reichman H, Itan M, Rozenberg P, Yarmolovski T, Brazowski E, Varol C, Gluck N, **Shapira S**, Arber N, Qimron U, Karo-Atar D, Lee JJ, Munitz A. Activated eosinophils exert antitumorigenic activities in colorectal cancer. *Cancer Immunol Res*. 2019;7(3):388-400.

Tzfon I, Chayo J, Shaked M, Bernstein E, Dekel R, Arber N, **Shapira S**. Pancreatic cancer in bloom syndrome. *SAGE Open Medical Case Reports*. 2019;7:1-2.

Chapter

Shapira S, Wolf I, Arber N. Looking into the crystal ball of prevention and early detection of CRC. In: R. Benamouzig and J. Galmiche. *Screening and Prevention of colorectal cancers*. Chapter 14: 143-152 (2018).

Grants

2018-2019	Co-Investigator ,Gassner Fund for Medical Research in Memory of Mr Yitzchak Gassner
2019	PI, Djerassi-Elias Institute of Oncology



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Malignant Cells-Derived Exosomes: Serving as Cancer Biomarkers

Positions

Senior Lecturer, 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 proteins 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.

Subsequently we have shown that the transcript of telomerase in sera exosomes of patients with cancer including colon cancer and Lynch syndrome, brain tumors and lung cancers may serve as a diagnostic marker.

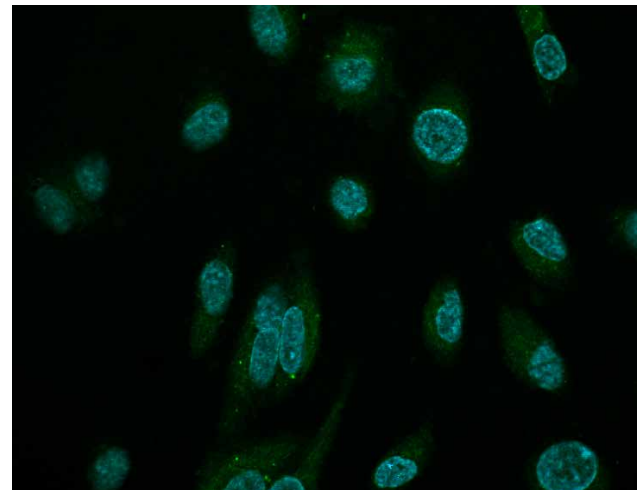


Figure 1. FITC-stained exosomes are taken up by HUVEC cells analyzed by fluorescent microscopy.

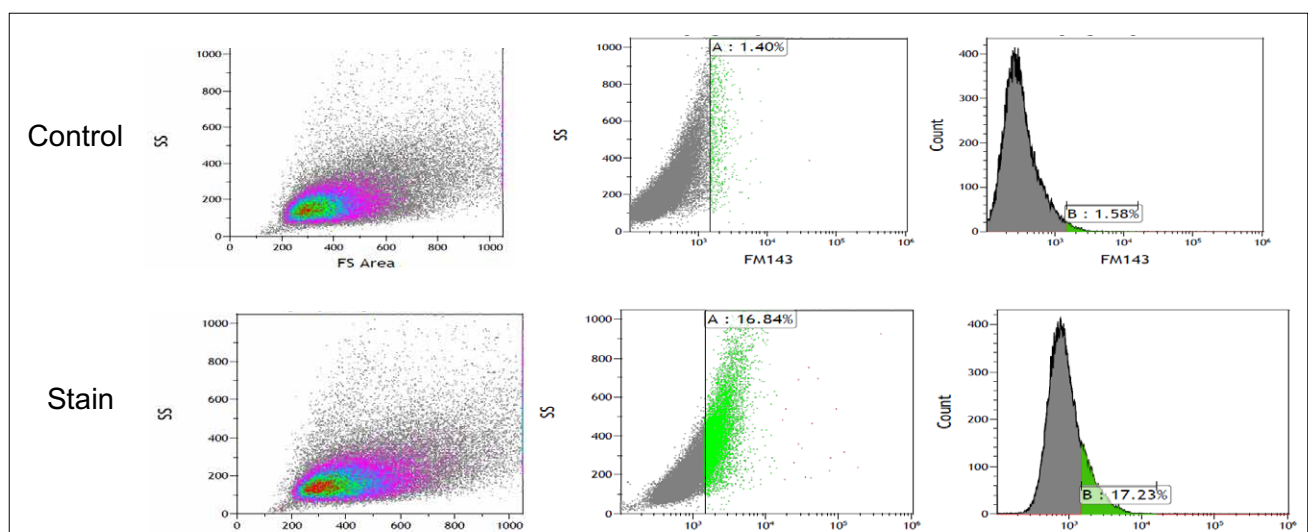


Figure 2. FM-134 stained exosomes are taken up by HUVEC cells analysed by flow cytometry.

In addition to the transcript of hTERT we have recently studied the presence of alternative splice factors in cancer cells derived exosomes and found very promising results as to their presence in the tested ex- vivo samples. We plan to elaborate this study to numerous other hematological as well as solid tumor derived exosomes.

In other set of projects, we have shown that chronic lymphocytic leukemia (CLL) –derived exosomes recruit endothelial cells and monocytes to secrete cytokines which are then taken up by the neoplastic cells, providing them with a protection from apoptosis through STAT-3 activation. In contrast, these exosomes induce cellular death in normal B lymphocytes, their counterpart competing on the same biological niche.

In addition to the above we have studied the role of polycythemia vera (PV)- derived exosomes in conferring thrombotic presentation to these patients by acting as "mini platelets" spreading the JAK2 mutated oncogene into other body tissues.

Another new venue of the lab is the resistance of patients with acute myeloid leukemia (AML) to the treatment of the BCL-2 inhibitor, venetoclax. We hypothesize that at least part of venetoclax resistance is mediated via stroma cells derived exosomes residing in the bone marrow of patients with AML.

A prerequisite of the exosomal mediated crosstalk between cells is the ability of the recipient cells to engulf these exosomes. In Fig. 2, we show the vicious circle initiated by CLL cells to acquire survival advantage.

Publications

Uziel O, Kanner A A., Beery E, Lev S, Lahav M, Horn-Fichman S, Har Nof S, Laviv Y, Yust Katz S, Amiel A, Abu Shakara R, Levi-Barda A, Raanani P, Sela Y, Cohen Z, Siegal T. Is blood-derived exosomal hTERT mRNA transcript a marker of oncogenic activity in primary brain tumors? An exploratory study. In Press, *Cancer Medicine*, 2023.

Orit Uziel, Lian Lipshtein, Zinab Sarsor, Einat Beery, Shaked Bogen, Meir Lahav, Vitali Kliminski, Roded Sharan, Asia Gervits, Lorenzo Federico Signorini, Shai Shimony, Pia Raanani & Uri Rozovski. CLL-derived exosomes educate endothelial cells to become IL-6 producing, CLL supportive cells. In Press, *BioMedicines*, 2023

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Lahav Y, Avidor S, Levy D, Ohry A, Zeilig G, Lahav M, Golander H, Chacham-Guber A, **Uziel O**, Defrin R. Shorter telomeres among individuals with physical disability: The moderating role of perceived stress. *J Gerontol B Psychol Sci Soc Sci*. 2022;77(8):1384-1393.

Lahav Y, Levy D, Ohry A, Zeilig G, Lahav M, Golander H, Chacham- Guber A, **Uziel O**, Defrin R. Chronic pain and premature aging – The moderating role of physical exercise. *J Pain*. 2021;22(2):209-218.

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.

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.

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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.

Uziel O, Beery E, Lahav M, Abu Shkara R, Yust-Katz S, Amiel A, Kanner AA, Laviv Y, Ben Zvi I, Siegal T. P01.019 Blood derived exosomal hTERT mRNA in glioblastoma: A potential circulating biomarker. *Neuro-Oncology* 20(Suppl 3): iii232, 2018.

Grants

2019-2020 Society for Hematology in Israel, The IGHV enigma: Why unmutated IGHV correlates with aggressive CLL?

2019-2020 Society for Liver Research, Circulating human telomerase (hTERT) mRNA in exosomes for early detection of hepatocellular carcinoma

2019-2020 Faculty of Medicine, Circulating human telomerase (hTERT) mRNA in exosomes for early detection of hepatocellular carcinoma

2019-2021 CBRC Dotan Award, The role of chronic lymphocytic leukemia (CLL)-derived exosomes in educating endothelial cells

2019-2020 Young Researchers Beilinson, The IGHV enigma: Why unmutated IGHV correlates with aggressive CLL?

2019-2020 Dotan dream award: Identify microRNA in the plasma of patients with DLBCL as a marker for relapse in the CNS

2019-2020 Faculty of Medicine: Identify microRNA in the plasma of patients with DLBCL as a marker for relapse in the CNS



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Department of Pathology, School of Medicine
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Developing Novel Adoptive Cell Therapies for Melanoma

Position

Senior Lecturer, Faculty of Medicine

Research

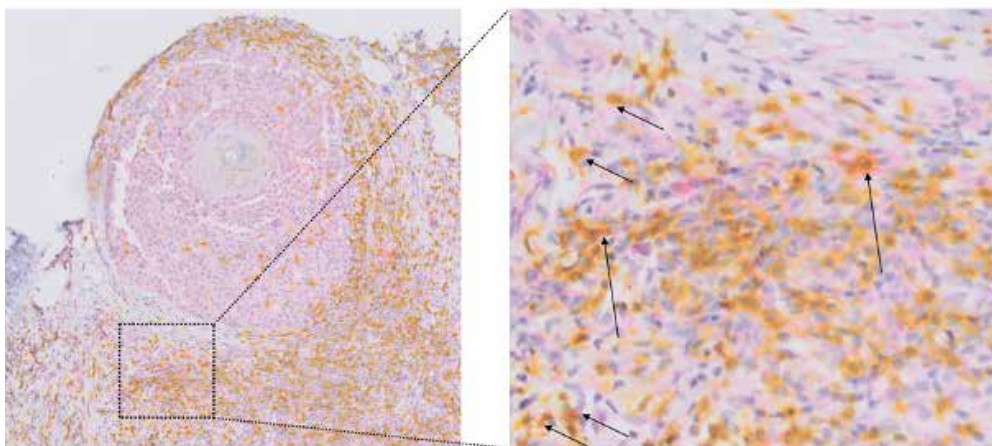
We perform cutting-edge translational research that can benefit melanoma patients, treated at the Sheba Medical Center. Our goal is to improve adoptive cell therapy (ACT) using human, autologous tumor-infiltrating lymphocytes (TILs), which is a well-established cell therapy for melanoma. While ACT was successful in treating melanoma prior to the era of immune checkpoint blockade (ICB), it is now frequently administered to patients who are refractory to ICB, and the success rates have dropped, indicating a development of resistance against ACT. Therefore, there is significant interest and an urgent need in the clinic to develop better TIL and T-cell products for patients with checkpoint inhibitor-refractory melanoma. We develop several technologies used to improve TIL anti-tumor capacities, using mRNA gene induction, CRISPR based gene deletion, metabolic reprogramming, establishing novel TCR therapies, and deciphering melanoma- TIL-microbiome interactions. We also work outside of melanoma, studying chimeric antigen receptor (CAR) T cell biology.

Publications

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Melanoma tumor margin. CD8+ T cells (depicted in yellow) in melanoma biopsy of a melanoma patient. PENK+CD8+ double positive cells are depicted in orange. Left, 10x; Right, 40x.

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Reviews

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Peri A., Salomon N, **Wolf Y***, Kreiter S*, Diken M*, Samuels Y*. The landscape of T cell antigens for cancer immunotherapy. *Nature Cancer*, doi: 10.1038/s43018-023-00588-x (2023). *Corresponding authors.

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* Corresponding authors

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Grants

2023-2025 Emerging Science Fund, Pfizer collaboration: “mRNA based T cell re-programming for cancer immunotherapy”

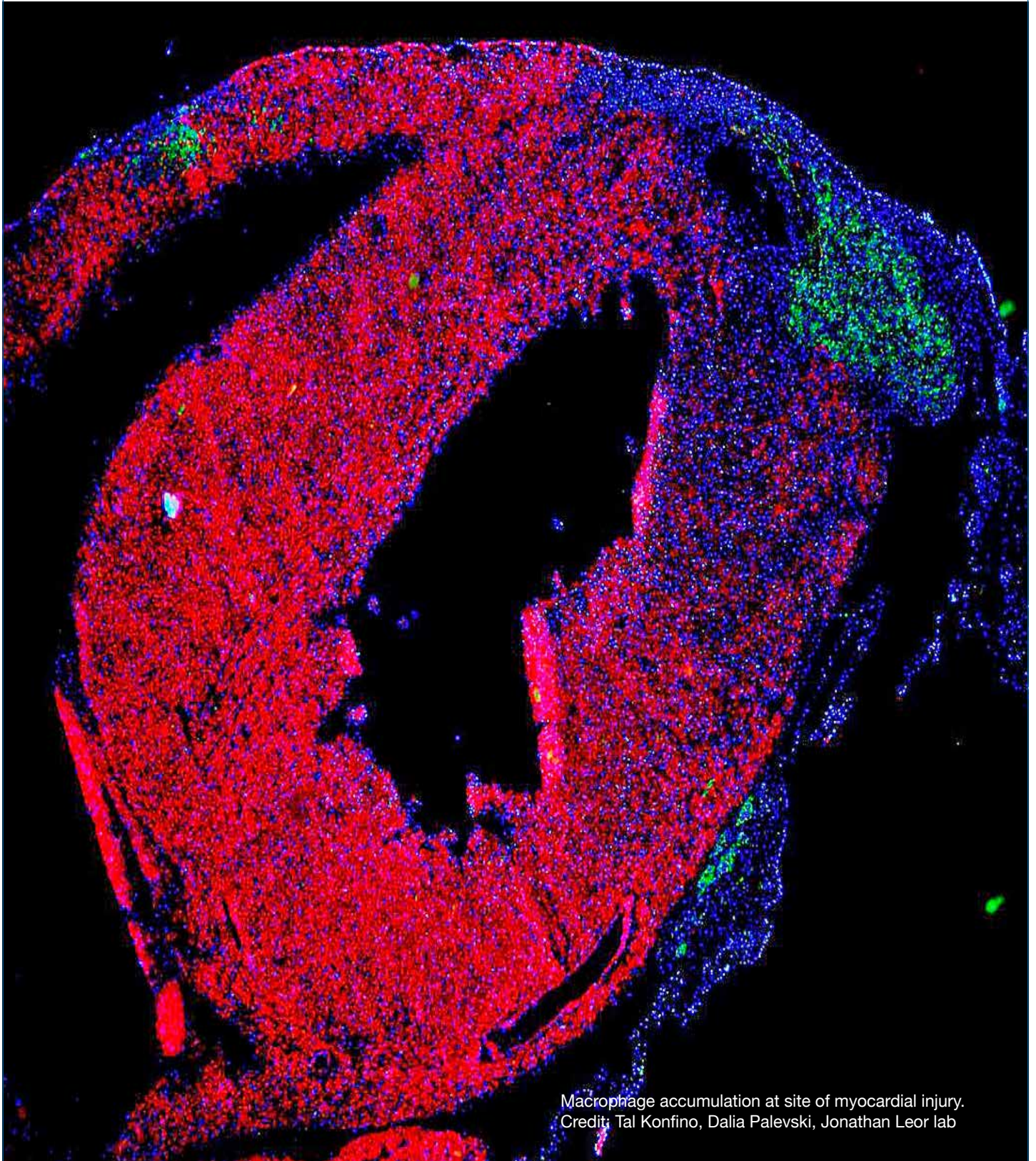
2023-2025 Sheba Medical Center/ Bar Ilan University joint research grant: “Deciphering the modulation of immunotherapy by the gut microbiota for improved cellular”

2022-2024 Sheba Medical Center Internal Grant- “Second chance”: “Identification and utilization of TCRs against recurrent mutations in uveal melanoma”

2022-2025 Melanoma Research Alliance/ Rosetrees Trust - Young Investigator Award: “mRNA-based re-programming of terminally differentiated TILs”

2021 Ongoing annual donation from the Lemelbaum Family

Cardiovascular System



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



Dr. Michal Entin-Meer, Ph.D.

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Cardiovascular Research Lab, Tel Aviv
Sourasky Medical Center; Lecturer,
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Elucidating the Molecular & Pathophysiological Mechanisms Leading to the Initiation and Progression of Cardiovascular Diseases

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.

Main ongoing research topics

The potential involvement of the cation channel TRPV2, which is highly abundant on peri-infarct

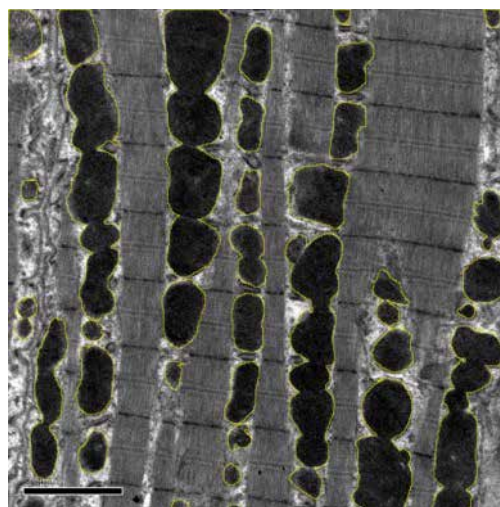
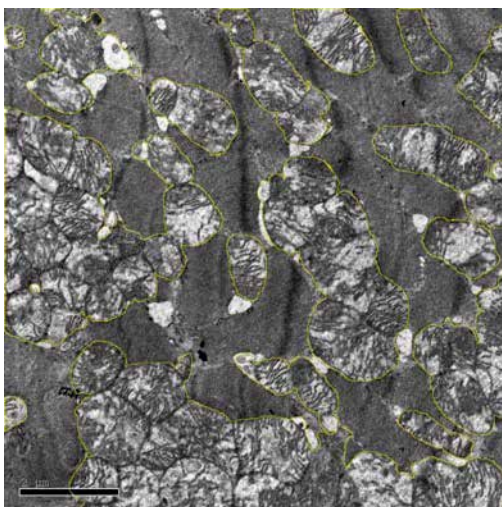
immune cells, in the recovery processes following an acute myocardial infarction.

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

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

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Grants

- | | |
|------------|---|
| 2018- 2021 | Weizmann-Ichilov joint grant. Can cardiac mitochondria represent a novel therapeutic target to attenuate progression to cardiorenal syndrome in chronic kidney disease? |
| 2018-2021 | Ministry of Health. The cation channel TRPV2 expressed on peri-infarct macrophages as a therapeutic target for patients with acute myocardial infarction. |
| 2019-2022 | Israel Innovation Authority - Kamin,. Development of a blocking agent to TRPV2 calcium channel as a treatment modality for inflammatory diseases and for acute myocardial infarction. |



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Stress and Inflammation in the Cardiovascular System

Positions

Senior Lecturer, Faculty of Medicine

Senior Researcher and Lab Head, Inflammation Research Lab, Department of Internal Medicine C" & E", Tel Aviv Sourasky Medical Center

Research

- Cholinergic regulation of stress and inflammation.
- Urinary protein secretion as a risk for metabolic syndrome.
- Determination of new set of control limits for the disease marker.

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 admitted 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, and biostatisticians.

Publications

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levels are associated with brain atrophy and cognitive decline in stroke survivors. results from the TABASCO prospective cohort study. *J Alzheimers Dis.* 2018;65(4):1365-1375.

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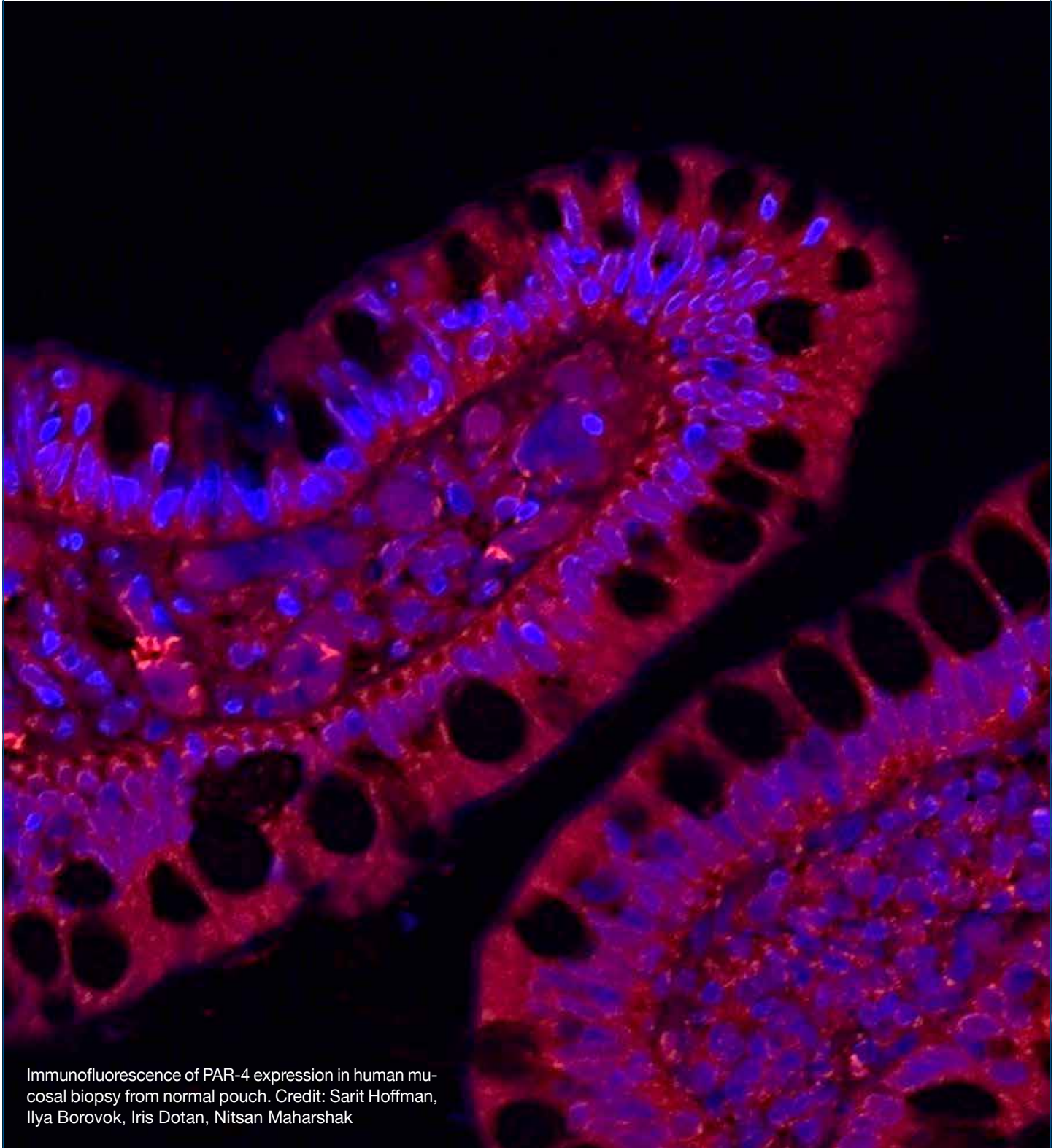
Grants

2019-2020 Urine proteomics differentiate between viral and bacterial infections. Israel Innovation Authority, Kamin Grant.

2019-2020 Non-alcoholic fatty liver and liver fibrosis progression predictive analytics: Risk prediction and machine learning techniques for improved prevention. The Israel National Institute for Health Policy Research.

2019-2020 Inflammatory makers, metabolic profile and GCase activity among patients with Parkinson's disease who carry mutations in the GBA gene and their unaffected relatives. The Michael J. Fox Foundation for Parkinson's Research.

Digestive System



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



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Innate Immunity of Digestive Tract and Liver Diseases

Positions

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

Director, Research Center for Digestive Tract & Liver Diseases

Editorial boards: Immunometabolism (Hapres), Frontiers in Immunology

Committee member in “Aldema” – non-profit organization for advancing research on the treatment and prevention of digestive tract diseases

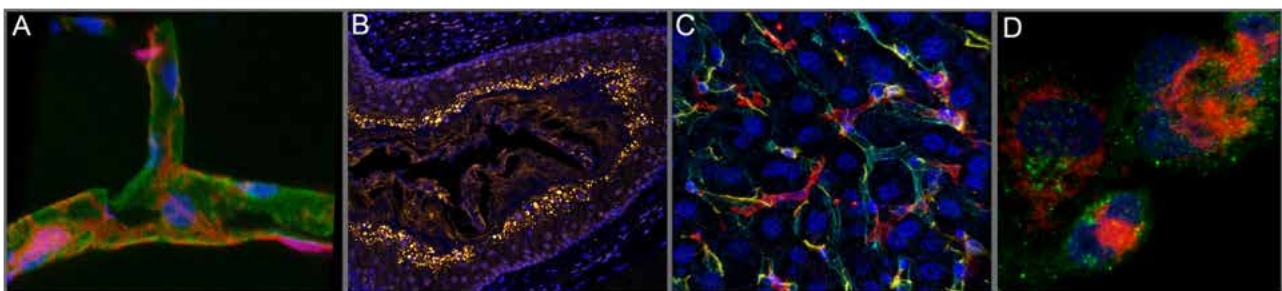
Research

Phagocytic type of innate immune cells, such as macrophages, monocytes and dendritic cells, play key tissue-specific homeostatic roles in organs of the digestive tract. Yet, they also fuel the pathological inflammatory sequence of digestive tract diseases, while preserving the potential to facilitate recovery. Our group strives to decipher the cell-specific immunoregulatory mechanisms that dictate the pathological versus restorative behavior of these innate immune cells in health and disease. We study the involvement of these cells in diseases of the digestive tract and metabolic syndrome, such as: liver fibrosis, metabolic dysfunction associated liver disease (MAFLD), obesity-induced type 2 diabetes,

eosinophilic esophagitis, inflammatory bowel diseases (IBD), colorectal cancer, and hepatocellular carcinoma. We combine state-of-the-art in vivo transgenic mouse models with human patient samples and apply advanced immunological, genetic, molecular and imaging approaches. Our studies have greatly contributed to the field of gut and liver immunology with the functional definition of distinct macrophage subsets in these organs and their involvement in the respective diseases. We believe that mechanistic insights derived from our research would enable the design of more sophisticated cell-specific therapeutic approaches.

Among our main research topics:

- Unravelling key immunoregulatory molecules dictating the inflammatory versus restorative activity of macrophages in various diseases of the digestive tract. Our studies have illuminated COMMD10 as a pivotal immunoregulator in macrophages, regulating their differentiation, inflammatory and metabolic activities, and survival during diseases of the digestive tract.
- GIP receptor (GIPR)–GLP1 receptor (GLP1R) multi-agonists are at the front of treatment for type 2 diabetes and metabolic syndrome diseases. In the last decade, our lab has unraveled a key beneficial



Studying innate immunity in digestive tract diseases. (A) Expression of GIP receptor (red) in perivascular adipose tissue macrophages in the visceral white adipose tissue. (B) Increased expression of the matrix metalloprotease ADAM8 (gold) in esophageal epithelial cells in mice subjected to EoE model. (C) Colocalization of liver resident macrophages – Kupffer cells (red) in their niche with hepatocytes (DAPI), hepatic stellate cells (yellow) and endothelial cells (cyan). (D) COMMD10 (green) localization in the cytoplasm, nucleus (DAPI) and mitochondria (red) of human macrophages.

immunometabolic roles for GIP during obesity, in supporting BM hematopoiesis and the restraining of adipose tissue macrophage inflammatory activity.

- We study the immunometabolic activities of the S100A8 and S100A9 alarmins in obesity and thermogenesis. Our lab has defined a deleterious role for S100A8/A9 in obesity and cold-induced adaptive thermogenesis, while S100A8 and S100A9 homodimers are beneficial.
- Eosinophilic esophagitis (EoE) is a rare, yet emerging, chronic type 2 immune-mediated disease, characterized by esophageal dysfunction. Utilizing a novel mouse model and our own EoE patient biobank, we study the association between EoE and an altered composition of the microbiome along the GI tract, as well as the cellular immune mechanisms that link between the microbiome and EoE development. We also study the role of S100A8 and S100A9 alarmins in the development and resolution of EoE.

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Grants

2019 – 2024 Israel Science Foundation (ISF).

2019 – 2022 Israel Science Foundation (ISF) – Canadian Institute of Health Research joint program

2022 – 2025 Azrieli Foundation



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Investigating the Mechanisms of Liver Steatosis, Obesity and Cholestatic Injury

Positions

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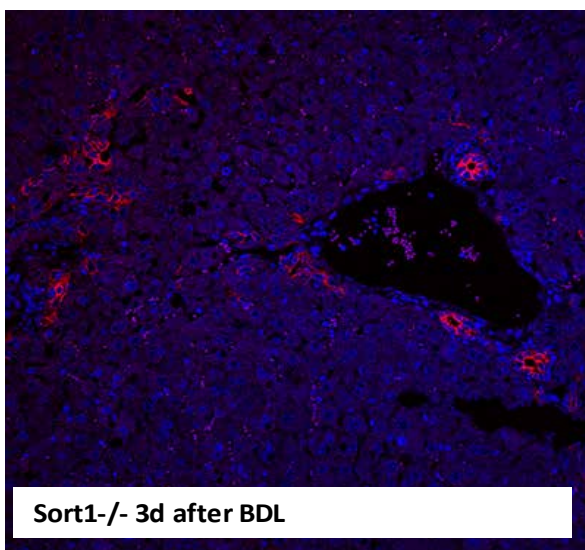
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Research

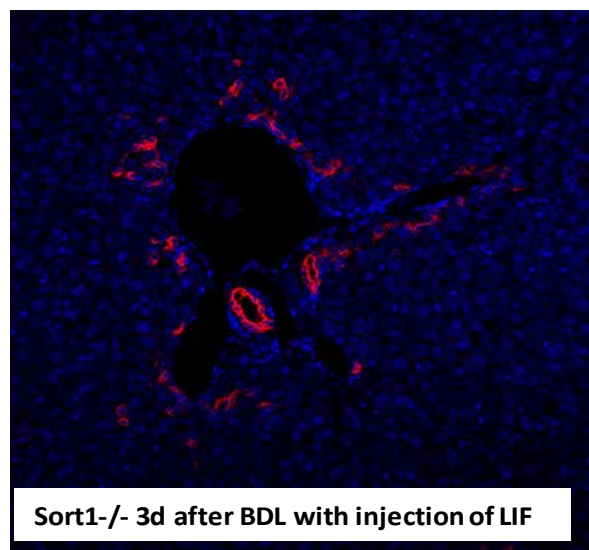
Our lab is investigating two main diseases, liver steatosis in models of diet-induced obesity and insulin resistance and cholestatic liver injury. Obesity and the metabolic syndrome accompanying it affect a large percentage of Western world population and the obesity epidemic is only expected to increase,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



Sort1^{-/-} 3d after BDL



Sort1^{-/-} 3d after BDL with injection of LIF

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

Publications

Rabinowich L*, Fishman S*, Hubel E, Thurm T, Park WJ, Pewzner-Jung Y, Futerman A, Halpern Z, **Zvibel I**. 2015. Sortilin deficiency improves the metabolic phenotype and reduces hepatic steatosis in a murine model of diet-induced obesity. *J Hepatol* 62:175-81. *equal authors.

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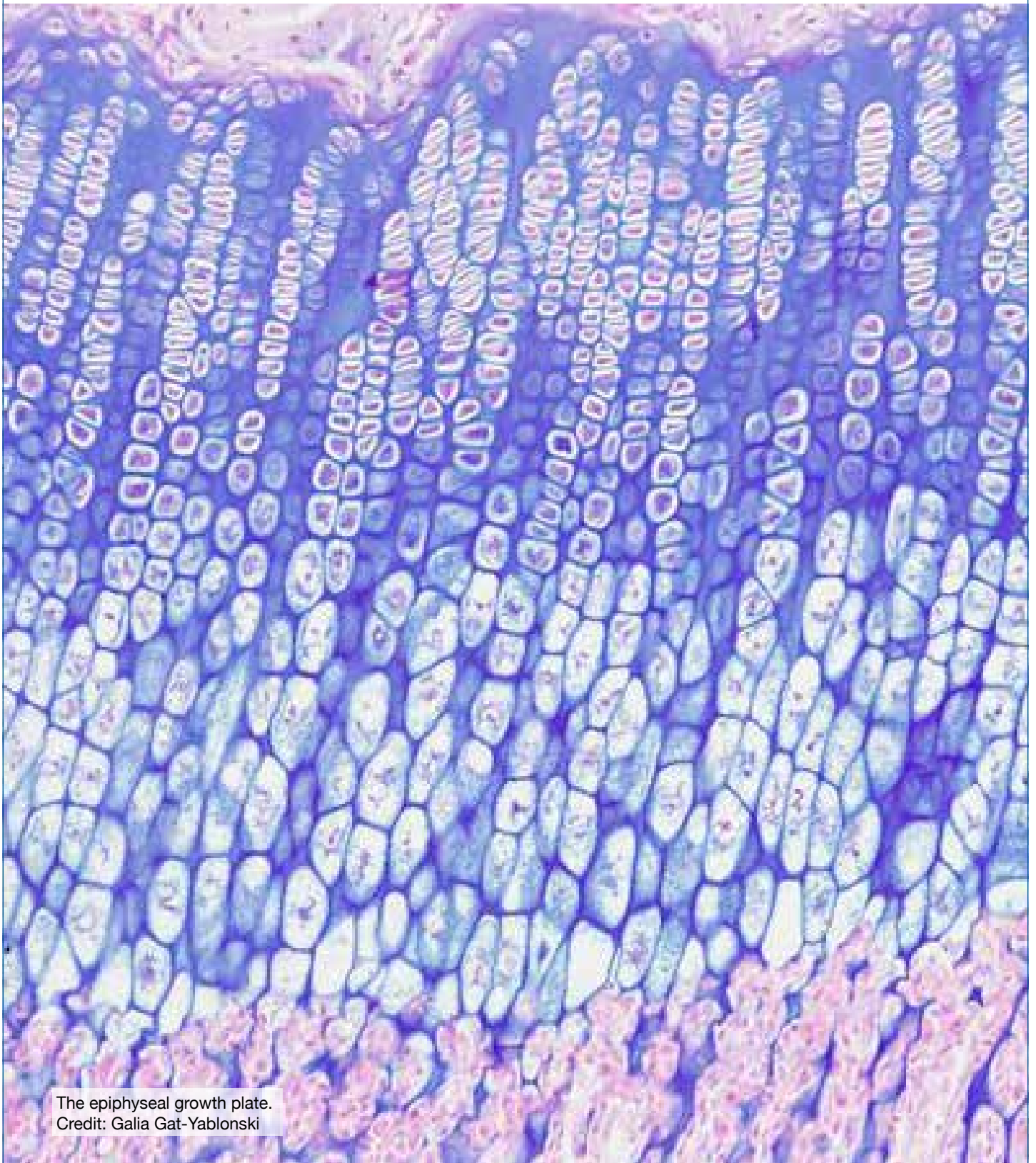
Mantelmacher FD*, **Zvibel I***, Cohen K, Epshtein A, Pasmanik- Chor M, Vogl T, Kuperman Y, Weiss S, Drucker DJ, Varol C, Fishman S. GIP regulates inflammation and body weight by restraining myeloid cell-derived S100A8/A9. *Nature Metab*, 2018; 1:19. *equal authors.

Grants

2019-2023

Israeli Science Foundation. Deciphering the role of sortilin, IL-6 and leukemia inhibitory factor signaling in the ductular reaction following cholestatic liver injury, PI

Endocrine Disease



The epiphyseal growth plate.
Credit: Galia Gat-Yablonski



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The Laboratory for Molecular Endocrinology and Diabetes

Positions

Senior Lecturer, Faculty of Medicine

Committee Member, Israel Endocrine Society

Research

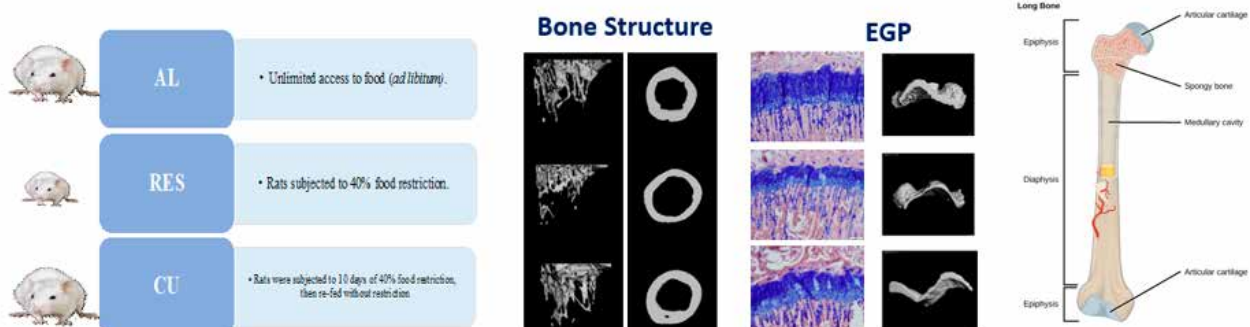
Our lab is studying the processes involved in linear growth in children, in close collaboration with the Institute for Endocrinology and Diabetes at the Schneider Children Medical Center. The study aims to decipher novel regulatory mechanisms for enabling the development of better monitoring and treatment modalities which are much needed in this field. Previously it was believed that hormones such as growth hormone and Insulin like growth factor 1 (IGF-1) are the most critical factor, however, most children with short stature that visit our institute, present a normal hormonal profile; therefore we decided to focus our attention on studying the target organ, the epiphyseal growth plate (EGP). Our model is based on the well-known connection between nutrition and linear growth.

We were the first to show that leptin, the satiety hormone secreted from adipocytes, directly activates the growth plate. We have shown that leptin administration to food restricted animals compensated for the reduced amount of food, leading to almost normal growth. We have further showed that leptin binds directly to specific receptors in the EGP and activates its known signal transduction pathways including Stat3/Jnk/ERK

and that it activates the regulatory pathway of *Ihh*/PthrP. Recently we found that high levels of leptin, especially during puberty activates the aromatase enzyme, which converts testosterone to estrogen. As estrogen leads to growth inhibition, this activation leads to growth cessation and premature closure of the EGP, culminating in short stature. These findings were supported by a clinical observation made in our clinic, showing that obese children may sometimes end up with short stature compared to their peers.

Short children may sometimes be treated with growth hormone even in the presence of adequate amount of the hormone, if they are very short. In order to follow their response to treatment, a sensitive biomarker is required, apart from height measuring, as this gives indication only after 6 months or more. We are studying different biomarkers in several setups in order to identify the most sensitive and specific ones.

Animal studies are performed to study the effect of nutrition on growth. We are using a model of food restriction induced growth attenuation followed by re-feeding in order to cause catch up growth, which is robust than average growth. We were studying the changes in gene expression, identifying the role of the transcription factor HIF1alpha, several micro RNAs and HDACs. A transgenic model we developed in which Sirt1 (an HDAC of family III) was specifically knocked down in the EGP showed that the affected animals had significantly less efficient growth and less efficient response to nutritional manipulation. Surprisingly, a



marked effect was identified in bone mineralization and structure of the cortical and trabecular bone compartments.

Microbiome analysis at different nutritional states revealed that food restriction led to significant changes in gut microbiota, similar to the differences reported between fat and lean humans. Using several different diets, we noted that specific ingredients in the diet, even when calories and macromolecules are similar, significantly affect gut microbiota and growth. These findings enable us to suggest future improvements to the growth stimulating formula that was developed by the clinic.

Quantitative proteomics of rat livers fed ad libitum or food restricted shows that unrestricted feeding is stressful for proteostasis with implications on life span. Over 1800 common proteins were significantly quantified in livers of ad libitum, restriction- and re-fed rats, which summed up into 92% of the total protein mass of the cells. Compared to restriction, ad libitum cells contained significantly less mitochondrial catabolic enzymes and more cytosolic and ER HSP90 and HSP70 chaperones, which are hallmarks of heat- and chemically-stressed tissues. Following re-feeding, levels of HSPs nearly reached ad libitum levels. The quantitative and qualitative protein values indicated that the restriction regimen was a least stressful condition that used minimal amounts of HSP-chaperones to maintain optimal protein homeostasis and sustain optimal life span. In contrast, the elevated levels of HSP-chaperones in ad libitum tissues were characteristic of a chronic stress, which in the long term could lead to early aging and shorter life span.

We have been studying the molecular background of the Maturity Onset Diabetes of the Young (MODY) in Israeli patients, and identified several mutations that are more prevalent in our population. We are currently involved in a clinical study on autoantibodies to type 1 diabetes. Collaborating with a group from the USA that developed an ultrasensitive method to identify autoantibodies we will follow children from the general population to identify the timing of autoantibodies appearance. These results will be used to educate the families that are at risk and maybe in the future will enable us to offer treatment that may postpone the appearance of the overt diabetes.

Publications

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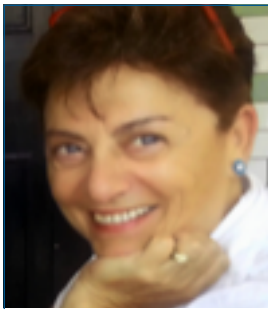
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Alpha Linolenic Acid (Essential Omega-3): Its Role in Pregnancy for Optimal Brain Development & Long-Term Prevention of Disease in Offspring

Positions

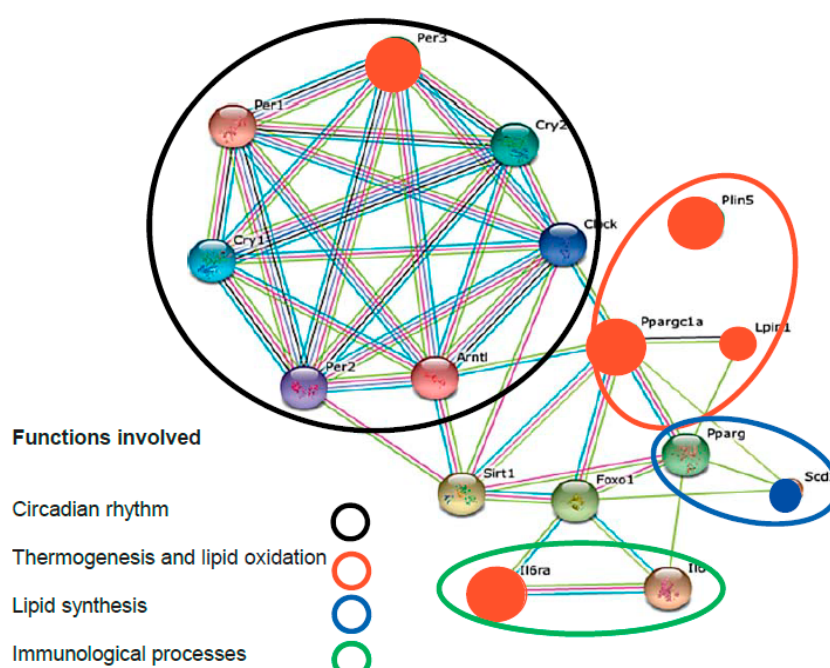
Associate Professor, CAMEA, Faculty of Medicine
Researcher at the Bert Strassburger Lipid Center,
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Research

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 world population and death.

Docosahexaenoic acid (DHA) is an omega-3 fat that can be made in the body from a precursor alpha



Protein interaction between products of genes upregulated (red full) or down-regulated (blue full) by ω 3 essential fatty acid (ALA) or saturated fatty acids (SFA). Enriched functions are marked using open colored circles.

linolenic acid (ALA) or consumed directly from fish. DHA is essential for normal brain function and its levels increase dramatically during brain development. Much of the world consumes diets lacking DHA and relies on synthesis from a dietary precursor. Under normal conditions, in adults, the synthesis of DHA from its precursor appears to be enough to supply the brain. It is even possible that the synthesis of DHA from its precursor is enough to supply the infant brain during its growth. However, it has now become apparent that certain dietary factors, stress and genetics can influence the body's ability to synthesize DHA, which could have long-term consequences on brain function. We have developed methods to study the synthesis of DHA from ALA in detail and we use mice to examine how different diets, stress and genetic factors influence the synthesis of DHA, brain DHA levels and brain function while the brain is developing. We are also examining human mothers in their fatty acid profiles compared to non-pregnant women, to establish a scientific basis for personalized needs of fatty acids during pregnancy for the wellbeing of both mother and child. We are contemplating the impact of maternal dietary ALA on the offspring's epigenetic impact.

Publications

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Grants

- | | |
|------|--|
| 2020 | Tel Hashomer Grant, The effect of Alpha Linolenic Acid (ALA) supplementation on fatty acids profile during pregnancy compared to other omega3 supplements and their influence on the metabolic –epigenetic status of the newborn in humans |
| 2020 | Tel Hashomer Grant, Alpha Linolenic Acid as a tool to improve BBB transport system |



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Investigating the Molecular Mechanisms of Vascular Dysfunction

Positions

Senior Lecturer, Faculty of Medicine

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Research

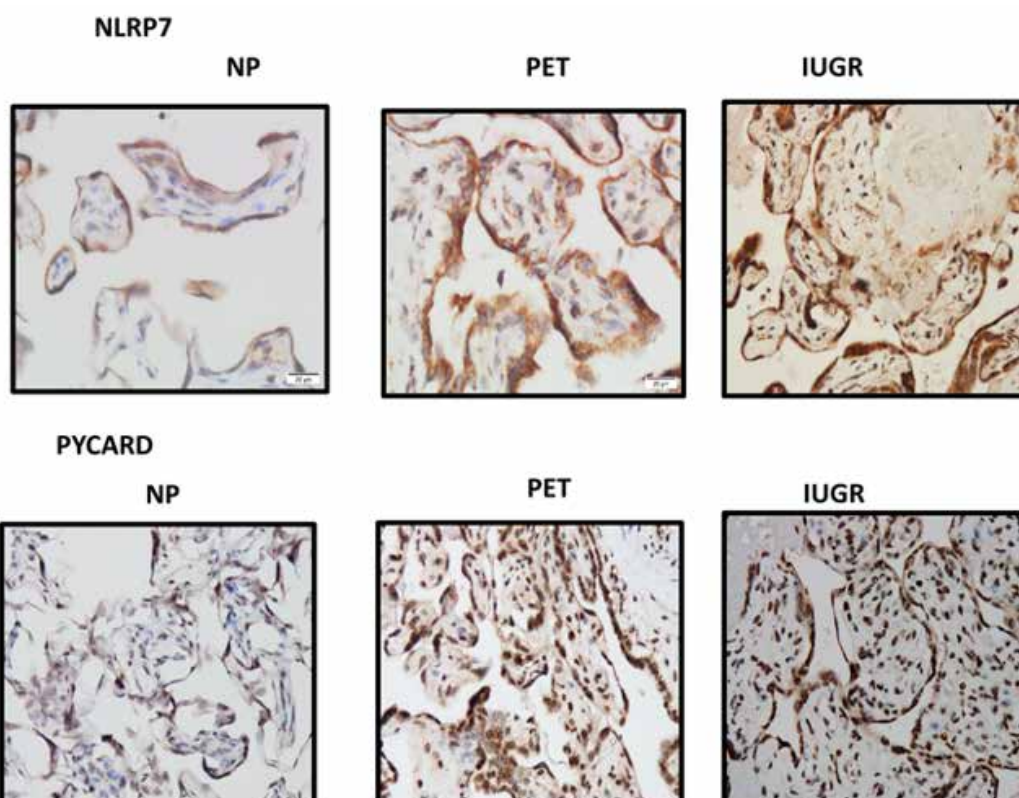
Diabetes: Investigate the anti-inflammatory response in *in vitro* models of endothelial cells and smooth muscle cells exposed to diabetic environments and in *in vivo* models of db/db mice.

Vascular calcification in kidney disease: Vascular calcification is a strong prognostic marker of cardiovascular disease mortality in patients with CKD. Vascular calcification has is a passive,

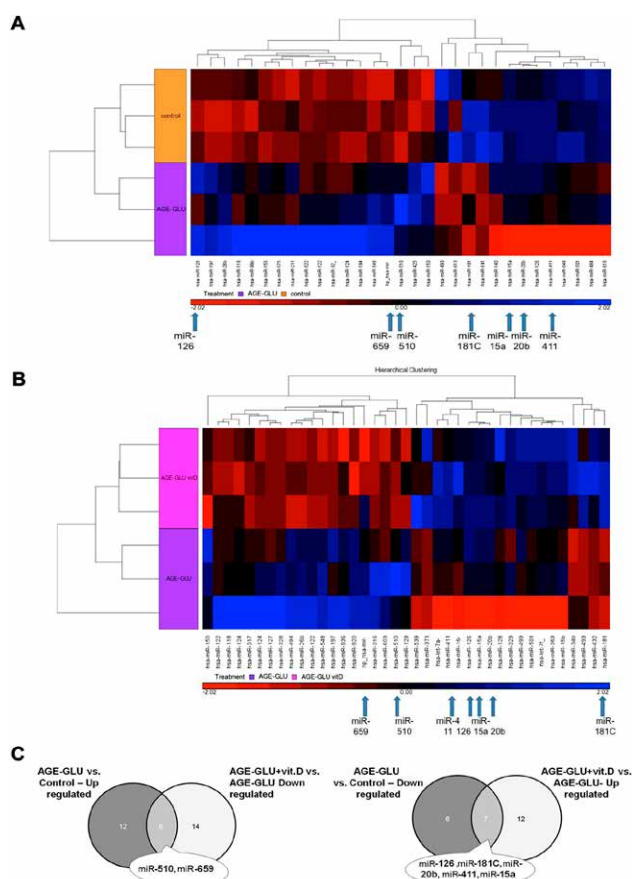
degenerative, end-stage process of atherosclerosis and inflammation. We evaluate changes in *in vitro* models of endothelial cells stimulated with uremic serum from hemodialysis patients. Also study the effect of plasma exosomes derived from hemodialysis, on vascular calcification.

Investigate gene and protein changes in normal and preeclamptic pregnancies, gestational diabetes and fetal growth restriction in maternal and blood cords, as well as placenta biopsy (in collaboration with the Department of Obstetrics and Gynecology).

Clinical and laboratory research – Collaborate with physicians in the Department of Nephrology, Meir Medical Center



NLRP7 and PYCARD protein expression in placental tissue (Silber et al. 2022 *American Journal of Reproductive Immunology*).



Publications

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Zitman-Gal T, Einbinder Y, Ohana M, Katzav A, Kartawy A, Benchetrit S. (2018) Effect of liraglutide on the Janus kinase/signal transducer and transcription activator (JAK/STAT) pathway in diabetic kidney disease in db/db mice and in cultured endothelial cells. *Journal of Diabetes*. 11:656-664.

Einbinder Y, Cohen-Hagai K, Shitrit P, **Zitman-Gal T**, Erez D, Benchetrit S, Korzets Z, Kotliroff A. (2019) ISPD guideline-driven retraining, exit site care and decreased peritonitis: a single-center experience in

Israel. *International Urology and Nephrology*. 4:723-727.

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Genetic Diseases & Genomics



Credit: Viktor Koen



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Epitranscriptomics: Gene Expression Regulation Through RNA Modifications

Positions

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Research

Epigenetic modifications regulate gene expression to determine cell fate and responses to environmental stimuli. The mechanisms that orchestrate the dynamic and reversible deposition of these DNA and histone modifications have been studied extensively, and it is known that they participate in the core regulation of gene expression. By contrast, the role of epitranscriptomic (RNA) modifications in the regulation of gene expression is only starting to be revealed.

RNA modifications were previously known to occur in highly abundant RNA species, such as ribosomal RNA and transfer RNA. However, in recent years, thank to studies by us and others, a growing number of modifications have been identified and characterized in low-abundance species of RNA such as mRNA and long non-coding RNA. These modifications regulate RNA processing events such as splicing, transport, translation and turnover.

The epitranscriptome, as these modifications are now collectively known, comprises a growing number of chemical adducts, such as *N*⁶-methyladenosine, *N*¹-methyladenosine, inosine, 5-methylcytidine, 5-hydroxymethylcytidine, pseudouridine, *N*⁶,2'-*O*-dimethyladenosine, *N*⁴-acetylcytidine, *N*⁷-methylguanosine, 8-oxoguanosine and 2'-*O*-methy. These modifications embed RNA transcripts with information additional to that carried in their sequence of bases. The discovery of dedicated cellular machineries that deposit, remove and recognize RNA modifications (known as writers, erasers and readers, respectively) has helped to reveal the essential roles of these modifications in cellular, developmental and disease processes.

Our group studies the effects of RNA modifications on gene expression by understanding the mechanisms responsible for their cellular decoding and the biological consequences in both normal physiology and disease. For example, modifications can change the charge of RNA bases and alter their base pairing properties, resulting in differential RNA folding. They can also form recognition elements embedded in the transcript's sequence that modulate protein-RNA interactions. For this purpose, we develop novel technologies to detect and sequence modifications and look for new components of the cellular machineries responsible for the metabolism of modifications in particular and mRNA more broadly.

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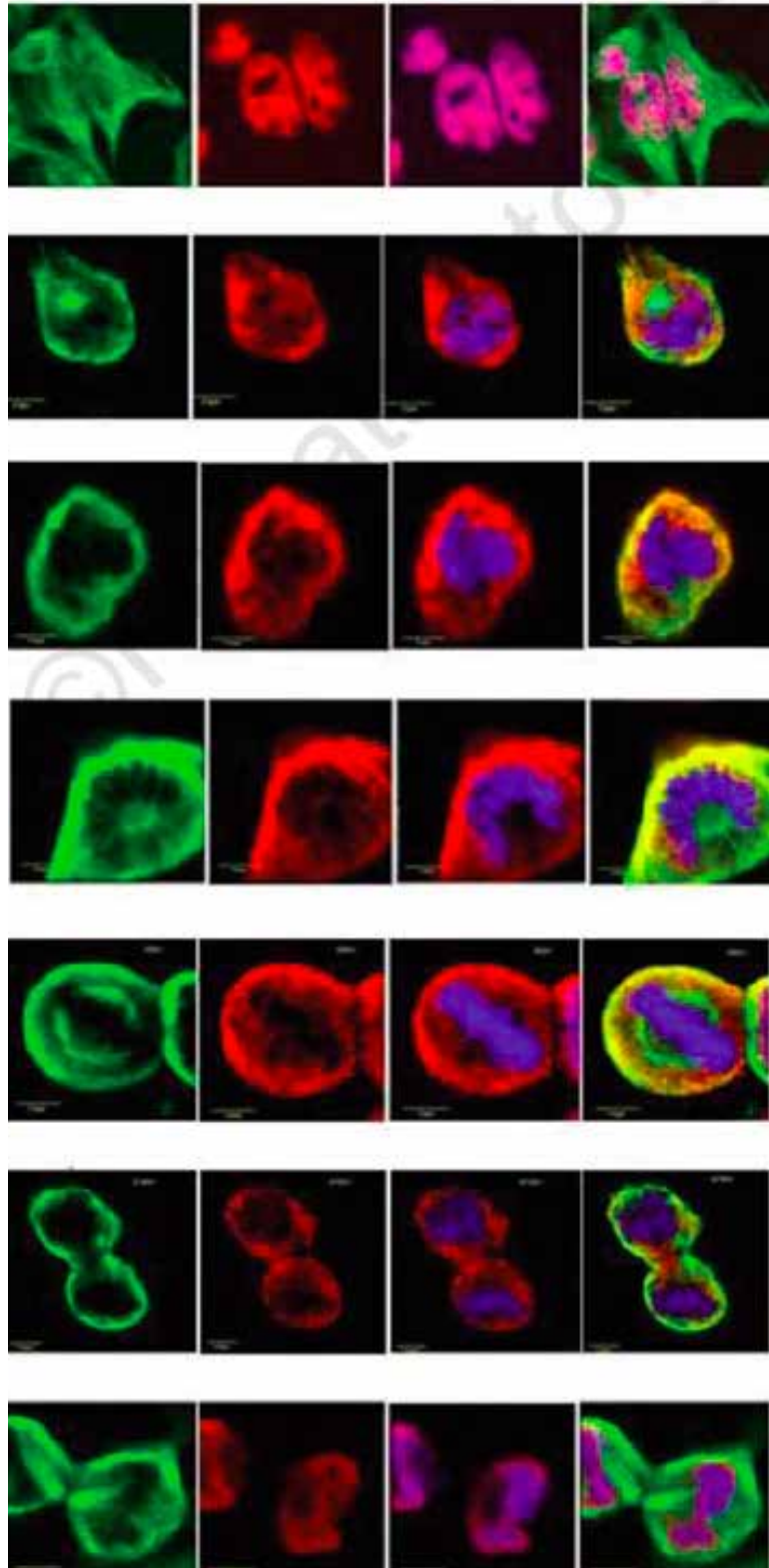
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Immunology & Hematology



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



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Extracellular Vesicles (EVs): A Biomarker and Therapeutic Tool

Positions

Senior Lecturer, Faculty of Medicine

Director, Hematology Research Laboratory for
Extracellular Vesicles, Tel-Aviv Sourasky Medical
Center

Research

Extracellular vesicles (EVs) are sub-micron membrane vesicles that shed from cells under various conditions. They found in body fluids of healthy individuals and their levels increase in a variety of diseases. EVs are divided according to size, synthesis route, and cell origin. EVs bear antigens reflecting their cellular origins, cytokines, fragments of DNA/RNA and miRNA that can be transfer to recipient cells, therefore play significant role in intercellular communication.

Over the past 18 years, our laboratory has made significant contributions to exploring the role of EVs in pregnancy complications, cancer (hematological malignancies: myeloma, AML, ALL and solid tumors such as breast cancer, colon cancer), in congenital disorders such as thalassemia and in trauma patients and patients with dementia. Additionally, the effects of EVs that shed from cell culture upon stimulation on other cells functions (such as endothelial, placental cells, airway epithelial, liver, pancreatic and ovary and breast cancer cell lines) were explored. We also

focused on the therapeutic side of EVs and significant progress was made in our study on EVs derived from CAR-T cells as a potential therapy for cancer. During this period, my team and I published above 40 publications describing our research work.

Publications

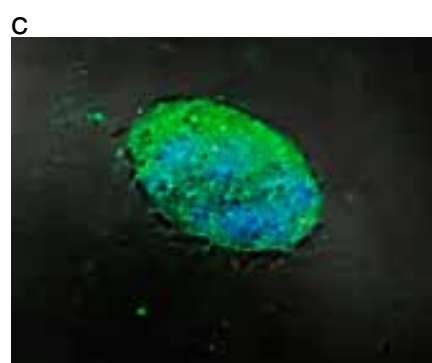
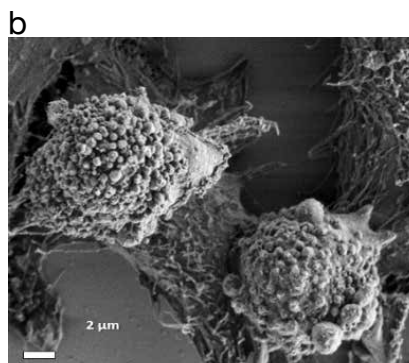
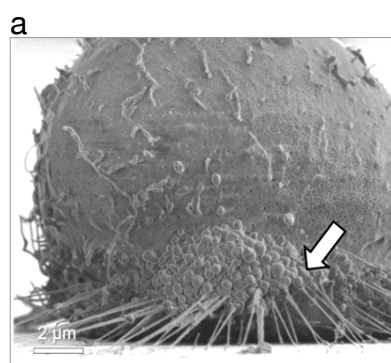
Manuscripts

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Scanning electronic microscopy (SEM) images of EVs shedding from breast cancer cells before stimulation (a) and post stimulation (b). *Aharon A. et al. Thromb Haemost* 2018.

c. CAR -T EVs (green) bind to cancer cell surface. *Aharon A. et al. Hum Gene Ther*. 2021

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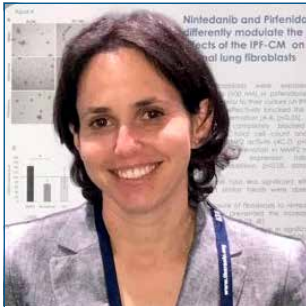
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Review

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Grants

KAMIN



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Investigating the Molecular Basis of Pulmonary Fibrosis

Positions

Lecturer, Faculty of Medicine

Principle Investigator, Pulmonary Disease Research Laboratory, Meir Medical Center, Kfar Saba

Research

We study the effects of the microenvironment on fibrotic disease progression. In our lab, we culture primary human lung fibroblasts derived from normal and IPF tissues to explore molecular markers and mechanisms involved in fibroblast to myofibroblast differentiation. Using an idiopathic pulmonary fibrosis (IPF) conditioned matrix (CM) model that we developed, we investigate fibroblast-extracellular (ECM) interactions. We found that culturing normal fibroblasts on the IPF-CM leads to their differentiation towards myofibroblasts. This platform also enables the study of new drug candidates for fibrosis.

Publications

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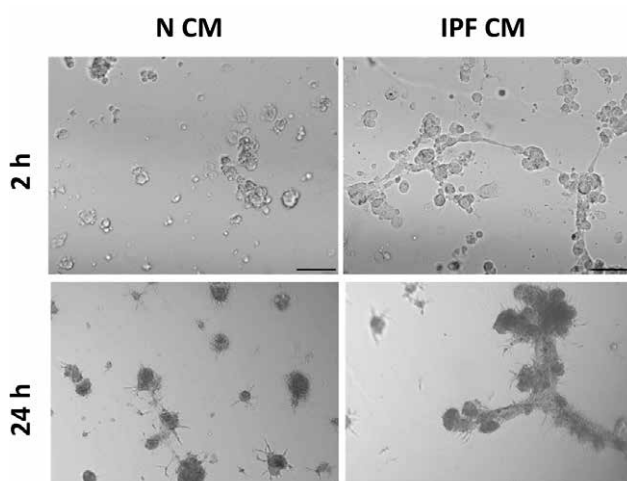
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Normal human lung fibroblasts cultured on control (N CM) and IPF CM. As shown on the right side, the normal cells become elongated (2h), migrate and finally cluster into large aggregates (24h) following their culture on the IPF-CM.

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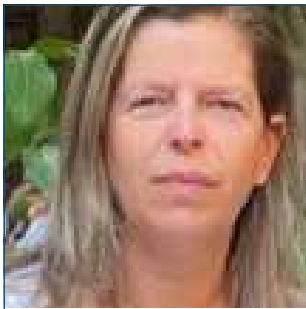
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Grants

2019-2020 Avalyn Pharma



Dr. Smadar Gertel, Ph.D.

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Precision Medicine in Rheumatology

Position

Dr. Smadar Gertel

Head of the Arthritis Research Laboratory

Lecturer, Faculty of Medicine

Position

Prof. Ori Elkayam

Head of the Rheumatology Department, Tel Aviv Sourasky Medical Center

Professor, Faculty of Medicine

Former Chairman, The Israeli Society of Rheumatology

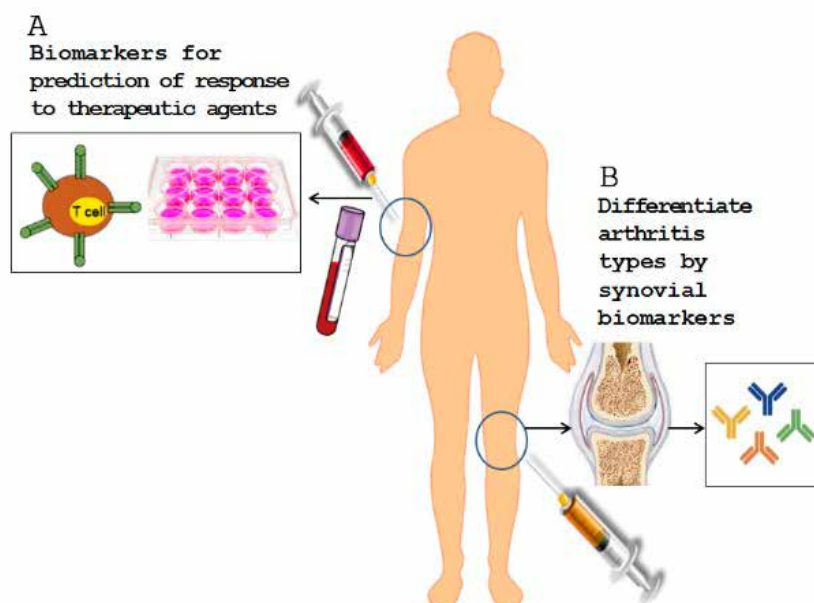
Research

Rheumatic diseases are prevalent diseases that include variety of disorders, the most common among them are: Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and Osteoarthritis (OA). Those diseases are characterized by pain, swelling and synovitis of the joints. Nowadays new classes of medications have greatly improved rheumatic disease

outcomes. However, biomarkers that will assist in the best therapeutic choice are lacking. Although, precision medicine is already in use in medicine fields, such as oncology, this field in rheumatology is lagging behind.

Our main research:

- Characterization of biomarkers for response to anti-rheumatic drugs – Generation of an assay to analyze patient's immune cells response to drugs using ex-vivo conditions. Diverse immune cell phenotype alterations in response to each drug are being characterized. Our aim is that such assays will assist in drug choices for the individual patient and will optimize rheumatic diseases patient's outcomes.
- Characterization of biomarkers to distinguish between different types of rheumatic diseases - The rheumatic diseases share common clinical presentation but also present differences in pathogenesis and radiographic findings. Those differences are translated into variances in the specificity and efficacy of therapies. Moreover, PsA disease diagnosis is based only on clinical



evaluation since diagnostic biomarkers are not available yet. Finding of new biomarkers may improve accuracy in the diagnosis of different diseases and may assist in therapy selection. The diagnosis may be helped by synovial fluid analysis. We aim to characterize synovial biomarkers that could differentiate between the different disease types.

Our laboratory is located in close proximity to the Rheumatology Clinic, allowing daily collaboration with the department and accessibility to human patient samples. We use advanced immunological and molecular approaches.

The scheme illustrates the lab main research fields: A. Development of ex-vivo assay to predict response to anti-rheumatic drugs based on immune phenotyping of patient immune cells. B. Identification of synovial biomarkers that will assist at diagnosis of different arthritis types.

Publications

Gertel S, Polachek A, Furer V, Levartovsky D, Sidis H, Pel S, et al. T cell functions of psoriatic arthritis patients are regulated differently by TNF, IL-17A and IL-6 receptor blockades in vitro. *Clin Exp Rheumatol*. 2021.

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Dr. Gilad Halpert, Ph.D.

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Improving Management of Inflammatory/Autoimmune & Rheumatic Diseases Using Extracellular Vesicles and Medical Cannabinoids

Positions

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

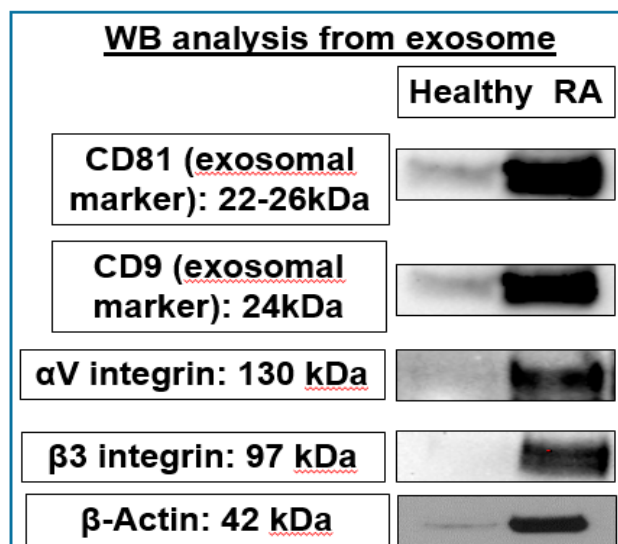
Research

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:

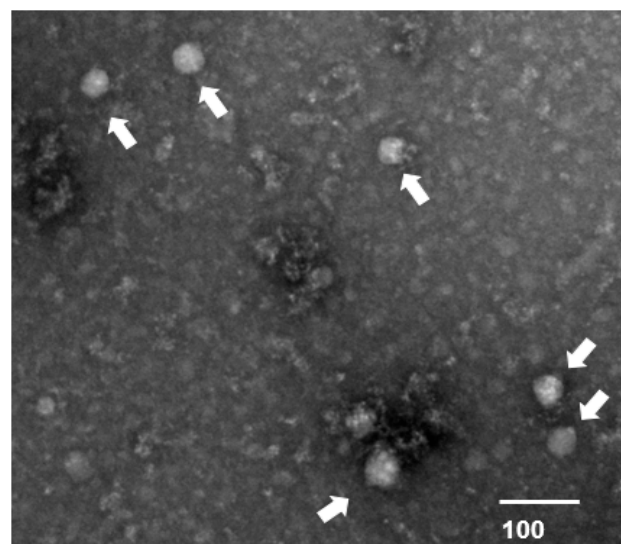
1. Improved drug delivery using specific tissue-homing small extracellular vesicles ('exosomes')

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 (immunomagnetic separation). The drug-loaded exosomes can be injected back

A



B



The specific synovial-homing receptor α v β 3 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, α v, β 3 (Santa Cruz Biotechnology) and β -actin (R&D system). Total 7 μ g protein were loaded into each well. B. Transmission Electron Microscopy (TEM) analysis shows a nano-size vesicle (~40nm) of exosomes derived from sera of RA mice.

to the diseased 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 diseases (Animal models of Collagen-induced arthritis, DSS-induced Colitis, 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 syndrome – through examination of the effect of various 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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Reviews

Halpert, G., and Sredni, B. (2014) The effect of the novel tellurium compound AS101 on autoimmune diseases, *Autoimmunity Rev* 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	2020-2022	Sheba Medical Center: Second chance: Improved drug delivery using gut-specific homing small extracellular vesicles for the treatment of inflammatory bowel diseases, Role: PI
2020-2021	Laboratory of Mosaic of Autoimmunity (LMA); Saint Petersburg State University; Role: Collaborator		



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CAR T Immunotherapy for Cancer and Beyond

Positions

Senior Scientist

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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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Zigler M, Shir A, Joubran S, Sagalov A, Klein S, Edinger N, Lau J, Yu SF, Mizraji G, **Globerson Levin A**, Sliwkowski MX, Levitzki A. HER2-Targeted Polyinosine/Polycytosine therapy inhibits tumor growth and modulates the tumor immune microenvironment. *Cancer Immunol Res*. 2016;4:688-97.

Grants

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





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The Coagulation Cascade: Hemostasis and Cellular Aspects

Position

Associate Professor, Faculty of Medicine

Head, TAU Amalia Biron Research Institute of Thrombosis and Hemostasis

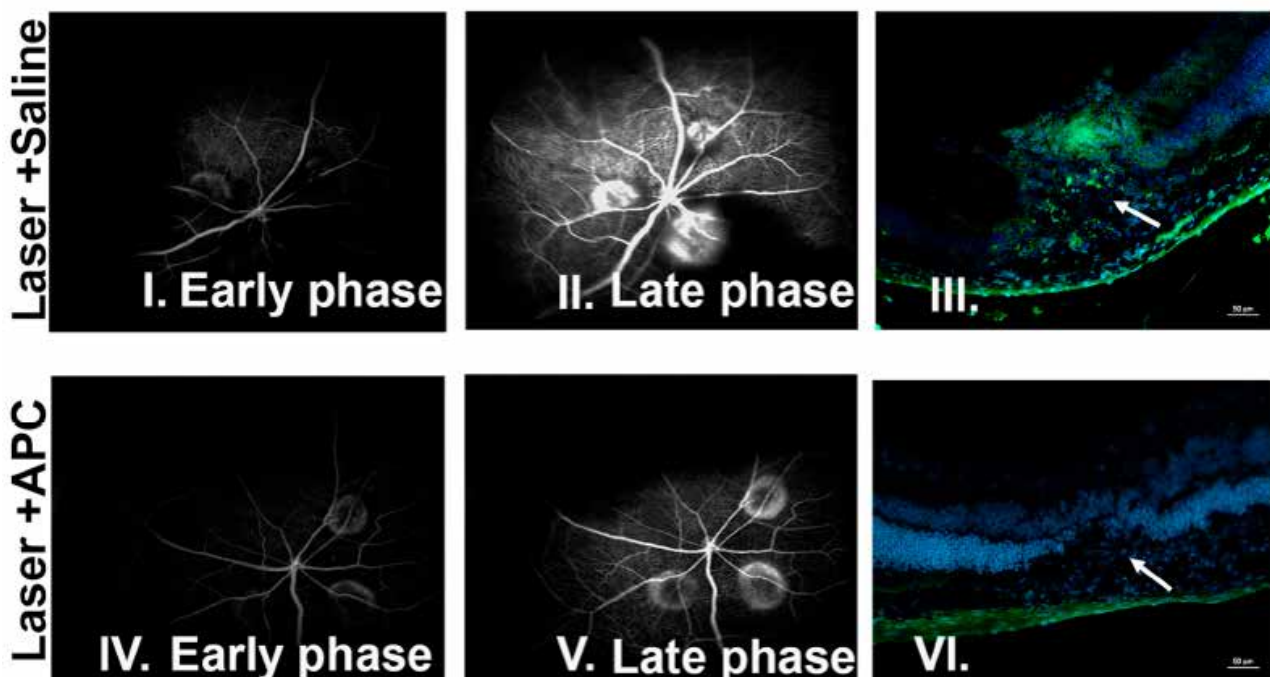
Research

Our research focuses upon the coagulation cascade and addresses two main topics:

Basic, clinical and translational evaluation of hemostasis among patients with bleeding disorders in order to define personalized treatment. There is no ultimate lab assay available in order to assess the hemostatic state of patients with bleeding disorders treated by various hemostatic agents or undergoing surgeries. Our studies focus on thrombin, the pivotal

factor in the coagulation cascade. Based on ex-vivo thrombin generation (TG) analysis, we are studying the ability of combined treatments, new drugs and innovative non- replacement approaches to induce hemostasis in patients' plasma. By exploring the coagulation cascade, we aim to predict the hemostatic state of patients, and to tailor personal therapies for patients with bleeding disorders. These studies also enable avoidance of hypercoagulability and potential thrombotic complications.

The coagulation system involvement in ocular pathologies. We explore the impact and significance of hemostatic pathways in the eye. We are focusing on ocular pathologies involving bleeding, impairment of blood retina barriers and growth of pathological blood vessels. Using cell cultures, an animal-based



Early and late fluorescein angiograph images of an eye with 3 laser spots treated with saline (I, II) or APC (IV, V) and images of histological sections labeled with FITC-dextran (green) and DAPI (blue) in saline (III) and APC (VI) treated eyes. Arrow indicates the laser spot area.

models and human samples we are trying to find a new therapeutic approach for ocular pathologies. Recently we found that the coagulation inhibitor Activated Protein C (APC) significantly inhibited choroidal neovascularization (CNV). Formation of CNV is a hallmark of age-related macular degeneration and a leading cause for blindness and our long-term goal is to develop a novel treatment for CNV.

Publications

Dan-Brezis I, Zahavi A, Axer-Siegel R, Nisgav Y, Dahbash M, Weinberger D, Ehrlich R, **Livnat T**. Inflammation, angiogenesis and coagulation interplay in a variety of retinal diseases. *Acta Ophthalmol*. 2019

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Dahbash M, Sella R, Megiddo-Barnir E, Nisgav Y, Tarasenko N, Weinberger D, Rephaeli A, **Livnat T**. The histone deacetylase inhibitor AN7, attenuates choroidal neovascularization in a mouse model. *Int J Mol Sci*. 2019; 20.

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Barg AA, Hauschner H, Luboshitz J, **Livnat T**, Straus T, Levy-Mendelovich S, Lubetsky A, Rosenberg N, Kenet G. From thrombasthenia to next generation thrombocytopenia: Neonatal alloimmune thrombocytopenia induced by maternal Glanzmann thrombasthenia. *Pediatr Blood Cancer*. 2018; 65:e27376.

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Grants

2019

Claire and Amédée Maratier Fund, Faculty of Medicine, Tel Aviv University. Activated protein C (APC) as a potential treatment for choroidal neovascularization (CNV); Is the anticoagulant activity necessary?



Dr. Shelly Tartakover Matalon, Ph.D.

Department of Internal Medicine, Faculty of Medicine, Tel Aviv University
Autoimmune Research Laboratory, Meir Medical Center



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Investigating Autoimmune Diseases: Progress Towards Personalized Medicine

Position

Senior Lecturer, Faculty of Medicine

Research

Our Laboratory focuses on autoimmune pathologies and especially in Systemic Sclerosis (Scleroderma), a connective-tissue disease characterized by vascular alterations and severe fibrosis. The Lab operates a biobank of more than 1100 sera and blood cells collected from rheumatic patients.

Research is conducted in several areas with the aim of promoting personalized medicine:

- 1) Discovering markers (such as young cells, autoantibodies and miRNAs) for evaluation, diagnosis and prediction of autoimmune diseases and their complications.
- 2) Understanding mechanisms underlying disease progression
- 3) Exploring the effectivity and mechanism of action of new treatments for autoimmune diseases.

Our laboratory work combines techniques of cellular and molecular biology. The studies are based on close collaborations between researchers and physicians, which promote access to human tissues and to up-to-date clinical approaches and novel strategies. The strength of the laboratory is its ability to combine in vitro experiments with primary cell cultures and the patients' blood samples with the patients' clinical / Laboratory data, to have a deeper understanding of the biological mechanisms involved in the different clinical complications.

Publications

Komemi O, Epstein Shochet G, Pomeranz M, Fishman A, Pasmanik-Chor M, Drucker L, **Tartakover Matalon S***, Lishner M*. Placenta conditioned extracellular matrix (ECM) prevents breast cancer cell attachment

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Naftali T, Bar-Lev Schleider L, Scklerovsky Benjaminov F, Konikoff FM, **Matalon ST**, Ringel Y. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial. *PLoS One*. 2021;16(2):e0246871.

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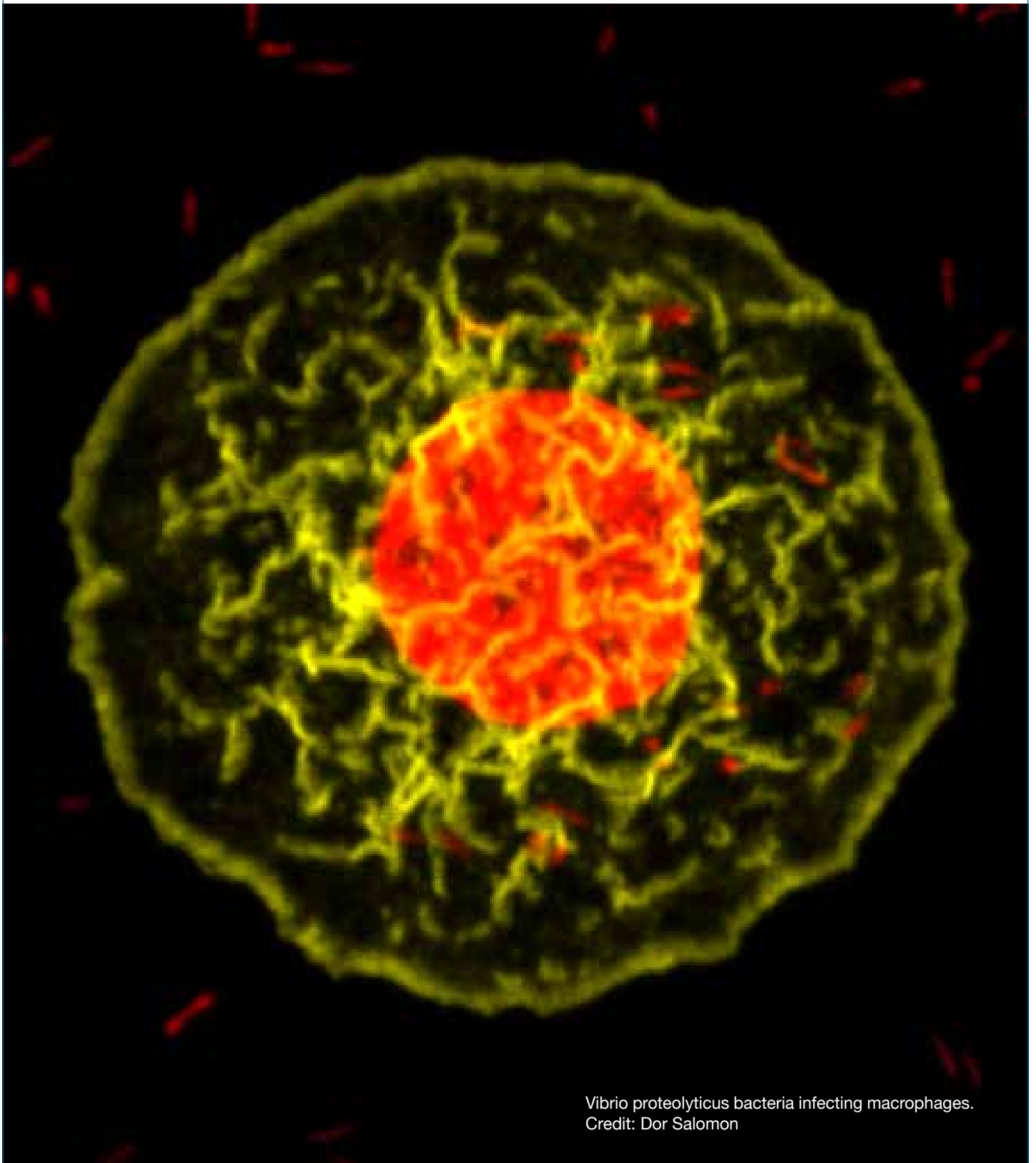
Pri-Paz Basson Y, Tayer-Shifman OE, Naser R, **Tartakover Matalon S**, Kimhi O, Gepstein R, Halperin T, Ziv-Baran T, Ziv A, Parikh R, Kivity S, Levy Y. Immunogenicity and safety of the mRNA-based BNT162b2 vaccine in systemic autoimmune rheumatic diseases patients. *Clin Rheumatol*. 2022;41(12):3879-3885

Kohon MY, Zaaroor Levy M, Hornik-Lurie T, Shalom A, Berl A, Drucker L, Yair L*, **Tartakover Matalon S***. $\alpha v \beta 3$ integrin as a linker between the development of fibrosis and thyroid hormones, *Int J Mol Sci*. 2023;24(10):8927.

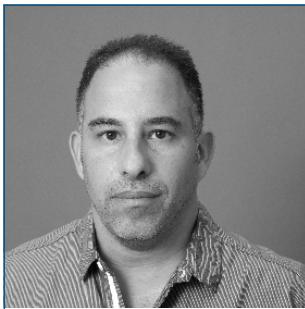
Grants

- | | |
|-----------|---|
| 2021-2023 | WSF & GILS Research Grant Program (World scleroderma foundation) In search of miRNAs that can identify and predict vascular disease in patients with Systemic Sclerosis |
| 2022-2023 | Chemomab: The effect of microenvironmental factors on endothelial cell dysfunction in systemic sclerosis: involvement of soluble and matrix embedded factors |

Infectious Diseases



Vibrio proteolyticus bacteria infecting macrophages.
Credit: Dor Salomon



Prof. Ohad Gal-Mor, Ph.D.

Infectious Diseases Research Laboratory,
Sheba Medical Center Department of Clinical
Microbiology and Immunology
Faculty of Medicine



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Studying the Molecular Basis of *Salmonella* Virulence and its Host-Pathogen Interactions

Positions

Head, Infectious Diseases Research Laboratory,
Sheba Medical Center.

Associate Professor, Department of Clinical
Microbiology and Immunology, Faculty of Medicine

Secretary, Israel Society for Microbiology.

Section Editor (Bacterial Pathogenesis), Virulence

Research

Our main research interests focus on the ubiquitous foodborne pathogen *Salmonella enterica* and the mechanisms this pathogen causes diseases, including the following subjects:

The role and function of *Salmonella* virulence factors in pathogenicity and host specificity.

Why and how different *Salmonella enterica* serovars (biotypes) vary in their host-specificity and clinical outcome (gastroenteritis, systemic or asymptomatic infections).

Virulence pathways regulation in *Salmonella* and regulatory response to physiological and environmental signals.

Mechanisms of population dynamics, emergence and evolution of new biotypes and the role of horizontal gene transfer in these events.

The molecular basis of unusual invasive and persistent *Salmonella* infections.

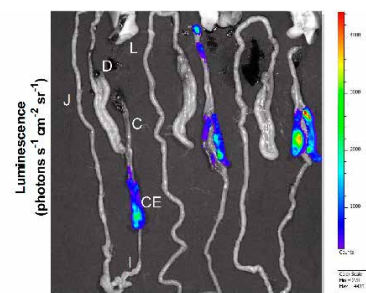
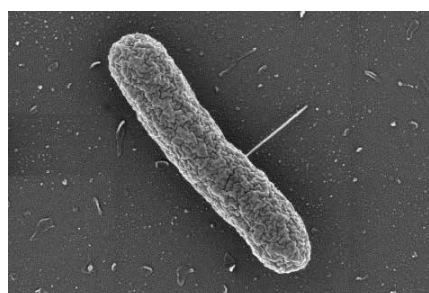
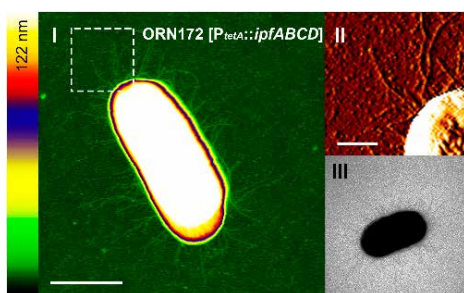
Publications

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Suwandi A, Galeev A, Riedel R, Sharma S, Seeger K, Sterzenbach T, García Pastor L, Boyle EC, **Gal-Mor O**, Hensel M, Casadesús J, Baines JF, Grassl GA. Std fimbriae-fucose interaction increases *Salmonella*-induced intestinal inflammation and prolongs colonization. PLoS Pathog. 2019;15:e1007915.

Aviv G, Cornelius A, Davidovich M, Cohen H, Suwandi A, Galeev A, Steck N, Azriel S, Rokney A, Valinsky L, Rahav G, Grassl GA, **Gal-Mor O**. Differences in the expression of SPI-1 genes pathogenicity and epidemiology between the emerging *Salmonella enterica* serovar Infantis and the model *Salmonella enterica* serovar Typhimurium. J Infect Dis. 2019;220:1071-1081.

Gal-Mor O. Persistent Infection and long-term carriage of typhoidal and nontyphoidal salmonellae. Clin Microbiol Rev. 2018;32(1).



(A) Imaging of the Ipf fimbriae of *Salmonella* Infantis using atomic force microscopy (AFM). (B) Imaging of the type IV secretion system using scanning electron microscopy (SEM). (C) Spatial expression of *ipf* genes in *S. Infantis* during infection in the chicken model.

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Aviv G, Rahav G, **Gal-Mor O**. Horizontal Transfer of the *salmonella enterica* serovar infantis resistance and virulence plasmid pesi to the gut microbiota of warm-blooded hosts. *mBio*. 2016;7(5).

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Grants

2019-2021	Research Cooperation Lower Saxony – Israel (The Volkswagen Foundation).
2019-2020	Israel Ministry of Science & Technology. Israel-Italy Collaboration on Microgravity Research (Antimicrobial Resistance Gene Transfer in Microgravity).
2019-2022	German-Israeli Foundation (GIF) for Scientific Research and Development
2018-2021	Joint Research Program of ISF-Broad Institute



Dr. Michal Mandelboim, Ph.D.

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Department of Epidemiology and Preventive
Medicine, School of Public Health, Faculty of
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Epidemiology of Respiratory Viruses

Positions

Assistant Professor, Epidemiology and Preventive
Medicine

Head, National Influenza and Other Respiratory
Viruses, Central Virology Laboratory, Ministry of Health

Research

We study Influenza, RSV, Adeno, hMPV, Parainfluenza, and Corona viruses, including MERS and the new corona virus nCoV 2019. Our laboratory is part of the World Health Organization (WHO) National Influenza Center (NICs) global network. As a national center, our lab is involved both in routine diagnostic and epidemiological work and in research and development, focusing on pathogenesis and epidemiology of respiratory viruses, and on development and evaluation of laboratory assays, vaccines and anti-viral drugs. We investigate several respiratory viruses in particular. These include: Influenza (including the pandemic influenza virus H1N1pdm), HMPV, MERS, SARS, nCoV 2019 and RSV.

Publications

Glatman-Freedman A, Pando R, Sefti H, Omer I, Rosenberg A, Drori Y, Nemet I, Mendelson E, Keinan-Boker L, **Mandelboim M**, Israeli Influenza Surveillance Network. Predominance of a drifted Influenza A (H3N2) clade and its association with age-specific influenza vaccine effectiveness variations, influenza season 2018-2019. *Vaccines (Basel)*. 2020;8(1).

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Kustin T, Ling G, Sharabi S, Ram D, Friedman N, Zuckerman N, Bucris ED, Glatman-Freedman A, Stern A, **Mandelboim M**. A method to identify respiratory virus infections in clinical samples using next-generation sequencing. *Sci Rep*. 2019;9:2606.

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Molecular Epidemiology of Human Viruses with Focus on HIV and Viral Hepatitis

Positions

Senior Scientist, Epidemiology and Preventive
Medicine Faculty of Medicine, Faculty of Medicine

Director, National HIV and Viral Hepatitis Reference
Laboratory; Head, Clinical Virology Laboratory, Central
Virology Laboratory, Israel Ministry of Health, Tel
Hashomer

Research

We study the molecular and clinical epidemiology of human viruses with focus on blood borne viruses including HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), hepatitis E virus (HEV) and also parvovirus B19 (B19). Recently we are also studying human papilloma viruses (HPV) especially at target populations such as men having sex with men (MSM) who are either HIV positive or negative. We focus on developing and implementation of new molecular or serological based tools for diagnosis of human viruses. We monitor the circulation and presence of HAV and HEV in Israel. We establish non-invasive biomarkers for monitoring of disease progression especially for HBV and HDV, regularly perform molecular resistance analysis of HIV, HCV and HBV patients following treatment failure, and maintain a national data base of our all results, enabling in-depth epidemiological research.

Publications

Manor Y, Lewis M, Ram D, Daudi N, **Mor O**, Savion M, Kra-Oz Z, Shemer Avni Y, Sheffer R, Shouval D, Mendelson E. Evidence for Hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. *J Infect Dis.* 2017;215(4):574-580.

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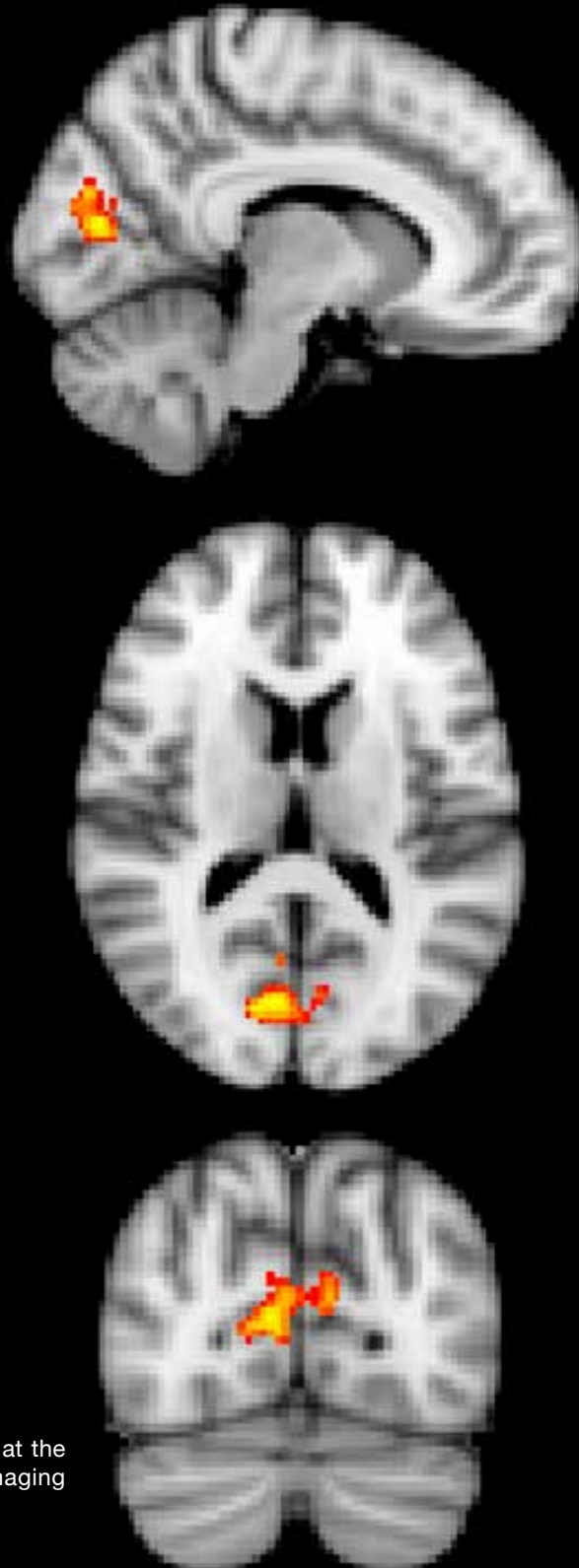
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Grants

2022 Recanati Foundation for Medical Research

Neurological & Psychiatric Diseases



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



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Mechanisms of Stress Vulnerability to Develop Post-Stroke Cognitive and Affective Deterioration

Positions

Senior Lecturer, Faculty of Medicine

Head of research group and lab: Focus on Stroke and Vascular Dementia, TASMC

Research

We study neuro-psychiatric complications after stroke. Stroke survivors are at high risk of developing a wide range of psychiatric symptoms: depression, anxiety, dementia and stress-related symptoms, which contribute significantly to poor recovery.

We conduct both translational and interventional clinical studies, in search for prodromal biomarkers for vulnerability to develop post-stroke dementia and affective deterioration, as well as novel therapeutic options.

In the last two years, we have founded a pioneer proof-of-concept trial funded by the Alzheimer's Association and the Gates Foundation. In this multi-center (five stroke centers in Israel) Phase-II trial we are investigating the potential of the licensed drug Maraviroc, a CCR5-antagonist, in preventing progression to vascular dementia. This interventional study is based on genetic and clinical results from our previous longitudinal TABASCO study. We investigate the hypothesis that blocking CCR5 modulate signaling cascades implicated in memory and in depression.

Recently, we have initiated another two interventional studies investigating Maraviroc in post-stroke depression and in major depression, as well as experimental model for blocking CCR5 in depression.

Publications

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Grants

2020-2024	The Alzheimer's Association and the Gates Foundation
2022-2025	Chief Scientist Office - Ministry of Health, Israel
2023-2026	Ministry of Innovation, Science & Technology, Division of Planning & Development
2023-2024	The Brain Division, Tel Aviv Medical Center
2023-2024	The Israel National Institute for Health Policy Research



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

Positions

Professor, 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

Associate Editor, Journal of NeuroEngineering & Rehabilitation

Associate Editor, Journals of Gerontology: Medical Sciences

Editorial Board, Gait & Posture

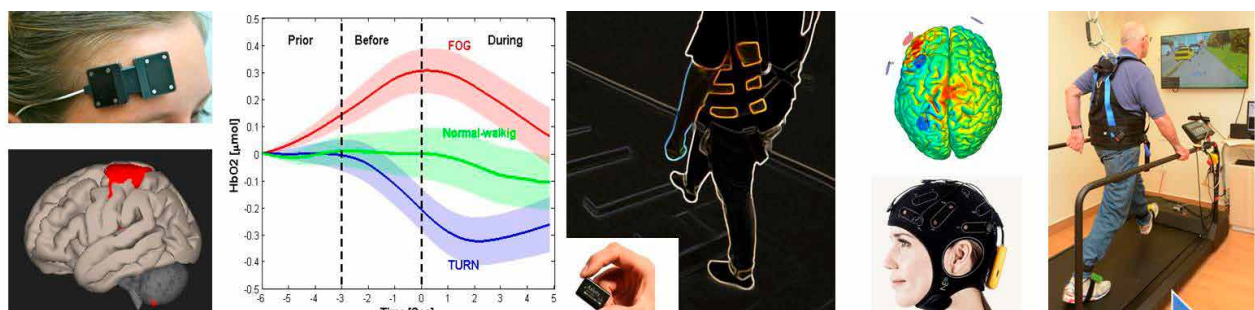
Review Editor in Movement Disorders, Frontiers in Neurology

American Federation of Aging Research's National Scientific Advisory Council

Task force member, Task Force on Global Guidelines for Falls in Older Adults

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 achieve 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



Mechanisms

Assessment

Treatment

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

includes the development of new “bio-markers” that can be used for early 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 negotiating 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

Ben AE, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Halleli H, Shopin L, Auriel E, Giladi N, Mike A, Halevy A, Weiss A, Mirelman A, Bornstein NM, **Hausdorff JM**. Gait measures as predictors of poststroke cognitive function: evidence from the TABASCO study. *Stroke* 46:1077-1083; 2015.

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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)

2016-2019 National Multiple Sclerosis Society, Virtual Reality-treadmill combined intervention for enhancing mobility and cognitive function in patients with Relapsing-Remitting Multiple Sclerosis (JM Hausdorff, PI)

2016-2019 Ministry of Science, Technology and Space, Development and validation a Smartphone-based system for improving gait, cognition and socialization in elderly (A Mirelman 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)

2016-2019 US-Israel Bi-National Science Foundation, Enhancing brain activity to improve dual task walking in older adult fallers: a functional near-infrared spectroscopy and transcranial direct current stimulation study (JM Hausdorff Israeli PI, L Lipsitz US PI).

2017-2019 Israel Science Foundation, The role of the frontal lobe in obstacle negotiation in patients with Parkinson's disease (JM Hausdorff, 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 Reference 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)



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Position

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Research

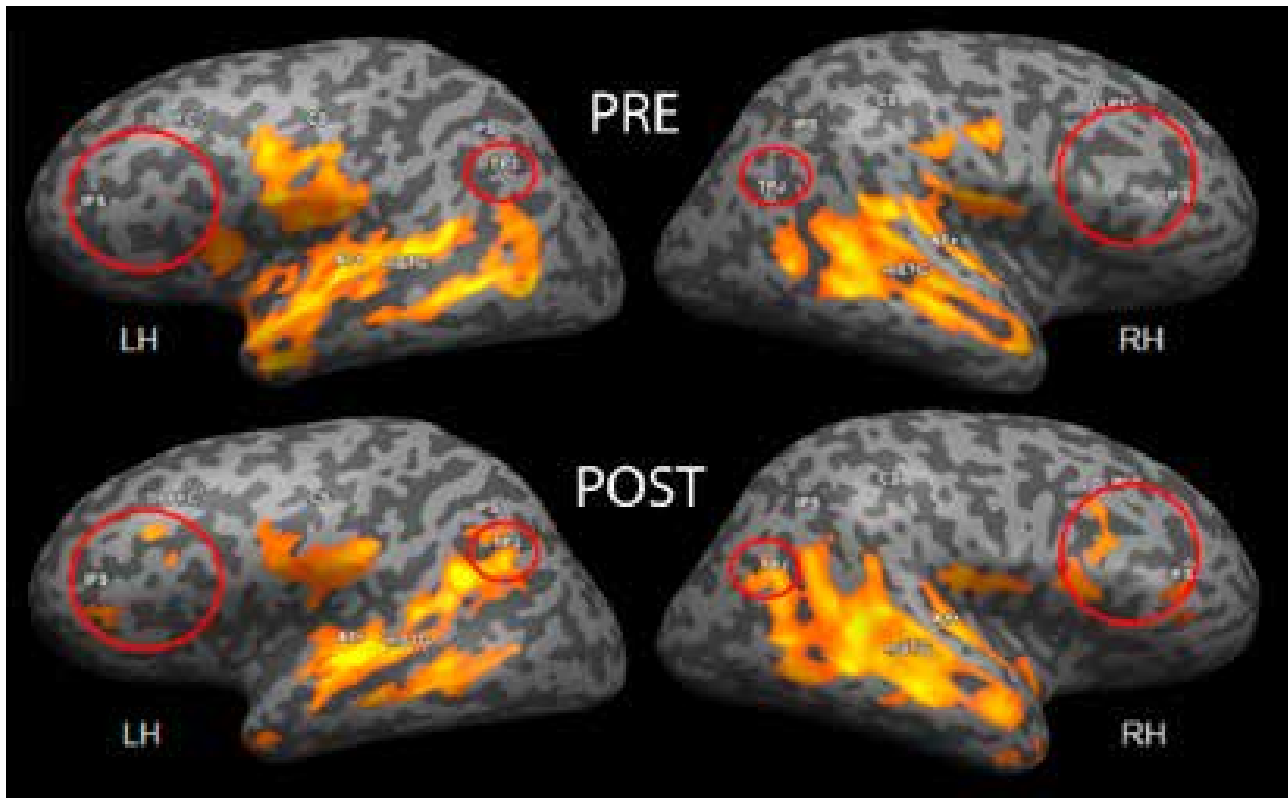
We focus on a multi-modal investigation of the human cognitive experience, using functional and structural brain imaging, behavioral rating and physiological measures. The main line of research is investigation of levels of information processing in healthy older adults and participants with amnesic mild cognitive impairment (a-MCI). In particular, we study the neuroprotective role of physical exercise and its physiological adaptations in older population and in individuals with a-MCI.

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Grants

2018-2022 Israel Science Foundation



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Functional Neuroimaging Laboratory

Positions

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Research

The functional neuroimaging lab focuses on the diagnosis and prognosis of brain pathologies, in particular the way the brain reorganizes due to acute and chronic neuro-pathologies and how such reorganization in both brain structure and function corresponds with cognitive outcome.

Our research applies multimodal neuroimaging acquisition and analytical techniques (structural, functional and connectivity) together with demographic, clinical, cognitive and genetic data aimed to identify disrupted brain networks and to improve prediction of prognosis in clinical populations such as traumatic brain injury, dementia, type-2 diabetes, and depression.

The objective of our research is to translate into clinical practice. Our translational research aims to improve

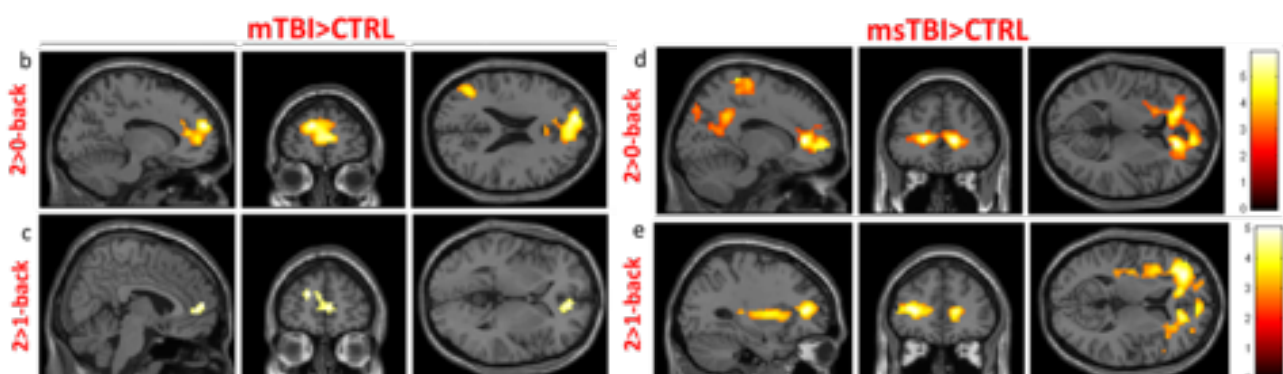
the diagnosis and prediction of brain pathology's progression, to plan medical and rehabilitative interventions for the well-being of patients with neuropathologies.

Our lab also provides support for all stages of presurgical clinical fMRI assessment, including paradigm building, fMRI scanning and data analysis. Presurgical clinical fMRI is used for functional mapping in patients with epilepsy and brain tumors in order to localize brain function.

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*. 2016; 34:1466-1472.

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Reviews

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

Grants

2016-2021	NIA R01 AG051545, Hyperbaric oxygen therapy for cognition in diabetic elderly at high dementia risk. Co-investigator
2018-2020	Israel Innovation Authority- Magneton Grant, Integration of eye tracking, BNA technologies and resting-state fMRI for predicting successful treatment in depression patients. Principal Investigator
2019-2020	Innovation Center Grant, Sheba Medical Center , Multimodal Connectome in Neuropathologies. Principal Investigator
2019-2020	Research Authority, Sheba Medical Center, "Second chance grant", MISTIC-Multimodal Imaging Study in Traumatic Brain Imaging in Children. Principal Investigator



Dr. Inbal Maidan, Ph.D.

Neurology and Neurosurgery
Faculty of Medicine



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Investigating the Underlying Neural Mechanisms that Contribute to Changes in Function

Positions

Lecturer, Faculty of Medicine

Research

We aim to investigate, identify, and quantify the underlying neural mechanisms that contribute to changes in mobility among older adults, people with Parkinson's disease (PD), and others with neurodegenerative disease. We focus on developing and applying several complementary neuroimaging methods as EEG and fNIRS to evaluate the compensatory brain mechanisms that are activated to enable mobility and function in the presence of aging and neurodegeneration. Our goals are to better understand the role of the CNS in every-day life function, to identify biomarkers reflecting disease, and to evaluate the utility of these biomarkers in identifying individuals with a high risk of developing neurodegenerative disease. Our research has important impacts on personalized medicine as it promises to describe the person's abilities and the compensatory mechanisms utilized on an individual level. This in turn could enable the tailoring of specific gait interventions, providing personalized medicine approaches to the benefit of the individual patient and the healthcare system.

Publications

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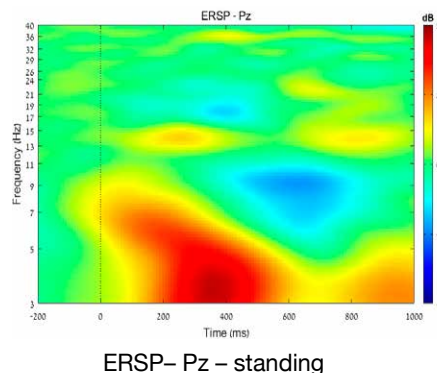
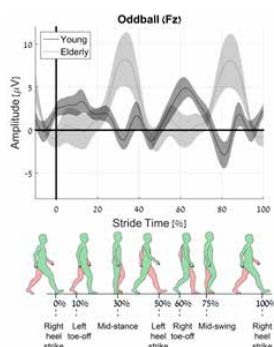
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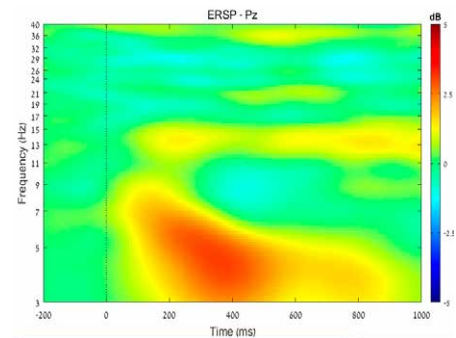
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ERSP- Pz – standing



ERSP- Pz – walking

A. Prefrontal cortex activation during obstacle negotiation: what's the effect size and timing? *Brain and Cognition* 2018; 122:45-51.

Maidan I, Nieuwhof F, Bernad-Elazari H, Bloem BR, Giladi N, Hausdorff JM, Claassen JAHR, Mirelman A. Evidence for differential effects of 2 forms of exercise on prefrontal plasticity during walking in Parkinson's disease. *Neurorehabil Neural Repair* 2018; 32:200-208.

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Maidan I, Fahoum F, Shustak S, Gazit E, Patashov D, Tchertov D, Giladi N, Hausdorff JM, Mirelman A. Changes in event-related potentials during dual task walking in aging and Parkinson's disease. *Clin Neurophysiol* 2019; 130:224-230.

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Possti D, Fahoum F, Sosnik R, Giladi N, Hausdorff JM, Mirelman A, **Maidan I**. Changes in the EEG spectral power during dual-task walking with aging and Parkinson's disease: initial findings using Event-Related Spectral Perturbation analysis. *J Neurol*; 2021;268:161-168.

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Sosnik R, Danziger-Schragenheim S, Possti D, Fahoum F, Giladi N, Hausdorff JM, Mirelman A, **Maidan I**. Impaired Inhibitory control during walking in Parkinson's Disease patients: An EEG study. *J Parkinsons Dis*. 2021.

Grants

2019-2020 Fugelnest Foundation

2020-2021 Parasol Foundation



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Laboratory for Early Markers of
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Investigating Early Markers of Neurodegeneration

Positions

Associate Professor, Neurological Department, School of Medicine

Faculty Member, Sagol School of Neuroscience

Director, Laboratory for Early Markers of Neurodegeneration, Tel Aviv Sourasky Medical Center

Research

Research in the LEMON lab is performed in a clinical setting. Our mission is to identify new markers of ageing and neurodegeneration. More specifically, we aim to better understand the pathological process of neurodegeneration and its progression. We investigate clinical, biological and neuronal markers using different tools such as neural-imaging (e.g., MRI, fMRI, EEG and fNIRS) and body fixed sensors with the overall aim of identifying sensitive measures that can quantify progression and predict neurodegeneration in prodromal and healthy individuals and populations at risk due to genetic mutations. In addition, we are exploring measures of successful ageing, ways to better understand the interplay between motor and cognition functions, methods to evaluate reserve capacity in health and disease and potential behavioral modifications that have the potential to increase the likelihood for successful ageing.

Publications

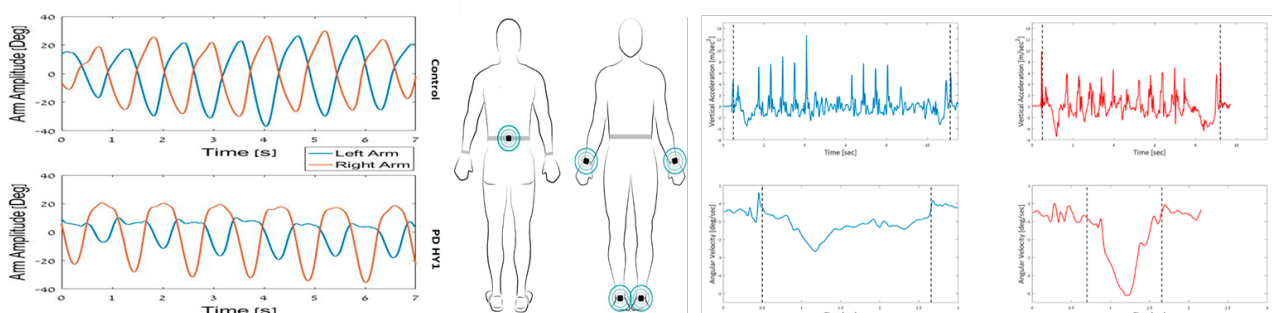
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Subtle changes in acceleration as collected by wearable sensors. The signals show different patterns of movement in a person with early stage Parkinson's disease and a healthy subject at risk for developing Parkinson's disease as compared to healthy age matched controls. Features such as these are explored in the context of additional measures (imaging and biological) to construct a cumulative predictive model of disease, disease progression and ageing.

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Maidan I, Zifman N, Hausdorff JM, Giladi N, Levy-Lamdan O, **Mirelman A**. A multimodal approach using TMS and EEG reveals neurophysiological changes in Parkinson's disease. *Parkinsonism Relat Disord*. 2021;89:28-33.

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Grants

2019-2024	European Commision- H2020 Program
2020-2024	US Department of Defense (DOD)
2022-2024	JPND Cognitive Propagation
2022-2025	Michael J Fox Foundation
2022-2025	Ministry of Justice (Ezvonot)
2023-2026	Michael J Fox Foundation



Dr. Michal Taler, Ph.D.

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Investigating the Biological Basis of Severe Mental Illness

Positions

Head, Pediatric Molecular Psychiatry Lab, Sheba Medical Center, Faculty of Medicine

Senior Lecturer, Faculty of Medicine

Research

Our laboratory, situated within the Sheba Medical Center, operates under the leadership of Prof. Doron Gothelf as part of the Division of Child and Adolescent Psychiatry. Our primary focus is utilizing molecular and genetic methodologies to enhance our understanding of the biological underpinnings associated with various psychiatric disorders and general pathological aspects of mental illness.

Specifically, our research delves into investigating the intricate relationship between the immune system, blood-brain barrier (BBB) permeability, oxidative stress (OS), 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.

Our lab is located at the heart of the intersection between basic science and clinical practice.

Extreme Childhood Irritability (ECI), characterized by agitation and violent outbursts, is one of the most prevalent reasons for children being referred to psychiatric care. It manifests across multiple childhood psychiatric disorders. In our laboratory, we assess various aspects of the immune system,

BBB permeability, OS, as well as the glutamate and GABA ratio in young children.

Our laboratory enjoys a prime position, as it's strategically located at the intersection of basic science research and clinical practice. Our affiliation with the Division of Child and Adolescent Psychiatry means that all our investigations revolve around human tissues, predominantly blood samples, accompanied by meticulous clinical observations. Our team consists of experienced clinical researchers and senior neuroscientists who work collaboratively, fostering a multidisciplinary approach to our research endeavors.

Publications

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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.

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.

Krivoy A, Hoshen M, Fischel T, **Taler M**, Segev A, Weizman A. There is room for improvement: the rate of clozapine use among patients with schizophrenia in Israel [Article in Hebrew]. *Harefuah*. 2019;158(7):449-452.

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. pii: S0889-1591(19)31330-3.

Erez T, Yirmiya ET, Ehud Mekori-Domachevsky E, Ronnie Weinberger R, Michal **Taler M**, Miri Carmel M, Doron Gothelf D. Exploring the potential association among sleep disturbances, cognitive impairments and immune activation in 22q11.2 Deletion Syndrome. *Am J Med Genet A*. 2020;182(3):461-468.

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 pro-inflammatory cytokine IL-6. *Int Clin Psychopharmacol*. 2020.

Taler M, Aronovich R, Henry Hornfeld S, Dar S, Sasson E, Weizman A, Hochman E. Regulatory effect of lithium on hippocampal blood-brain barrier integrity in a rat model of depressive-like behavior. *Bipolar Disord*. 2020;23:55-65

Taler M, Mekori-Domachevsky E, Vergaalen E, Claes S, Serur Y, Dar S, Levy-Shraga Y, Weizman A, Swillen A, Gothelf D. Blood brain barrier permeability increases with age in individuals with 22q11.2 deletion syndrome. *World J Biol Psychiatry* 2021:1-26

Taler M, Gil-Ad I, Brenner I, Hornfeld SH, Weizman A. Complex effects of sertraline and citalopram on in vitro murine breast cancer proliferation and on in vivo progression and anxiety level. *Int J Mol Sci*. 2022;23(5):2711

Hochman E, **Taler M**, Flug R, Gur S, Dar S, Bormant G, Blattberg D, Nitzan U, Krivoy A, Weizman A. Serum claudin-5 levels among patients with unipolar and bipolar depression in relation to the pro-inflammatory cytokine tumor necrosis factor-alpha levels. *Brain Behav Immun*. 2023;109:162-167.

Matalon, N., Vergaalen, E., Shani, S., Dar, S., Mekori-Domachevsky, E., Segal-Gavish H., Hochberg, Y., Gothelf, D., Swillen, A., **Taler, M**. The relationship between oxidative stress and psychotic disorders in 22q11.2 deletion syndrome. *Brain Behav Immun*. 2023, 114:16-21.

Grants

2022–2024	National Institute of Psychobiology in Israel
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Dr. Ariel Tankus, Ph.D.

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Faculty of Medicine



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The Neuronal Encoding of Human Speech

Positions

Senior Lecturer, Faculty of Medicine and Sagol School of Neuroscience

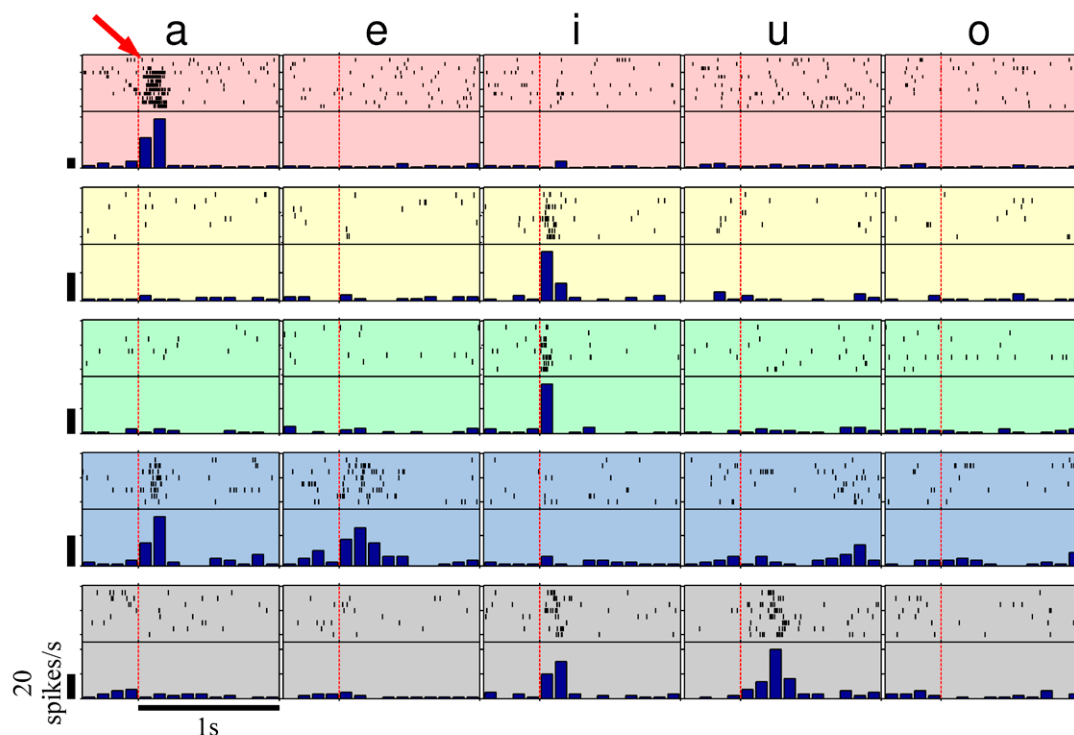
Senior Researcher and Neurophysiologist, Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center ("Ichilov")

Research

The goal of our research is to understand how speech is represented in the human brain at the single neuron level in health and neurological disorders. We take advantage of a unique clinical "opportunity" to work with neurosurgical patients undergoing implantation of electrodes for clinical reasons. Experiments are

conducted intraoperatively with awake patients with movement disorders or in the ward, with epilepsy patients. We investigate multiple levels of speech constructs, for example the acoustic, phonetic and phonological levels, during the production, perception and imagery of speech. . We focus on three aims:

1. Understanding the encoding of speech features by single neurons (see Figure 1 for an example).
2. Exploring the degradation in the neuronal representation of speech due to neurological disorders, for example in Parkinson's disease.
3. Developing brain-machine interfaces for restoring speech faculties in completely paralyzed persons



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).

by decoding their neuronal activity (i.e., inferring speech contents solely from neuronal activity).

Our research is a first step towards therapeutic intervention to alleviate speech disorders in Parkinson's disease and avoid speech-related side effects of deep brain stimulation. Our studies therefore bears enormous potential to greatly improve the quality of life of millions of people around the globe.

Publications

O. Perez, R. Mukamel, **A. Tankus**, Y. Yeshurun and I. Fried: Preconscious prediction of a driver's decision using intracranial recordings. *Journal of Cognitive Neuroscience*, 27(8):1492–1502, 2015.

T. Iluz, A. Weiss, E. Gazit, **A. Tankus**, M. Brozgal, M. Dorfman, A. Mirelman, N. Giladi, J.M. Hausdorff: Can a body-fixed sensor reduce Heisenberg's uncertainty when it comes to the evaluation of mobility? Effects of aging and fall risk on transitions in daily living. *Journals of Gerontology: Medical Sciences*, 1–9, 2015.

A. Tankus. Exploring human epileptic activity at the single neuron level. *Epilepsy & Behavior*, 58:11–17, 2016.

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.

A. Tankus, I. Fried. Degradation of neuronal encoding of speech in the subthalamic nucleus in Parkinson's disease. *Neurosurgery*, 84:378–387, 2019.

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*, 130:1835–1840, 2019.

Chapter

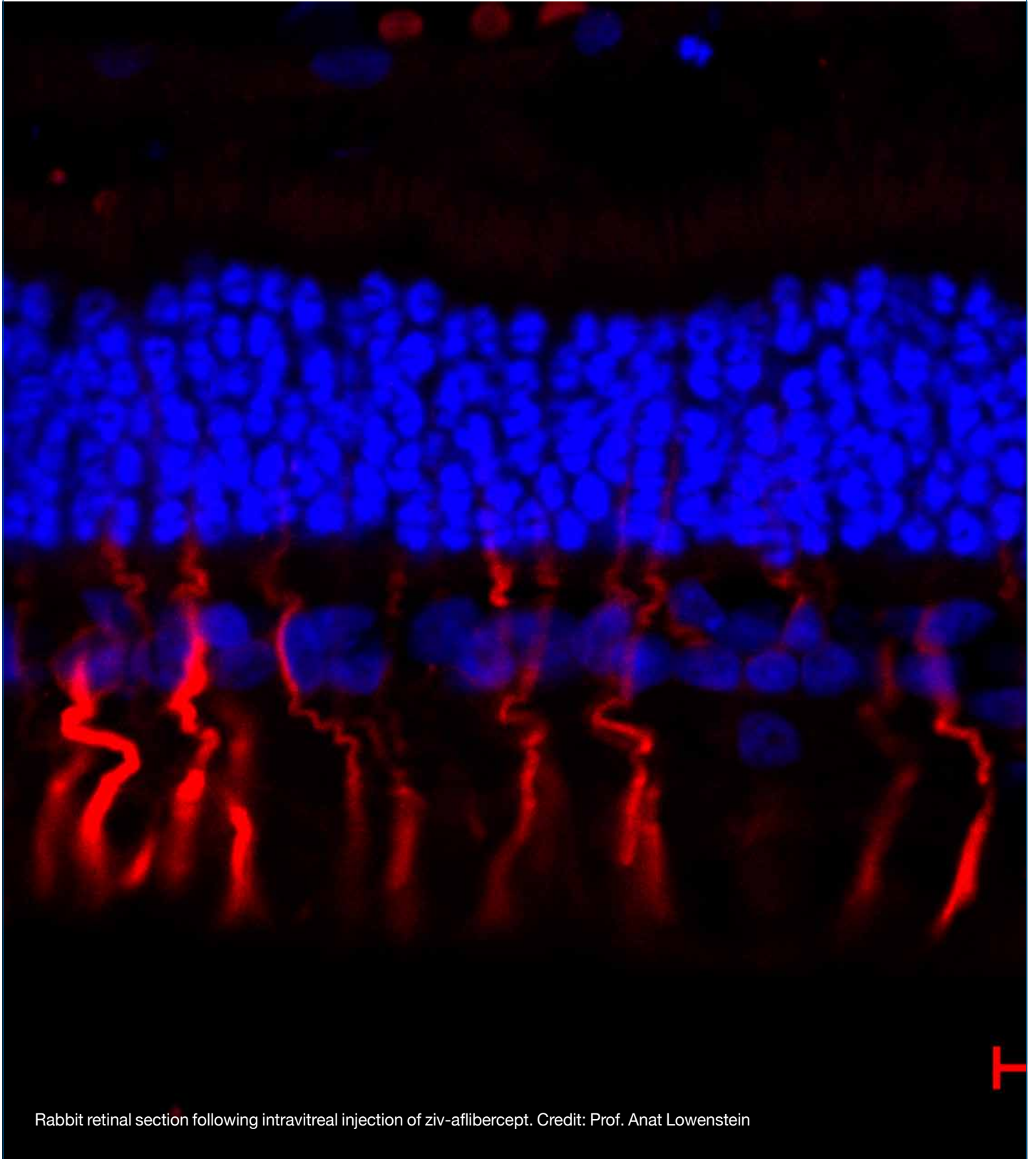
A. Tankus and J.M. Hausdorff. Deep brain stimulation in Parkinson's disease: effects on gait and postural control. In F.A. Barbieri and R. Vitorio, editors, *Locomotion and Posture in Older Adults – The Role of Aging and Movement Disorders*, Springer, Chapter 25, pages 385–396, 2017.

Grants

2019 – 2020 Speech Representations by Single Neurons in the Thalamus, GPi and STN and Their Degradation due to Parkinson's Disease, Dr. Herman Schauder Research Fund

2019 – 2020 Synthetic Lethality for Personalized Therapy-based Stratification In Acute Leukemia, EU (EraPerMed) grant (Israeli partner: Ministry of Health).

Ophthalmology



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



Dr. Ifat Sher, Ph.D.

Goldschleger Eye Institute, Faculty of Medicine
Sheba Medical Center, Tel Hashomer



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health.gov.il

Neurodegeneration in the Eye and Brain

Positions

Head, Restorative Retinal Research Laboratory,
Goldschleger Eye Institute, Sheba Medical Center,
Tel Hashomer

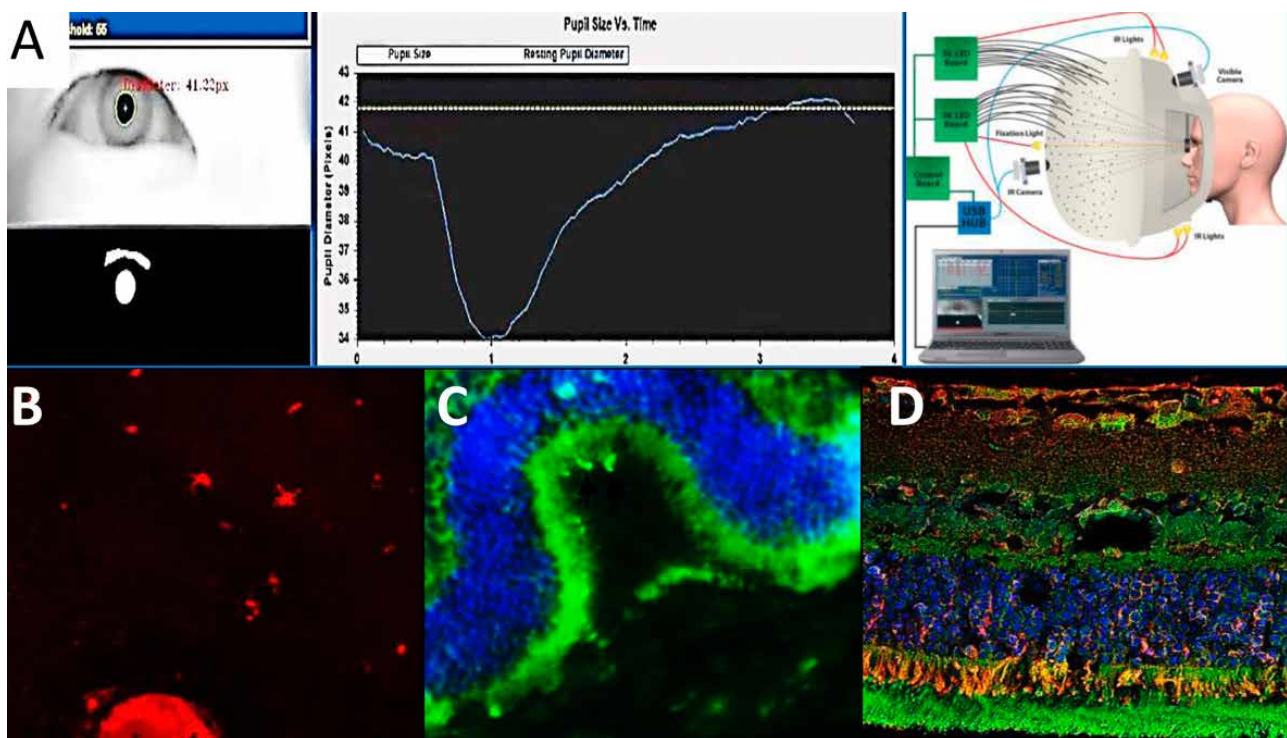
Member, Animals in Research Committee (ARC) of
Association for Research in Vision and Ophthalmology
(ARVO)

Co-Founder, Epitech-Mag Ltd., Israel

Co-Founder, Everads Therapy Ltd., Israel

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



(A) Chromatic pupilloperimetry – an innovative technology for noninvasive measurement of spatial & temporal changes in neuroretinal circuitry (B) Migration of retinal microglial cells into the sub-retina in a retinal degeneration mouse model; (C) Retinal cultures for semi-high throughput drug screening; (D) Expression patterns of coagulation factors in the neuro-retina in health and disease conditions.

delivery and diagnostic platforms for studying these leading incurable diseases.

Current research projects include:

- Neuroretinal circuitry function in Multiple Sclerosis and Parkinson's disease
- The immune system in retinal degeneration
- Semi-high throughput drug screening for neuroretinal degeneration
- The coagulation system in diabetic retinopathy and retinal degeneration

Publications

Rotenstreich Y, Tzameret A, Kalish SE, Belkin M, Meir A, Treves AJ, Nagler A, **Sher I**. A novel system for minimally invasive transplantation of bone marrow derived stem cells as a thin layer in the subretina and extravascular spaces of the choroid for treatment of retinal degeneration. *Harefua*. 2015; 154(2):84-88.

Levy I, **Sher I**, Corem-Salkmon E, Ziv O, Meir A, Treves AJ, Nagler A, Kalter-Leibovici O, Margel S, Rotenstreich Y. Bioactive magnetic near Infra-Red fluorescent core-shell iron oxide/human serum albumin nanoparticles for controlled release of growth factors for augmentation of human mesenchymal stem cell growth and differentiation. *J Nanobiotech*. 2015; 13:34.

Tzameret A, **Sher I**, Belkin M, Treves AJ, Meir A, Nagler A, Levkovitch-Verbin H, Rotenstreich Y*, Solomon AS*. (* Equal contribution, corresponding authors) Epiretinal transplantation of human bone marrow mesenchymal stem cells rescues retinal and vision function in a rat model of retinal degeneration. *Stem Cell Res*. 2015;15(2):387-94.

Chibel R, **Sher I**, BenNer D, Mahajna M, Achiron A, Haj-Yahia S, Skaat A, Berchenko Y, Oberman B, Kalter-Leibovici O, Freedman L, Rotenstreich Y. Chromatic multifocal pupillometer for objective perimetry and diagnosis of patients with Retinitis Pigmentosa. *Ophthalmology*. 2016 (123):1898-1911.

Rotenstreich Y, Tzameret A, Kalish SA, Bubis Ettel, Belkin M, Moroz I, Rosner M, Levy I, Margel S, **Sher I**. A minimally invasive adjustable-depth blunt injector for delivery of pharmaceuticals into the posterior pole. *Acta Ophthalmologica*. 2017;95(3):e197-e205.

Tzameret A, Kalish SA, **Sher I**, Meir A, Levy I, Margel S, Moroz I, Rosner M, Treves AJ, Nagler A, Belkin M, Rotenstreich Y. Long term-safety of transplantation of human bone-marrow mesenchymal stem cells in the extravascular spaces of the choroid of rabbits. *Stem Cells International* 2017:4061975.

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Sher I, Tzameret A, Szalapak AM, Carmeli T, Derazne E, Avni-Zauberman N, Marcovich AL, Simon GB, Rotenstreich Y. Multimodal assessment of corneal erosions using optical coherence tomography and automated grading of fluorescein staining in a rabbit dry eye model. *Transl Vis Sci Technol*. 2019;8(1):27.

Bubis E, **Sher I**, Skaat A, Sharvit-Ginon I, Szalapak AM, Moroz I, Kalter-Leibovici O, Rotenstreich Y. Blue autofluorescence fundus imaging for monitoring retinal degeneration in Royal College of Surgeons Rats. *Transl Vis Sci Technol*. 2019;8(1):26.

Tzameret A, **Sher I**, Edelshtain V, Belkin M, Kalter-Leibovici O, Solomon AS, Rotenstreich Y. Evaluation of visual function in Royal College of Surgeon rats using a depth perception visual cliff test. *Vis Neurosci*. 2019;36:E002.

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after cataract extraction surgery. *J Glaucoma*. 2019;28(8):727-731.

Ben Ner D, **Sher I**, Hamburg A, Mhajna MO, Chibel R, Derazne E, Sharvit-Ginon I, Pras E, Newman H, Levy J, Khateb S, Sharon D, Rotenstreich Y. Chromatic pupilloperimetry for objective diagnosis of Best vitelliform macular dystrophy. *Clin Ophthalmol*. 2019;13:465-475.

Sher I, Tzameret A, Goldberg Z, Bubis E, Avni-Zauberman N, Kalter-Leibovici O, Marcovich AL, Ben Simon G, Rotenstreich Y. Repetitive magnetic stimulation protects corneal epithelium in a rabbit model of short-term exposure keratopathy. *Ocul Surf*. 2020;18(1):64-73

Peled A, Afek A, Twig G, Pras E, Rotenstreich Y, **Sher I**, Derazne E, Tzur D, Gordon B. Myopia and childhood migration: A study of 607862 adolescents. *Ophthalmology*. 2019.

Grants

2018-2021 Israeli Ministry of Science and Technology, The association between gut and oral microbiota and retinitis pigmentosa phenotype, Co-I

2019 – 2022 Israeli Ministry of Science and Technology, Novel treatments for Retinitis Pigmentosa, Co-I

Pediatrics





Dr Laurence Elbaz Mangel, PhD

Department of Neonatology, Dana Dwek
Children's Hospital, Tel-Aviv Sourasky
Medical Center



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Human Milk Research

Position

Senior Researcher

Research

The ongoing research at our department focuses on Human Milk (HM) and lactation. HM is dynamic and provides macronutrients (fats, carbohydrates and proteins), micronutrients (vitamins and minerals) and non-nutritive bioactive factors (Human milk oligosaccharides, immunoglobulins, cells, growth factors, etc.) that promote survival and healthy development of the infant. Our laboratory is equipped with a Human Milk Analyzer from MIRIS.

We study the influence of various environmental, maternal and neonatal variables upon HM macronutrient composition. These include collection and storage conditions of HM, nasogastric-tube-feeding, seasonal variation, fenugreek diet supplementation, pre-pregnancy BMI, gestational diabetes mellitus, maternal anxiety, physical activity and age, between-breast differences, length of lactation, the practice of tandem-breastfeeding (two or more offspring of different ages who are breastfed by their mother at the same time), infant's gender, status of Small for Gestational Age versus Appropriate for Gestational Age of preterm infants, and singleton versus twin pregnancies effects. We also look into the use of aluminum-based antiperspirants on HM aluminum content, the HM content of Covid-19-specific-antibodies following Covid-19 vaccination during pregnancy or following maternal Covid-19 infection and the correlation between levels of lutein in HM and the occurrence and severity of retinopathy of prematurity (ROP) in preterm infants.

Publications

Ovental A, Doyev R, **Mangel L**, Herzlich J, Hadanny A, Marom R. Neonatal morbidity among African refugee women in Israel: a case-control study. *BMJ Open*. 2021;11(12):e050778.

Rosenberg G, **Mangel L**, Mandel D, Marom R, Lubetzky R. Tandem breastfeeding and human milk macronutrients: A prospective observational study. *J Hum Lact*. 2021;37(4):723-729.

Rochman M, **Mangel L**, Mandel D, Berkovitch M, Kohn E, Abu Hamad R, Lubetzky R. Aluminum content of human milk and antiperspirant use. *Breastfeed Med*. 2021;16(8):654-659.

Zommerfroind I, Moran-Lev H, Mandel D, Mimouni FB, **Mangel L**, Lubetzky R. Changes in macronutrients of human milk after bolus feeding: a simulation study. *J Perinatol*. 2021;41(5):1069-1073.

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Blumovich A, **Mangel L**, Yochpaz S, Mandel D, Marom R. Risk factors for readmission for phototherapy due to jaundice in healthy newborns: a retrospective, observational study. *BMC Pediatr*. 2020 May 26;20(1):248.

Fridman E, **Mangel L**, Mandel D, Beer G, Kapusta L, Marom R. Effects of maternal aspirin treatment on hemodynamically significant patent ductus arteriosus in preterm infants - pilot study. *J Matern Fetal Neonatal Med*. 2020; 6:1-6.

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Shapira D, Mandel D, Mimouni FB, Moran-Lev H, Marom R, **Mangel L**, Lubetzky R. The effect of gestational diabetes mellitus on human milk macronutrients content. *J Perinatol*. 2019;39(6):820-823.

Orbach R, Mandel D, **Mangel L**, Marom R, Lubetzky R. The effect of deep freezing on human milk macronutrients content. *Breastfeed Med*. 2019;14(3):172-176.

Mangel L, Mimouni FB, Feinstein-Goren N, Lubetzky R, Mandel D, Marom R. The effect of maternal habitus on macronutrient content of human milk colostrum. *J Perinatol*. 2017;37(7):818-21.

Grants

2021

Materna Research Institute, Investigation of vaccine or disease induced anti COVID-19 antibodies in breast milk and neonatal serum.

Public Health





Prof. Lizy Fireman, Ph.D.

Laboratory for Occupational and
Environmental Lung Disease
Tel Aviv Sourasky Medical Center



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<http://www.tasmc.org.il/InternalMed/Pulmonary/Pages/allergy-lab.aspx>

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 of inflammatory and structural cells in occupational lung diseases were made in studies using fiberoptic bronchoscopy in conjunction with bronchoalveolar lavage (BAL). The relative invasiveness of this technique, however, has restricted the use of bronchoscopy to a limited

Biological monitoring by measurement of micro range particles in induced sputum samples

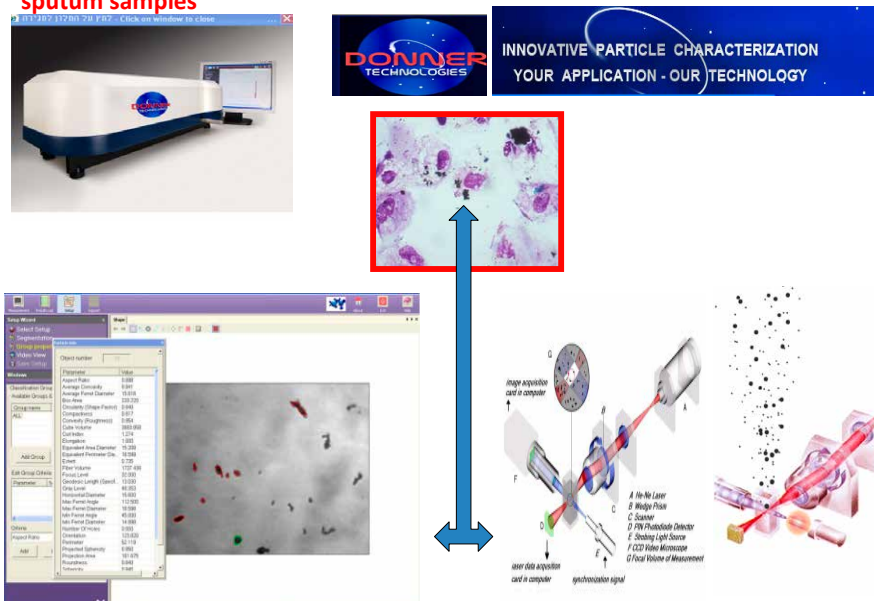


Figure 1

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

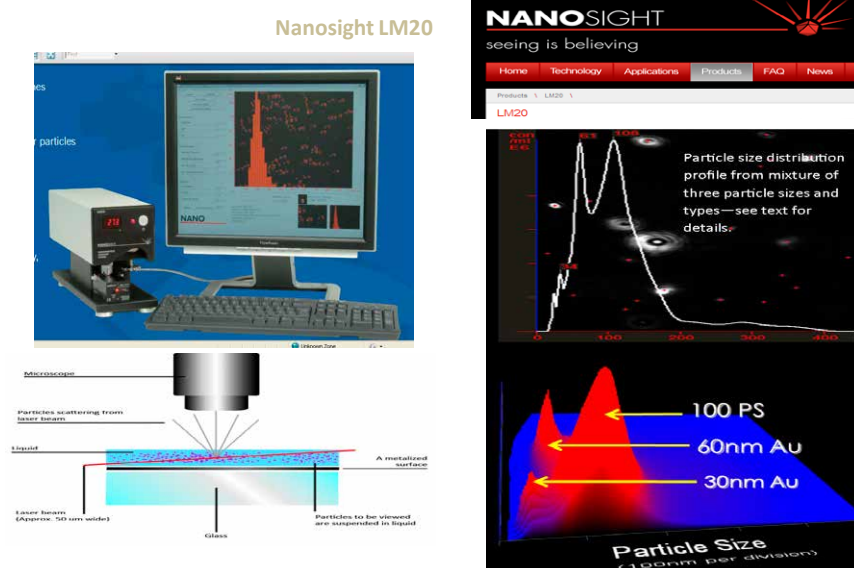


Figure 2

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 Eyetechn 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.

Fireman E, Alcalay Y, Ophir N, Kivity S, Stejskal V Identification of metal sensitization in sarcoid-like metal-exposed patients by the MELISA® lymphocyte proliferation test — a pilot study. *Journal of Occupational Medicine and Toxicology*. 2016 2: 00086

Litinsky I, **Fireman E**, Paran D, Polachek A, Broide A, Sharabi A, Anouk M, Elkayam O. Induced sputum

analysis in subjects with systemic sclerosis. *Respir Care*. 2016;61(10):1369-73.

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Ophir N, Shai AB, Alkalay Y, Israeli S, Korenstein R, Kramer MR, **Fireman E**. Artificial stone dust-induced functional and inflammatory abnormalities in exposed workers monitored quantitatively by biometrics. *ERJ Open Res*. 2016.

Survival following lung transplantation for artificial stone silicosis relative to idiopathic pulmonary fibrosis. Rosengarten D, Fox BD, **Fireman E**, Blanc PD, Rusanov V, Fruchter O, Raviv Y, Shtraichman O, Saute M, Kramer MR. *Am J Ind Med*. 2017;60(3):248-254

Differential pattern of deposition of nanoparticles in the airways of exposed workers. **Fireman E**, Edelheit R, Stark M, Shai AB. *J Nanopart Res*. 2017;19(2):30.

Rosengarten D, Fox BD, **Fireman E**, Blanc PD, Rusanov V, Fruchter O, Raviv Y, Shtraichman O, Saute M, Kramer MR. Survival following lung transplantation for artificial stone silicosis relative to idiopathic pulmonary fibrosis. *Am J Ind Med*. 2017;60:248-254

Fireman E, Edelheit R, Stark M, Shai AB. Differential pattern of deposition of nanoparticles in the airways of exposed workers. *J Nanopart Res*. 2017;19:30

Ophir N*, Bar-Shai A*, Kramer MR, Grubstein A, Israeli-Shani L, **Fireman E**. HO-1 protects smokers exposed to artificial stone dust for pulmonary function tests deterioration. *Sarcoidosis Vasculitis and Diffuse Lung Diseases* 2018; 35:3.

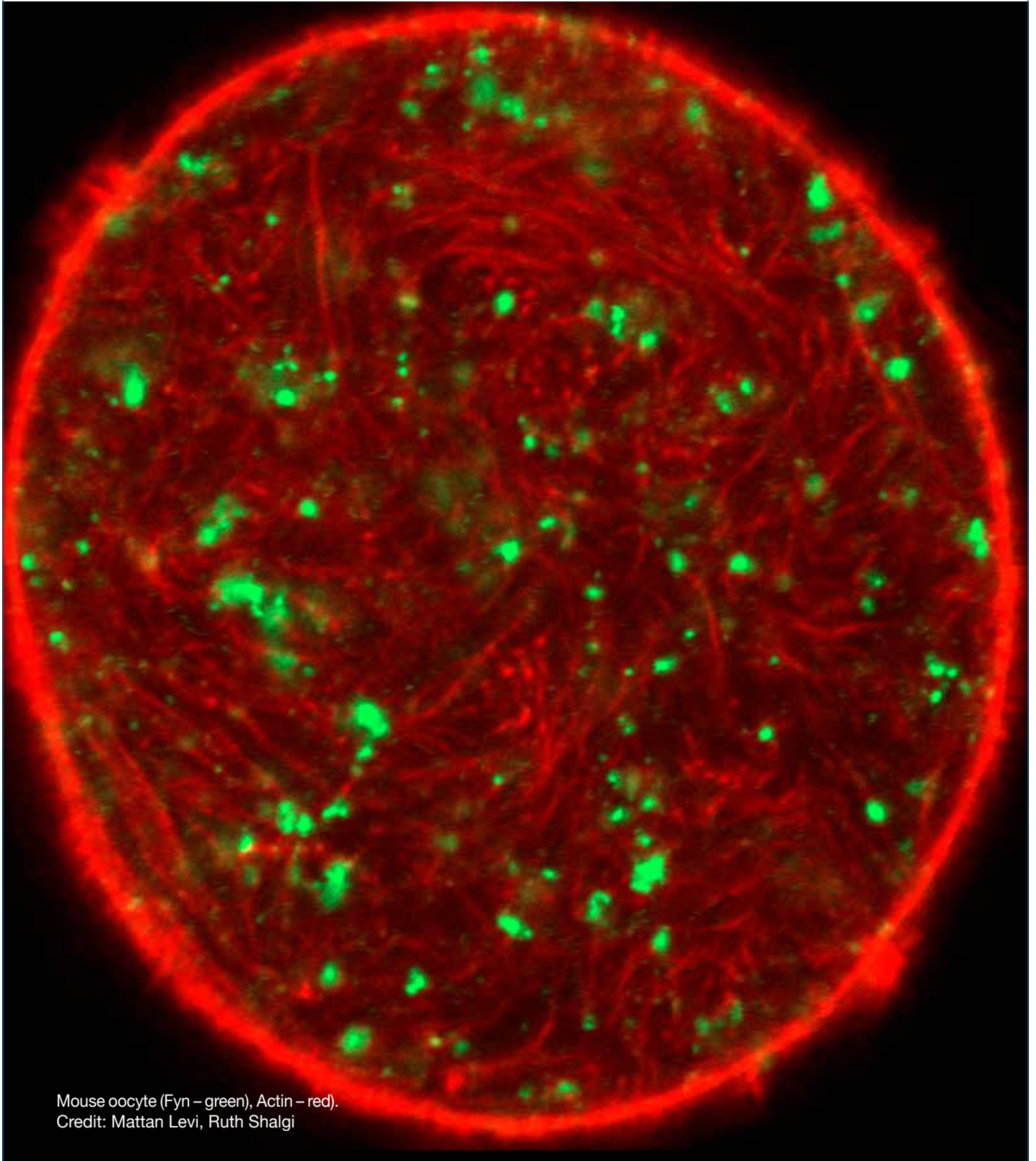
Ophir N, Bar Shai A, Korenstein R, Kramer M, **Fireman E**. Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure. *Occup Environ Med* 2019; 76: 875-879.

Udi Shapira U, Brezinski RY, Rogowski O, Zeltser D , Berliner S, Shapira I, Shenhar-Tsarfaty S, **Fireman E**. Association between elevated serum bilirubin levels with preserved lung function under conditions of exposure to air pollution. *BMC Pulm Med* 2021;21(1):119.

Grants

- | | |
|-----------|--|
| 2021 | Haifa Bay Municipal Association for Environmental Protection, Biological monitoring of air pollution impact |
| 2020-2022 | The use of bio-monitoring to assess and protect workers exposed to nano-scale materials, The Israeli Ministry of Science |

Reproduction



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



Dr. Sandra E. Kleiman, Ph.D.

Male Fertility and Sperm Bank,
Lis Maternity Hospital
Tel Aviv-Sourasky Medical Center
School of Medicine



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Genetic and Epigenetic Regulation of Spermatogenesis for Personalized Diagnosis and Treatment of Male Infertility

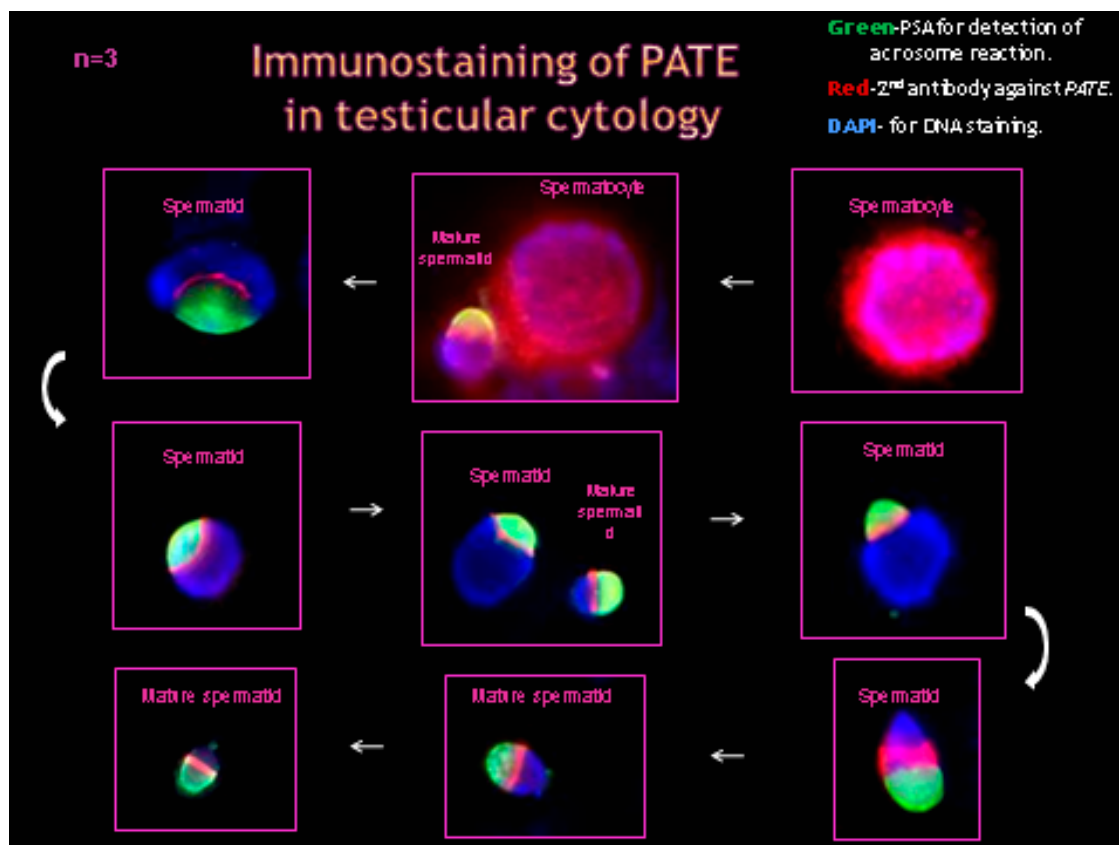
Position

Senior Lecturer, Faculty of Medicine

Research

Our lab works towards uncovering the etiology of male infertility. Our goal is to better understand the spermatogenetic process and improve the diagnosis and the treatment of men with infertility and subfertility. We are applying genetic approaches, combined with endocrinology, histological and cytological approaches in human specimens and mice models. By focusing on the Israeli Jewish and Arab population, our study has

identified three new genes, each one playing a pivotal role in different critical processes occurring during spermatogenesis. We are employing deep sequencing to identify additional new genes mutated in infertility and subfertility. Batteries of genes are exclusively expressed at specific stages during spermatogenesis. By studying meiosis, gene expression and gene regulation, we identified testicular molecular markers that predict the presence of sperm in the testis. At present, we are working on detecting markers in semen that can predict testicular sperm cells by studying the seminal small RNA transcriptome and



Expression pattern of PATE protein during spermatogenesis. Immunofluorescence analysis reveals the cell stages and the location in which the PATE protein is detected.

unravelling insights into small RNA regulation in spermatogenesis.

Publications

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Grants

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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.



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hESCs in Development, Genetic Disorders and Cell Therapy

Positions

Director, IVF Lab and Wolfe PGD-Stem Cell Lab, Tel Aviv Sourasky Medical Center

Professor, Department of Cell and Developmental Biology, 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 preimplantation 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.

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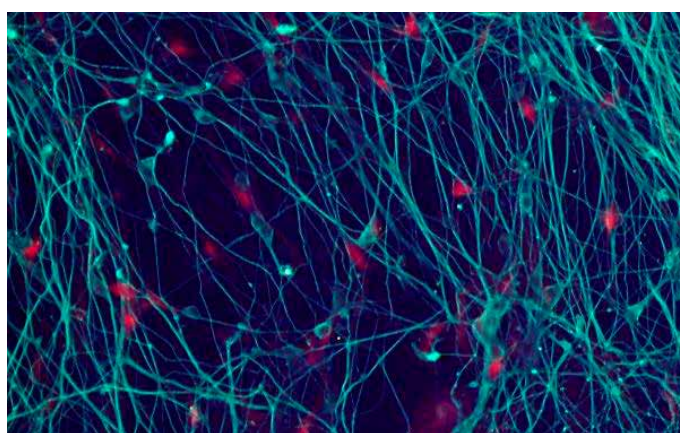
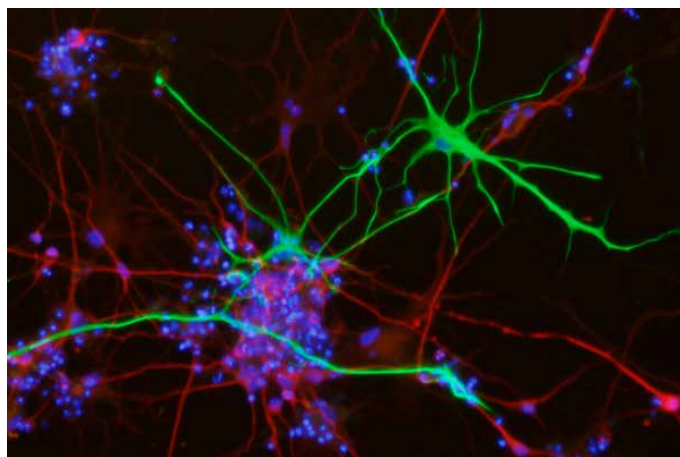
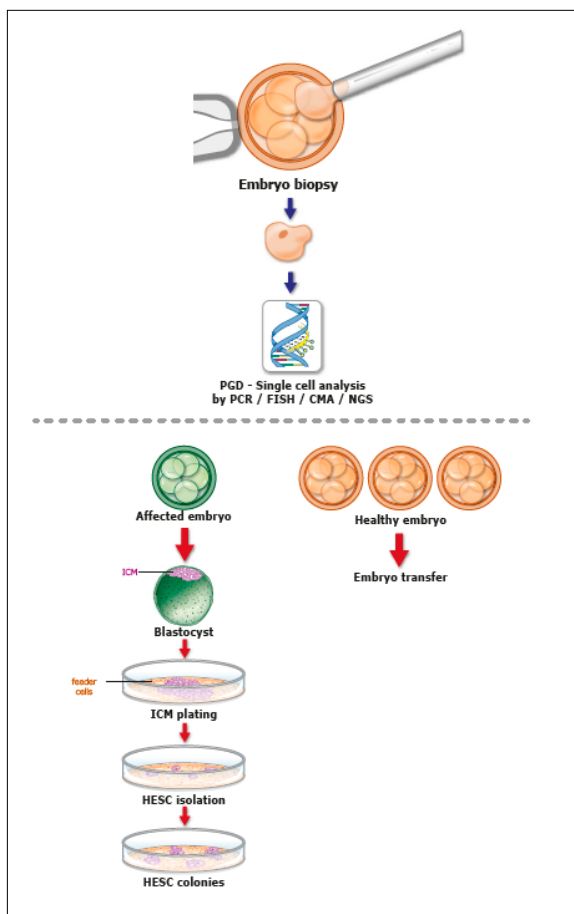
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Left: HESCs are derived from PGD embryos affected by genetic disorders. Right: Neurons derived from HESCs: A. Neurons (MAP2, red) and glia (GFAP, green) from fragile X HESCs at day 128 of differentiation. B, C Neurons (Tuj1, green) from normal HESCs 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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