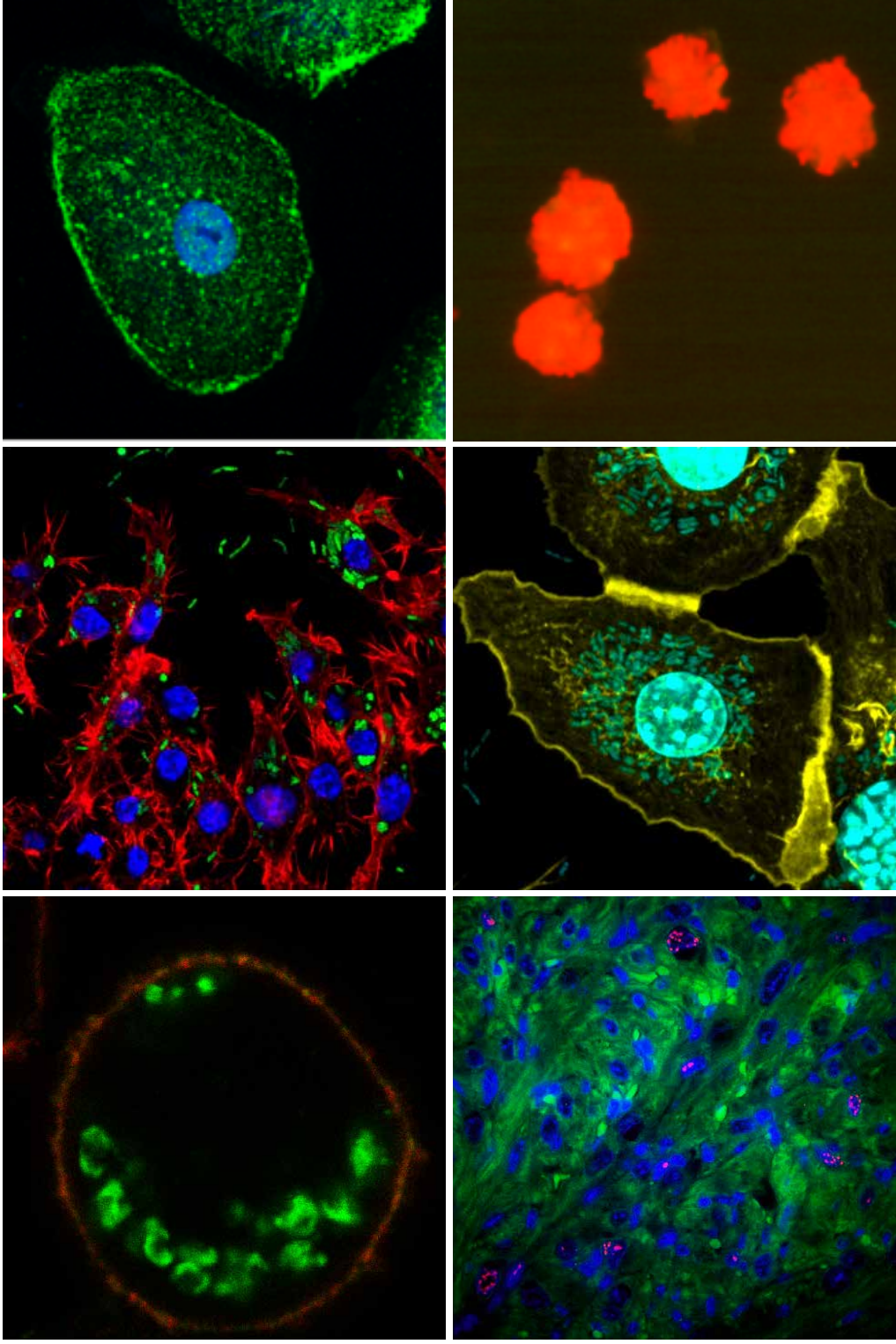

TEL AVIV UNIVERSITY
Pursuing the Unknown

Sackler Faculty of Medicine

Hospital-Based PhD Research 2022

Sections

Cover images (from bottom left, clockwise):

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

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

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

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

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

Editor: Prof. Karen Avraham
Graphic design: Michal Semo Kovetz, TAU Graphic Design Studio
February 2022

The Sackler Faculty of Medicine

The Tel Aviv University Faculty of Medicine is Israel's largest medical research and training complex. The Sackler Faculty of Medicine of Tel Aviv University (TAU) was founded in 1964. 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 imited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians and PhD researchers in 181 affiliated departments and institutes in 17 hospitals hold academic appointments at TAU. The Gitter-Smolarz Life Sciences and Medicine Library serves students and staff and is the center of a consortium of 15 hospital libraries.

The student body is made up of 750 Israeli students enrolled in the 6-year M.D. degree program, 300 American and Canadian students enrolled in a 4-year M.D. program chartered by the State of New York and accredited by the State of Israel, and a 4-year program for Israeli students for the M.D. degree, with 260 students. Approximately 200 students study dental medicine in a six-year program where they are awarded the D.M.D. degree and another 2,000 students are enrolled in the health professions programs where they will earn degrees in Communications Disorders, Nursing, Physical Therapy and Occupational Therapy. 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. Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Ami Fishman, Prof. Arnon Wiznitzer, and Assistant to the Dean, Michal Gilboa.

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

Prof. Ehud Grossman, MD,
Dean

Prof. Karen B. Avraham, PhD,
Vice Dean (Preclinical)

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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 Biochemstry, Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

osnataf@gmail.com

Investigating Hormone Metabolism in Cancer

Positions

Associate Professor, Sackler Faculty of Medicine

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

Research

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

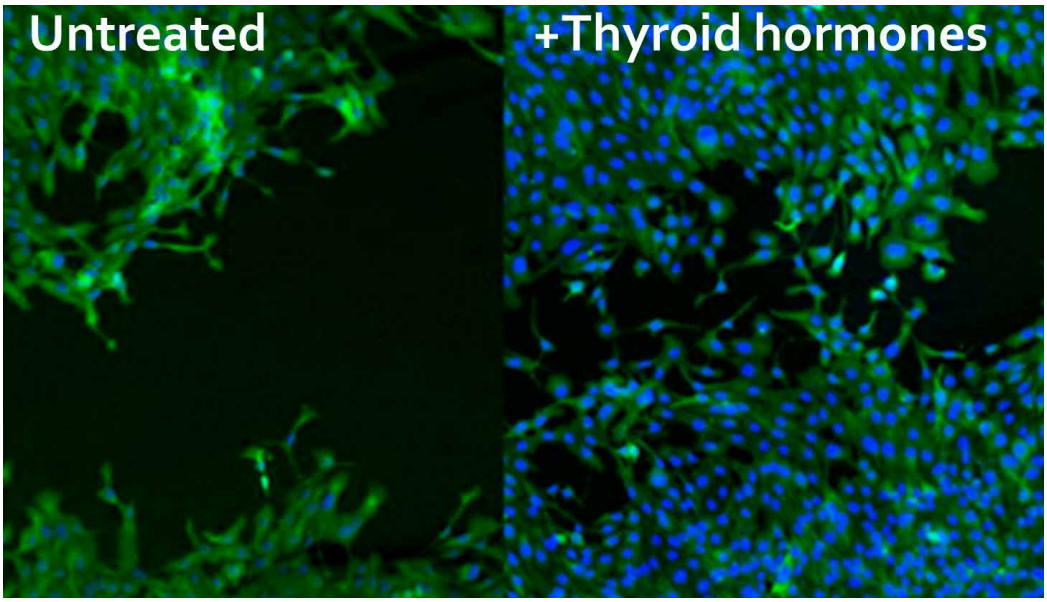
Publications

Ellis M, Krashin E, Hamburger-Avnery O, Gan S, Elis A and **Ashur-Fabian O**. The anti-leukemic and lipid lowering effects of imatinib are not hindered by statins in CML: a retrospective clinical study and in vitro assessment of lipid-genes transcription. *Leuk. & Lymph*, 58(5):1172-1177, 2017.

Redko B, Tuchinsky H, Segal T, Tobi D, Luboshits G, **Ashur-Fabian O**, Pinhasov A, Gerlitz G, Gellerman G.Toward the development of a novel non-RGD cyclic peptide drug conjugate for treatment of human metastatic melanoma. Oncotarget. 8(1):757-768, 2017.

Shinderman-Maman E, Cohen K, Moskovich D, Hercbergs A, Werner H, Davis PJ, Ellis M, **Ashur-Fabian O**. Thyroid hormones derivatives reduce proliferation and induce cell death and DNA damage in ovarian cancer. Scientific Reports 28;7(1):16475, 2017.

Weingarten C, Jenudi Y, Tshuva RY, Moskovich D, Alfandari A, Hercbergs A, Davis PJ, Ellis M and **Ashur-Fabian O**. The interplay between epithelial-mesenchymal transition (EMT) and the thyroid hormones-avb3 axis in ovarian cancer. Hormones and Cancer, 2017.



Ovarian cancer cell proliferation and migration is enhanced by thyroid hormones

Krashin E, Ellis M, Cohen K, Viner M, Neumark E, Rashid G and **Ashur-Fabian O**. Chemical and Metabolic Profile of the Bone Marrow Interstitial Fluid in Plasma Cell Dyscrasias and Other Hematologic Disorders. Hematological Oncology, 2017.

Shinderman-Maman E, Weingarten C, Moskovich D, Werner H, Hercbergs A, Davis PJ, Ellis M, **Ashur-Fabian O**. Molecular insights into the transcriptional regulatory role of thyroid hormones in ovarian cancer. Mol Carcinog. 57(1):97-105, 2018.

Cohen K, Abadi U, Hercbergs A, Davis PJ, Ellis M, **Ashur-Fabian O**. The induction of myeloma cell death and DNA damage by tetrac, a thyroid hormone derivative. Endocr Relat Cancer. 25(1):21-34, 2018.

Mousa SA, Glinsky GV, Lin HY, **Ashur-Fabian O**, Hercbergs A, Keating KA, Davis PJ. contributions of thyroid hormone to cancer metastasis. Biomedicines, 6, 2018.

Ashur-Fabian O, Zloto O, Fabian I, Tsarfaty G, Ellis M, Steinberg DM, Hercbergs A, Davis PJ, Fabian ID. Tetrac delayed the onset of ocular melanoma in an orthotopic mouse model. Front Endocrinol (Lausanne), 9:775, 2019.

Dayan A, Fleminger G, **Ashur-Fabian O**. Targeting the Achilles' heel of cancer cells via integrin-mediated delivery of ROS-generating dihydrolipoamide dehydrogenase. Oncogene, 38:5050-5061, 2019.

Seraya-Bareket C, Weisz A, Shinderman-Maman E, Teper-Roth S, Stamler D, Arbib N, Kadan Y, Fishman A, Kidron D, Edelstein E, Ellis M and **Ashur-Fabian O**. The identification of nuclear αvβ3 integrin in ovarian cancer: non-paradigmal localization with cancer promoting actions. *Oncogenesis*, 9(7):69, 2020.

Moskovich D, Alfandari A, Finkelshtein Y, Weisz A, Katzav A, Kidron D, Edelstein E, Veroslavski D, Perets R, Arbib N, Kadan Y, Fishman A, Lerer B, Ellis M and Ashur-Fabian O. DIO3, the thyroid hormone inactivating enzyme, promotes tumorigenesis and metabolic reprogramming in high grade serous ovarian cancer. *Cancer Letters*, 31;501:224-233, 2021.

Weitzner O, Seraya-Bareket C, Biron-Shental T, Fishman A, Yagur Y, Tzadikevitch-Gefen K, Farladansky-Gershnabel S, Kidron D, Ellis M and **Ashur-Fabian O**. Enhanced expression of αVβ3 integrin in extravillus trophoblasts of placenta accrete. *Arch Gynecol Obstet* (ARCH), 303(5):1175-1183, 2021.

Krashin E, Silverman B, Steinberg DM, Yekutieli D, Giveon S, Fabian O, Hercbergs A, Davis PJ, Ellis M and **Ashur-Fabian O**. Opposing effects of thyroid hormones on cancer risk based on patient age and tumor type: A population-based study. *Eur J Endocrinol*, 184(3):477-486, 2021.

Abadi U, Weisz A, Kidron D, Katzav A, Hercbergs A, Davis PJ, Ellis M and **Ashur-Fabian O**. αvβ3 integrin expression and mitogenic effects by thyroid hormones in chronic lymphocytic leukemia. *J Clin Med*, 19;10(8):1766, 2021.

Krashin E, Silverman B, Steinberg DM, Yekutieli D, Giveon S, Fabian O, Hercbergs A, Davis PJ, Ellis M, **Ashur-Fabian O**. Pre-diagnosis thyroid hormone dysfunction is associated with cancer mortality. *Endocrine Related Cancer*, 28(11):705-713, 2021.

Weisz A, Abadi U, Mausbach L, Gurwitz D, Ellis M and **Ashur-Fabian O**. Nuclear αvβ3 integrin expression, post translational modifications and regulation in hematological malignancies. Accepted for publication, *Hematological Oncology*, Sep 2021.

Moskovich D, Finkelshtein Y, Alfandari A, Rosemarin A, Lifschytz T, Weisz A, Mondal S, Ungati H, Katzav A, Kidron D, Mugesh G, Ellis M, Lerer B and **Ashur-Fabian O**. Targeting the DIO3 enzyme using first-in-class inhibitors effectively suppresses tumor growth: A new paradigm in ovarian cancer treatment. *Oncogene*, 40(44):6248-6257, 2021.

Reviews

Krashin E, Piekiełko-Witkowska A, Ellis M, **Ashur-Fabian O**. Thyroid hormones and cancer: A comprehensive review of preclinical and clinical studies. Front Endocrinol (Lausanne), 10:59, 2019.

Davis PJ, **Ashur-Fabian O**, Incerpi S, Mousa SA. Editorial: Non genomic actions of thyroid hormones in cancer. Front Endocrinol (Lausanne), 10:847, 2019.

Grants

2020-2022	Tel Aviv University Data Science Center, Diagnostic and prognostic scores for pancreatic cancer using big medical data
2021-2022	The Dotan Hemato-Oncology Seed Award, Thyroid-based Predictive and Prognostic Models for AML

Dr. Liat Drucker, Ph.D.

Department of Pathology, Sackler Faculty of Medicine, Tel Aviv University
Oncogenetics Laboratory, Meir Medical Center

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Multiple Myeloma in its Bone Marrow Niche

Positions

Senior Lecturer, Sackler 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.

Publications

Attar-Schneider O, Pasmanik-Chor M, Tartakover Matalon S, **Drucker L***, Lishner M*. eIF4E and eIF4GI have distinct and differential imprints on multiple myeloma's proteome and signaling. Oncotarget, 28;6:4315-29, 2015

Epstein Shochet G, **Drucker L**, Pasmanik-Chor M, Pomeranz M, Fishman A, Tartakover Matalon S*,Lishner M*. First trimester human placental factors induce breast cancer cell autophagy. Breast Cancer Research and Treatment, 149:645-54, 2015

Epstein Shochet G, **Drucker L**, Pasmanik-Chor M, Pomeranz M, Fishman A, Tartakover Matalon S*,Lishner M*. First trimester human placental factors induce breast cancer cell autophagy. Breast Cancer Research and Treatment, 149:645-54, 2015

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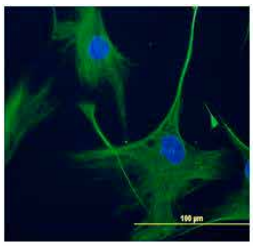
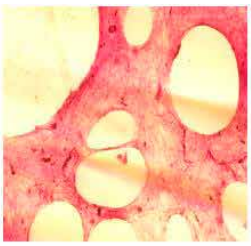
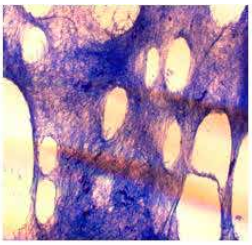


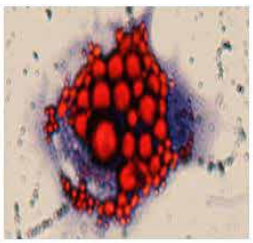
Primary human mesenchymal stem cells (MSCs)



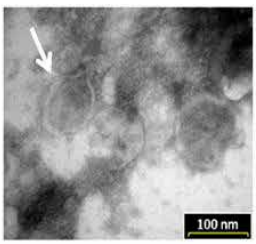
MSCs' extracellular matrix (elastin)



MSCs' extracellular matrix (collagen)



MCS differentiated into adipocyte



MSCs' microvesicles

Marcus H, Attar-Schneider O, Dabbah M, Zismanov V, Tartakover-Matalon S, *Lishner M, ***Drucker L**. Mesenchymal stem cells secretomes' affect multiple myeloma translation initiation. Cell Signal 28:620-30, 2016

Dabbah M, Attar-Schneider O, Zismanov V, Tartakover Matalon S, *Lishner M, ***Drucker L**. Multiple myeloma cells promote migration of bone marrow mesenchymal stem cells by altering their translation initiation. J Leuk Biol 100:761-770, 2016

Attar-Schneider O, ***Drucker L**, *Gottfried M. Migration and epithelial to mesenchymal transition of lung cancer can be targeted via translation initiation factors eIF4E and eIF4GI. Lab Invest 96:1004-15, 2016

Epstein Shochet G, Komemi O, Sadeh-Mestechkin D, Pomeranz M(Fishman A, **Drucker L**, Lishner M, Tartakover Matalon S. Heat shock protein-27 (HSP27) regulates STAT3 and eIF4G levels in first trimester human placenta. J Mol Histol 47:555-563, 2016

Epstein Shochet G, **Drucker L**, Pasmanik-Chor M, Pomeranz M, Fishman A, Tartakover Matalon S*,Lishner M*. First trimester human placenta prevents breast cancer cells attachment to the matrix: the role of extracellular matrix. Mol Carcinogenesis 56:62-74, 2017

Dabbah M, Attar-Schneider O, Tartakover Matalon S, Shefler I, Jarchowsky O, *Lishner M, ***Drucker L**. Microvesicles derived from bone marrow mesenchymal stem cells differentially modulate multiple myeloma cells' phenotype and translation initiation according to their normal or pathological source. Carcinogenesis 38:708-716, 2017

Attar-Schneider O, ***Drucker L**, *Gottfried M. The effect of mesenchymal stem cells' secretome on lung cancer progression is contingent on their origin: primary or metastatic niche. Lab Invest 98:1549-1561, 2018

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 and activates their survival mechanisms: a key for future distant metastases. Int J Cancer 144:1633-1644, 2018

Ibraheem A, Dolberg Jarchowsky O, Attar-Schneider O, Dabbah M, Tartakover Matalon S, *Lishner M, ***Drucker L**. BM-MS derived ECM modifies multiple myeloma phenotype and drug response in a source dependent manner. Translational Research 207:83-95, 2019, 2019

Bar M, Komemi O, Pomeranz M, Fishman A, **Drucker L**, *Lishner M, *Tartakover Matalon S. Placental supernatants' enhancement of the metastatic potential of breast cancer cells: Is estrogen receptor (ERα) essential for this phenomenon? Archives of Gynecology and Obstetrics 300:981-991, 2019

Dabbah M, Jarchowsky-Dolberg O, Attar-Schneider O, Tartakover Matalon S, Pasmanik-Chor M, ***Drucker L**, *Lishner M. CD49d on multiple myeloma mesenchymal stem cells microvesicles: prognostic marker and selective therapeutic target. Carcinogenesis 7: 60698–60711, 2019

Tartakover Matalon S, Ringel Y, Konikoff F, **Drucker L**, Pery S, Naftali T. Cannabinoid Receptor 2 (CB2) agonist promotes parameters implicated in mucosal healing in Inflammatory Bowel Disease patients. United European Gastroenterology, 2019

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

Kilionsky DJ et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy 2;12:1-222, 2016

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
Tel Aviv Sourasky Medical Center

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benzik@tlvmc.gov.il

Development of B-Cell Malignancies

Positions

Senior Lecturer, Sackler Faculty of Medicine

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

Research

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

Publications

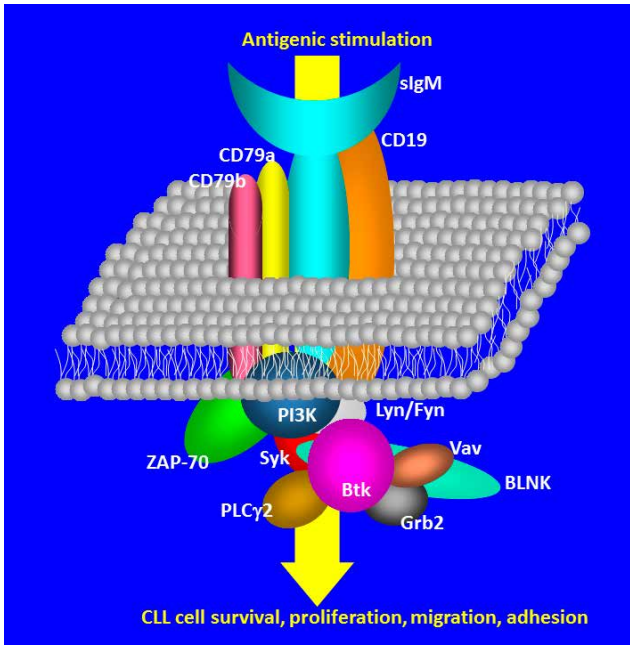
Herishanu, Y., **Katz, B.-Z**. *Cryoglobulins mimicking platelet recovery in a mantle cell lymphoma patient treated with chemoimmunotherapy.* (2015) Blood 125:1047.

Sarid, N., **Katz, B.-Z**. *Dividing plasma cells in the cerebrospinal fluid of a patient with refractory multiple myeloma.* (2015) Blood 126:2162.

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

Dezorella, N.*, **Katz, B.-Z**.*, Shapiro, M., Polliack, A., Perry, C., Herishanu, Y. *SLP76 integrates into the B-Cell receptor signaling cascade in chronic lymphocytic leukemia cells and is associated with aggressive disease course.* (2016) Haematologica 101:1553-1562. * Equal contributors

Shapiro, M., Herishanu, Y., **Katz, B.-Z**., Dezorella, N., Sun, C., Kay, S., Polliack, A., Avivi, I., Wiestner, A., Perry, C. *Lymphocyte activation gene 3- A novel therapeutic target in chronic lymphocytic leukemia.* (2017) *Haematologica* 102:874-882.



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.

Katz, B.-Z., Herishanu, Y. Fragility of sub-cellular structures in chronic lymphocytic leukemia. (2017) *Int. J. Hematol*. 105:707-708.

Dezorella, N., Ashkenazi, E., Shapiro, M., Perry, C., Kamdjou, T., **Katz, B.-Z.**, Herishanu Y. Wide-range effects of the MALT-1 inhibitor Mi-2 in CLL cells results in apoptosis. (2018) *Leuk Lymphoma*. 4:1-4.

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 Scopio 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
Sackler Faculty of Medicine

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Drug Delivery into the Brain, Brain Tumors and Brain MRI

Positions

Associate Professor, Sackler 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.

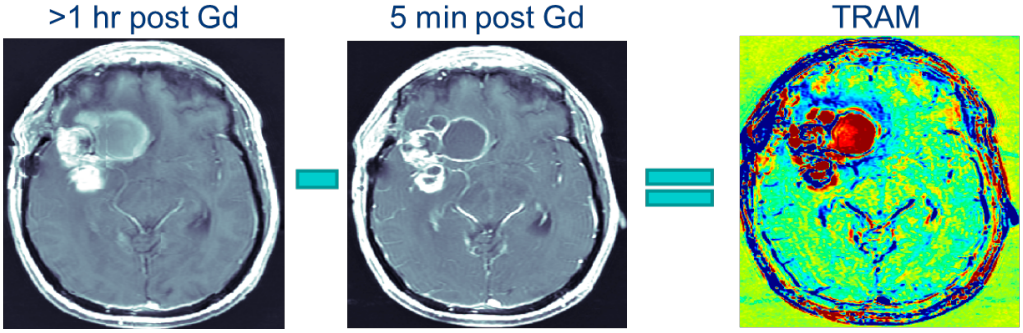
Publications

Nordling-David MM, Yaffe R, Guez D, Meirow H, Last D, Grad E, Salomon S, Sharabi S, Levi-Kalisman Y, Golomb G, **Mardor Y**. Liposomal temozolomide drug delivery using convection enhanced delivery. J Control Release. 2017;261:138-146.

Peretz S, Orion D, Last D, **Mardor Y**, Kimmel Y, Yehezkely S, Lotan E, Itsekson-Hayosh Z, Koton S, Guez D, Tanne D. Incorporation of relative cerebral blood flow into CT perfusion maps reduces false 'at risk' penumbra. J Neurointerv Surg. 2018;10:657-662.

Daniels D, Sharabi S, Last D, Guez D, Salomon S, Zivli Z, Castel D, Volovick A, Grinfeld J, Rachmilevich I, Amar T, Liraz-Zaltsman S, Sargsyan N, **Mardor Y**, Harnof S. Focused ultrasound-induced suppression

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

of auditory evoked potentials in vivo. Ultrasound Med Biol. 2018;44:1022-1030.

Sharabi S, Daniels D, Last D, Guez D, Zivli Z, Castel D, Levy Y, Volovick A, Grinfeld J, Rachmilevich I, Amar T, **Mardor Y**, Harnof S. Non-thermal focused ultrasound induced reversible reduction of essential tremor in a rat model. Brain Stimul. 2018; 12:1-8.

Elhaik Goldman S, Goez D, Last D, Naor S, Liraz Zaltsman S, Sharvit-Ginon I, Atrakchi-Baranes D, Shemesh C, Twitto-Greenberg R, Tsach S, Lotan R, Leikin-Frenkel A, Shish A, **Mardor Y**, Schnaider Beeri M, Cooper I. High-fat diet protects the blood-brain barrier in an Alzheimer's disease mouse model. Aging Cell. 2018; 17:e12818.

Guez D, Last D, Daniels D, Sharabi S, Nass D, Nissim O, Spiegelmann R, Tzarfaty G, Hoffmann C, Talianski A, Shoshan Y, Fellig Y, Harnof S, Cohen ZR, Zach L, **Mardor Y.** Radiation-induced vascular malformations in the brain, mimicking tumor in MRI-based treatment response assessment maps (TRAMs). Clin Transl Radiat Oncol. 2018; 15:1-6.

Shavit-Stein E, Sheinberg E, Golderman V, Sharabi S, Wohl A, Gofrit SG, Zivli Z, Shelestovich N, Last D, Guez D, Daniels D, Gera O, Feingold K, Itsekson-Hayosh Z, Rosenberg N, Tamarin I, Dori A, Maggio N, **Mardor Y**, Chapman J, Harnof S. A novel compound targeting Protease Receptor 1 activators for the treatment of glioblastoma. Front Neurol. 2018;9:1087.

Tzameret A, Ketter-Katz H, Edelshtain V, Sher I, Corem-Salkmon E, Levy I, Last D, Guez D, **Mardor Y**, Margel S, Rotenstrich Y. In vivo MRI assessment of bioactive magnetic iron oxide/human serum albumin nanoparticle delivery into the posterior segment of the eye in a rat model of retinal degeneration. J Nanobiotechnology. 2019;17:3.

Sharabi S, Bresler Y, Ravid O, Shemesh C, Atrakchi, Schnaider-Beeri M, Gosselet F, Dehouck L, Last D, Guez D, Daniels D, **Mardor Y**, Cooper I. Transient blood–brain barrier disruption is induced by low pulsed electrical fields in vitro: an analysis of permeability and trans-endothelial electric resistivity. Drug Deliv. 2019; 26:459-469.

Sharabi S, Guez D, Daniels D, Cooper I, Atrakchi D, Liraz-Zaltsman S, Last D, **Mardor Y**. The application of point source electroporation and chemotherapy for the treatment of glioma: a randomized controlled rat study. Sci Rep. 2020;10(1):2178.

Sharabi S, Last D, Daniels D, Liraz Zaltsman S, **Mardor Y**. The effects of point-source electroporation on the blood-brain barrier and brain vasculature in rats: An MRI and histology study. Bioelectrochemistry. 2020 134:107521.

Sharabi S, Last D, Daniels D, Fabian ID, Atrakchi D, Bresler Y, Liraz-Zaltsman S, Cooper I, **Mardor Y.** Non-invasive low pulsed electrical fields for inducing BBB disruption in mice-feasibility demonstration. Pharmaceutics. 2021 13(2):169.

Porper K, Shpatz Y, Plotkin L, Pechthold RG, Talianski A, Champ CE, Furman O, Shimoni-Sebag A, Symon Z, Amit U, Hemi R, Kanety H, **Mardor Y**, Cohen ZR, Jan E, Genssin H, Anikster Y, Zach L, Lawrence YR. A Phase I clinical trial of dose-escalated metabolic therapy combined with concomitant radiation therapy in high-grade glioma. J Neurooncol. 2021 153(3):487-496.

Shelly S, Liraz Zaltsman S, Ben-Gal O, Dayan A, Ganmore I, Shemesh C, Atrakchi D, Garra S, Ravid O, Rand D, Israelov H, Alon T, Lichtenstein G, Sharabi S, Last D, Gosselet F, Rosen V, Burstein G, Friedlander A, Harel R, Vogel G, Schnaider Beeri M, **Mardor Y**, Lampl Y, Fleminger G, Cooper I. Potential neurotoxicity of titanium implants: Prospective, in-vivo and in-vitro study. Biomaterials. 2021 doi: 10.1016/j.biomaterials.

Krivoy A, Shrot S, Avrahami M, Fischel T, Weizman A, **Mardor Y**, Guez D, Daniels D, Katelaris A, Last D, Hoffmann C. Brain motor region diffusion tensor imaging in patients with catatonic schizophrenia: A case-control study. Isr Med Assoc J. 2021;23(10):625-630.

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

Dr. Ilan Volovitz, Ph.D.

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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, Sackler Faculty of Medicine

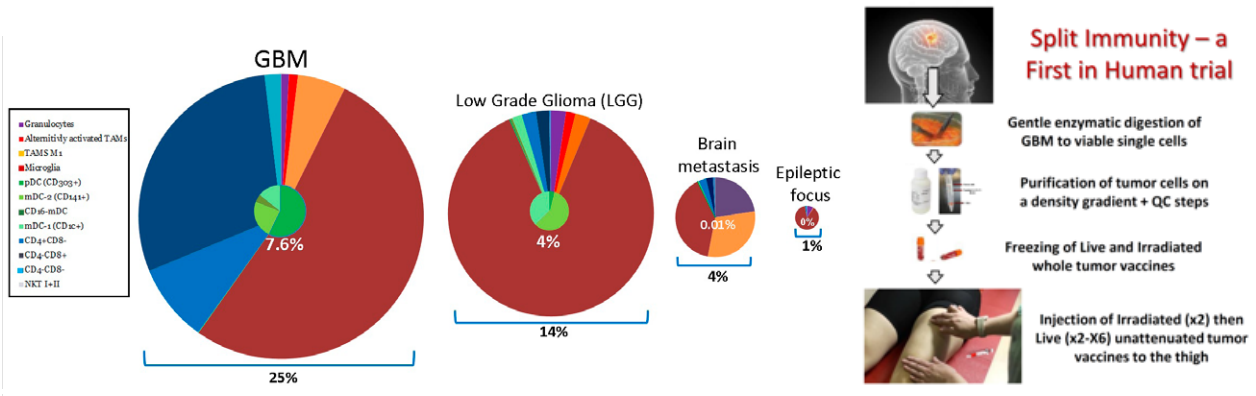
Former Chairman, Tumor Section of European Association of Neurosurgical Societies

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.



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

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

Solodeev I, Meilik B, **Volovitz I**, Sela M, Manheim S, Yarkoni S, Zipori D, Gur E, Shani N.Fas-L promotes the stem cell potency of adipose-derived mesenchymal cells. *Cell Death Dis*. 2018 Jun 11;9(6):695.

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 Neurosc*i. 2016

Volovitz I, Melzer S, Amar S, Bocsi J, Bloch M, Efroni S, Ram Z, Tárnok A. Dendritic cells in the context of human tumors: biology and experimental tools. *Int Rev Immunol*. 2016

Sela M, Tirza G, Ravid O, **Volovitz I**, Solodeev I, Friedman O, Zipori D, Gur E, Krelin Y, Shani N. NOX1-induced accumulation of reactive oxygen species in abdominal fat-derived mesenchymal stromal cells impinges on long-term proliferation. *Cell Death Dis*. 2015

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)

Dr. Galit Granot, Ph.D.

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Hematological Malignancies

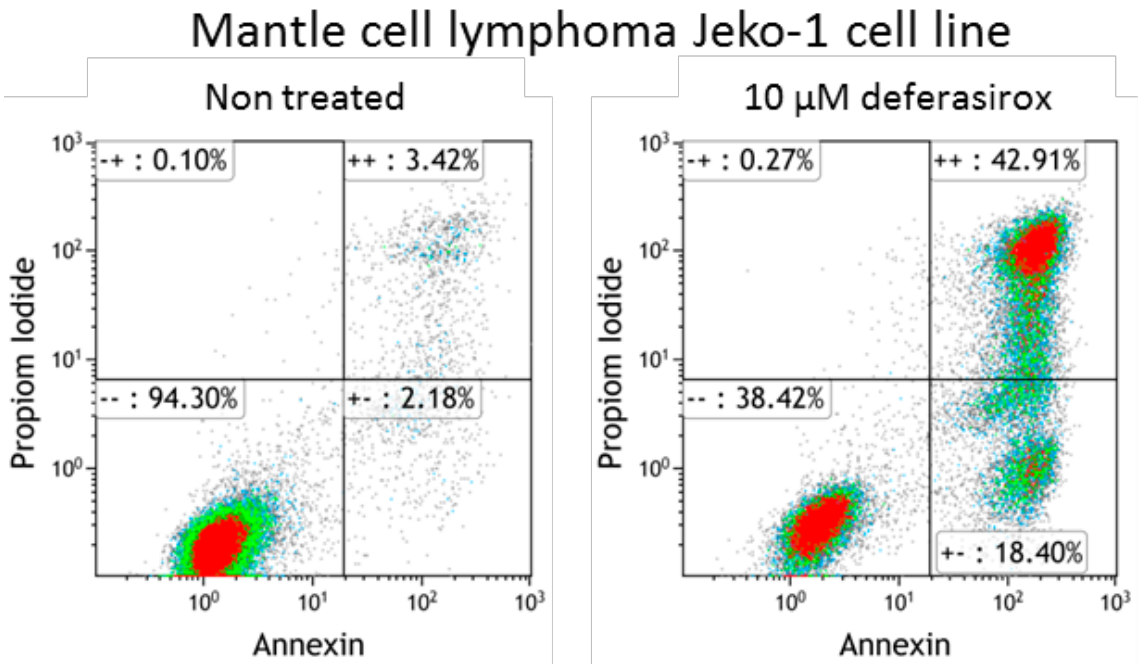
Research

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 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 HIF1α expression. *Exp Hematol*. 2019;70:55-69.

Gover-Proaktor A, **Granot G**, Pasmanik-Chor M, Pasvolsky O, Shapira S, Raz O, Raanani P, Leader A. Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib differentially affect the vascular molecular pathways and functionality of human endothelial cells. *Leuk Lymphoma*. 2019;60:189-199.



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

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

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

Hershkovitz-Rokah O, Modai S, Pasmanik-Chor M, Toren A, Shomron N, Raanani P, Shpilberg O, **Granot G**. Restoration of miR-424 suppresses BCR-ABL activity and sensitizes CML cells to imatinib treatment. Cancer Lett. 2015;360(2):245-56.

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

Raanani P, **Granot G**, Ben-Bassat I. Is cure of chronic myeloid leukemia in the third millennium a down to earth target (ed) or a castle in the air? Cancer Lett. 2014;352(1):21-7.

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

Dr. Shiran Shapira, Ph.D.

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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

Dolkart O, Amar E, **Shapira S**, Marmor S, Steinberg EL, Weinbroum AA . Protective effects of rosuvastatin in a rat model of lung contusion: Stimulation of the cyclooxygenase 2-prostaglandin E-2 pathway. Surgery. 2015; 157:944-53.

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.

Leshno A, **Shapira S**, Liberman E, Kraus S, Sror M, Harlap-Gat A, Avivi D, Galazan L, David M, Maharshak N, Moanis S, Arber N, Moshkowitz M. The APC I1307K allele conveys a significant increased risk for cancer . Int J Cancer. 2015;138(6):1361-7

Shapira S, Ben-Amotz O, Sher O, Kazanov D, Mashiah J, Kraus S, Gur E, Arber N. Delayed wound healing in Heat Stable Antigen (HSA/CD24)-deficient mice . PLoS One. 2015;10.

Shapira S, Pleban S, Kazanov D, Tirosh P, Arber N. Terpinen 4-ol: A novel and promising therapeutic agent for human gastrointestinal cancers . PLoS One. 2016;11(6):e0156540.

Shapira S, Shapira A, Kazanov D, Hevroni G, Kraus S, Arber.N Selective eradication of cancer cells by delivery of adenovirus-based toxins. Oncotarget. 2017;8(24):38581-38591.

Shapira S*, Leshno A*, Katz D, Maharshak N, Hevroni G, Jean-David M, Kraus S, Galazan L, Aroch I, Kazanov D, Hallack A, Becker S, Umanski M, Moshkowitz M, Dotan I, Arber N. Of mice and men: a novel dietary supplement for the treatment of ulcerative colitis. Ther Adv Gastroenterol. 2017; 8: 38581–38591.

Avivi-Arber L, Avivi D, Perez M, Arber N, **Shapira S**. Impaired bone healing at tooth extraction sites in CD24-deficient mice: A pilot study. PLoS One. 2018;13:e0191665.

Vaks L,Litvak-Greenfeld D, Dror S, Matatov G, Nahary L, **Shapira S**, Hakim R, Alroy I, Benhar I. Design principles for bispecific IgGs, opportunities and pitfalls of 3 artificial disulfide bonds. Antibodies.2018 7(3), 27.

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.

Tzfoni 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

Dr. Orit Uziel, Ph.D.

The Felsenstein Medical Research Center
Rabin Medical Center and
Sackler Faculty of Medicine

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Malignant Cells-Derived Exosomes: Mechanisms to Acquire Survival Advantage and the Use as Cancer Biomarkers

Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

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

Currently we are focused on the potential use of exosomal hTERT as a cancer biomarker. We follow

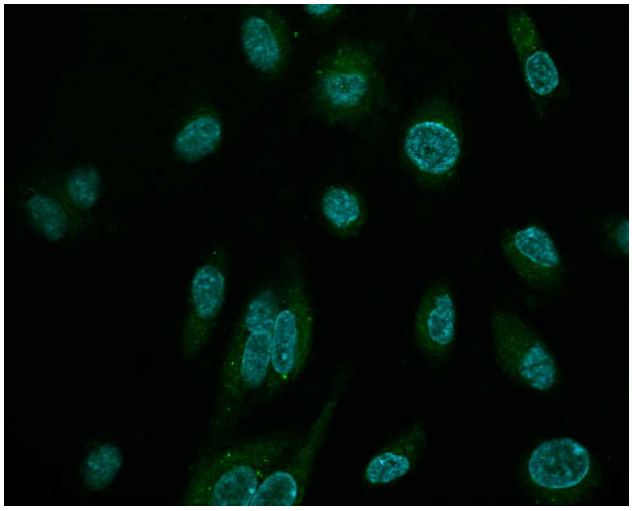


Figure 1. FITC-stained exosomes are taken up by HUVEC cells analyzed by fluoresent microscopy.

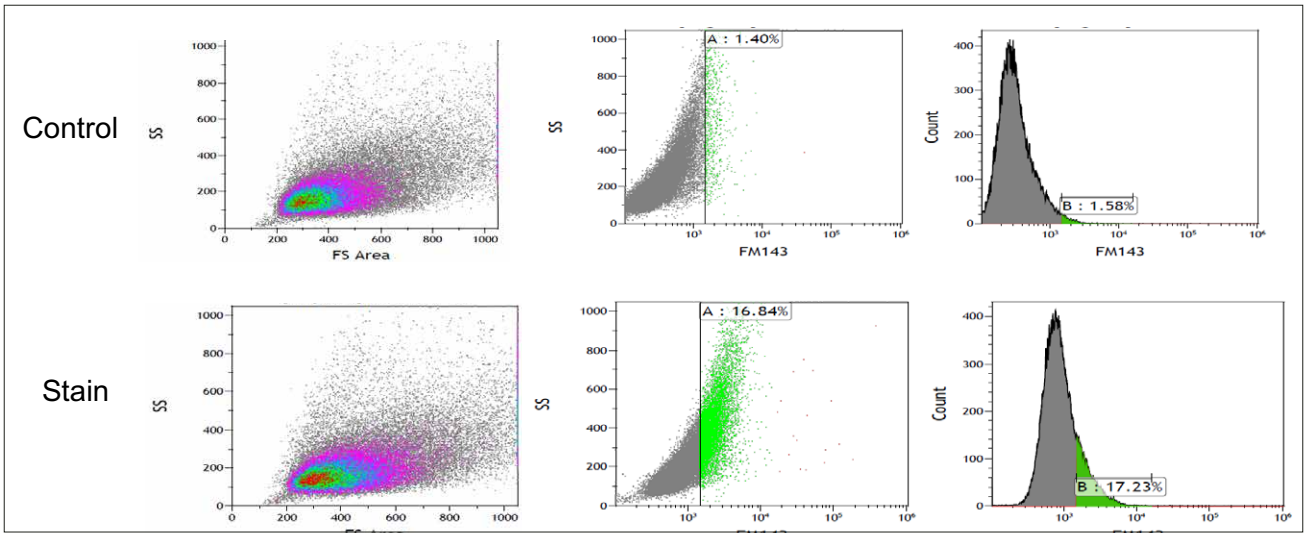


Figure 2. FM-134 stained exosomes are taken up by HUVEC cells analysed by flow cytometry.

the presence of telomerase in exosomes isolated from patients with cancer in response to treatment. This followup is conducted on exosomes derived from patients with lung cancer, breast cancer and glioblastoma multiforme in which we also correlate the disease stage with the presence of mutations present at telomerase promoter as well. We study also other types of cargos that are delivered by exosomes as well.

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

Publications

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.

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

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

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

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

Stein JY, Levin Y, Lahav, Y., **Uziel, O**., Abumock, H., & Solomon, Z. Perceived social support, loneliness and later life telomere length following wartime captivity. *Health Psychology* 37, 1067-1076, 2018.

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.

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

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

Solomon Z, Tsur N, Levin Y, **Uziel O**, Lahav M, Ohry A. The implications of war captivity and long-term psychopathology trajectories for telomere length. Psychoneuroendocrinology. 81, 122-128, 2017.

Kliminski V, **Uziel O**, Kessler-Icekson G. Popdc1/Bves Functions in the Preservation of Cardiomyocyte Viability While Affecting Rac1 Activity and Bnip3 Expression. J Cell Biochem. 118, 1505-1517, 2017.

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

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

Uziel O, Lahav M. Proteomic and microRNA data clarifying the effects of telomere shortening on Cancer cells. Data in Brief. 48–51, 2015.

Shepshelovich D, Ram R, **Uziel O**, Kushnir M, Lithwick Yanai G, Hoshen M, Feinmesser M, Beeri O, Lahav M. MicroRNA signature is indicative of long term prognosis in diffuse large B cell lymphoma. Leukemia Research. 39, 632-7, 2015.

Uziel O, Yosef N, Sharan R, Ruppin E, Kupiec M, Kushnir M, Beery E, Cohen-Diker T, Nordenberg J, Lahav M. Effects of telomere shortening on cancer cells: Network model of proteomic and microRNA analysis. Genomics. 105, 5–16, 2015.

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

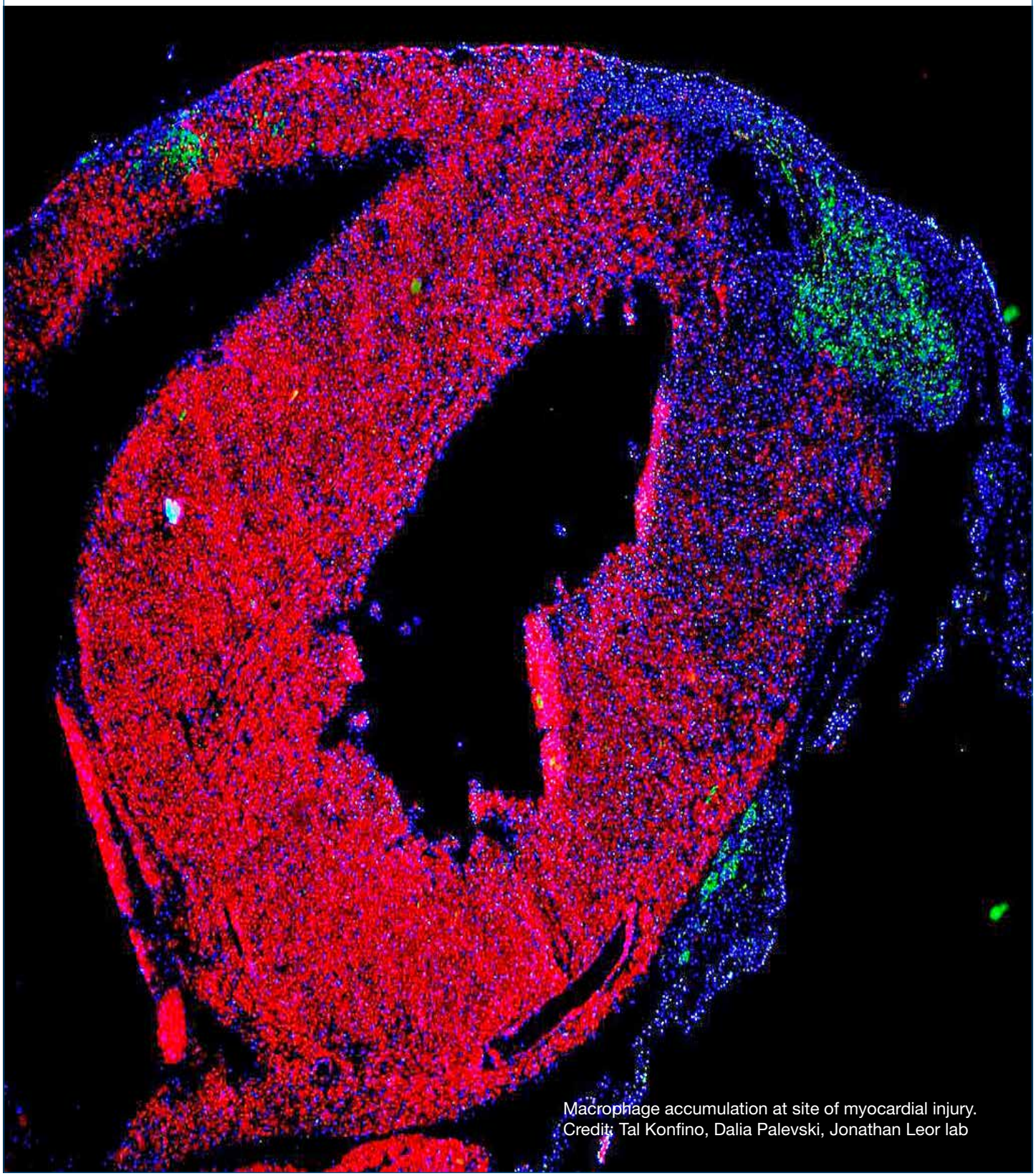
2019-2021 CBRC Dotan Award, The role of chronic lymphocytic leukemia (CLL)-derived exosomes in educating endothelial cells

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

Cardiovascular System



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

Dr. Michal Entin-Meer, Ph.D.

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

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

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

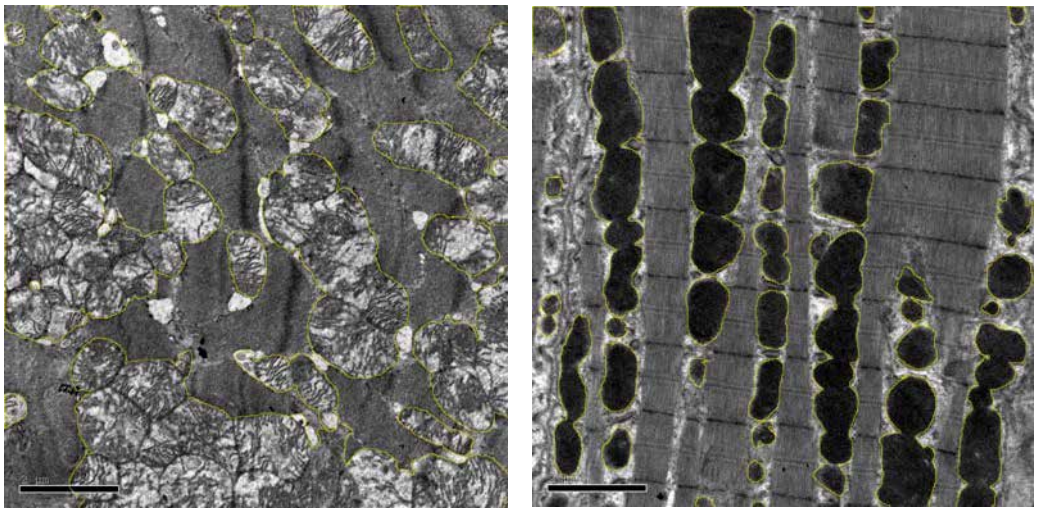
The potential involvement of the cation channel TRPV2, which is highly abundant on peri-infarct immune cells, in the recovery processes following an acute myocardial infarction.

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

Rofe MT, Levi1 R, Hertzberg-Bigelman E, Goryainov P, Barashi R, Ben-Shoshan J, Keren G, **Entin-Meer M**. Chronic kidney disease leads to cardiac hypertrophy



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

with no apparent induction of cardiac cell death. Isr Med Assoc J. 2015, 17(12):744-9.

Barzelay A, Levy R, Kohn E, Sella M, Shani N, Meilik B, **Entin-Meer M**, Gur E, Loewenstein A, Barak A. Power-Assisted Liposuction Versus Tissue Resection for the Isolation of Adipose Tissue-Derived Mesenchymal Stem Cells: Phenotype, Senescence, and Multipotency at Advanced Passages. Aesthet Surg J. 2015, 35(7):NP230-40.

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

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

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

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

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

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

Bigelman E, Cohen L, Aharon-Hananel G, Levy R, Rozenbaum Z, Saada A, Keren G, **Entin-Meer M.** Pathological presentation of cardiac mitochondria in a rat model of chronic kidney disease. *PLoS ONE*. 2018, 13:e0198196.

Cohen L, Bigelman E, Sagi I, Keren G, **Entin-Meer M**. Specific MMP-9 and MMP-2 inhibition by novel MMP antibody attenuates LV remodeling secondary to volume overload. *Suppl to Eur Heart J.* 2018; 586, P2821.

Rozenbaum Y, Topilsky I, Khoury S, Milwidsky A, Balchyunayte A, Laufer-Perl M, Berliner S, Pereg D, **Entin-Meer M***, Havakuk O* (equal authorship). Relationship between climate and hemodynamics according to echocardiography. *J Appl Physiol.* 2018; 126:322-329.

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

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

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.

Dr. Joseph Roitelman, Ph.D.

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Intracellular Regulation of Cholesterol Homeostasis

Positions

Senior Lecturer, Department of Human Genetics and Biochemistry, Sackler School of Medicine

Laboratory Director, Bert W. Strassburger Lipid Center, Sheba Medical Center

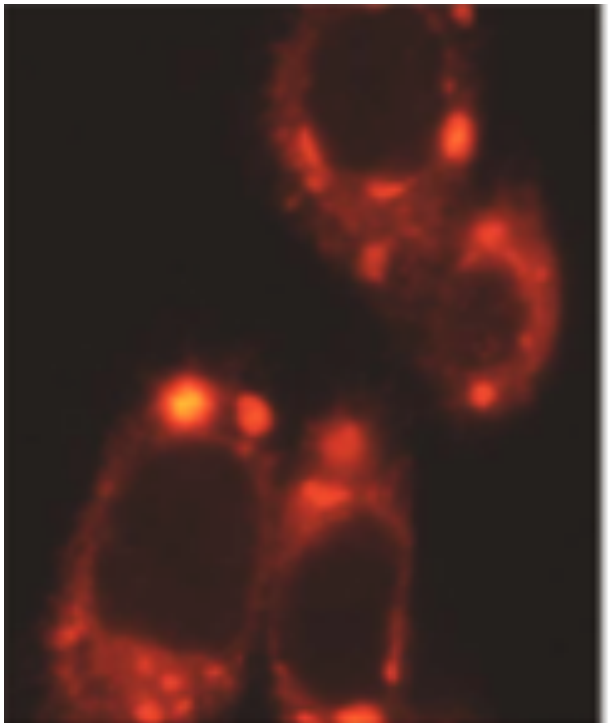
The levels of cholesterol in mammalian cells are tightly regulated by cholesterol itself via multitude of negative feedback mechanisms that coordinate its uptake from plasma lipoproteins and endogenous production in the mevalonate pathway. The major rate-limiting step in the mevalonate pathway is catalyzed by the enzyme HMG-CoA reductase, the target of statins class of cholesterol-lowering drugs.

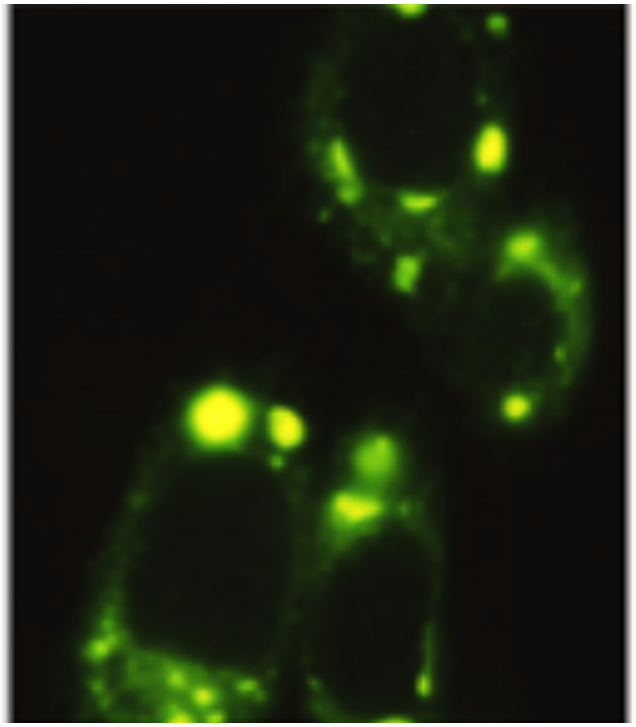
The intracellular abundance, hence activity, of HMG-CoA reductase is strictly controlled by cholesterol and intermediates of the mevalonate pathway, and the research in our laboratory is aimed to unravel the molecular events and cellular factors that operate in the degradation of HMG-CoA reductase protein.

Our studies have wider implications to our understanding of atherosclerosis and neoplastic processes, and afford new perspectives for devising novel therapeutic modalities to combat these diseases.

Publications

Loregger A, Raaben M, Tan J, Scheij S, Moeton M, van den Berg M, Gelberg-Etel H, Stickel E, **Roitelman J**, Brummelkamp T, Zelcer N. Haploid mammalian genetic screen identifies UBXD8 as a key determinant of HMGCR degradation and cholesterol biosynthesis. Arterioscler Thromb Vasc Biol. 2017;37(11):2064-2074.





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Stress and Inflammation in the Cardiovascular System

Positions

Senior Lecturer, Sackler 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

Ben Assayag E, **Shenhar-Tsarfaty S**, Korczyn AD, Kliper E, Hallevi H, Shopin L, et al. Gait measures as predictors of poststroke cognitive function: evidence from the TABASCO study. Stroke. 46, 1077-1083, 2015.

S Shenhar-Tsarfaty, N Yayon, N Waiskopf, I Shapira, S Toker, D Zaltser, S Berliner, Y Ritov, H Soreq. Fear and C-reactive protein cosynergize annual pulse increases in healthy adults. P Natl Acad Sci USA (PNAS), 112, E467-471, 2015.

E Leshem-Rubinow, **S Shenhar-Tsarfaty**, A Milwidsky, S Toker, **I Shapira**, S Berliner, Y Benyamini, S Melamed, O Rogowski. Self-rated health is associated with elevated C-reactive protein even among apparently healthy individuals. IMAJ, 17, 213-217, 2015.

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

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

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

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

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

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

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

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

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

Solomon Z, Levin Y, Assayag EB, Furman O, **Shenhar-Tsarfaty S**, Berliner S, Ohry A. The implication of combat stress and PTSD trajectories in metabolic syndrome and elevated C-reactive protein levels: A longitudinal study. J Clin Psychiatry. 2017;78(9):e1180-e1186.

Ben Assayag E, Eldor R, Korczyn AD, Kliper E, **Shenhar-Tsarfaty S**, Tene O, Molad J, Shapira I, Berliner S, Volfson V, Shopin L, Strauss Y, Hallevi H, Bornstein NM, Auriel E. Type 2 Diabetes Mellitus and impaired renal function are associated with brain alterations and poststroke cognitive decline. Stroke. 2017;48(9):2368-2374.

Brzezinski RY, Etz-Hadar I, Grupper A, Ehrenwald M, Shapira I, Zeltser D, Berliner S, Rogowski O, Eldor R, **Shenhar-Tsarfaty S**. Sex difference in the risk for exercise-induced albuminuria correlates with hemoglobin A1C and abnormal exercise ECG test findings. Cardiovasc Diabetol. 2017;16(1):79.

Ziv-Baran T, **Shenhar-Tsarfaty S**, Etz-Hadar I, Goldiner I, Gottreich A, Alcalay Y, Zeltser D, Shapira I, Angel Y, Friedensohn L, Ehrenwald M, Berliner S, Rogowski O. The ability of the wide range CRP assay to classify individuals with low grade inflammation into cardiovascular risk groups. Clin Chim Acta. 2017;471:185-190.

Ben Assayag E, Tene O, Korczyn AD, Shopin L, Auriel E, Molad J, Hallevi H, Kirschbaum C, Bornstein NM, **Shenhar-Tsarfaty S**, Kliper E, Stalder T. High hair cortisol concentrations predict worse cognitive outcome after stroke: Results from the TABASCO prospective cohort study. Psychoneuroendocrinology. 2017;82:133-139.

Brzezinski RY, Berliner S, **Shenhar-Tsarfaty S**. Letter by Brzezinski et al Regarding Article, "Prediabetes and Type 2 diabetes are associated with generalized microvascular dysfunction: The Maastricht Study". Circulation. 2017;135(14):e860-e861.

Molad J, Kliper E, Korczyn AD, Ben Assayag E, Ben Bashat D, **Shenhar-Tsarfaty S**, Aizenstein O, Shopin L, Bornstein NM, Auriel E. Only white matter hyperintensities predicts post-stroke cognitive performances among cerebral small vessel disease markers: results from the TABASCO Study. J Alzheimers Dis. 2017;56(4):1293-1299.

Herishanu Y, Polliack A, **Shenhar-Tsarfaty S**, Weinberger R, Gelman R, Ziv-Baran T, Zeltser D, Shapira I, Berliner S, Rogowski O. Increased serum C-reactive protein levels are associated with shorter survival and development of second cancers in chronic lymphocytic leukemia. Ann Med. 2017;49(1):75-82.

Brzezinski RY, Fisher E, Cohen N, Zwang E, Shefer G, Stern N, Zeltser D, Shapira I, Berliner S, Rogowski O, **Shenhar-Tsarfaty S**. Total serum cholinesterase activity predicts hemodynamic changes during exercise and associates with cardiac troponin detection in a sex-dependent manner. Mol Med. 2018;24(1):63.

Hod K, Sperber AD, Maharshak N, Ron Y, Shapira I, David Z, Rogowski O, Berliner S, **Shenhar-Tsarfaty S**, Dekel R. Serum cholinesterase activity is elevated in female diarrhea-predominant irritable bowel syndrome patients compared to matched controls. Neurogastroenterol Motil. 2018;30(12):e13464.

Bar-Shai A, **Shenhar-Tsarfaty S**, Ahimor A, Ophir N, Rotem M, Alcalay Y, Fireman E. A novel combined score of biomarkers in sputum may be an indicator for lung cancer: A pilot study.Clin Chim Acta. 2018;487:139-144.

Grupper A, Schwartz D, Berliner S, Shashar M, Grupper A, Baruch R, Schwartz IF, Weinstein T, Ben-Bassat OK, Rogowski O, Zeltser D, Shapira I, **Shenhar-Tsarfaty S**. Normal-range albuminuria in healthy subjects increases over time in association with hypertension and metabolic outcomes.J Am Soc Hypertens. 2018;12(11):759-767.

Tene O, Hallevi H, Korczyn AD, Shopin L, Molad J, Kirschbaum C, Bornstein NM, **Shenhar-Tsarfaty S**, Kliper E, Auriel E, Usher S, Stalder T, Ben Assayag E. The price of stress: High bedtime salivary cortisol 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.

Brzezinski RY, Fisher E, Ehrenwald M, Shefer G, Stern N, Shapira I, Zeltser D, Berliner S, **Shenhar-Tsarfaty S**, Milwidsky A, Rogowski O. Elevated high-sensitive troponin T in negative stress test individuals. Eur J Clin Invest. 2018;48(6):e12930

Ziv-Baran T, Wasserman A, Shteinvil R, Zeltser D, Shapira I, **Shenhar-Tsarfaty S**, Meilik A, Goldiner I, Rogowski O, Berliner S, Halpern P. C-reactive protein and emergency department seven days revisit.Clin Chim Acta. 2018;481:207-211.

Coster D, Wasserman A, Fisher E, Rogowski O, Zeltser D, Shapira I, Bernstein D, Meilik A, Raykhshtat E, Halpern P, Berliner S, **Shenhar-Tsarfaty S,** Shamir R. Using the kinetics of C-reactive protein response to improve the differential diagnosis between acute bacterial and viral infections. Infection. 2019.

Ehrenwald M, Wasserman A, **Shenhar-Tsarfaty S**, Zeltser D, Friedensohn L, Shapira I, Berliner S, Rogowski O. Exercise capacity and body mass index - important predictors of change in resting heart rate. BMC Cardiovasc Disord. 2019;19(1):307.

Steuerman Y, Wasserman A, Zeltser D, Shapira I, Trotzky D, Halpern P, Meilik A, Raykhshtat E, Berliner S, Rogowski O, Gat-Viks I, **Shenhar-Tsarfaty S**. Anemia measurements to distinguish between viral and bacterial infections in the emergency department. Eur J Clin Microbiol Infect Dis. 2019;38(12):2331-2339.

Angel Y, Zeltser D, Berliner S, Ingbir M, Shapira I, **Shenhar-Tsarfaty S**, Rogowski O. Hospitalization as an opportunity to correct errors in anticoagulant treatment in patients with atrial fibrillation. Br J Clin Pharmacol. 2019;85(12):2838-2847.

Grupper A, Ehrenwald M, Schwartz D, Berliner S, Shashar M, Baruch R, Schwartz IF, Rogowski O, Zeltser D, Shapira I, **Shenhar-Tsarfaty S.** Hypertension is associated with increased post-exercise albuminuria, which may be attenuated by an active lifestyle.J Clin Hypertens (Greenwich). 2019;21(8):1171-1179.

Krubiner M, Shapira U, Zeltser D, Shapira I, Berliner S, **Shenhar-Tsarfaty S**, Rogowski O, Bar-Shai A. Lung function deterioration predicts elevated troponin levels in apparently healthy individuals throughout a 5-year follow-up.Respir Med. 2019;154:63-68.

Cohen N, Brzezinski RY, Ehrenwald M, Shapira I, Zeltser D, Berliner S, **Shenhar-Tsarfaty S**, Milwidsky A, Rogowski O. Familial history of heart disease and increased risk for elevated troponin in apparently healthy individuals. Clin Cardiol. 2019;42(8):760-767

Nachmias N, Langier S, Brzezinski RY, Siterman M, Stark M, Etkin S, Avriel A, Schwarz Y, **Shenhar-Tsarfaty S**, Bar-Shai A. NLRP3 inflammasome activity is upregulated in an in-vitro model of COPD exacerbation.PLoS One. 2019;14(5):e0214622.

Ziv-Baran T, Wasserman A, Goldiner I, Stark M, **Shenhar-Tsarfaty S**, Shapira I, Zeltser D, Mailis I, Berliner S, Rogowski O. Characteristics of apparently healthy individuals with a very low C-reactive protein. Clin Chim Acta. 2019;495:221-226.

Brzezinski RY, Milwidsky A, **Shenhar-Tsarfaty S**. Exercise-induced cardiac troponin in the era of high sensitivity assays: What makes our heart sweat? Int J Cardiol. 2019;288:19-21.

Shapira U, Krubiner M, Ehrenwald M, Shapira I, Zeltser D, Berliner S, Rogowski O, **Shenhar-Tsarfaty S**, Bar-Shai A. Eosinophil levels predict lung function deterioration in apparently healthy individuals. Int J Chron Obstruct Pulmon Dis. 2019 Mar 7;14:597-603.

Grupper A, Angel Y, Baruch A, Schwartz IF, Schwartz D, Nakache R, Goykhman Y, Katz P, Nachmany I, Lubezky N, Weinstein T, Shashar M, Ben-Bassat OK, Berliner S, Rogowski O, Zeltser D, Shapira I, **Shenhar-Tsarfaty S**. Long term metabolic and renal outcomes of kidney donors compared to controls with excellent kidney function. BMC Nephrol. 2019;20(1):30.

Fisher E, Brzezinski RY, Ehrenwald M, Shapira I, Zeltser D, Berliner S, Marcus Y, Shefer G, Stern N, Rogowski O, Halperin E, Rosset S, **Shenhar-Tsarfaty S**. Increase of body mass index and waist circumference predicts development of metabolic syndrome criteria in apparently healthy individuals with 2 and 5 years follow-up. Int J Obes (Lond). 2019;43(4):800-807.

Wasserman A, Karov R, **Shenhar-Tsarfaty S**, Paran Y, Zeltzer D, Shapira I, Trotzky D, Halpern P, Meilik A, Raykhshtat E, Goldiner I, Berliner S, Rogowski O. Septic patients presenting with apparently normal C-reactive protein: A point of caution for the ER physician. Medicine (Baltimore). 2019;98(2):e13989.

Milwidsky A, Fisher E, Brzezinski RY, Ehrenwald M, Shefer G, Stern N, Shapira I, Zeltser D, Rosenbaum Z, Greidinger D, Berliner S, **Shenhar-Tsarfaty S**,

Rogowski O. Metabolic syndrome is associated to high-sensitivity cardiac troponin T elevation. Biomarkers. 2019;24(2):153-158.

Shenhar-Tsarfaty S, Sherf-Dagan S, Berman G, Webb M, Raziel A, Keidar A, Goitein D, Sakran N, Zwang E, Shapira I, Zeltser D, Berliner S, Rogowski O, Shibolet O, Zelber-Sagi S. Obesity-related acetylcholinesterase elevation is reversed following laparoscopic sleeve gastrectomy.Int J Obes (Lond). 2019;43(2):297-305.

Ziv-Baran T, Wasserman A, Goldiner I, Stark M, **Shenhar-Tsarfaty S**, Shapira I, Zeltser D, Mailis I, Berliner S, Rogowski O. The association between C-reactive protein and common blood tests in apparently healthy individuals undergoing a routine health examination. Clin Chim Acta. 2020;501:33-41.

Furer V, **Shenhar-Tsarfaty S**, Berliner S, Arad U, Paran D, Mailis I, Rogowski O, Zeltser D, Shapira I, Matz H, Elkayam O. Prevalence of high-sensitivity cardiac troponin T in real-life cohorts of psoriatic arthritis and general population: a cross-sectional study.Rheumatol Int. 2020;40(3):437-444.

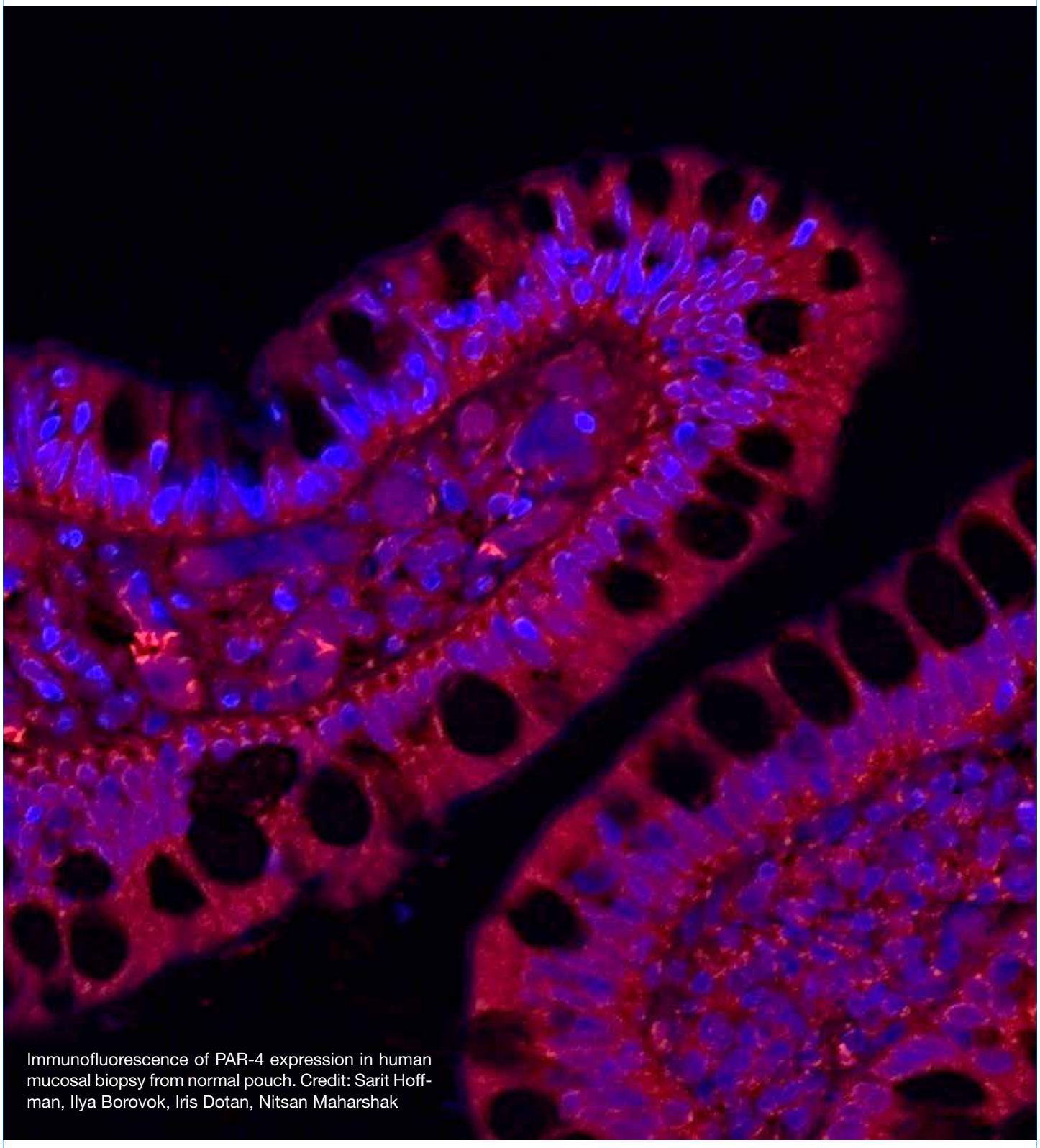
Grants

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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Mononuclear Phagocytes in Digestive Tract Diseases and Metabolic Syndrome

Positions

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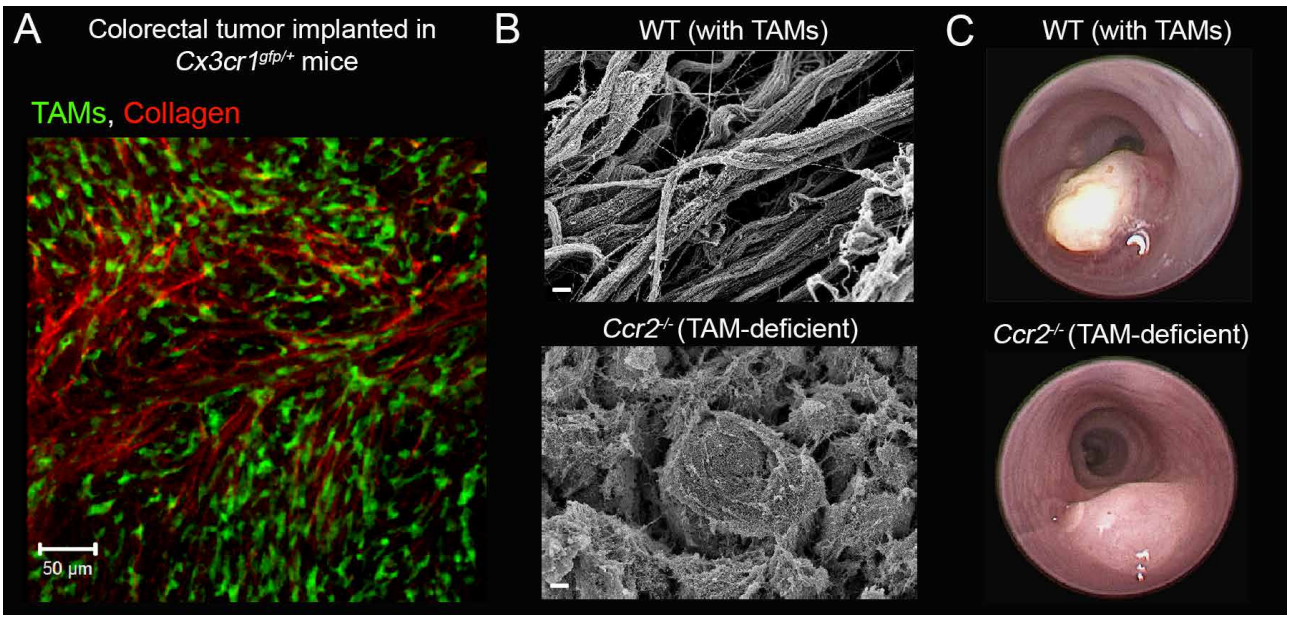
Director, Research Center for Digestive Tract & Liver Diseases

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

Mononuclear phagocytic type of immune cells, including monocytes, macrophages, and dendritic cells, play key homeostatic tissue specific roles in their tissue of residence. Yet, they also play important roles in the pathogenesis and resolution of various diseases of the digestive tract and the metabolic syndrome. Our group strives to decipher the cell-specific immunoregulatory mechanisms that dictate the behavior of these immune cells in health and disease. In particular, we study the involvement of these cells in diseases of the digestive tract and metabolic syndrome, such as: cancer, inflammatory bowel diseases (IBD), liver fibrosis, non-alcoholic steatohepatitis (NASH) and obesity-induced type 2 diabetes. 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 by the functional definition of different phagocyte subsets in these organs and



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

their involvement in the respective diseases. We hope that the mechanistic insights derived from our research will enable us to design novel therapeutic and diagnostic tools for these diseases.

Among our main research topics:

- The interplay between phagocytic immune cells and extracellular matrix (ECM) remodeling in the pathogenesis of IBD, colorectal cancer, liver fibrosis and obesity. Specifically, we study the contribution of phagocyte cell-derived matrix enzymes such as ADAMs to the pathophysiology of these diseases.
- Studying the roles of different immunoregulatory molecules in dictating the inflammatory versus restorative activity of monocytes and macrophage during drug-induced liver injury, liver fibrosis & IBD.

Studying the mechanistic roles and therapeutic potential of molecules that operate at the interface between immunity and metabolism, such as the GIP incretin hormone, S100A8/A9 (Calprotectin) and others.

Publications

Chen Varol, Alexander Mildner and Steffen Jung. Macrophages: development and tissue specialization. 2015. *Annual Review in Immunology*. 33:643-75.

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

Ran Afik*, Ehud Zigmond*, Milena Vugman, Mordehay Klepfish, Elee Shimshoni, Metsada Pasmanik Chor, Anjana Shenoy, Elad Bassat, Zamir Halpern, Tamar Geiger, Irit Sagi* and **Chen Varol***. Tumor macrophages are pivotal constructors of tumor collagenous matrix. 2016. *Journal of Experimental Medicine .* First co-authors equally contributed*

Fernanda Dana Mantelmacher, Sigal Fishman, Keren Cohen, Metsada Pasmanik Chor, Yuichiro Yamada, Isabel Zvibel, **Chen Varol**. Glucose-dependent insulinotropic polypeptide (GIP) receptor deficiency leads to impaired BM hematopoiesis. 2017. *Journal of Immunology*. 198: 000.

Helena Shifrin, Odelia Mouhadeb , Nathan Gluck, **Chen Varol**, Marta Weinstock. Cholinergic anti-inflammatory pathway does not contribute to prevention of ulcerative colitis by novel indoline carbamates. 2017. *The Journal of Neuroimmune Pharmacology. doi:10.1007/s11481-017-9735-8*

Shlomo Magdassi, Shoshi Bar-David, Yael Friedman-Levi, Ehud Zigmond, **Chen Varol**, Guy Lahat, Joseph Klausner, Sara Eyal, Eran Nizri. Intraoperative Localization of Rectal Tumors Using Liposomal Indocyanine Green. 2017. *Surg Innov*. 24:139-144

Odelia Mouhadeb, Shani Ben Shlomo, Keren Cohen, Inbal Farkash, Shlomo Gruber, Nitsan Maharshak, Zamir Halpern, Ezra Burstein, Nathan Gluck, **Chen Varol**. Impaired COMMD10-mediated regulation of Ly6Chi monocyte-driven inflammation disrupts gut barrier function. 2018. Front Immunol. 9:2623.

Debby Reuveni, Yael Gore, Patric S. C. Leung, Yael Lichter, Itay Moshkovits, Ayelet Kaminitz,

Eli Brazowski, Eric Lefebvre, Pamela Vig, **Chen Varol**, Zamir Halpern, Oren Shibolet, Merrill Eric Gershwin, Ehud Zigmond. The critical role of chemokine (C-C Motif) receptor 2-positive monocytes in autoimmune cholangitis. 2018. Front Immunol. 9:1852.

Chen Varol, Irit Sagi. Phagocyte-extracellular matrix crosstalk empowers tumor development and dissemination. 2018. FEBS J. 285(4):734-51.

Tammi Arbel Rubinstein, Shiri Shahmoon, Ehud Zigmond, Tal Etan, Keren Merenbakh-Lamin,

Metsada Pasmanik-Chor, Gil Har-Zahav, Iris Barshack, Gliad W Vainer, Nir Skalka, Rina Rosin-

Arbesfeld, **Chen Varol**, Tamar Rubinek, Ido Wolf. Klotho suppresses colorectal cancer through modulation of the unfolded protein response. 2019. Oncogene. 38(6):794-807.

Hadar Reichman, Michal Itan, Perri Rozenberg, Tal Yarmolovski, Eli Brazowski, **Chen Varol**,

Nathan Gluck, Shiran Shapira, nadir Arber, Udi Qimron, Danielle Karo-Atar, James J Lee, Ariel Munitz. Activated eosinophils exert antitumorigenic activities in colorectal cancer. 2019. Cancer Immunol Res. 7(3):388-400.

Shoshi Bar-David, Liraz Larush, Noam Goder, Asaf Aizic, Ehud Zigmond, **Chen Varol**, Joseph Klausner, Shlomo Magdassi, Eran Nizri. Size and lipid modification determine liposomal Indocyanine green performance for tumor imaging in a model of rectal cancer. 2019. Sci Rep. 9(1):8566.

Dana Fernanda Mantelmacher, Isabel Zvibel, Keren Cohen, Metsada Pasmanik- Chor, Thomas Vogl, Yael Kuperman, Shai Weiss, Daniel J Drucker, **Chen Varol*,** Sigal Fishman*. An enteroendocrine-myeloid cell S100A8/A9 axis controls inflammation and body

weight. 2019. Nature Metabolism. 1, 58–69. * Co-corresponding authors.

Shani Ben Shlomo, Odelia Mouhadeb, Keren Cohen, **Chen Varol***, Nathan Gluck*. COMMD10-Guided Phagolysosomal Maturation Promotes Clearance of Staphylococcus aureus in Macrophages. 2019. iScience. 14:147-63. * Co-corresponding authors.

Chen Varol. Tumorigenic Interplay between macrophages and collagenous matrix in the tumor microenvironment. 2019. Methods in Molecular Biology. New York, NY: Springer; 203-20.

Sigal Fishman, Isabel Zvibel, **Chen Varol**. Incretin Hormones in the Control of Immunometabolism. 2019. Immunometabolism. 1(1).

Mordechay Klepfish, Tamar Gross, Milena Vugman, Nikos A Afratis, Sapir Havusha, Eli Brazowski, Inna Solomonov, **Chen Varol*,** Irit Sagi *. LOXL2 inhibition paves the way for macrophage-mediated collagen degradation in liver fibrosis. 2020. Front Immunol. *in press.* * Co-corresponding authors.

Grants

2016 – 2019	Israel Science Foundation (ISF).
2018 – 2021	Azrieli Foundation.
2019 – 2024	Israel Science Foundation (ISF).
2019 – 2022	Israel Science Foundation (ISF) – Canadian Institute of Health Research joint program

Dr. Isabel Zvibel, Ph.D.

Department of Internal Medicine; Sackler Faculty of Medicine; Research Center for Digestive Tract and Liver Diseases
Tel Aviv Sourasky Medical Center

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Investigating the Mechanisms of Liver Steatosis, Obesity and Cholestatic Injury

Positions

Principal investigator, Research Center for Digestive Tract and Liver Diseases

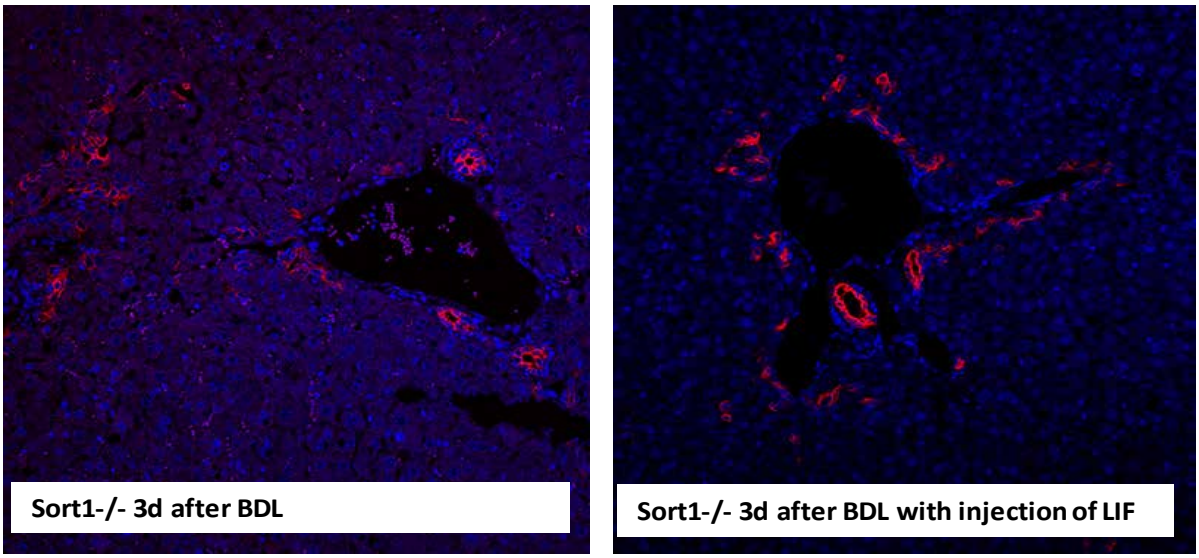
Tel Aviv Sourasky Medical Center

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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



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

Publications

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.

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

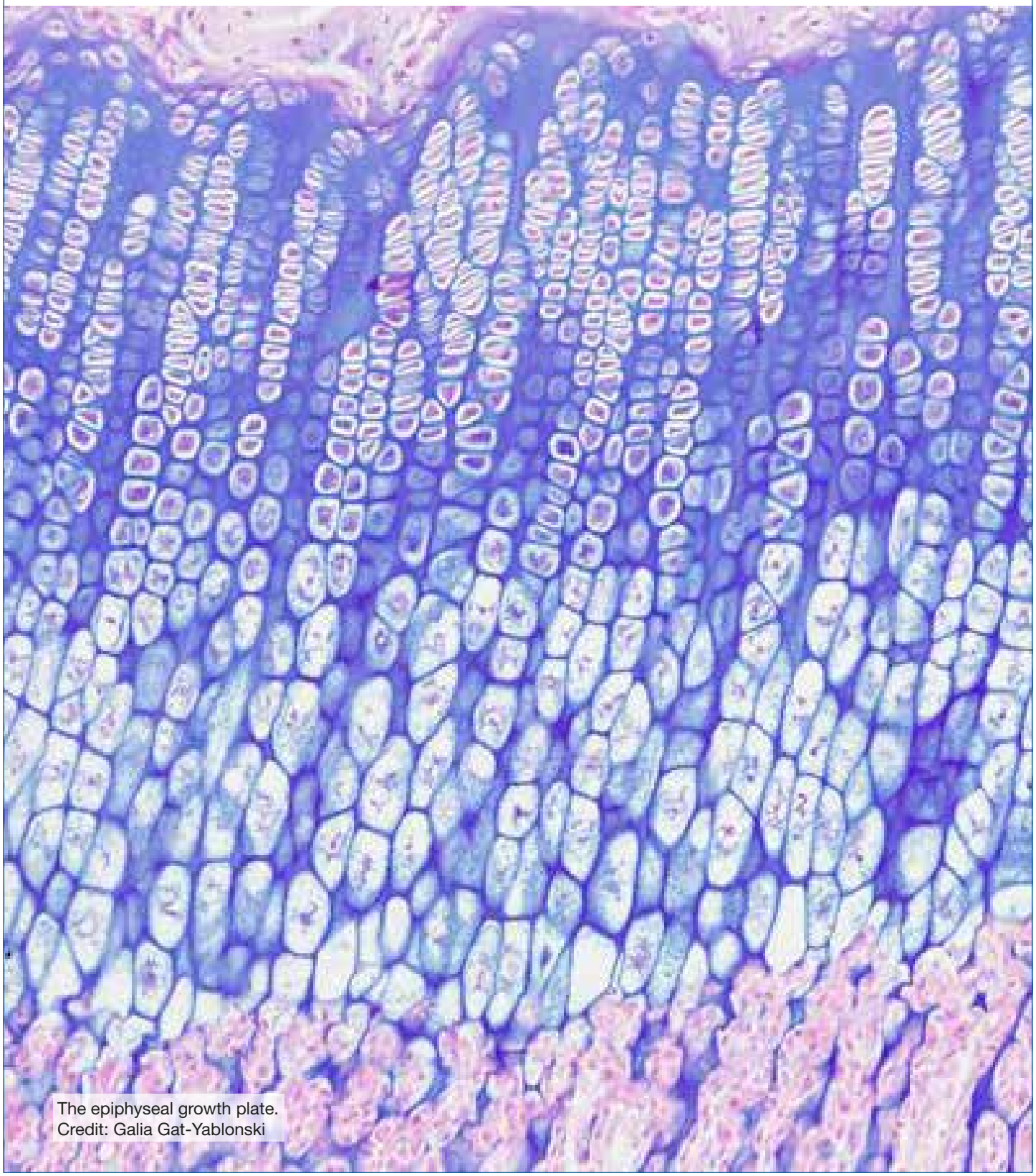
Mantelmacher FD, Fishman S, Cohen K, Pasmanik Chor M, Yamada Y, **Zvibel I***, Varol C*. Glucose-Dependent Insulinotropic Polypeptide Receptor Deficiency Leads to Impaired Bone Marrow Hematopoiesis. *J Immunol*. 2017; 198:3089-3098. * equal senior authors.

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

Dr. Galia Gat-Yablonski, Ph.D.

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The Laboratory for Molecular Endocrinology and Diabetes

Positions

Senior Lecturer, Sackler Faculty of Medicine

Committee Member, Israel Endocrine Society

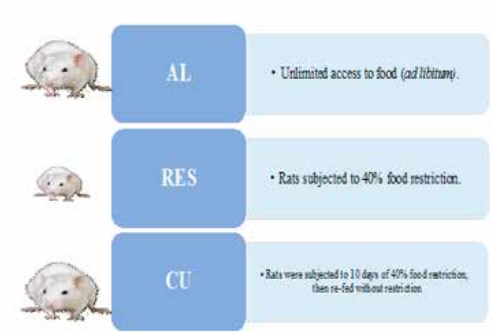
Research

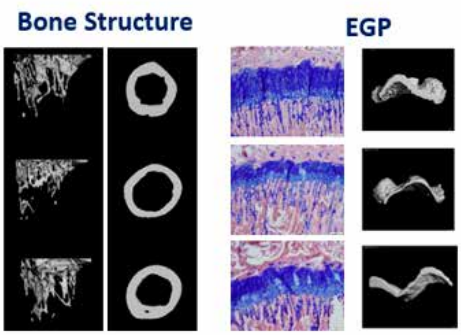
Our lab is studying the processes involved in linear growth in children, in close collaboration with the Institute for Endocrinology and Diabetes at the Schneider Children Medical Center. The study aims to decipher novel regulatory mechanisms for enabling the development of better monitoring and treatment 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.

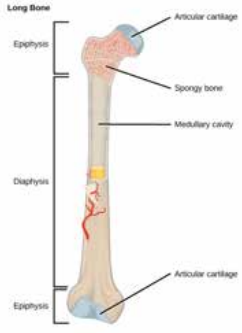
We were the first to show that leptin, the satiety hormone secreted from adipocytes, directly activates the growth plate. We have shown that leptin administration to food restricted animals compensated for the reduced amount of food, leading to almost normal growth. We have further showed that leptin 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 coverts 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 finding 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

Fuchs S, **Gat-Yablonski G**, Shtaif B, Lazar L, Phillip M, Lebenthal Y. Vascular endothelial growth factor (VEGF) levels in short, GH treated children: a distinct pattern of VEGF-C in Noonan syndrome J Endocrinol Invest. 2015; 38: 399-406

Heneberg P, Malá M, Yorifuji T, **Gat-Yablonski G**, Lebenthal Y, Tajima T, Nogaroto V, Rypáčková B, Kocková L, Urbanová J,Anděl M. Low frequencies of autoimmunity-associated PTPN22 polymorphisms in MODY patients, including those transiently expressing islet cell autoantibodies. Int Arch Allergy Immunol. 2015;166:189-98.

Levy T, Bloch Y, Bar-Maisels M, **Gat-Yablonski G**, Djalovski A, Borodkin K, Apter A. Salivary oxytocin in adolescents with conduct problems and callous-unemotional traits. Eur Child Adolesc Psychiatry.2015; 24: 1543-51.

Shtaif B, Dror N, Bar-Maisels M, Phillip M, **Gat-Yablonski G**. Growth without growth hormone: can growth and differentiation factor 5 be the mediator? Growth Factors. 2015; 33:309-18

Pinto G, Shtaif B, Phillip M, **Gat-Yablonski G**. Growth attenuation is associated with histone deacetylase 10-induced autophagy in the liver.J Nutr Biochem.. 2016;27:171-80.

Masarwi M, Gabet Y, Dolkart O, Brosh T, Shamir R, Phillip M, **Gat-Yablonski G.** Skeletal effect of casein and whey protein intake during catch-up growth in young male Sprague-Dawley rats. Br J Nutr. 2016;18:1-11

Gat-Yablonski G, Finka A, Pinto G, Quadroni M, Shtaif B, Goloubinoff P. Quantitative proteomics of rat livers shows that unrestricted feeding is stressful for proteostasis with implications on life span. Aging (Albany NY). 2016;8(8):1735-58.

Levy T, Apter A, Djalovski A, Peskin M, Fennig S, **Gat-Yablonski G**, Bar-Maisels M, Borodkin K, Bloch Y. The reliability, concurrent validity and association with salivary oxytocin of the self-report version of the Inventory of Callous-Unemotional Traits in adolescents with conduct disorder. Psychiatry Res. 2017 256:124-129

Bar-Maisels M, Gabet Y, Shamir R, Hiram-Bab S, Pasmanik-Chor M, Phillip M, Bar-Yoseph F, **Gat-Yablonski G**. Beta palmitate improves bone length and quality during catch-up growth in young rats. Nutrients 2017;9(7).

Masarwi M, Solnik HI, Phillip M, Yaron S, Shamir R, Pasmanic-Chor M, **Gat-Yablonski G**. Food restriction followed by refeeding with a casein- or whey-based

diet differentially affects the gut microbiota of pre-pubertal male rats. J Nutr Biochem. 2018;51:27-39

Lebenthal Y, Fisch Shvalb N, Gozlan Y, Tenenbaum A, Tenenbaum-Rakover Y, Vaillant E, Froguel P, Vaxillaire M, **Gat-Yablonski G**. The unique clinical spectrum of maturity onset diabetes of the young type 3.Diabetes Res Clin Pract. 2018;135:18-22.

Masarwi M, Shamir R, Phillip M, **Gat-Yablonski G**. Leptin stimulates aromatase in the growth plate: limiting catch-up growth efficiency. J Endocrinol. 2018. pii: JOE-18-0028

Yackobovitch-Gavan M, **Gat-Yablonski G**, Shtaif B, Hadani S, Abargil S, Phillip M, Lazar L. Growth hormone therapy in children with idiopathic short stature - the effect on appetite and appetite-regulating hormones: a pilot study. Endocr Res. 2018:1-11

Aviram A, Shtaif B, **Gat-Yablonski G**, Yogev Y. The association between adipocytokines and glycemic control in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2018:1-201

Yackobovitch-Gavan M, **Gat-Yablonski G**, Shtaif B, Hadani S, Abargil S, Phillip M, Lazar L.Growth hormone therapy in children with idiopathic short stature - the effect on appetite and appetite-regulating hormones: a pilot study. Endocr Res. 2019;44(1-2):16-26.

Aviram A, Shtaif B, **Gat-Yablonski G**, Yogev Y. The association between adipocytokines and glycemic control in women with gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2020;33(2):177-183.

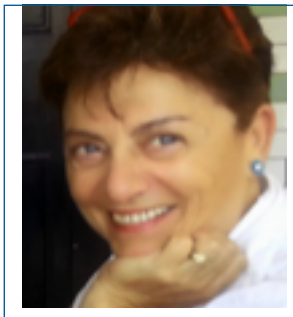
Reviews

Gat-Yablonski G, Phillip M. Nutritional catch up growth. Nutrients. 2015 ;7(1):517-51.

Yackobovitch-Gavan M, Phillip M, **Gat-Yablonski G**. How milk and its proteins affect growth, bone health, and weight. Horm Res Paediatr. 2017;88(1):63-69.

Gat-Yablonski G, De Luca F. Effect of nutrition on statural growth. Horm Res Paediatr. 2017 88(1):46-62

Gat-Yablonski G, Yackobovitch-Gavan M, Phillip M. Which dietary components modulate longitudinal growth? Curr Opin Clin Nutr Metab Care. 2017 ;20(3):211-216



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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

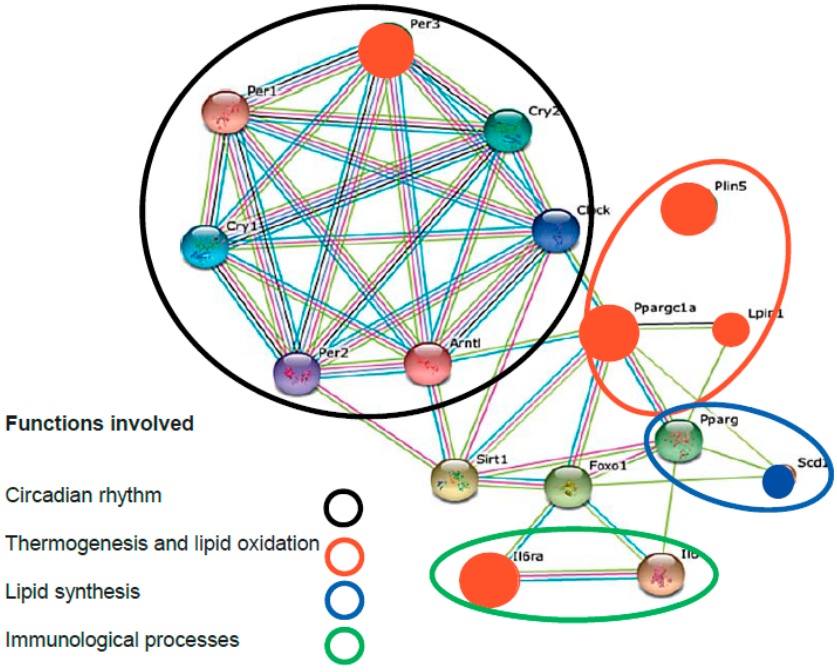
Positions

Associate Professor, CAMEA, Sackler Faculty of Medicine

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

Research

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



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

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

Mahler L, Hararia A, Harats D,A Ben-Amotz A, Peled M, **Leikin-Frenkel A**, Kandel Kfir M, Kamaria Y, Shaish A. (2019) Combined treatment with 9-cis β-carotene and 22R-hydroxycholesterol augments cholesterol efflux in macrophages. Algal Research 44.

Harari A, **Leikin-Frenkel A**, Sagee A, et al. (2019) Addition of fish-oil to atherogenic-high-fat diet inhibited atherogenesis while olive oil did not, in LDL receptor-KO mice. Advances in Biology. 1(1): 1-10.

Almog, T., Kandel Kfir, M., Levkovich, H., Shlomai, G., Barshack, I., Stienstra, R., Lustig, Y., **Leikin Frenkel, A.**, Harari, A., Bujanover, Y., Apte, R., Shaish, A., Harats, D., Kamari, Y. (2018) Interleukin-1α deficiency reduces adiposity, glucose intolerance and hepatic de-novo lipogenesis in diet-induced obese mice. BMJ Open Diabetes Research and Care. 7: e000650.

Yehuda I, Madar A, **Leikin-Frenkel A**, Tamir S. 2015. Glabridin, an isoflavan from licorice root, down-regulates iNOS expression and activity under high glucose stress and inflammation. Molecular Nutrition & Food Research 59: 1041-1052.

L Shomonov Wagner, A Raz, **A Leikin-Frenkel**. 2015. Alpha linolenic acid in maternal diet halts the lipid disarray due to saturated fatty acids in the liver of mice offspring at weaning Lipids Health Dis. 26:14-14.

ML Kagan, AR Levy, **A Leikin-Frenkel**. 2015. Comparative study of tissue deposition of omega-3 fatty acids from polar-lipid rich oil of the microalgae *Nannochloropsis oculata* with krill oil in rats. Food Funct. 6:186-92.

Yehuda I, Madar Z, **Leikin-Frenkel A**, Szuchman-Sapir A, Magzal F, Markman G, Tamir S 2015. Glabridin, an isoflavan from licorice root, up-regulates paraoxonase 2 expression under hyperglycemia and protects it from oxidation. Molecular Nutrition & Food Research 10: 287-299.

Leikin-Frenkel A, Shomonov-Wagner L, Juknat A, Pasmanik-Chore M. 2015. Maternal Diet Enriched with Alpha Linolenic or Saturated Fatty Acids Differentially Regulates Gene Expression in Mice Offspring's liver. J Nutrigenet Nutrigenomics; 8:185-194.

Review

Leikin-Frenkel A. 2016. Is there A Role for Alpha-Linolenic Acid in the Fetal Programming of Health? Journal of Clinical Medicine 5:40.

Leikin-Frenkel A. Perinatal Lipid Nutrition. Cordero Sanchez P and Vinci Guerra M. Molecular Nutrition,Elsevier (2020).

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

Dr. Tali Zitman-Gal, Ph.D.

Nephrology Laboratory
Department of Nephrology and Hypertension
Meir Medical Center, Kfar Saba

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Investigating the Molecular Mechanisms of Vascular Dysfunction

Positions

Lecturer, Sackler Faculty of Medicine

Head of Nephrology Laboratory, Meir Medical Center

Research

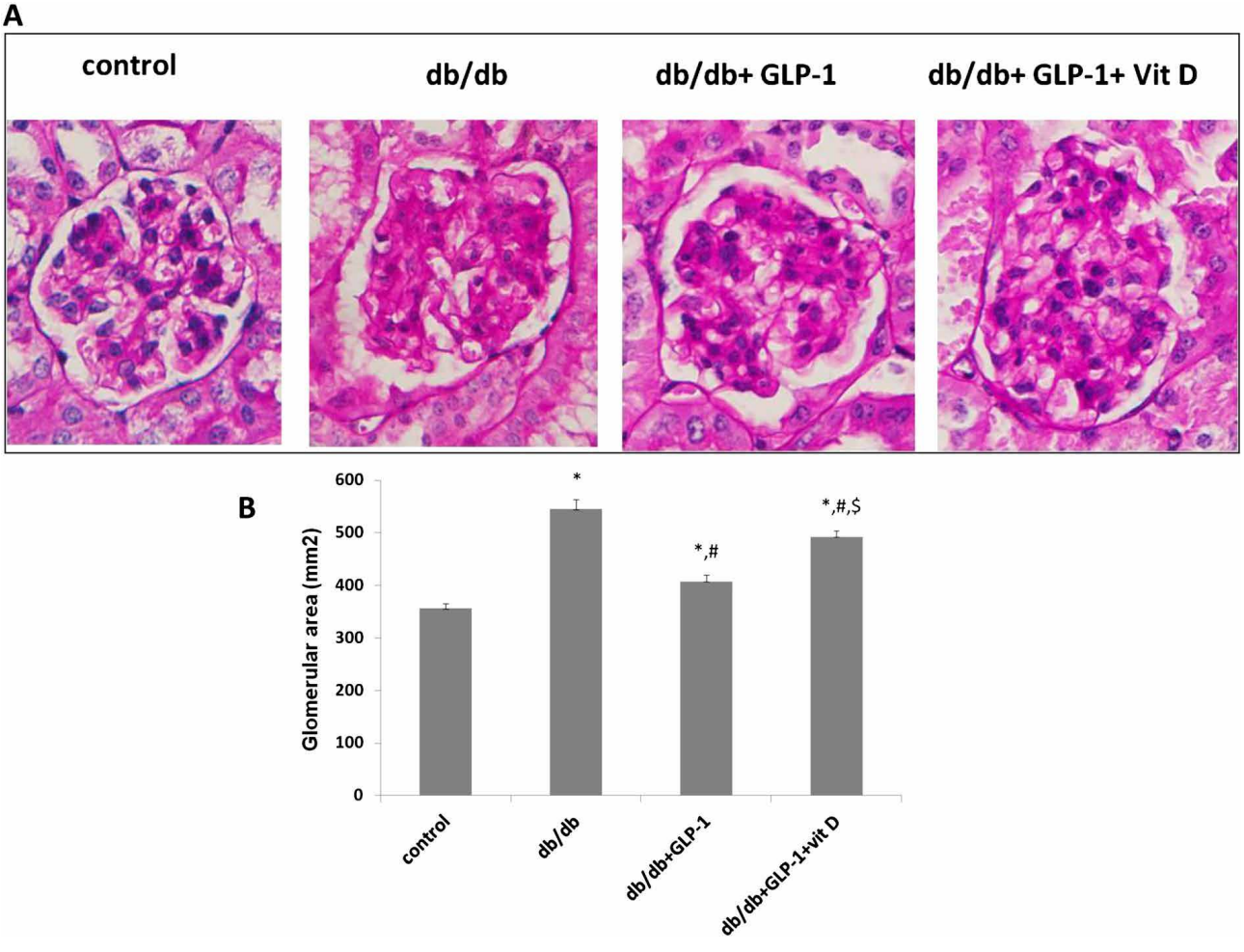
Diabetes - We study the anti-inflammatory response in *in vitro* models of endothelial and smooth muscle cells exposed to a diabetic-like environment and in *in vivo* models of *db/db* mice

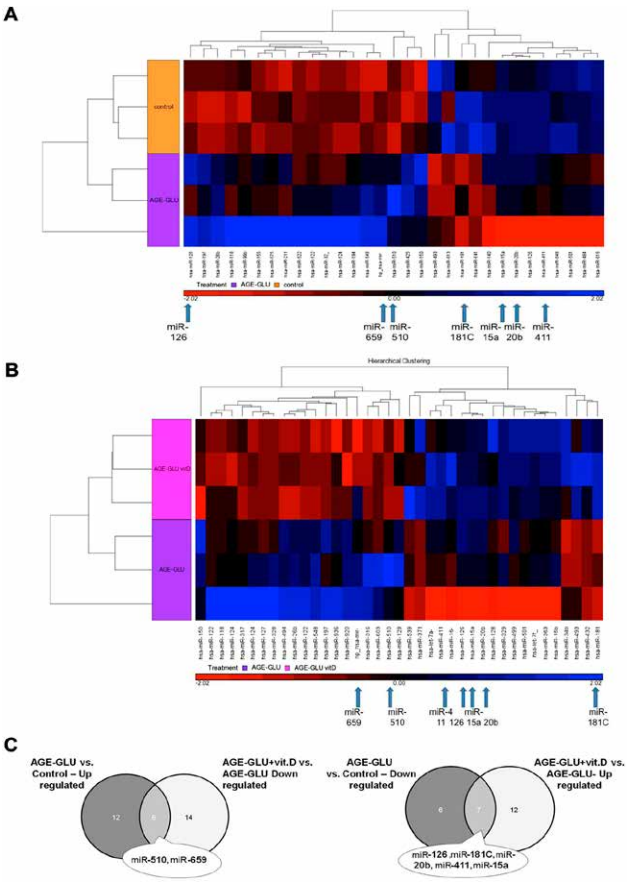
Normal and preeclamptic pregnancies and gestational diabetes - HDL composition and function, as well as evaluate vascular gene and protein changes in maternal and cord blood and placental biopsies, in collaboration with the Department of Obstetrics and Gynecology

Chronic kidney disease - Stratify blood levels of Galectin-3 in patients with CKD and investigate the potential association with deterioration in renal function

Hemodialysis - Correlate cell-free DNA and other blood markers with hemodialysis patient outcomes, in collaboration with the Department of Nephrology, Soroka Hospital

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





Publications

Zitman-Gal T, Green J, Korzets Z, Bernheim J, Benchetrit S (2015) Kruppel-like factors in an endothelial and vascular smooth muscle cell coculture model: impact of a diabetic environment and vitamin D. *In Vitro Cellular & Developmental Biology - Animal***.** 51:470-478.

Einbinder Y, Ohana M, Benchetrit S, Zehavi T, Nacasch N, Bernheim J, **Zitman-Gal T** (2016) Glucagon-like-peptide-1 and vitamin D: anti-inflammatory response in diabetic kidney disease in db/db mice and in cultured endothelial cells. Diabetes Metab Res Rev. 32:805-815.

Cohen-Hagai K, Rozenberg I, Korzets Z, **Zitman-Gal T**, Einbinder Y, Benchetrit S. (2016) Upper respiratory tract infection among dialysis patients. IMAJ. 18.

Cohen-Hagai K, Rashid G, Einbinder Y, Ohana M, Benchetrit S, **Zitman-Gal T**.(2017) Effect of vitamin D status on Von Willebrand factor and ADAMTS13 in diabetic patients on chronic hemodialysis. Ann Lab Med. 37:155-158.

Einbinder Y, Benchetrit S, Golan E, **Zitman-Gal T** (2017). Comparison of intact PTH and bio-intact PTH assays among non-dialysis dependent chronic kidney disease patients. Ann Lab Med. 2017 37:381-387.

Cohen-Hagai K, Rashid G, Ohana M, Benchetrit S, **Zitman-Gal T** (2017).[The effect of vitamin D on the expression of ADAMT13 in cultured endothelial cells exposed to a diabetic-like environment]. Harefuah. 156:486-489. Hebrew.

Einbinder Y, Biron-Shental T, Agassi-Zaitler M, Tzadikevitch-Geffen K, Vaya J, Khatib S, Ohana M, Benchetrit S, **Zitman-Gal T** (PI) (2018). High-density lipoproteins (hdl) composition and function in preeclampsia. Archives of Gynecology and Obstetrics. 298(2):405-413.

Einbinder Y, Agur T, Davidov K, **Zitman-Gal T**, Golan E, Benchetrit S. (2018) Anemia management among hemodialysis patients with high ferritin levels. IMAJ. 20(7):405-411.

Cohen-Hagai K, Kotliroff A, Rozenberg I, Korzets Z, **Zitman-Gal T**, Benchetrit S (2018). Effectiveness of influenza vaccine in hemodialyzed patients – A retrospective study. Therapeutic Apheresis and Dialysis. 23(1):38-43.

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.

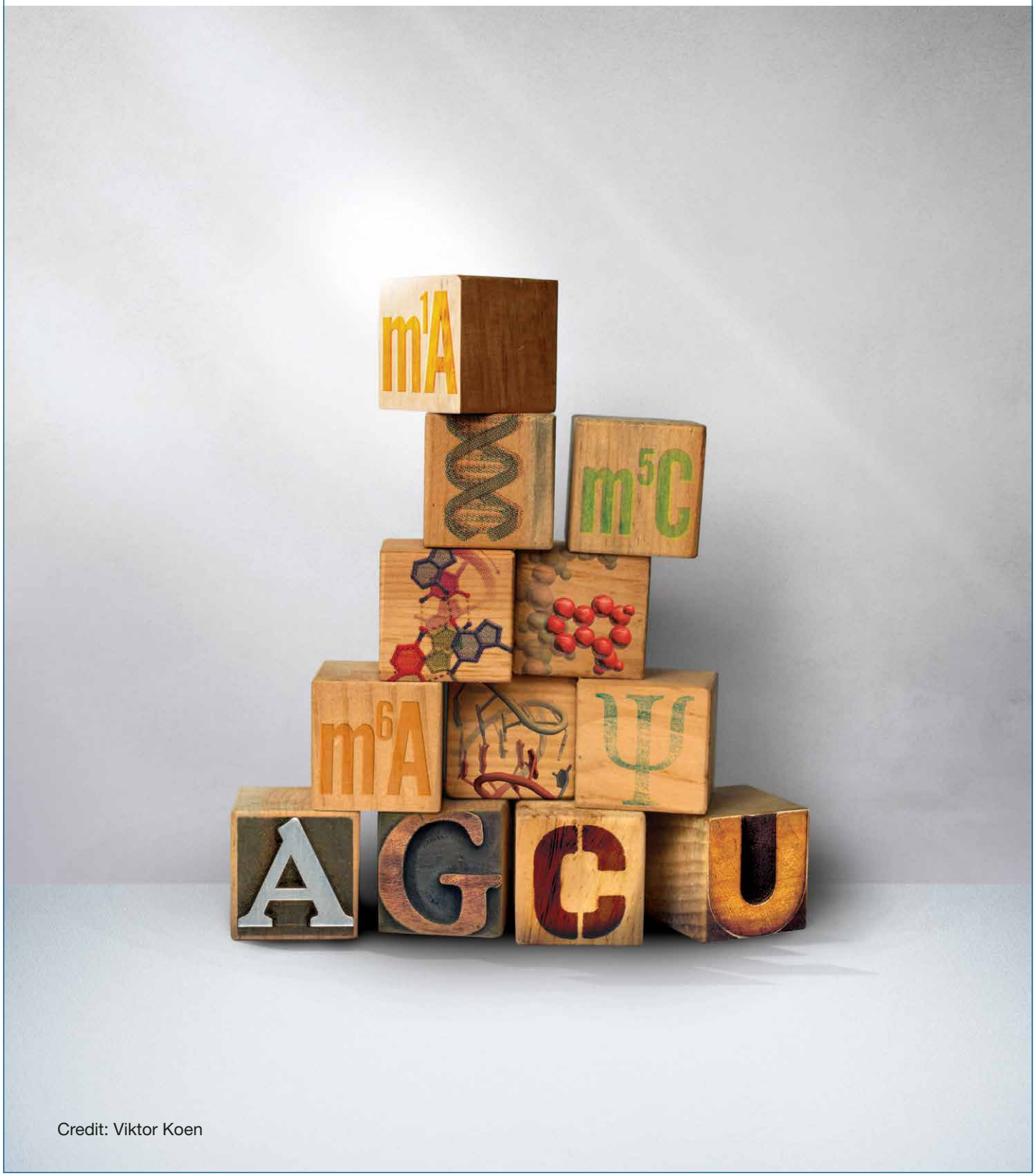
Cohen-Hagai K, Nacasch N, Rozenberg I, Korzets Z, Einbinder Y, **Zitman-Gal T**, Benchetrit, S. (2019) Clinical outcomes of stroke in hemodialysis patients: a retrospective single-center study. International Urology and Nephrology. 51:1435-1441.

Pasternak Y, Ohana M, Biron-Shental T, Cohen-Hagai K, Benchetrit S, **Zitman-Gal T**. (2019) Thioredoxin, Thioredoxin interacting protein and transducer and activator of transcription 3 in gestational diabetes. Molecular Biology Reports. 47:1199-1206.

Grants

2019-2020 ISNH – Israeli Society of Nephrology and Hypertension

Genetic Diseases & Genomics



Credit: Viktor Koen

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Epitranscriptomics: Gene Expression Regulation Through RNA Modifications

Positions

Deputy Director, Cancer Research Center, Chaim Sheba Medical Center

Senior Lecturer, Faculty of Medicine, Tel Aviv University

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 consequenes 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.

Publications

Greenbaum L, Barel O, Nikitin V, Hersalis-Eldar A, Kol N, Reznik-Wolf H, **Dominissini D**, Pras E, Dori A. Identification of a homozygous VRK1 mutation in two patients with adult-onset distal hereditary motor neuropathy. *Muscle Nerve*. 2019

Dominissini D, Rechavi G. N4-acetylation of cytidine in mRNA by NAT10 regulates stability and translation. *Cell.* 2018;175:1725-1727.

Hsu PJ, Fei Q, Dai Q, Shi H, **Dominissini D**, Ma L, He C. Single base resolution mapping of 2'-O-methylation sites in human mRNA and in 3' terminal ends of small RNAs. *Methods*. 2019;156:85-90.

Hesser CR, Karijolich J, **Dominissini D**, He C, Glaunsinger BA. N6-methyladenosine modification and the YTHDF2 reader protein play cell type specific roles in lytic viral gene expression during Kaposi's sarcoma-associated herpesvirus infection. *PLoS Pathog*. 2018;14:e1006995.

Choi J, Indrisiunaite G, DeMirci H, Ieong KW, Wang J, Petrov A, Prabhakar A, Rechavi G, **Dominissini**

D, He C, Ehrenberg M, Puglisi JD. 2'-O-methylation in mRNA disrupts tRNA decoding during translation elongation. *Nat Struct Mol Biol*. 2018;25:208-216.

Dominissini D, Rechavi G. 5-methylcytosine mediates nuclear export of mRNA. *Cell Res*. 2017;27:717-719.

Dai Q, Moshitch-Moshkovitz S, Han D, Kol N, Amariglio N, Rechavi G, **Dominissini D**, He C. Nm-seq maps 2'-O-methylation sites in human mRNA with base precision. *Nat Methods*. 2017;14:695-698.

Clark WC, Evans ME, **Dominissini D**, Zheng G, Pan T. tRNA base methylation identification and quantification via high-throughput sequencing. *RNA*. 2016;22:1771-1784.

Dominissini D, Nachtergaele S, Moshitch-Moshkovitz S, Peer E, Kol N, Ben-Haim MS, Dai Q, Di Segni A, Salmon-Divon M, Clark WC, Zheng G, Pan T, Solomon O, Eyal E, Hershkovitz V, Han D, Doré LC, Amariglio N, Rechavi G, He C. The dynamic N(1)-methyladenosine methylome in eukaryotic messenger RNA. *Nature.* 2016;530:441-6.

Choi J, Ieong KW, Demirci H, Chen J, Petrov A, Prabhakar A, O'Leary SE, **Dominissini D**, Rechavi G, Soltis SM, Ehrenberg M, Puglisi JD. N(6)-methyladenosine in mRNA disrupts tRNA selection and translation-elongation dynamics. *Nat Struct Mol Biol*. 2016;23:110-5.

Dominissini D, Moshitch-Moshkovitz S, Amariglio N, Rechavi G. Transcriptome-wide mapping of N^6-methyladenosine by m^6A-seq. *Methods Enzymol*. 2015;560:131-47.

Geula S, Moshitch-Moshkovitz S, **Dominissini D**, Mansour AA, Kol N, Salmon-Divon M, Hershkovitz V, Peer E, Mor N, Manor YS, Ben-Haim MS, Eyal E, Yunger S, Pinto Y, Jaitin DA, Viukov S, Rais Y, Krupalnik V, Chomsky E, Zerbib M, Maza I, Rechavi Y, Massarwa R, Hanna S, Amit I, Levanon EY, Amariglio N, Stern-Ginossar N, Novershtern N, Rechavi G, Hanna JH. Stem cells. m^6A mRNA methylation facilitates resolution of naïve pluripotency toward differentiation. *Science*. 2015;347:1002-6.

Chen K, Lu Z, Wang X, Fu Y, Luo GZ, Liu N, Han D, **Dominissini D**, Dai Q, Pan T, He C. High-resolution N(6)-methyladenosine (m(6) A) map using photo-crosslinking-assisted m(6) A sequencing. *Angew Chem Int Ed Engl*. 2015;54:1587-90.

Review

Livneh I, Moshitch-Moshkovitz S, Amariglio N, Rechavi G, **Dominissini D**. The m6A epitranscriptome: transcriptome plasticity in brain development and function. *Nat Rev Neurosci*. 2020;21:36-51.

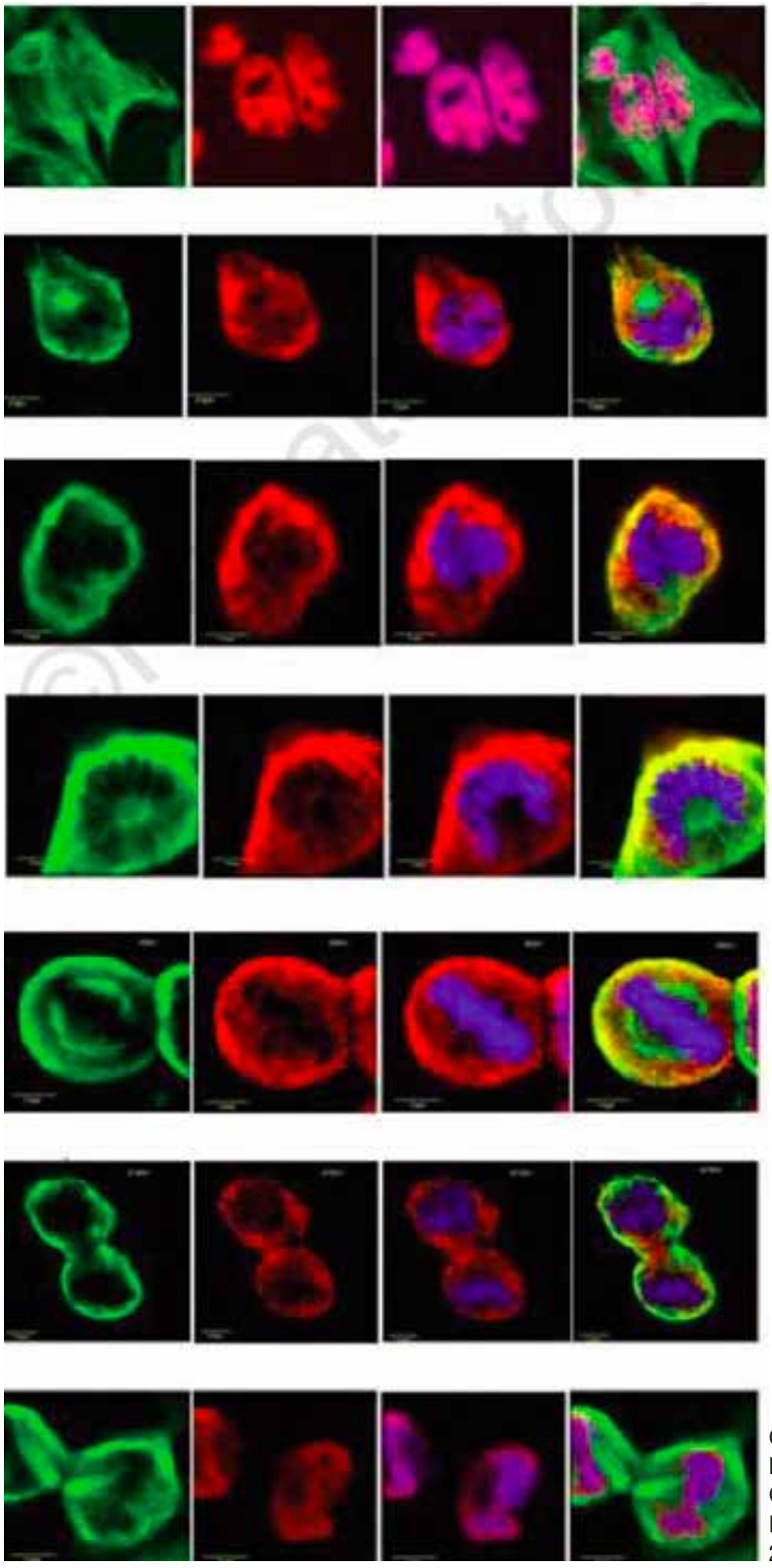
Peer E, Moshitch-Moshkovitz S, Rechavi G, **Dominissini D**. The epitranscriptome in translation regulation. *Cold Spring Harb Perspect Biol*. 2019;11.

Dominissini D, Rechavi G. Epitranscriptome regulation. Nat Struct Mol Biol. 2018.

Peer E, Rechavi G, **Dominissini D**. Epitranscriptomics: regulation of mRNA metabolism through modifications. *Curr Opin Chem Biol*. 2017;41:93-98.

Dominissini D, Rechavi G. Loud and clear epitranscriptomic m1A signals: Now in single-base resolution. *Mol Cell*. 2017 Dec 7;68825-826.

Immunology & Hematology



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

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Investigating the Molecular Basis of Pulmonary Fibrosis

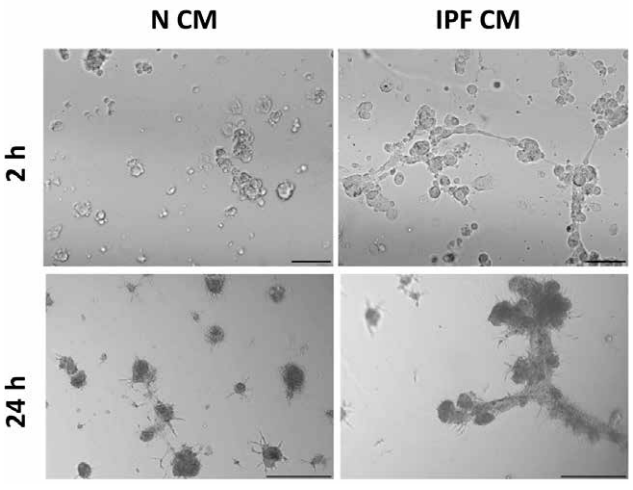
Positions

Lecturer, Sackler 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.



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.

Publications

Epstein Shochet G, Israeli-Shani L, Koslow M, Shitrit D. Nintedanib (BIBF 1120) blocks the tumor promoting signals of lung fibroblast soluble microenvironment. *Lung Cancer*. 2016;96:7-14

Epstein Shochet G, Komemi O, Sadeh-Mestechkin D, Pomeranz M, Fishman A, Drucker L, Lishner M, Tartakover Matalon S. Heat shock protein-27 (HSP27) regulates STAT3 and eIF4G levels in first trimester human placenta. *J Mol Histol*. 2016;47(6):555-563

Epstein Shochet G, Brook E, Israeli-Shani L, Edelstein E, Shitrit D. Fibroblast paracrine TNF-α signaling elevates integrin A5 expression in idiopathic pulmonary fibrosis (IPF). *Respir Res*. 2017;19;18(1):122

Markevitz N*, **Epstein Shochet G***, Levi Y, Israeli-Shani L, Shitrit D. Sarcoidosis in Israel: Clinical outcome status, organ involvement, and long-term follow-up. *Lung* 2017;195: 419-424.

Koslow M, **Epstein Shochet G**, Matveychuk A, Israeli-Shani L, Guber A, Shitrit D. The role of bacterial culture by bronchoscopy in patients with lung cancer: a prospective study. *J Thorac Dis* 2017;9(12):5300-5305

Epstein Shochet G, Wollin L, Shitrit D. The matrix-fibroblast interplay: Nintedanib and Pirfenidone modulate the effect of IPF fibroblast conditioned matrix on normal fibroblast phenotype. *Respirology*. 2018;23(8):756-763

Bar-Gil Shitrit A, Chen-Shuali C, Adar T, Koslowsky B, Shteingart S, Paz K, Grisaru-Granovsky S, Goldin E, **Epstein Shochet G** and Shitrit D. Sleep disturbances can be prospectively observed in patients with an inactive Inflammatory Bowel Disease. *Dig Dis Sci.* 2018;63(11):2992-2997

Shitrit D, Adir Y, Avriel Y, King D, **Epstein Shochet G**, Guber A, Schnaer S, Kassirer M, D. Blanc P, Abramovich A. EBUS-TBNA is sufficient for

successful diagnosis of silicosis with mediastinal lymphadenopathy. *Lung*. 2018;196(4):441-445

Komemi O, **Epstein Shochet G**, Pomeranz M, Fishman A, Pasmanik-Chor M, Drucker L, Tartakover Matalon S, Lishner M. Placenta-conditioned extracellular matrix (ECM) activates breast cancer cell survival mechanisms: a key for future distant metastases. *Int J Cancer*. 2019:1;144(7):1633-1644

Levy Y, Israeli-Shani L, Kuchuk M, **Epstein Shochet** G, Koslow M, Shitrit D. Rheumatological assessment is important to interstitial lung disease diagnosis. *J Rheumatol*. 2018;45(11):1509-1514.

Dahan D, **Epstein Shochet G**, Fizitsky E, Almagor M and Shitrit D. Acute infection in ventilated patients in the intensive care unit: Association between resting energy expenditure and C-reactive protein. *Isr Med Assoc J*. 2018;20(10):604-607.

Wand O, Guber E, Guber A, **Epstein Shochet G,** Israeli-Shani L, and Shitrit D. Inhaled Tranexamic Acid for hemoptysis treatment: A randomized controlled trial. *Chest*. 2018;154(6):1379-1384.

Epstein Shochet G, Brook E, Eyal O, Edelstein E, Shitrit D. Epidermal growth factor receptor (EGFR) paracrine upregulation in idiopathic pulmonary fibrosis (IPF) fibroblasts is blocked by nintedanib. *Am J Physiol Lung Cell Mol Physiol*. 20191;316(6):L1025-L1034.

Erez D, Koslow M, **Epstein Shochet G**, Dovrish Z, Israeli-Shani L, Dahan D, King D, Shitrit D. Computed tomography angiography findings in pulmonary embolism patients vary following thrombolytic treatment. *Isr Med Assoc J*. 2019;21(3):203-207.

Guber A, **Epstein Shochet G**, Kohn S, Shitrit D. wrist-sensor pulse oximeter enables prolonged patient monitoring in chronic lung diseases. *J Med Syst*. 201914;43(7):230.

Koslow M, Shitrit D, Israeli-Shani L, Uziel O, Beery E, Osadchy A, Refaely Y, **Epstein Shochet G**, Amiel A. Peripheral blood telomere alterations in ground glass opacity (GGO) lesions may suggest malignancy *Thorac Cancer*. 2019;10(4):1009-1015

Koslow M, **Epstein Shochet G**, Fenadka F, Neuman Y, Osadchy A, Shitrit D. Systemic thrombolysis therapy is associated with improved outcomes among patients with acute pulmonary embolism and respiratory failure. *Am J Med Sci* 2020;28;S0002-9629(20)30161-0.

Epstein Shochet G, Brook E, Bardenstein-Wald B, Shitrit D. TGF-β pathway activation by Idiopathic Pulmonary Fibrosis (IPF) Fibroblast derived soluble factors is mediated by IL-6 trans-signaling. *Respir Res* 2020;21(1):56.

Epstein Shochet G, Brook E, Bardenstein-Wald B, Grobe H, Edelstein E, Israeli-Shani L and Shitrit D. Integrin alpha-5 silencing leads to myofibroblastic differentiation in IPF-derived human lung fibroblasts. *Ther Adv Chronic Di* 2020;11: 1–12

Grants

2019-2020 Avalyn Pharma

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Precision Medicine in Rheumatology

Position

Dr. Smadar Gertel

Head of the Arthritis Research Laboratory

Lecturer, Sackler Faculty of Medicine

Position

Prof. Ori Elkayam

Head of the Rheumatology Department, Tel Aviv Sourasky Medical Center

Professor, Sackler Faculty of Medicine

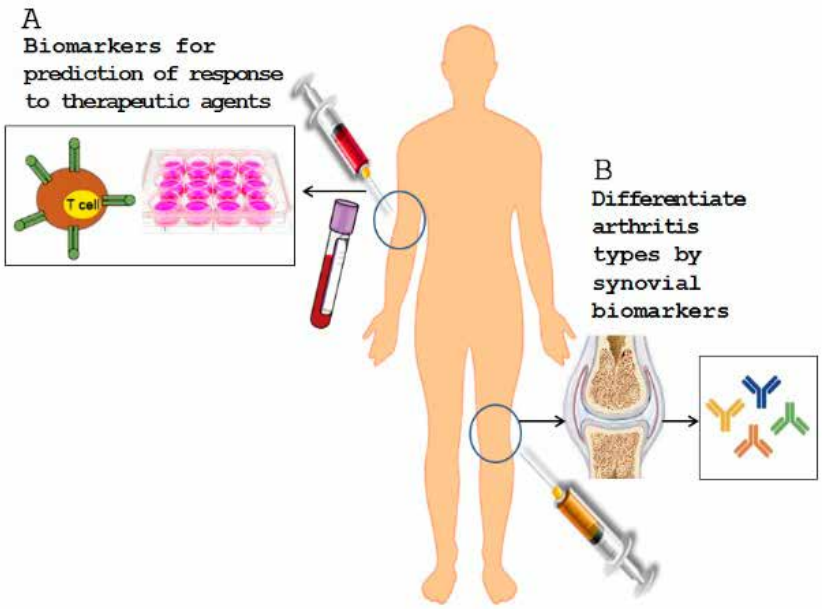
Former Chairman, The Israeli Society of Rheumatology

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.

Gertel S, Polachek A, Furer V, Levartovsky D, Elkayam O. CD4(+) LAG-3(+) T cells are decreased in active psoriatic arthritis patients and their restoration in vitro is mediated by TNF inhibitors. *Clin Exp Immunol.* 2021;206:173-83.

Chorin E, Hochstadt A, Arad U, Ghantous E, **Gertel S**, Levartovsky D, et al. Soluble ST2 and CXCL-10 may serve as biomarkers of subclinical diastolic dysfunction in SLE and correlate with disease activity and damage. *Lupus*. 2020;29:1430-7.

Gibor G, Ilan N, Journo S, Sharabi A, Dreyer J, **Gertel S**, et al. Heparanase is expressed in adult human osteoarthritic cartilage and drives catabolic responses in primary chondrocytes. *Osteoarthritis Cartilage*. 2018;26:1110-7.

Dr. Gilad Halpert, Ph.D.

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

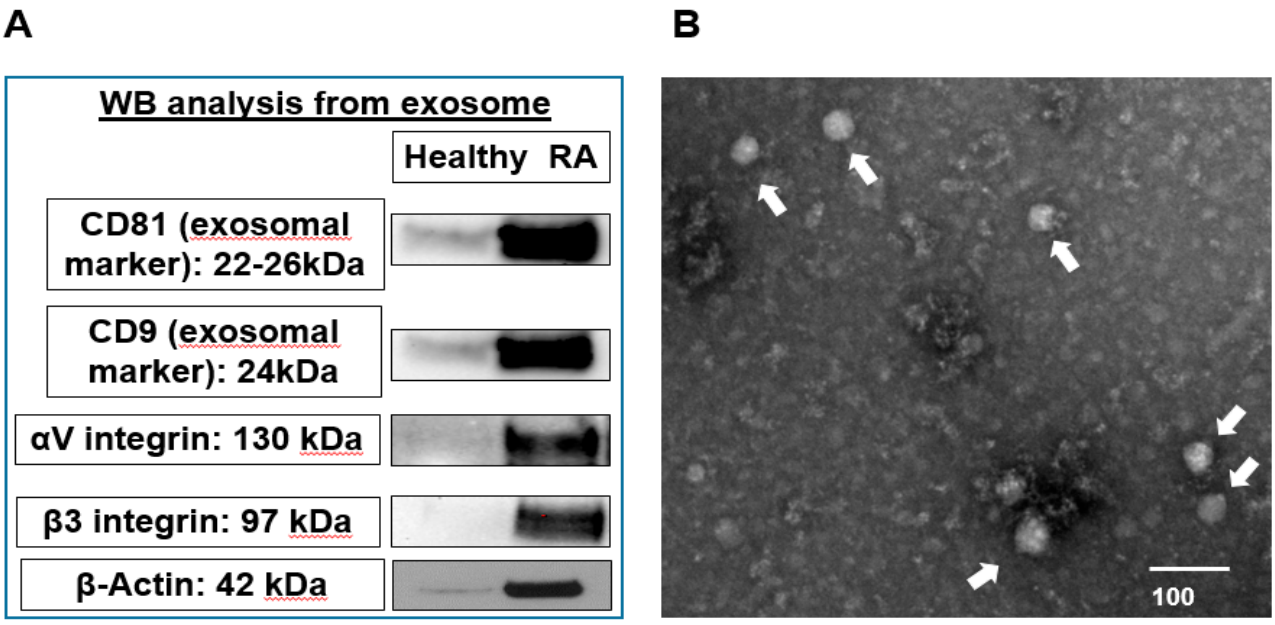
Positions

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



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

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

Publications

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

Halpert, G., Amital, H., and Shoenfeld, Y. (2020) [Silicone Breast Implants - Historical Medical Error], *Harefuah 159*, 697-702.

Borodina, E., Katz, I., Antonelly, A., Gzgzyan, A. M., Dzhemlikhanova, L. K., Ostriski, Y., Niauri, D., Jamilya, K., Bitsadze, V., Makatsariya, A., Tincani, A., Nalli, C., Churilov, L. P., Shovman, O., **Halpert, G**., Blank, M., Shoenfeld, Y., and Amital, H. (2020) The pathogenic role of circulating Hashimoto's Thyroiditis-derived TPO positive IgG on fetal loss in naive mice, *Am J Reprod Immunol*, e13331.

Kagan, P., **Halpert, G.**, Amital, H., Shapira, R., and Shoenfeld, Y. (2020) Autoimmune/Inflammatory Syndrome induced by adjuvant associated with a metal implant in the mouth; explantation was followed by recovery, *Isr Med Assoc J 9*, 516-517.

Ben-Ami Shor, D., Lachnish, J., Bashi, T., Dahan, S., Shemer, A., Segal, Y., Shovman, O., **Halpert, G.**, Volkov, A., Barshack, I., Amital, H., Blank, M., and Shoenfeld, Y. (2019) Immunomodulation of murine chronic DSS-induced colitis by tuftsin-phosphorylcholine, *J Clin Med 9*.

Huang, X., Zhuang, J., Chung, S. W., Huang, B., **Halpert, G.**, Negron, K., Sun, X., Yang, J., Oh, Y., Hwang, P. M., Hanes, J., and Suk, J. S. (2019) Hypoxia-tropic protein nanocages for modulation of tumor- and chemotherapy-associated hypoxia, *ACS Nano 13*, 236-247.

Date, A. A.*, Halpert, G.*, Babu, T., Ortiz, J., Kanvinde, P., Dimitrion, P., Narayan, J., Zierden, H., Betageri, K., Musmanno, O., Wiegand, H., Huang, X., Gumber, S., Hanes, J., and Ensign, L. M. (2018) Mucus-penetrating budesonide nanosuspension enema for local treatment of inflammatory bowel disease, *Biomaterials 185*, 97-105.

Date, A. A., Rais, R., Babu, T., Ortiz, J., Kanvinde, P., Thomas, A. G., Zimmermann, S. C., Gadiano, A. J., **Halpert, G.**, Slusher, B. S., and Ensign, L. M. (2017) Local enema treatment to inhibit FOLH1/GCPII as a novel therapy for inflammatory bowel disease, *J Control Release 263*, 132-138.

Dardik, R.*, Livnat, T.*, Halpert, G.*, Jawad, S., Nisgav, Y., Azar-Avivi, S., Liu, B., Nussenblatt, R. B., Weinberger, D., and Sredni, B. (2016) The small tellurium-based compound SAS suppresses inflammation in human retinal pigment epithelium, *Mol Vis 22*, 548-562.

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

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

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

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Immunology-Research.aspx

CAR T Immunotherapy for Cancer and Beyond

Positions

Senior Scientist

Laboratory Manager and Head, Tel Aviv Sourasky Medical Center

Research

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

Publications

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

Globerson Levin A, Kronik N, Shiloach T, Waks T, Eshhar Z, Vainstein V. Less is more: reducing the number of administered chimeric antigen receptor T cells in a mouse model using a mathematically guided approach. Cancer Immunol Immunother 2020; 69:1165-1175.

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

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

Dr. Tami Livnat, Ph.D.

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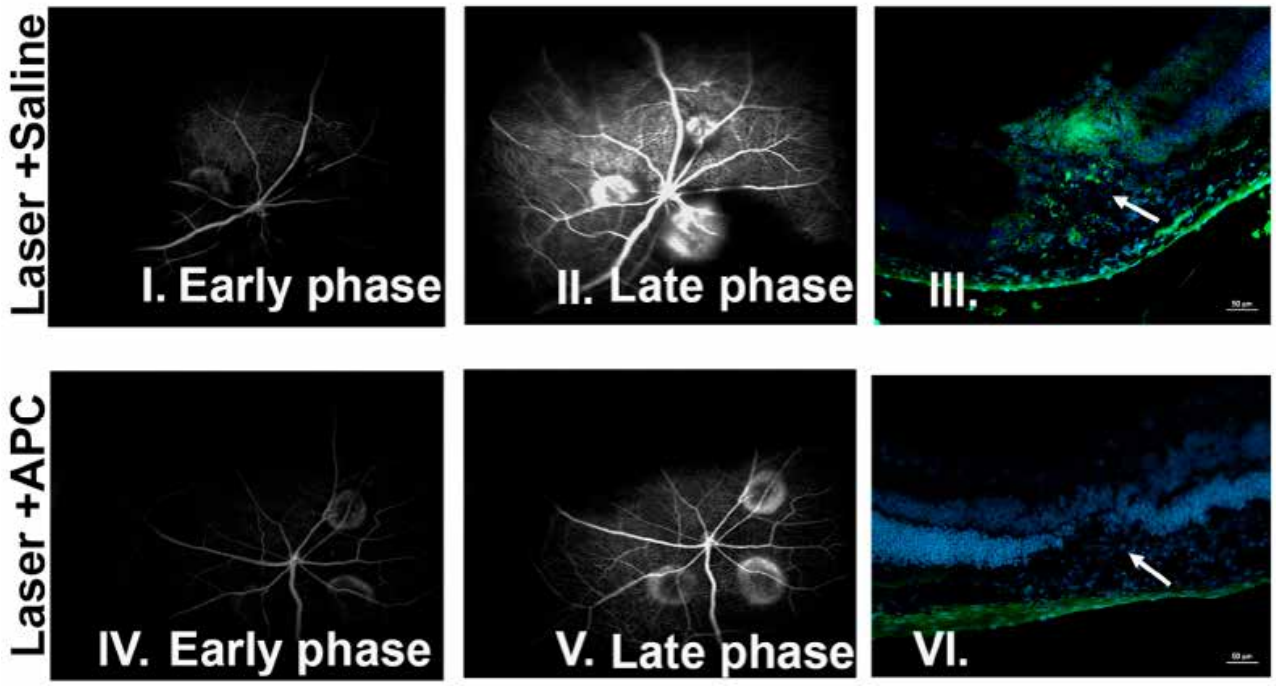
The Coagulation Cascade: Hemostasis and Cellular Aspects

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 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.



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.

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

Salomon O, Budnik I, Avishai E, Tamarin I, Bashari D, Dardik R, **Livnat T**. Single low dose of rfviia combined with antifibrinolytic agent is a simple and safe treatment for factor xi-deficient patients undergoing surgery. *Thromb Haemost*. 2019; 119:1927-1932

Barg AA, Avishai E, Budnik I, Levy-Mendelovich S, Barazani TB, Kenet G, **Livnat T** Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors-a single-center cohort. *Pediatr Blood Cancer*. 2019; 66:e27886.

Livnat T, Weinberger Y, Budnik I, Deitch I, Dahbash M, Sella R, Dardik R, Kenet G, Nisgav Y, Weinberger D. Activated protein C induces suppression and regression of choroidal neovascularization- A murine model. *Exp Eye Res*. 2019; 186:107695.

Eiger-Moscovich M, Livny E, Sella R, Gal-Or O, Nisgav Y, **Livnat T**, Bahar I Comparison of Subconjunctival Aflibercept and Betamethasone for the Treatment of Formed Corneal Neovascularization in a Rabbit Model. *Ophthalmic Res*. 2019; 6:116-122

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.

Levy-Mendelovich S, Levy T, Budnik I, Barg AA, Rosenberg N, Seligsohn U, Kenet G, **Livnat T**. Low concentrations of recombinant factor VIIa may improve the impaired thrombin generation of Glanzmann thrombasthenia patients. *Thromb Haemost*. 2019; 119:117-127.

Barg AA, Levy-Mendelovich S, Avishai E, Dardik R, Misgav M, Kenet G, **Livnat T**. Alternative treatment options for pediatric hemophilia B patients with high-responding inhibitors: A thrombin generation-guided study. *Pediatr Blood Cancer*. 2018; 65:e27381.

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.

Bar-Ilan A, **Livnat T**, Hoffmann M, Binder L, Zakar M, Guy R, Felikman Y, Moschcovich L, Shenkman B, Monroe D, Hershkovitz O, Kenet G, Hart G. In vitro characterization of MOD-5014, a novel long-acting carboxy-terminal peptide (CTP)-modified activated FVII. *Haemophilia.* 2018; 24:477-486.

Levy-Mendelovich S, Barg AA, Rosenberg N, Avishai E, Luboshitz J, Misgav M, Kenet G, **Livnat T**. Treatment tailoring for factor V deficient patients and perioperative management using global hemostatic coagulation assays. *Blood Cells Mol Dis*. 2018; 71:5-10.

Barliya T, Dardik R, Nisgav Y, Dachbash M, Gaton D, Kenet G, Ehrlich R, Weinberger D, **Livnat T**. Possible involvement of NETosis in inflammatory processes in the eye: Evidence from a small cohort of patients. *Mol Vis*. 2017; 23:922-932.

Weinberger D, Bor-Shavit E, Barliya T, Dahbash M, Kinrot O, Gaton DD, Nisgav Y, **Livnat T**. Mobile laser indirect ophthalmoscope: for the induction of choroidal neovascularization in a mouse model. *Curr Eye Res*. 2017;42:1545-1551.

Tal K, Dotan A, Nisgav Y, Dachbash M, Gal-Or O, Ehrlich R, Gaton DD, Weinberger D, **Livnat T.** Retinal penetration of intravitreally injected tissue plasminogen activator: a rat model study. *Ophthalmic Res*. 2018;59:235-240

Livnat T, Budnik I, Levy-Mendelovich S, Avishai E, Misgav M, Barg AA, Lubetsky A, Brutman-Barazani T, Kenet G. Combination of hemostatic therapies for treatment of patients with hemophilia A and inhibitors. *Blood Cells Mol Dis*. 2017;66:1-5.

Ehrlich R, Zahavi A, Axer-Siegel R, Budnik I, Dreznik A, Dahbash M, Nisgav Y, Megiddo E, Kenet G, Weinberger D, **Livnat T**. Correlation between interleukin-6 and thrombin-antithrombin iii complex levels in retinal diseases. *Curr Eye Res*. 2017;42:1269-1272.

Barliya T, Ofri R, Sandalon S, Weinberger D, **Livnat T**. Changes in retinal function and cellular remodeling following experimental retinal detachment in a rabbit model. *J Ophthalmol*. 2017;2017:4046597.

Leiba M, Malkiel S, Budnik I, Rozic G, Avigdor A, Duek A, Nagler A, Kenet G, **Livnat T**. Thrombin generation as a predictor of thromboembolic events in multiple myeloma patients. Blood *Cells Mol Dis.* 2017;65:1-7.

Schaap-Fogler M, Bahar I, Rephaeli A, Dahbash M, Nudelman A, Livny E, Barliya T, Nisgav Y, **Livnat T**. Effect of Histone Deacetylase inhibitor, Butyroyloxymethyl-Diethyl Phosphate (AN-7), on corneal neovascularization in a mouse model. J *Ocul Pharmacol Ther*. 2017;33:480-486.

Kuperman AA, Barg AA, Fruchtman Y, Shaoul E, Rosenberg N, Kenet G, **Livnat T**. Primary prophylaxis for children with severe congenital factor VII deficiency - Clinical and laboratory assessment. *Blood Cells Mol Dis*. 2017;67:86-90.

Sherman S, Rabizadeh E, Moyal L, **Livnat T**, Ziv E, Cherny I, Inbal A, Hodak E. Fibrinogen-like Protein 2 Activity as a Potential Biomarker for Diagnosis of Early Mycosis Fungoides. *Acta Derm Venereol.* 2017;97:370-372.

Dardik R, **Livnat T**, Halpert G, Jawad S, Nisgav Y, Azar-Avivi S, Liu B, Nussenblatt RB, Weinberger D, Sredni B. The small tellurium-based compound SAS suppresses inflammation in human retinal pigment epithelium. *Mol Vis*. 2016;22:548-62.

Gal-Or O, Livny E, Sella R, Nisgav Y, Weinberger D, **Livnat T**, Bahar I. Efficacy of subconjunctival aflibercept versus bevacizumab for prevention of corneal neovascularization in a rat model. *Cornea*. 2016;35:991-6.

Rainy N, Etzion T, Alon S, Pomeranz A, Nisgav Y, **Livnat T**, Bach M, Gerstner CD, Baehr W, Gothilf Y, Stiebel-Kalish H. Knockdown of unc119c results in visual impairment and early-onset retinal dystrophy in zebrafish. *Biochem Biophys Res Commun*. 2016;473:1211-1217

Dotan A, Kremer I, Gal-Or O, L**ivnat T**, Zigler A, Bourla D, Weinberger D. Scleral cross-linking using riboflavin and ultraviolet-a radiation for prevention of axial myopia in a rabbit model. *J Vis Exp*. 2016;110:e53201.

Sella R, Gal-Or O, Livny E, Dachbash M, Nisgav Y, Weinberger D, **Livnat T**, Bahar I. Efficacy of topical aflibercept versus topical bevacizumab for the prevention of corneal neovascularization in a rat model. *Exp Eye Res*. 2016;146:224-32.

Gal-Or O, Dotan A, Dachbash M, Tal K, Nisgav Y, Weinberger D, Ehrlich R, **Livnat T**. Bevacizumab clearance through the iridocorneal angle following intravitreal injection in a rat model. *Exp Eye Res*. 2016;145:412-416.

Fruchtman Y, Dardik R, Barg AA, **Livnat T**, Feldman Z, Rubinstein M, Grinberg G, Rosenberg N, Kenet G. Spinal epidural hematoma following cupping glass treatment in an infant with hemophilia A. *Pediatr Blood Cancer*. 2016;63:1120-2

Sidlik R, Strauss T, Morag I, Shenkman B, Tamarin I, Lubetsky A, **Livnat T**, Kenet G. Assessment of functional fibrinolysis in cord blood using modified thromboelastography. *Pediatr Blood Cancer*. 2016;63:839-43.

Maharshak I, Salomon-Zimri S, Antes R, Liraz O, Nisgav Y, **Livnat T**, Weinberger D, Colton CA, Solomon AS, Michaelson DM. The effects of the apoE4 genotype on the developing mouse retina. *Exp Eye Res*. 2016;145:17-25.

Livnat T, Shenkman B, Martinowitz U, Zivelin A, Dardik R, Tamarin I, Mansharov R, Budnik I, Salomon O. The impact of thrombin generation and rotation thromboelastometry on assessment of severity of factor XI deficiency. *Thromb Res*. 2015;136:465-73.

Antes R, Salomon-Zimri S, Beck SC, Garcia Garrido M, **Livnat T**, Maharshak I, Kadar T, Seeliger M, Weinberger D, Michaelson DM. VEGF mediates ApoE4-induced neovascularization and synaptic pathology in the choroid and retina. *Curr Alzheimer Res*. 2015;12:323-34.

Shenkman B, Einav Y, **Livnat T**, Budnik I, Martinowitz U. Rotation thromboelastometry analysis of clot formation and fibrinolysis in severe thrombocytopenia: effect of fibrinogen, activated prothrombin complex concentrate, and thrombin- activatable fibrinolysis inhibitor. Int *J Lab Hematol*. 2015;37:521-9

Reviews

Barg AA, **Livnat T**, Kenet G. Inhibitors in hemophilia: Treatment challenges and novel options. *Semin Thromb Hemost*. 2018; 44:544-550.

Barg AA, **Livnat T**, Kenet G. An extra X does not prevent acquired hemophilia - Pregnancy-associated acquired hemophilia A. *Thromb Res*. 2017; 151 Suppl 1:S82-S85.

Livnat T, Barg AA, Levy-Mendelovich S, Kenet G Rare bleeding disorders-old diseases in the era of novel options for therapy. *Blood Cells Mol Dis*. 2017; 67:63-68.

Grants

2019 Claire and Amédée Maratier Fund, Sackler 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, Sackler 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, Sackler Faculty of Medicine

Research

Our laboratory focuses on pathologies where the immune system of subject attacks its own body components, such as Systemic Sclerosis (a disease of connective tissue).

Our research is conducted in several areas with the aim of promoting personalized medicine: 1) Discovering markers (glycosylated proteins, young cells, autoantibodies, miRNA) for evaluation and diagnosis of rare autoimmune diseases. 2) Understanding mechanisms underlying disease progression in order to find new therapeutic targets and exploring the effectivity and mechanisms of action of new therapy for autoimmune diseases. 3) Studying the complex relationship between cancer and autoimmune diseases.

Our laboratories work combines techniques of cellular and molecular biology. The studies are based on close collaboration between researchers and physicians, which promotes access to up-to-date clinical approaches and novel strategies under development as well as to human tissues.

The Lab also operates a biobank of sera collected from patients with autoimmune diseases.

The strength of the laboratory is its ability to combine ongoing studies using primary cells and blood samples with the clinical data of the patients In order to reach a deeper understanding of the relationship between the biological mechanisms involved and the clinical condition of the patients.

Publications

Attar-Schneider O, Pasmanik-Chor M, **Tartakover Matalon S**, Drucker L*, Lishner M*. eIF4E and eIF4GI have distinct and differential imprints on multiple myeloma's proteome and signaling. Oncotarget, 28;6(6):4315-29, 2015

Epstein Shochet G, Drucker L, Pasmanik-Chor M, Pomeranz M, Fishman A, **Tartakover Matalon S*,** Lishner M*. First trimester human placental factors induce breast cancer cell autophagy. Breast Cancer Research and Treatment, 149(3):645-54, 2015

Marcus H, Attar-Schneider O, Dabbah M, Zismanov V, **Tartakover-Matalon S**, *Lishner M, *Drucker L. Mesenchymal stem cells secretomes' affect multiple myeloma translation initiation. Cell Signal 28(6):620-30, 2016

Dabbah M, Attar-Schneider O, Zismanov V, **Tartakover Matalon S**, *Lishner M, *Drucker L. Multiple myeloma cells promote migration of bone marrow mesenchymal stem cells by altering their translation initiation. J Leuk Biol 100(4):761-770, 2016

Epstein Shochet G, Komemi O, Sadeh-Mestechkin D, Pomeranz M (Fishman A, Drucker L, Lishner M, **Tartakover Matalon S.** Heat shock protein-27 (HSP27) regulates STAT3 and eIF4G levels in first trimester human placenta. J Mol Histol 47(6):555-563, 2016

Epstein Shochet G, Drucker L, Pasmanik-Chor M, Pomeranz M, Fishman A, **Tartakover Matalon S***, Lishner M*. First trimester human placenta prevents breast cancer cells attachment to the matrix: the role of extracellular matrix. Mol Carcinogenesis 56(1):62-74, 2017

Dabbah M, Attar-Schneider O, **Tartakover Matalon S**, Shefler I, Jarchowsky O, *Lishner M, *Drucker L. Microvesicles derived from bone marrow mesenchymal stem cells differentially modulate multiple myeloma cells' phenotype and translation initiation according to their normal or pathological source. Carcinogenesis 38(7):708-716, 2017

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 and activates their survival mechanisms: a key for future distant metastases. Int J Cancer 144(7):1633-1644, 2018

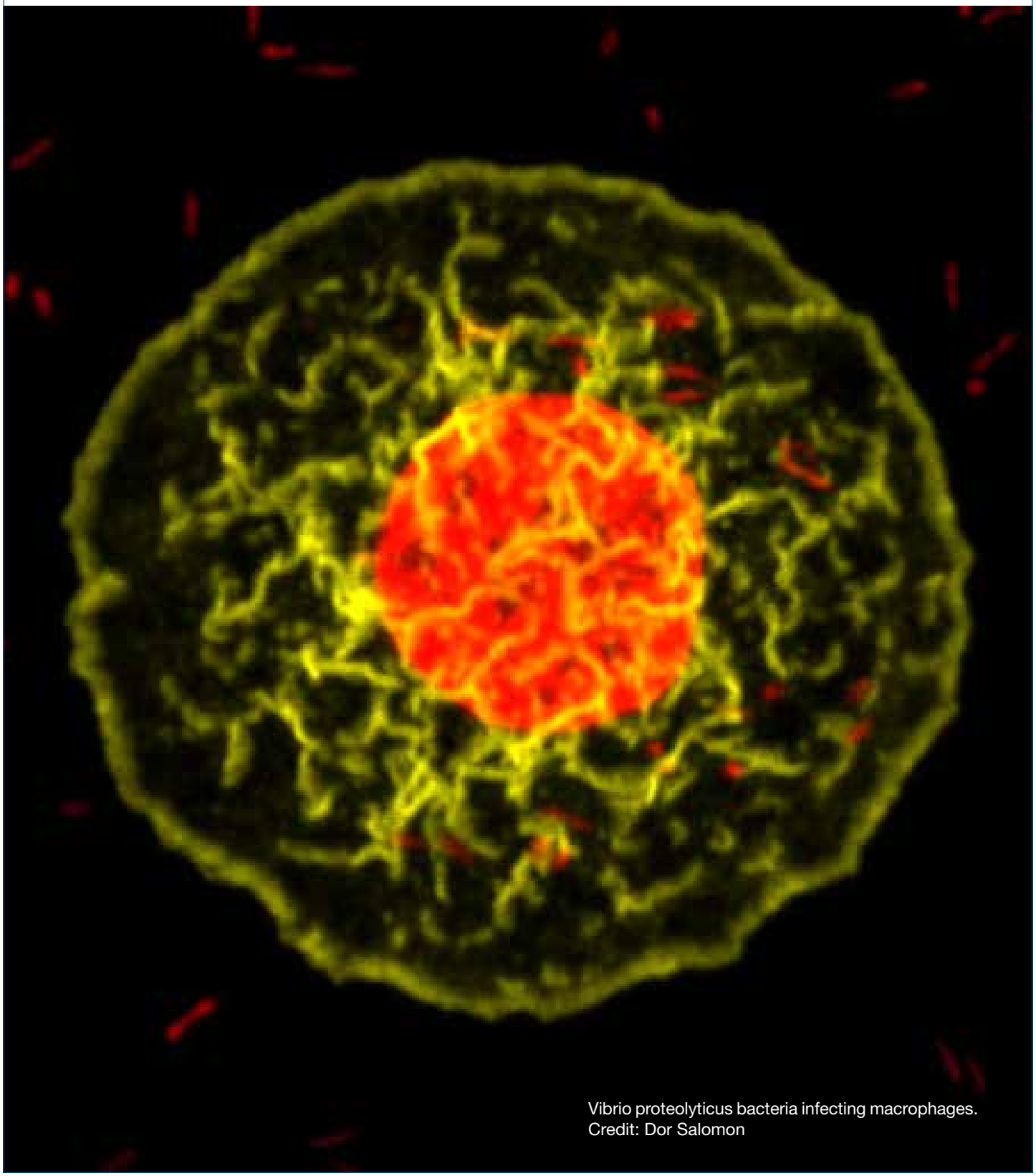
Ibraheem A, Dolberg Jarchowsky O, Attar-Schneider O, Dabbah M, **Tartakover Matalon S**, *Lishner M, *Drucker L. BM-MS derived ECM modifies multiple myeloma phenotype and drug response in a source dependent manner. Translational research 207:83-95, 2019, 2019

Bar M, Komemi O, Pomeranz M, Fishman A, Drucker L, *Lishner M, ***Tartakover Matalon S.** Placental supernatants' enhancement of the metastatic potential of breast cancer cells: Is estrogen receptor (ERα) essential for this phenomenon? Archives of Gynecology and Obstetrics 300(4):981-991, 2019

Tartakover Matalon S, Ringel Y, Konikoff F, Drucker L, Pery S, Naftali T. Cannabinoid Receptor 2 (CB2) agonist promotes parameters implicated in mucosal healing in Inflammatory Bowel Disease patients. United European Gastroenterology, 2019

Dabbah M, Jarchowsky-Dolberg O, Attar-Schneider O, **Tartakover Matalon S,** Pasmanik-Chor M, Drucker L, Lishner M, Multiple myeloma BM-MSCs increase the tumorigenicity of MM cells via transfer of VLA4-enriched microvesicles. Carcinogenesis. 2020;41(1):100-110

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
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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.

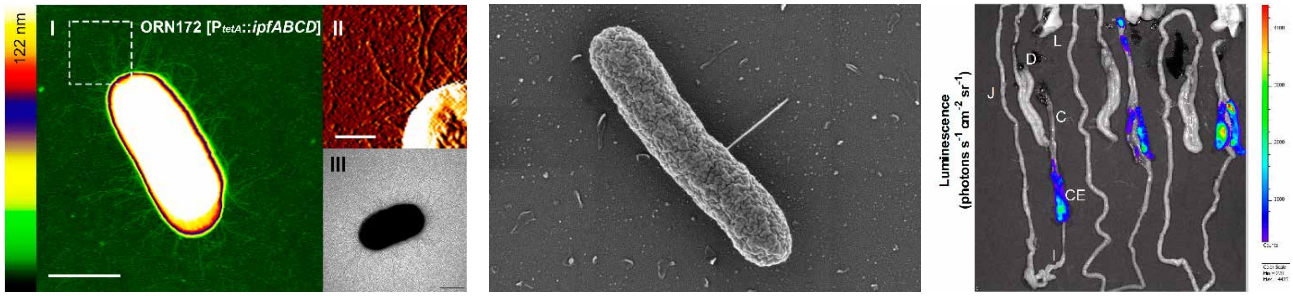
Publications

Cohen E, Davidovich M, Rokney A, Valinsky L, Rahav G, **Gal-Mor O**. Emergence of new variants of antibiotic resistance genomic islands among multidrug-resistant *Salmonella enterica* in poultry. Environ Microbiol. 2019.

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) Spatiall expression of *ipf* genes in *S.* Infantis during infection in the chicken model.

Regev-Yochay G, Smollan G, Tal I, Pinas Zade N, Haviv Y, Nudelman V, **Gal-Mor O**, Jaber H, Zimlichman E, Keller N, Rahav G. Sink traps as the source of transmission of OXA-48-producing *Serratia marcescens* in an intensive care unit. Infect Control Hosp Epidemiol. 2018;39:1307-1315.

Aviv G, **Gal-Mor O**. Western blotting against tagged virulence determinants to study bacterial pathogenicity. Methods Mol Biol. 2018;1734:47-54.

Aviv G, **Gal-Mor O**. lacZ Reporter System as a Tool to Study Virulence Gene Regulation in Bacterial Pathogens. Methods Mol Biol. 2018;1734:39-45.

Aviv G, **Gal-Mor O**. Usage of a Bioluminescence Reporter System to Image Promoter Activity During Host Infection. Methods Mol Biol. 2018;1734:33-38.

Aviv G, **Gal-Mor O**. Real-Time Reverse Transcription PCR as a Tool to Study Virulence Gene Regulation in Bacterial Pathogens. Methods Mol Biol. 2018;1734:23-32.

Azriel S, Goren A, Shomer I, Aviv G, Rahav G, **Gal-Mor O**. The Typhi colonization factor (Tcf) is encoded by multiple non-typhoidal *Salmonella* serovars but exhibits a varying expression profile and interchanging contribution to intestinal colonization. Virulence. 2017;8:1791-1807.

Aviv G, Elpers L, Mikhlin S, Cohen H, Vitman Zilber S, Grassl GA, Rahav G, Hensel M, **Gal-Mor O**. The plasmid-encoded Ipf and Klf fimbriae display different expression and varying roles in the virulence of *Salmonella enterica* serovar Infantis in mouse vs. avian hosts. PLoS Pathog. 2017;13:e1006559.

Shomer I, Avisar A, Desai P, Azriel S, Smollan G, Belausov N, Keller N, Glikman D, Maor Y, Peretz A, McClelland M, Rahav G, **Gal-Mor O**. Genetic and phenotypic characterization of a *salmonella enterica* serovar enteritidis emerging strain with superior intra-macrophage replication phenotype. Front Microbiol. 2016;7:1468.

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).

Baker KS, Dallman TJ, Behar A, Weill FX, Gouali M, Sobel J, Fookes M, Valinsky L, **Gal-Mor O**, Connor TR, Nissan I, Bertrand S, Parkhill J, Jenkins C, Cohen D, Thomson NR. Travel- and Community-based transmission of multidrug-resistant *shigella sonnei* lineage among international Orthodox Jewish communities. Emerg Infect Dis. 2016;22:1545-53.

McClelland M, Marzel A, Desai PT, **Gal-Mor O**. Reply to Yue. Clin Infect Dis. 2016;62:1326-7.

Elhadad D, Desai P, Grassl GA, McClelland M, Rahav G, **Gal-Mor O**. Differences in host cell invasion and salmonella pathogenicity island 1 expression between *salmonella enterica* serovar paratyphi a and nontyphoidal s. typhimurium. Infect Immun. 2016;84:1150-1165.

Marzel A, Desai PT, Goren A, Schorr YI, Nissan I, Porwollik S, Valinsky L, McClelland M, Rahav G, **Gal-Mor O**. Persistent infections by nontyphoidal *salmonella* in humans: Epidemiology and Genetics. Clin Infect Dis. 2016;62:879-886.

Azriel S, Goren A, Rahav G, **Gal-Mor O**. The stringent response regulator dksa is required for *salmonella enterica* serovar typhimurium growth in minimal medium, motility, biofilm formation, and intestinal colonization. Infect Immun. 2015;84:375-84.

Elhadad D, Desai P, Rahav G, McClelland M, **Gal-Mor O**. Flagellin Is required for host cell invasion and normal *salmonella* pathogenicity island 1 expression by *salmonella enterica* serovar paratyphi A. Infect Immun. 2015;83:3355-68.

Ihadad D, McClelland M, Rahav G, **Gal-Mor O**. Feverlike temperature is a virulence regulatory cue controlling the motility and host cell entry of typhoidal *salmonella*. J Infect Dis. 2015;212:147-56.

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, Sackler Faculty of Medicine

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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, Sefty 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).

Mook P, Meerhoff T, Olsen SJ, Snacken R, Adlhoch C, Pereyaslov D, Broberg EK, Melidou A, Brown C, Penttinen P; Collective of the WHO European Region, European Influenza Surveillance Network. Alternating patterns of seasonal influenza activity in the WHO European Region following the 2009 pandemic, 2010-2018. Influenza Other Respir Viruses. 2020.

Furer V, Zisman D, Kaufman I, Arad U, Berman M, Sarbagil-Maman H, Elias M, Hadad A, Paran D, Drori Y, Friedman N, **Mandelboim M**, Elkayam O. Immunogenicity and safety of vaccination against seasonal influenza vaccine in patients with psoriatic arthritis treated with secukinumab. Vaccine. 2020;38:847-851.

Shasha D, Valinsky L, Hershkowitz Sikron F, Glatman-Freedman A, **Mandelboim M**, Toledano A, Paran Y, Ben-Ami R, Goldman D. Quadrivalent versus trivalent influenza vaccine: clinical outcomes in two influenza seasons, historical cohort study. Clin Microbiol Infect. 2020;26:101-106.

Pomeranz G, Pando R, Hindiyeh M, Sherbany H, Meningher T, Sharabi S, Kolet L, Pomeranz A, Mendelson E, **Mandelboim M**. Rhinovirus infections in infants suggest that early detection can prevent unnecessary treatment. J Clin Virol. 2019 ;115:11-17.

Frishberg A, Peshes-Yaloz N, Cohn O, Rosentul D, Steuerman Y, Valadarsky L, Yankovitz G, **Mandelboim M**, Iraqi FA, Amit I, Mayo L, Bacharach E, Gat-Viks I. Cell composition analysis of bulk genomics using single-cell data. Nat Methods. 2019;16:327-332.

Segaloff H, Melidou A, Adlhoch C, Pereyaslov D, Robesyn E, Penttinen P, Olsen SJ; Who European Region and The European Influenza Surveillance Network. Co-circulation of influenza A(H1N1) pdm09 and influenza A(H3N2) viruses, World Health Organization (WHO) European Region, October 2018 to February 2019. Euro Surveill. 2019;24(9).

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.

Hindiyeh M, Mor O, Pando R, Mannasse B, Kabat A, Assraf-Zarfati H, Mendelson E, Sofer D, **Mandelboim**

M. Comparison of the new fully automated extraction platform eMAG to the MagNA PURE 96 and the well-established easyMAG for detection of common human respiratory viruses. PLoS One. 2019;14:e0211079.

Korem M, Orenbuch-Harroch E, Ben-Chetrit E, Israel S, Cohen MJ, Sviri S, Levin PD, **Mandelboim M**, Wolf DG. Intensive care admissions and associated severity of Influenza B versus A during Influenza B vaccine-mismatched seasons. Clin Infect Dis. 2019;69:1049-1052.

Winkler R, Gillis E, Lasman L, Safra M, Geula S, Soyris C, Nachshon A, Tai-Schmiedel J, Friedman N, Le-Trilling VTK, Trilling M, **Mandelboim M**, Hanna JH, Schwartz S, Stern-Ginossar N. Publisher Correction: m6A modification controls the innate immune response to infection by targeting type I interferons. Nat Immunol. 2019;20:243.

Winkler R, Gillis E, Lasman L, Safra M, Geula S, Soyris C, Nachshon A, Tai-Schmiedel J, Friedman N, Le-Trilling VTK, Trilling M, **Mandelboim M**, Hanna JH, Schwartz S, Stern-Ginossar N. m(6)A modification controls the innate immune response to infection by targeting type I interferons. Nat Immunol. 2019;20:173-182.

Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, Klein NP, Chung H, Effler PV, Feldman BS, Simmonds K, Wyant BE, Dawood FS, Jackson ML, Fell DB, Levy A, Barda N, Svenson LW, Fink RV, Ball SW, Naleway A; PREVENT Workgroup. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: A multi-country retrospective test negative design study, 2010-2016. Clin Infect Dis. 2019;68:1444-1453.

Brosh-Nissimov T, Hindiyeh M, Azar R, Smollan G, Belausov N, **Mandelboim M**, Rahav G, Keller N, Gefen-Halevi S. A false-positive Trichomonas vaginalis result due to Trichomonas tenax presence in clinical specimens may reveal a possible T. tenax urogenital infection. Clin Microbiol Infect. 2019;25:123-124.

Friedman N, Alter H, Hindiyeh M, Mendelson E, Shemer Avni Y, **Mandelboim M**. Human Coronavirus infections in Israel: Epidemiology, clinical symptoms and summer seasonality of HCoV-HKU1. Viruses. 2018;10(10).

Jornist I, Muhsen K, Ram D, Lustig Y, Levy V, Orzitser S, Azar R, Weil M, Indenbaum V, Sofer D, Mendelson E, **Mandelboim M**, Hindiyeh M. Characterization of human parainfluenza virus-3 circulating in Israel, 2012-2015. J Clin Virol. 2018; 107:19-24.

Regan AK, Klein NP, Langley G, Drews SJ, Buchan S, Ball S, Kwong JC, Naleway A, Thompson M, Wyant BE, Levy A, Chung H, Feldman B, Katz MA; PREVENT Group. Respiratory syncytial virus hospitalization during pregnancy in 4 high-income countries, 2010-2016. Clin Infect Dis. 2018;67(12):1915-1918.

Yaron-Yakoby H, Sefty H, Pando R, Dichtiar R, Katz MA, Stein Y, **Mandelboim M**, Mendelson E, Shohat T, Glatman-Freedman A; The Israeli Influenza Surveillance Network (IISN). Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenzaseasons 2014/15 and 2015/16. Euro Surveill. 2018;23(7).

Sharabi S, Bassal R, Friedman N, Drori Y, Alter H, Glatman-Freedman A, Hindiyeh M, Cohen D, Mendelson E, Shohat T, **Mandelboim M**. Forty five percent of the Israeli population were infected with the influenza B Victoria virus during the winter season 2015-16. Oncotarget. 2017;9(5):6623-6629.

Pando R, Sharabi S, **Mandelboim M**. Exceptional influenza morbidity in summer season of 2017 in Israel may predict the vaccine efficiency in the coming winter. Vaccine. 2018;36(11):1326-1329.

Stein Y, **Mandelboim M**, Sefty H, Pando R, Mendelson E, Shohat T, Glatman-Freedman A; Israeli Influenza Surveillance Network (IISN). Seasonal influenza vaccine effectiveness in preventing laboratory-confirmed influenza in primary care in Israel, 2016-2017 Season: Insights into novel age-specific analysis. Clin Infect Dis. 2018;66(9):1383-1391.

Glasner A, Isaacson B, Viukov S, Neuman T, Friedman N, **Mandelboim M**, Sexl V, Hanna JH, Mandelboim O. Increased NK cell immunity in a transgenic mouse model of NKp46 overexpression. Sci Rep. 2017;7(1):13090.

Bar-On Y, Charpak-Amikam Y, Glasner A, Isaacson B, Duev-Cohen A, Tsukerman P, Varvak A, **Mandelboim M**, Mandelboim O. NKp46 recognizes the Sigma1 protein of reovirus: Implications for reovirus-based cancer therapy. J Virol. 2017;91(19).

Glatman-Freedman A, Drori Y, Beni SA, Friedman N, Pando R, Sefty H, Tal I, McCauley J, Rahav G, Keller N, Shohat T, Mendelson E, Hindiyeh M, **Mandelboim M**. Genetic divergence of Influenza A(H3N2) amino acid substitutions mark the beginning of the 2016-2017 winter season in Israel. J Clin Virol. 2017;93:71-75.

Fraenkel M, Yitshak-Sade M, Beacher L, Carmeli M, **Mandelboim M**, Siris E, Novack V. Is the association between hip fractures and seasonality modified

by influenza vaccination? An ecological study. Osteoporos Int. 2017;28(9):2611-2617.

Friedman N, Drori Y, Pando R, Glatman-Freedman A, Sefty H, Bassal R, Stein Y, Shohat T, Mendelson E, Hindiyeh M, **Mandelboim M**. A(H1N1)pdm09 influenza infection: vaccine inefficiency. Oncotarget. 2017;8(20):32856-32863.

Kovalyuk N, Kaiserman I, Mimouni M, Cohen O, Levartovsky S, Sherbany H, **Mandelboim M**. Treatment of adenoviral keratoconjunctivitis with a combination of povidone-iodine 1.0% and dexamethasone 0.1% drops: a clinical prospective controlled randomized study. Acta Ophthalmol. 2017;95(8):e686-e692.

Diab M, Glasner A, Isaacson B, Bar-On Y, Drori Y, Yamin R, Duev-Cohen A, Danziger O, Zamostiano R, **Mandelboim M**, Jonjic S, Bacharach E, Mandelboim O. NK-cell receptors NKp46 and NCR1 control human metapneumovirus infection. Eur J Immunol. 2017;47(4):692-703.

Pando R, Drori Y, Friedman N, Glatman-Freedman A, Sefty H, Shohat T, Mendelson E, Hindiyeh M, **Mandelboim M**. Influenza A(H1N1)pdm 2009 and influenza B virus co-infection in hospitalized and non-hospitalized patients during the 2015-2016 epidemic season in Israel. J Clin Virol. 2017;88:12-16.

Weil M, **Mandelboim M**, Mendelson E, Manor Y, Shulman L, Ram D, Barkai G, Shemer Y, Wolf D, Kra-Oz Z, Weiss L, Pando R, Hindiyeh M, Sofer D. Human enterovirus D68 in clinical and sewage samples in Israel. J Clin Virol. 2017;86:52-55.

Talmi-Frank D, Altboum Z, Solomonov I, Udi Y, Jaitin DA, Klepfish M, David E, Zhuravlev A, Keren-Shaul H, Winter DR, Gat-Viks I, **Mandelboim M**, Ziv T, Amit I, Sagi I. Extracellular Matrix Proteolysis by MT1-MMP Contributes to Influenza-Related Tissue Damage and Mortality. Cell Host Microbe. 2016;20(4):458-470.

Diab M, Vitenshtein A, Drori Y, Yamin R, Danziger O, Zamostiano R, **Mandelboim M**, Bacharach E, Mandelboim O. Suppression of human metapneumovirus (HMPV) infection by the innate sensing gene CEACAM1. Oncotarget. 2016;7(41):66468-66479.

Sharabi S, Drori Y, Micheli M, Friedman N, Orzitzer S, Bassal R, Glatman-Freedman A, Shohat T, Mendelson E, Hindiyeh M, **Mandelboim M**. Epidemiological and Virological Characterization of Influenza B Virus Infections. PLoS One. 2016;11(8):e0161195.

Bercovich-Kinori A, Tai J, Gelbart IA, Shitrit A, Ben-Moshe S, Drori Y, Itzkovitz S, **Mandelboim M**, Stern-Ginossar N. A systematic view on influenza induced host shutoff. Elife. 2016;5. pii: e18311.

Salama M, Amitai Z, Nutman A, Gottesman-Yekutieli T, Sherbany H, Drori Y, Mendelson E, Carmeli Y, **Mandelboim M**. Corrigendum to "Outbreak of adenovirus type 55 infection in Israel" J Clin Virol. 2016;82:183.

Scheuerman O, Barkai G, **Mandelboim M**, Mishali H, Chodick G, Levy I. Human metapneumovirus (hMPV) infection in immunocompromised children. J Clin Virol. 2016;83:12-6.

Lustig Y, Mannasse B, Koren R, Katz-Likvornik S, Hindiyeh M, **Mandelboim M**, Dovrat S, Sofer D, Mendelson E. Superiority of West Nile Virus RNA Detection in Whole Blood for Diagnosis of Acute Infection. J Clin Microbiol. 2016;54(9):2294-7.

Yaari R, Katriel G, Stone L, Mendelson E, **Mandelboim M**, Huppert A. Model-based reconstruction of an epidemic using multiple datasets: understanding influenza A/H1N1 pandemic dynamics in Israel. J R Soc Interface. 2016;13(116). pii: 20160099.

Salama M, Amitai Z, Amir N, Gottesman-Yekutieli T, Sherbany H, Drori Y, Mendelson E, Carmeli Y, **Mandelboim M**. Outbreak of adenovirus type 55 infection in Israel. J Clin Virol. 2016;78:31-5. Erratum in: J Clin Virol. 2016;82:183.

Duev-Cohen A, Bar-On Y, Glasner A, Berhani O, Ophir Y, Levi-Schaffer F, **Mandelboim M**, Mandelboim O. The human 2B4 and NTB-A receptors bind the influenza viral hemagglutinin and co-stimulate NK cell cytotoxicity. Oncotarget. 2016;7(11):13093-105.

Mandelboim M, Glatman-Freedman A, Drori Y, Sherbany H, Pando R, Sefty H, Zadka H, Shohat T, Keller N, Mendelson E. Ineffectiveness of the 2014-2015 H3N2 influenza vaccine. Oncotarget. 2016;7:1185-92.

Ablin JN, Aloush V, Brill A, Berman M, Barzilai M, Caspi D, **Mandelboim M**, Levartovsky D, Polachek A, Wolman Y, Paran D, Barkagan M, Elkayam O. Influenza vaccination is safe and effective in patients suffering from fibromyalgia syndrome. Reumatismo. 2015;67:57-61.

Perry Markovich M, Glatman-Freedman A, Bromberg M, Augarten A, Sefty H, Kaufman Z, Sherbany H, Regev L, Chodick G, Mendelson E, Shohat T, **Mandelboim M**; Israel Pediatric Upper Respiratory Infection Network (IPURIN). Back-to-school upper respiratory infection in preschool and primary school-age children in Israel. Pediatr Infect Dis J. 2015;34:476-81.

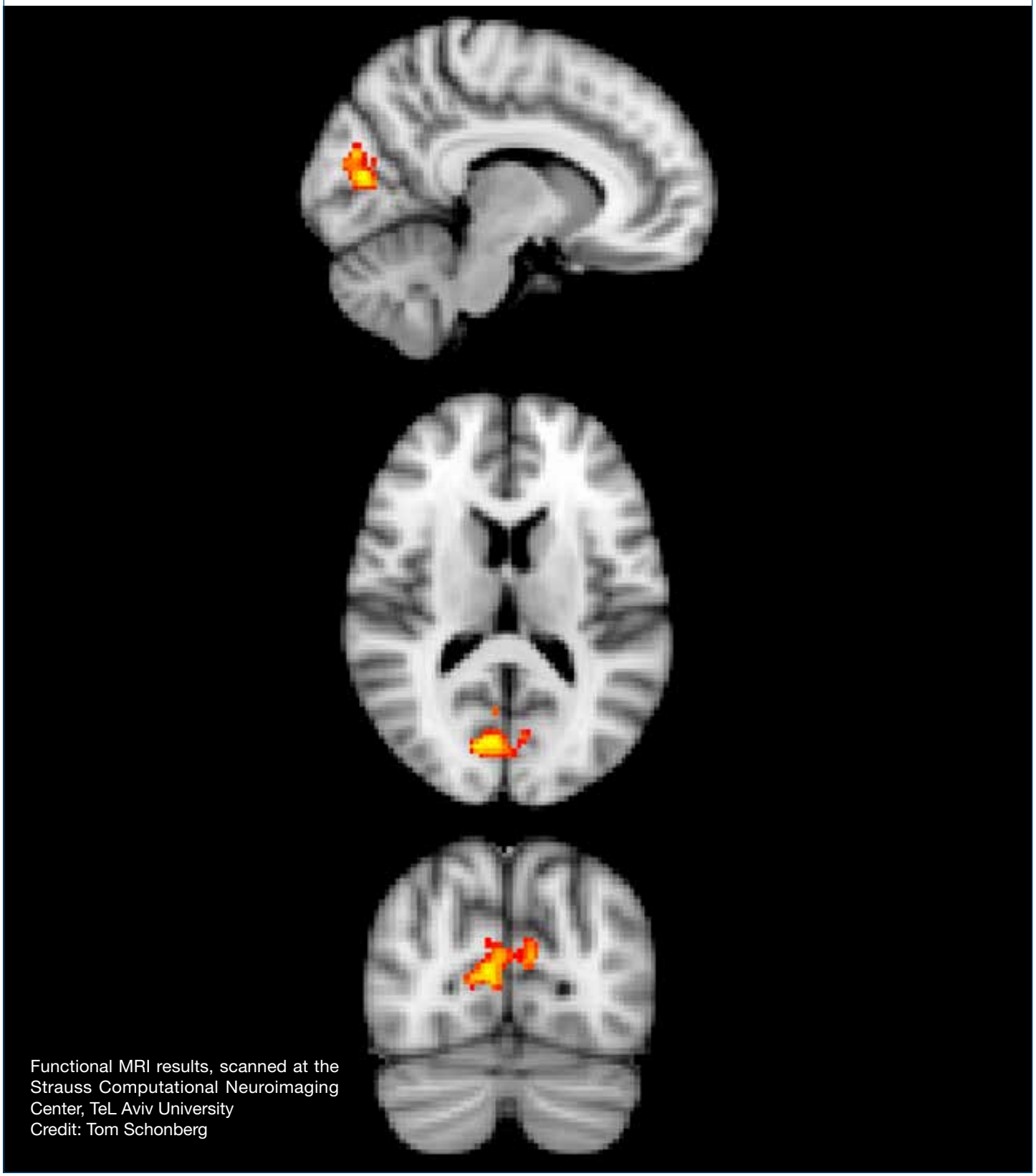
Polachek A, Korobko U, Mader-Balakirski N, Arad U, Levartovsky D, Kaufman I, Anouk M, Litinsky I, Wigler I, Mendelson E, Paran D, Matz H, Caspi D, **Mandelboim M**, Elkayam O. Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis. Clin Exp Rheumatol. 2015;33:181-6.

Broberg E, Snacken R, Adlhoch C, Beauté J, Galinska M, Pereyaslov D, Brown C, Penttinen P; WHO European Region and the European Influenza Surveillance Network. Start of the 2014/15 influenza season in Europe: drifted influenza A(H3N2) viruses circulate as dominant subtype. Euro Surveill. 2015;20.

Sherbany H, McCauley J, Meningher T, Hindiyeh M, Dichtiar R, Markovich MP, Mendelson E, **Mandelboim M**. Return of pandemic H1N1 influenza virus. BMC Infect Dis. 2014;14:710.

Tasher D, Stein M, Solomon C, Shachor-Meyouhas Y, Glikman D, **Mandelboim M**, Kassis I, Somekh E. Children hospitalised with influenza-associated pneumonia during the 2009 pandemic displayed increased disease severity. Acta Paediatr. 2015;104:e100-5.

Neurological & Psychiatric Diseases



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

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

Positions

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

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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

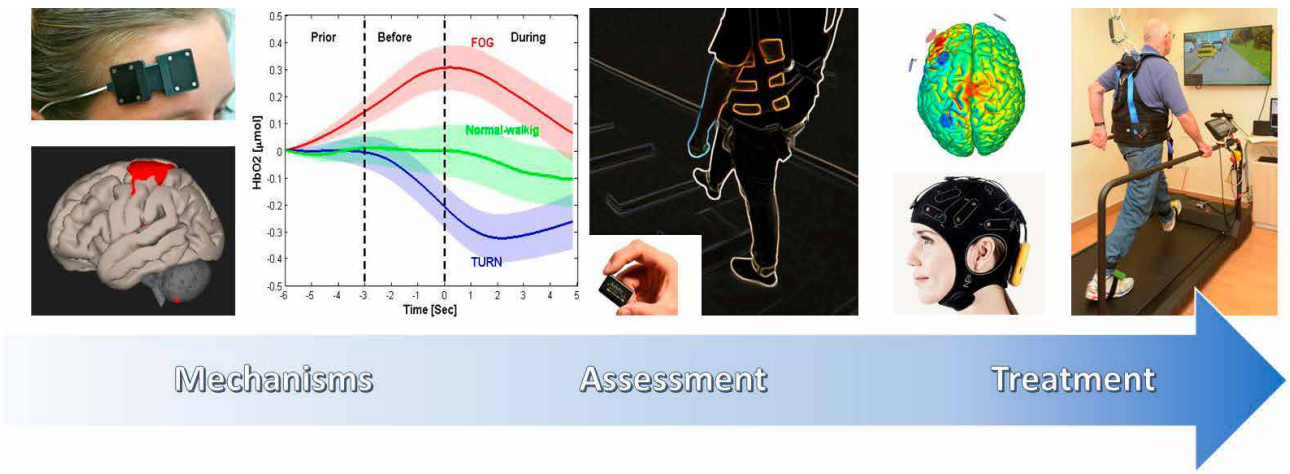
Review Editor in Movement Disorders, Frontiers in Neurology

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 achive three main objectives: 1) acquire new understandings of the *mechanisms* that contribute to cognitive and motor function and their changes with aging and disease; 2) construct and validate new methods and tools for early *detection* and *tracking* of cognitive and motor decline associated with aging and neuro-



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

degeneration. This 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 negotiationg obstacles; b) virtual-reality based intervention for gait and cognitive function in older adults and patients with multiple sclerosis; c) transcranial direct current stimulation to study the mechanisms and to ameliorate freezing of gait in patients with Parkinson's disease; d) Smartphone-based intervention to improve gait and cognition and to reduce fall risk in older adults; e) transcranial direct current stimulation to study the mechanisms and to reduce fall risk and the effects of dual tasking in older adults; f) investigation of genetic contributions to gait and mobility; g) 24/7 monitoring of gait and mobility using body-fixed sensors to study the effects of osteoarthritis on mobility and to identify early markers of Parkinson's disease. h) neural network studies of cognitive aging and mobility; i) effects of high intensity exercise on cognition, gait and mobility in older adults with mild cognitive impairment.

Publications

Manuscripts

Ben AE, Shenhar-Tsarfaty S, Korczyn AD, Kliper E, Hallevi 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.

Herman T, Weiss A, Brozgol M, Wilf-Yarkoni A, Giladi N, **Hausdorff JM**. Cognitive function and other non-motor features in non-demented Parkinson's disease motor subtypes. *J Neural Transm (Vienna)* 122:1115-1124; 2015.

Ihlen EA, Weiss A, Helbostad JL, **Hausdorff JM**. The Discriminant Value of Phase-Dependent Local Dynamic Stability of Daily Life Walking in Older Adult Community-Dwelling Fallers and Nonfallers. *Biomed Res Int* 2015:402596; 2015.

Klucken J, Friedl KE, Eskofier BM, **Hausdorff JM**. Guest Editorial: Enabling Technologies for Parkinson's Disease Management. *IEEE J Biomed Health Inform* 19:1775-1776; 2015.

Maidan I, Bernad-Elazari H, Gazit E, Giladi N, **Hausdorff JM**, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson disease: an fNIRS study of transient motor-cognitive failures. *J Neurol* 262:899-908; 2015.

Mazilu S, Calatroni A, Gazit E, Mirelman A, **Hausdorff JM**, Troster G. Prediction of Freezing of Gait in Parkinson's From Physiological Wearables: An Exploratory Study. *IEEE J Biomed Health Inform* 19:1843-1854; 2015.

Mirelman A, Bernad-Elazari H, Nobel T, Thaler A, Peruzzi A, Plotnik M, Giladi N, **Hausdorff JM**. Effects of Aging on Arm Swing during Gait: The Role of Gait Speed and Dual Tasking. *PLoS One* 10:e0136043; 2015.

Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, Giladi N, Hendler T, **Hausdorff JM**. Fall risk is associated with amplified functional connectivity of the central executive network in patients with Parkinson's disease. *J Neurol* 262:2448-2456; 2015.

Trojaniello D, Ravaschio A, **Hausdorff JM**, Cereatti A. Comparative assessment of different methods for the estimation of gait temporal parameters using a single inertial sensor: application to elderly, post-stroke, Parkinson's disease and Huntington's disease subjects. *Gait Posture* 42:310-316; 2015.

Walsh JN, Manor B, **Hausdorff JM**, Novak V, Lipsitz L, Gow B, Macklin EA, Peng CK, Wayne PM. Impact of Short- and Long-term Tai Chi Mind-Body Exercise Training on Cognitive Function in Healthy Adults: Results From a Hybrid Observational Study and Randomized Trial. *Glob Adv Health Med* 4:38-48; 2015.

Wayne PM, **Hausdorff JM**, Lough M, Gow BJ, Lipsitz L, Novak V, Macklin EA, Peng CK, Manor B. Tai Chi Training may Reduce Dual Task Gait Variability, a Potential Mediator of Fall Risk, in Healthy Older Adults: Cross-Sectional and Randomized Trial Studies. *Front Hum Neurosci* 9:332; 2015.

Weiss A, Herman T, Giladi N, **Hausdorff JM**. Association between Community Ambulation Walking Patterns and Cognitive Function in Patients with Parkinson's Disease: Further Insights into Motor-Cognitive Links. *Parkinsons Dis* 2015:547065; 2015.

Weiss A, Herman T, Giladi N, **Hausdorff JM**. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. *J Neural Transm (Vienna)* 122:403-410; 2015.

Bernad-Elazari H, Herman T, Mirelman A, Gazit E, Giladi N, **Hausdorff JM**. Objective characterization of daily living transitions in patients with Parkinson's disease using a single body-fixed sensor. *J Neurol* 263:1544-1551; 2016.

Dockx K, Bekkers EM, Van dB, V, Ginis P, Rochester L, **Hausdorff JM**, Mirelman A, Nieuwboer A. Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst Rev* 12:CD010760; 2016.

Ginis P, Nieuwboer A, Dorfman M, Ferrari A, Gazit E, Canning CG, Rocchi L, Chiari L, **Hausdorff JM**, Mirelman A. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinson's disease: A pilot randomized controlled trial. *Parkinsonism Relat Disord* 22:28-34; 2016.

Ihlen EAF, Weiss A, Beck Y, Helbostad JL, **Hausdorff JM**. A comparison study of local dynamic stability measures of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech* 49:1498-1503; 2016.

Ihlen EAF, Weiss A, Bourke A, Helbostad JL, **Hausdorff JM**. The complexity of daily life walking in older adult community-dwelling fallers and non-fallers. *J Biomech* 49:1420-1428; 2016.

Iluz T, Weiss A, Gazit E, Tankus A, Brozgol M, Dorfman M, Mirelman A, Giladi N, **Hausdorff JM**. 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. *J Gerontol A Biol Sci Med Sci* 71:1459-1465; 2016.

James EG, Leveille SG, You T, **Hausdorff JM**, Travison T, Manor B, McLean R, Bean JF. Gait coordination impairment is associated with mobility in older adults. *Exp Gerontol* 80:12-16; 2016.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, **Hausdorff JM**, Mirelman A. Altered brain activation in complex walking conditions in patients with Parkinson's disease. *Parkinsonism Relat Disord* 25:91-96; 2016.

Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, Deutsch JE, **Hausdorff JM**, Claassen JA, Mirelman A. The role of the frontal lobe in complex walking among patients with Parkinson's disease and healthy older adults: An fNIRS study. *Neurorehabil Neural Repair* 30:963-971; 2016.

Mirelman A, Rochester L, Maidan I, Del DS, Alcock L, Nieuwhof F, Rikkert MO, Bloem BR, Pelosin E, Avanzino L, Abbruzzese G, Dockx K, Bekkers E, Giladi N, Nieuwboer A, **Hausdorff JM**. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet* 388:1170-1182; 2016.

Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, Saunders-Pullman R, Raymond D, Doan N, Bressman SB, Marder KS, Alcalay RN, Rao AK, Berg D, Brockmann K, Aasly J, Waro BJ, Tolosa E, Vilas D, Pont-Sunyer C, Orr-Urtreger A, **Hausdorff JM**, Giladi N. Arm swing as a potential new prodromal marker of Parkinson's disease. *Mov Disord* 31:1527-1534; 2016.

Nieuwhof F, Reelick MF, Maidan I, Mirelman A, **Hausdorff JM**, Olde Rikkert MG, Bloem BR, Muthalib M, Claassen JA. Measuring prefrontal cortical activity during dual task walking in patients with Parkinson's disease: feasibility of using a new portable fNIRS device. *Pilot Feasibility Stud* 2:59; 2016.

Pelosin E, Ogliastro C, Lagravinese G, Bonassi G, Mirelman A, **Hausdorff JM**, Abbruzzese G, Avanzino L. Attentional Control of Gait and Falls: Is Cholinergic Dysfunction a Common Substrate in the Elderly and Parkinson's Disease? *Front Aging Neurosci* 8:104; 2016.

Rosenberg-Katz K, Maidan I, Jacob Y, Giladi N, Mirelman A, **Hausdorff JM**. Alterations in conflict monitoring are related to functional connectivity in Parkinson's disease. *Cortex* 82:277-286; 2016.

Rosenberg-Katz K, Herman T, Jacob Y, Kliper E, Giladi N, **Hausdorff JM**. Subcortical Volumes Differ in Parkinson's Disease Motor Subtypes: New Insights into the Pathophysiology of Disparate Symptoms. *Front Hum Neurosci* 10:356; 2016.

van der Leeuw G, Eggermont LH, Shi L, Milberg WP, Gross AL, **Hausdorff JM**, Bean JF, Leveille SG. Pain and cognitive function among older adults living in the community. *J Gerontol A Biol Sci Med Sci* 71:398-405; 2016.

Weiss A, Brozgol M, Giladi N, **Hausdorff JM**. Can a single lower trunk body-fixed sensor differentiate between level-walking and stair descent and ascent in older adults? Preliminary findings. *Med Eng Phys* 38:1146-1151; 2016.

Weiss A, Mirelman A, Giladi N, Barnes LL, Bennett DA, Buchman AS, **Hausdorff JM**. Transition between the timed up and go turn to sit subtasks: is timing everything? *J Am Med Dir Assoc* 17:864; 2016.

Arie L, Herman T, Shema-Shiratzky S, Giladi N, **Hausdorff JM**. Do cognition and other non-motor symptoms decline similarly among patients with Parkinson's disease motor subtypes? Findings from

a 5-year prospective study. *J Neurol* 264:2149-2157; 2017.

Arndt H, Burkard S, Talavera G, Garcia J, Castells D, Codina M, **Hausdorff JM**, Mirelman A, Harte R, Casey M, Glynn L, Di RM, Rossi L, Stara V, Rosevall J, Rusu C, Carenas C, Breuil F, Reixach E, Carrabina J. Real-Time Constant Monitoring of Fall Risk Index by Means of Fully-Wireless Insoles. *Stud Health Technol Inform* 237:193-197; 2017.

Broom L, Ellison BA, Worley A, Wagenaar L, Sorberg E, Ashton C, Bennett DA, Buchman AS, Saper CB, Shih LC, **Hausdorff JM**, VanderHorst VG. A translational approach to capture gait signatures of neurological disorders in mice and humans. *Sci Rep* 7:3225; 2017.

Brozgol M, Arbiv M, Mirelman A, Herman T, **Hausdorff JM**, Vaisman N. Vertical ground reaction force during standing and walking: Are they related to bone mineral density left-right asymmetries? *Gait Posture* 54:174-177; 2017.

Dagan M, Herman T, Mirelman A, Giladi N, **Hausdorff JM**. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. *Exp Brain Res* 235:2463-2472; 2017.

Dawe RJ, Leurgans SE, Yang J, Bennett JM, **Hausdorff JM**, Lim AS, Gaiteri C, Bennett DA, Buchman AS. Association between quantitative gait and balance measures and total daily physical activity in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* ; 2017.

Di RM, **Hausdorff JM**, Stara V, Rossi L, Glynn L, Casey M, Burkard S, Cherubini A. Concurrent validation of an index to estimate fall risk in community dwelling seniors through a wireless sensor insole system: A pilot study. *Gait Posture* 55:6-11; 2017.

Dockx K, Alcock L, Bekkers E, Ginis P, Reelick M, Pelosin E, Lagravinese G, **Hausdorff JM**, Mirelman A, Rochester L, Nieuwboer A. Fall-prone older people's attitudes towards the use of virtual reality technology for fall prevention. *Gerontology* 63:590-598; 2017.

Gow BJ, **Hausdorff JM**, Manor B, Lipsitz LA, Macklin EA, Bonato P, Novak V, Peng CK, Ahn AC, Wayne PM. Can Tai Chi training impact fractal stride time dynamics, an index of gait health, in older adults? Cross-sectional and randomized trial studies. *PLoS One* 12:e0186212; 2017.

James EG, Leveille SG, **Hausdorff JM**, Barton B, Cote S, Karabulut M, Conatser P, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Coordination impairments are associated with falling among older adults. *Exp Aging Res* 43:430-439; 2017.

James EG, Conatser P, Karabulut M, Leveille SG, **Hausdorff JM**, Cote S, Tucker KL, Barton B, Bean JF, Al SS, Markides KS. Mobility limitations and fear of falling in non-English speaking older Mexican-Americans. *Ethn Health* 22:480-489; 2017.

James EG, Leveille SG, **Hausdorff JM**, Travison T, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Rhythmic Interlimb Coordination Impairments and the Risk for Developing Mobility Limitations. *J Gerontol A Biol Sci Med Sci* 72:1143-1148; 2017.

James EG, Leveille SG, **Hausdorff JM**, Travison T, Cote S, Conatser P, Karabulut M, Mendes AC, Kennedy DN, Tucker KL, Al SS, Markides KS, Bean JF. Rhythmic interlimb coordination impairments are associated with mobility limitations among older adults. *Exp Aging Res* 43:337-345; 2017.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, **Hausdorff JM**, Mirelman A. Disparate effects of training on brain activation in Parkinson disease. *Neurology* 89:1804-1810; 2017.

Maidan I, Bernad-Elazari H, Giladi N, **Hausdorff JM**, Mirelman A. When is higher level cognitive control needed for locomotor tasks among patients with Parkinson's Disease? *Brain Topogr* 30:531-538; 2017.

Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, **Hausdorff JM**. Effects of aging on prefrontal brain activation during challenging walking conditions. *Brain Cogn* 115:41-46; 2017.

Nieuwhof F, Bloem BR, Reelick MF, Aarts E, Maidan I, Mirelman A, **Hausdorff JM**, Toni I, Helmich RC. Impaired dual tasking in Parkinson's disease is associated with reduced focusing of cortico-striatal activity. *Brain* 140:1384-1398; 2017.

Palmerini L, Rocchi L, Mazilu S, Gazit E, **Hausdorff JM**, Chiari L. Identification of characteristic motor patterns preceding freezing of gait in Parkinson's Disease using wearable sensors. *Front Neurol* 8:394; 2017.

Stuart S, Hunt D, Nell J, Godfrey A, **Hausdorff JM**, Rochester L, Alcock L. Do you see what I see? Mobile eye-tracker contextual analysis and inter-rater reliability. *Med Biol Eng Comput*; 2017.

Tankus A, Strauss I, Gurevich T, Mirelman A, Giladi N, Fried I, **Hausdorff JM**. Subthalamic neurons encode both single- and multi-limb movements in Parkinson's Disease patients. *Sci Rep* 7:42467; 2017.

van der Leeuw G, Leveille SG, Jones RN, **Hausdorff JM**, McLean R, Kiely DK, Gagnon M, Milberg WP. Measuring attention in very old adults using the Test

of Everyday Attention. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 24:543-554; 2017.

Hausdorff JM, Hillel I, Shustak S, Del Din S, Bekkers E MJ, Pelosin E, Nieuwhof F, Rochester L Mirelman A. Everyday stepping quantity and quality among older adult fallers with and without mild cognitive impairment: Initial evidence for new motor markers of cognitive deficits? *J Gerontol Med Sci* ePub ahead of print, 2017.

Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, Giladi N, Mirelman A, **Hausdorff JM**. Age-associated changes in obstacle negotiation strategies: Does size and timing matter? *Gait Posture* 59:242-247; 2018.

Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, Manor B, **Hausdorff JM**. Multi-target transcranial direct current stimulation for freezing of gait in Parkinson's disease: A step forward? *Mov Disord,* in press 2018.

Alcock L, Galna B, **Hausdorff JM**, Lord S, Rochester L. Gait & Posture Special Issue: Gait adaptations in response to obstacle type in fallers with Parkinson's disease. *Gait Posture*: 61: 368-374; 2018.

Beck Y, Herman T, Brozgol M, Giladi N, Mirelman A, **Hausdorff JM**. SPARC: a new approach to quantifying gait smoothness in patients with Parkinson's disease. *J Neuroeng Rehabil*: 15: 49; 2018.

Bertoli M, Cereatti A, Trojaniello D, Avanzino L, Pelosin E, Del DS, Rochester L, Ginis P, Bekkers EMJ, Mirelman A, **Hausdorff JM**, Della CU. Estimation of spatio-temporal parameters of gait from magneto-inertial measurement units: multicenter validation among Parkinson, mildly cognitively impaired and healthy older adults. *Biomed Eng Online*: 17: 58; 2018.

Dagan M, Herman T, Zhou J, Manor B, **Hausdorff JM**. Reply to "Anodal tDCS Over Prefrontal Cortex Improves Dual-Task Walking in Patients With Freezing". *Mov Disord*: 33: 1973-1974; 2018.

Dawe RJ, Leurgans SE, Yang J, Bennett JM, **Hausdorff JM**, Lim AS, Gaiteri C, Bennett DA, Buchman AS. Association Between Quantitative Gait and Balance Measures and Total Daily Physical Activity in Community-Dwelling Older Adults. *J Gerontol A Biol Sci Med Sci*: 73: 636-642; 2018.

Gao C, Sun H, Wang T, Tang M, Bohnen NI, Muller MLTM, Herman T, Giladi N, Kalinin A, Spino C, Dauer W, **Hausdorff JM**, Dinov ID. Model-based and Model-free Machine Learning Techniques for Diagnostic Prediction and Classification of Clinical Outcomes in Parkinson's Disease. *Sci Rep*: 8: 7129; 2018.

Herman T, Shema-Shiratzky S, Arie L, Giladi N, **Hausdorff JM**. Who will remain tremor dominant? The possible role of cognitive reserve in the time course of two common Parkinson's disease motor subtypes. *J Neural Transm (Vienna)*: 125: 1007-1011; 2018.

Hunt D, Stuart S, Nell J, **Hausdorff JM**, Galna B, Rochester L, Alcock L. Do people with Parkinson's disease look at task relevant stimuli when walking? An exploration of eye movements. *Behav Brain Res*: 348: 82-89; 2018.

Jor'dan AJ, Manor B, **Hausdorff JM**, Lipsitz LA, Habtemariam D, Novak V, Wayne PM. Long-term Tai Chi Training Is Associated With Better Dual-task Postural Control and Cognition in Aging Adults. *Adv Mind Body Med*: 32: 4-11; 2018.

Ko SU, Jerome GJ, Simonsick EM, Studenski S, **Hausdorff JM**, Ferrucci L. Differential associations between dual-task walking abilities and usual gait patterns in healthy older adults-Results from the Baltimore Longitudinal Study of Aging. *Gait Posture*: 63: 63-67; 2018.

Li KZH, Bherer L, Mirelman A, Maidan I, **Hausdorff JM**. Cognitive Involvement in Balance, Gait and Dual-Tasking in Aging: A Focused Review From a Neuroscience of Aging Perspective. *Front Neurol*: 9: 913; 2018.

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*: 32: 200-208; 2018.

Maidan I, Shustak S, Sharon T, Bernad-Elazari H, Geffen N, Giladi N, **Hausdorff JM**, Mirelman A. Prefrontal cortex activation during obstacle negotiation: What's the effect size and timing? *Brain Cogn*: 122: 45-51; 2018.

Galperin I, Hillel I, Del DS, Bekkers EMJ, Nieuwboer A, Abbruzzese G, Avanzino L, Nieuwhof F, Bloem BR, Rochester L, Della CU, Cereatti A, Giladi N, Mirelman A, **Hausdorff JM**. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. *Parkinsonism Relat Disord*: 62: 85-90; 2019.

Gazit E, Buchman AS, Dawe R, Curran TA, Mirelman A, Giladi N, **Hausdorff JM**. What happens before the first step? A New Approach to Quantifying Gait Initiation Using a Wearable Sensor. *Gait Posture*: 76: 128-135; 2019.

Herman T, Shema-Shiratzky S, Arie L, Giladi N, **Hausdorff JM**. Depressive symptoms may increase the risk of the future development of freezing of gait in patients with Parkinson's disease: Findings from a 5-year prospective study. *Parkinsonism Relat Disord*: 60: 98-104; 2019.

Hillel I, Gazit E, Nieuwboer A, Avanzino L, Rochester L, Cereatti A, Croce UD, Rikkert MO, Bloem BR, Pelosin E, Del DS, Ginis P, Giladi N, Mirelman A, **Hausdorff JM**. Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24/7 monitoring. *Eur Rev Aging Phys Act*: 16: 6; 2019.

Ma Y, Wu CW, Peng CK, Ahn A, Bertisch SM, Lipsitz LA, Yeh GY, Manor B, Novak V, **Hausdorff JM**, Gow B, Wayne PM. Complexity-Based Measures of Heart Rate Dynamics in Older Adults Following Long- and Short-Term Tai Chi Training: Cross-sectional and Randomized Trial Studies. *Sci Rep*: 9: 7500; 2019.

Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, Higgins JP, Jacobs DR, **Hausdorff JM**, Lloyd-Jones DM, Sorond FA. Cumulative Blood Pressure Exposure During Young Adulthood and Mobility and Cognitive Function in Midlife. *Circulation*: 2019.

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*: 130: 224-230; 2019.

Maidan I, Jacob Y, Giladi N, **Hausdorff JM**, Mirelman A. Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease. *Parkinsonism Relat Disord*: 63: 77-82; 2019.

Maidan I, Patashov D, Shustak S, Fahoum F, Gazit E, Shapiro B, Levy A, Sosnik R, Giladi N, **Hausdorff JM**, Mirelman A. A new approach to quantifying the EEG during walking: Initial evidence of gait related potentials and their changes with aging and dual tasking. *Exp Gerontol*: 126: 110709; 2019.

Mancini M, Weiss A, Herman T, **Hausdorff JM**. Turn Around Freezing: Community-Living Turning Behavior in People with Parkinson's Disease. *Front Neurol*: 9: 18; 2018.

Manor B, Zhou J, Harrison R, Lo OY, Travison TG, **Hausdorff JM**, Pascual-Leone A, Lipsitz L. Transcranial Direct Current Stimulation May Improve Cognitive-Motor Function in Functionally Limited Older Adults. *Neurorehabil Neural Repair*: 32: 788-798; 2018.

Parashos SA, Bloem BR, Browner NM, Giladi N, Gurevich T, **Hausdorff JM**, He Y, Lyons KE, Mari Z, Morgan JC, Post B, Schmidt PN, Wielinski CL. What predicts falls in Parkinson disease?: Observations from the Parkinson's Foundation registry. *Neurol Clin Pract*: 8: 214-222; 2018.

Stuart S, Hunt D, Nell J, Godfrey A, **Hausdorff JM**, Rochester L, Alcock L. Do you see what I see? Mobile eye-tracker contextual analysis and inter-rater reliability. *Med Biol Eng Comput*: 56: 289-296; 2018.

Tankus A, Mirelman A, Giladi N, Fried I, **Hausdorff JM**. Pace of movement: the role of single neurons in the subthalamic nucleus. *J Neurosurg*: 1-6; 2018.

Thaler A, Kliper E, Maidan I, Herman T, Rosenberg-Katz K, Bregman N, Gurevich T, Shiner T, **Hausdorff JM**, Orr-Urtreger A, Giladi N, Mirelman A. Cerebral Imaging Markers of GBA and LRRK2 Related Parkinson's Disease and Their First-Degree Unaffected Relatives. *Brain Topogr*: 31: 1029-1036; 2018.

Thumm PC, Maidan I, Brozgol M, Shustak S, Gazit E, Shema SS, Bernad-Elazari H, Beck Y, Giladi N, **Hausdorff JM**, Mirelman A. Treadmill walking reduces pre-frontal activation in patients with Parkinson's disease. *Gait Posture*: 62: 384-387; 2018.

van der Leeuw G, Leveille SG, Dong Z, Shi L, Habtemariam D, Milberg W, **Hausdorff JM**, Grande L, Gagnon P, McLean RR, Bean JF. Chronic Pain and Attention in Older Community-Dwelling Adults. *J Am Geriatr Soc*: 66: 1318-1324; 2018.

Vergara-Diaz G, Osypiuk K, **Hausdorff JM**, Bonato P, Gow BJ, Miranda JG, Sudarsky LR, Tarsy D, Fox MD, Gardiner P, Thomas CA, Macklin EA, Wayne PM. Tai Chi for Reducing Dual-task Gait Variability, a Potential Mediator of Fall Risk in Parkinson's Disease: A Pilot Randomized Controlled Trial. *Glob Adv Health Med*: 7: 2164956118775385; 2018.

Zivotofsky AZ, Bernad-Elazari H, Grossman P, **Hausdorff JM**. The effects of dual tasking on gait synchronization during over-ground side-by-side walking. *Hum Mov Sci*: 59: 20-29; 2018.

Buchman AS, Dawe RJ, Leurgans SE, Curran TA, Truty T, Yu L, Barnes LL, **Hausdorff JM**, Bennett DA. Different combinations of mobility metrics derived from a wearable sensor are associated with distinct health outcomes in older adults. *J Gerontol A Biol Sci Med Sci*: 2019.

Dawe RJ, Yu L, Leurgans SE, Truty T, Curran T, **Hausdorff JM**, Wimmer MA, Block JA, Bennett DA, Buchman AS. Expanding instrumented gait testing in the community setting: A portable, depth-sensing

camera captures joint motion in older adults. *PLoS One*: 14: e0215995; 2019.

Del DS, Galna B, Godfrey A, Bekkers EMJ, Pelosin E, Nieuwhof F, Mirelman A, **Hausdorff JM**, Rochester L. Analysis of Free-Living Gait in Older Adults With and Without Parkinson's Disease and With and Without a History of Falls: Identifying Generic and Disease-Specific Characteristics. *J Gerontol A Biol Sci Med Sci*: 74: 500-506; 2019.

Espay AJ, **Hausdorff JM**, Sanchez-Ferro A, Klucken J, Merola A, Bonato P, Paul SS, Horak FB, Vizcarra JA, Mestre TA, Reilmann R, Nieuwboer A, Dorsey ER, Rochester L, Bloem BR, Maetzler W. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord*: 34: 657-663; 2019.

Eyal S, Kurz I, Mirelman A, Maidan I, Giladi N, **Hausdorff JM**. Successful Negotiation of Anticipated and Unanticipated Obstacles in Young and Older Adults: Not All Is as Expected. *Gerontology*: 1-10; 2019.

Reviews

Ogawa EF, Shi L, Bean JF, **Hausdorff JM**, Dong Z, Manor B, McLean RR, Leveille SG. Chronic Pain Characteristics and Gait in Older Adults: The MOBILIZE Boston Study II. *Arch Phys Med Rehabil*: 2019.

Patashov D, Menahem Y, Ben-Haim O, Gazit E, Maidan I, Mirelman A, Sosnik R, Goldstein D, **Hausdorff JM**. Methods for Gait Analysis During Obstacle Avoidance Task. *Ann Biomed Eng*: 2019.

Pelosin E, Cerulli C, Ogliastro C, Lagravinese G, Mori L, Bonassi G, Mirelman A, **Hausdorff JM**, Abbruzzese G, Marchese R, Avanzino L. A multimodal training modulates short-afferent inhibition and improves complex walking in a cohort of faller older adults with an increased prevalence of Parkinson's disease. *J Gerontol A Biol Sci Med Sci*: 2019.

Shema-Shiratzky S, Gazit E, Sun R, Regev K, Karni A, Sosnoff JJ, Herman T, Mirelman A, **Hausdorff JM**. Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis. *J Neurol*: 266: 3022-3030; 2019.

Shema-Shiratzky S, Brozgol M, Cornejo-Thumm P, Geva-Dayan K, Rotstein M, Leitner Y, **Hausdorff JM**, Mirelman A. Virtual reality training to enhance behavior and cognitive function among children with attention-deficit/hyperactivity disorder: brief report. *Dev Neurorehabil*: 22: 431-436; 2019.

Sunderaraman P, Maidan I, Kozlovski T, Apa Z, Mirelman A, **Hausdorff JM**, Stern Y. Differential Associations Between Distinct Components of Cognitive Function and Mobility: Implications for Understanding Aging, Turning and Dual-Task Walking. *Front Aging Neurosci*: 11: 166; 2019.

von CR, Dawe RJ, Leurgans SE, Curran TA, Truty T, Yu L, Barnes LL, Shulman JM, Shulman LM, Bennett DA, **Hausdorff JM**, Buchman AS. Quantitative mobility metrics from a wearable sensor predict incident parkinsonism in older adults. *Parkinsonism Relat Disord*: 65: 190-196; 2019.

Vizcarra JA, Sanchez-Ferro A, Maetzler W, Marsili L, Zavala L, Lang AE, Martinez-Martin P, Mestre TA, Reilmann R, **Hausdorff JM**, Dorsey ER, Paul SS, Dexheimer JW, Wissel BD, Fuller RLM, Bonato P, Tan AH, Bloem BR, Kopil C, Daeschler M, Bataille L, Kleiner G, Cedarbaum JM, Klucken J, Merola A, Goetz CG, Stebbins GT, Espay AJ. The Parkinson's disease e-diary: Developing a clinical and research tool for the digital age. *Mov Disord*: 34: 676-681; 2019.

Weiss A, Herman T, Mirelman A, Shiratzky SS, Giladi N, Barnes LL, Bennett DA, Buchman AS, **Hausdorff JM**. The transition between turning and sitting in patients with Parkinson's disease: A wearable device detects an unexpected sequence of events. *Gait Posture*: 67: 224-229; 2019.

Amboni M, Barone P, **Hausdorff JM**. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord* 28:1520-1533; 2013.

Ambrose AF, Paul G, **Hausdorff JM**. Risk factors for falls among older adults: a review of the literature. *Maturitas* 75:51-61; 2013.

Herman T, Giladi N, **Hausdorff JM**. Neuroimaging as a window into gait disturbances and freezing of gait in patients with Parkinson's disease. *Curr Neurol Neurosci Rep* 13:411; 2013.

Rosso AL, Studenski SA, Chen WG, Aizenstein HJ, Alexander NB, Bennett DA, Black SE, Camicioli R, Carlson MC, Ferrucci L, Guralnik JM, **Hausdorff JM**, Kaye J, Launer LJ, Lipsitz LA, Verghese J, Rosano C. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci* 68:1379-1386; 2013.

Mirelman A, Giladi N, **Hausdorff JM**. Body-fixed sensors for Parkinson Disease. *JAMA* 314:873-874; 2015.

Sorond FA, Cruz-Almeida Y, Clark DJ, Viswanathan A, Scherzer CR, De JP, Csiszar A, Laurienti PJ, **Hausdorff JM**, Chen WG, Ferrucci L, Rosano C, Studenski SA, Black SE, Lipsitz LA. Aging, the central

nervous system, and mobility in older adults: Neural mechanisms of mobility impairment. *J Gerontol A Biol Sci Med Sci* 70:1526-1532; 2015.

Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, Eskofier BM, Merola A, Horak F, Lang AE, Reilmann R, Giuffrida J, Nieuwboer A, Horne M, Little MA, Litvan I, Simuni T, Dorsey ER, Burack MA, Kubota K, Kamondi A, Godinho C, Daneault JF, Mitsi G, Krinke L, **Hausdorff JM**, Bloem BR, Papapetropoulos S. Technology in Parkinson's disease: Challenges and opportunities. *Mov Disord* 31:1272-1282; 2016.

Varma VR, **Hausdorff JM**, Studenski SA, Rosano C, Camicioli R, Alexander NB, Chen WG, Lipsitz LA, Carlson MC. Aging, the Central nervous system, and mobility in older adults: Interventions. *J Gerontol A Biol Sci Med Sci* 71:1451-1458; 2016.

Fasano A, Canning CG, **Hausdorff JM**, Lord S, Rochester L. Falls in Parkinson's disease: A complex and evolving picture. *Mov Disord* 32:1524-1536; 2017.

Song R, Grabowska W, Park M, Osypiuk K, Vergara-Diaz GP, Bonato P, **Hausdorff JM**, Fox M, Sudarsky LR, Macklin E, Wayne PM. The impact of Tai Chi and Qigong mind-body exercises on motor and non-motor function and quality of life in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism Relat Disord* 41:3-13; 2017.

Wajda DA, Mirelman A, **Hausdorff JM**, Sosnoff JJ. Intervention modalities for targeting cognitive-motor interference in individuals with neurodegenerative disease: A systematic review. *Expert Rev Neurother* 17:251-261; 2017.

Grants

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

2016-2019 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 Refernce Ability Neural Networks (Y Stern PI; JM Hausdorff Israeli PI)

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

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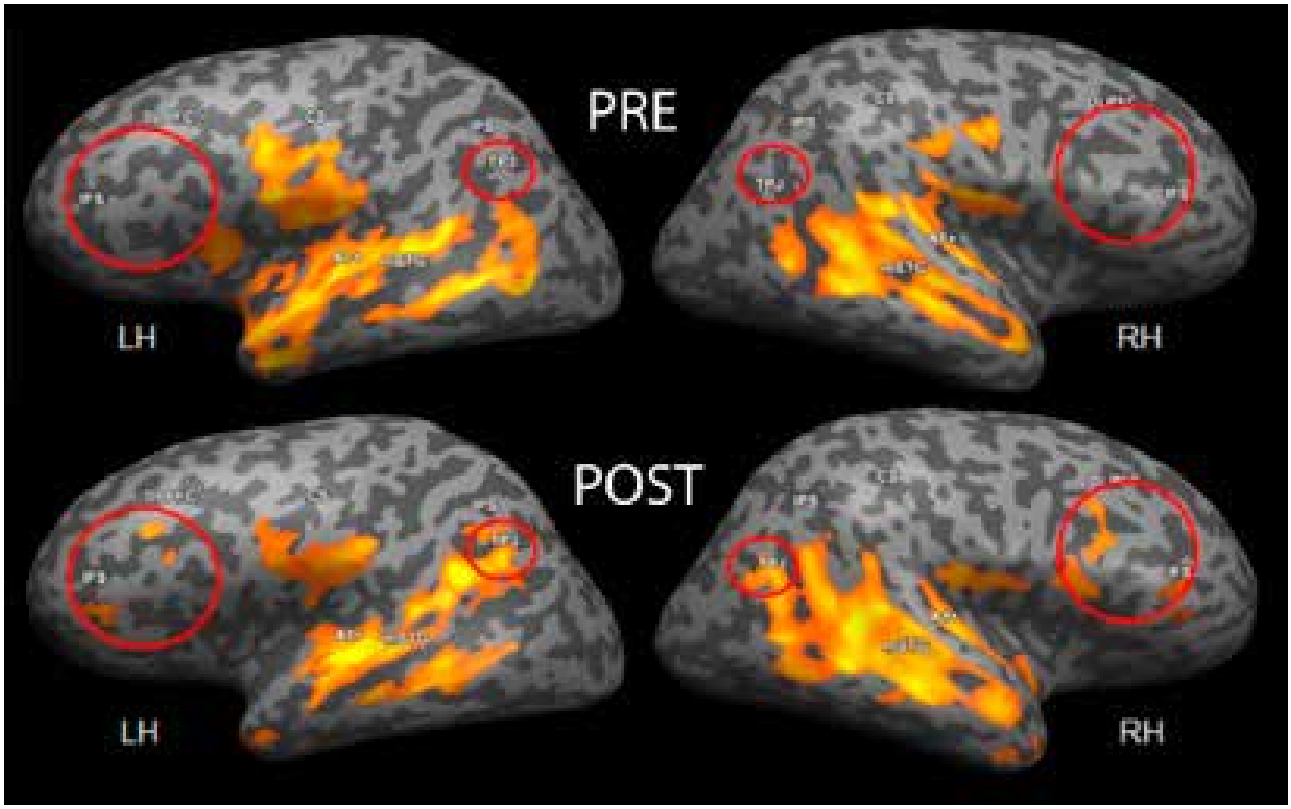
We focus on a multi-modal investigation of the human cognitive experience, using functional and structural brain imaging, behavioral rating and physiological measures. The main line of research is investigation of levels of information processing in healthy older adults and participants with amnestic 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.

Publications

Eisenstein T., Giladi N., Hendler T., Havakuk O., **Lerner Y.** (2022) Hippocampal and non-hippocampal correlates of physically active lifestyle and their relation to episodic memory in older adults. *Neurobiol Aging*, 109, 100-112.

Eisenstein T., Giladi N., Hendler T., **Lerner Y.** (2021) Physically active lifestyle is associated with attenuation of hippocampal dysfunction in cognitively intact older adults. *Front Aging Neurosci*, 13.

Lerner Y., Scherf K.S., Katkov M., Hasson U., Behrmann M. (2021) Changes in cortical coherence supporting complex visual and social processing in adolescence. *J Cogn Neurosci*, 33(11), 2215-2230.



Inter–subject correlations of responses across participants from the aerobic group that listened to the narrated story. After 4 months of aerobic training program, participants demonstrated reliable responses (high inter-SC) to story in the parietal (e.g. temporo-parietal junction) and frontal (e.g. inferior frontal gyrus) areas. Moreover, this pattern was close to those shown by healthy older adults.

Yogev-Seligmann G., Eisenstein T., Ash E., Giladi N., Sharon H., Nachman S., Bregman N., Kodesh E., Hendler T., **Lerner Y.** (2021) Functional brain plasticity following physical exercise in older adults with amnestic mild cognitive impairment. *J Alzheimers Dis*, 81 (1), 91-112.

Eisenstein T., Yogev-Seligmann G., Ash E., Giladi N., Sharon H., Shapira-Lichter, I. Nachman S., Hendler T., **Lerner Y.** (2021) Maximal aerobic capacity is associated with hippocampal cognitive reserve in older adults with amnestic mild cognitive impairment. *Hippocampus*, 31(3), 305-320.

Oren N., Ash E.L., Shapira-Lichter, I**.**, Elkana O., Reichman-Eisikovits O., Chomsky L., **Lerner Y.** (2019) Resting-state functional connectivity of the hippocampus and its relations to subsequent memory decline in older age – a longitudinal fMRI study. *Frontiers Neuroscience,* 11, 163.

Nir T.*, Or-Borichev A.*, Izraitel E., Hendler T., **Lerner Y.**, Matot, I. (2019) Transient subcortical functional connectivity upon emergence from propofol sedation in human male volunteers: evidence for active emergence. *British Journal of Anaesthesia*, 123, 298-308.

Lerner Y., Bleich-Cohen M., Eisenstein T., Madah W., Roseman L., Solnik S., Yogev-Seligmann G., Kremer I., Hendler T. (2018) Abnormal neural hierarchy in processing of verbal information in patients with schizophrenia. *Neuroimage*: *Clinical* 17, 1047-1060.

Marron T.R., **Lerner Y.**, Berant E., Kinreich S., Shapira-Lichter I., Hendler T., Faust M. (2018) Chain Free association, creativity, and the default mode network. *Neuropsychologia,* 118, 40-58.

Oren N., Shapira-Lichter, I., **Lerner Y.**, Hendler T., Giladi N., Ash E.L. (2018) How attention modulates encoding of dynamic stimuli in older adults. *Behavioural Brain Research,* 347, 209-218.

Golland Y., Levit-Binnun N., Hendler., **Lerner Y**. (2017) Neural dynamics underlying emotional transmissions between individuals. *SCAN* 12, 1249-1260.

Oren N., Shapira-Lichter, I., **Lerner Y.**, Tarrasch R., Hendler T., Giladi N., Ash E.L. (2017) Schema benefit vs. proactive interference: Contradicting behavioral outcomes and coexisting neural patterns. *Neuroimage,* 158, 271-281.

Grants

2018-2022 Israel Science Foundation

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

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.

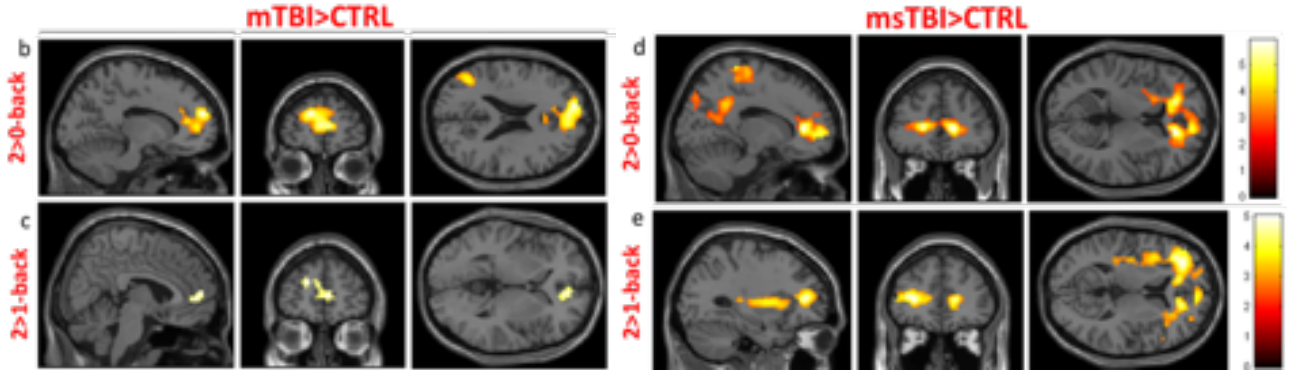
The objective of our research is to translate into clinical practice. Our translational research aims to improve the diagnosis and prediction of brain pathology's progression, to plan medical and rehabilitative interventions for the well-being of patients with neuropathologies.

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.

Weinstein A., **Livny A.,** Weizman A. Brain imaging studies on the cognitive, pharmacological and



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

neurobiological effects of cannabis in humans: Evidence from studies of adult users. Current Pharmaceutical Design. 2016.

Livny A., Ravona Springer R., Heymann T., Priess R. Kushnir T., Tsarfaty G., Rabinov L., Moran R., Hoffman H., Cooper I., Greenbaum L., Silverman J., Sano M., Johnson S., Bendlin B., Schnaider Beeri M. Long-term variability in glycemic control is associated with white matter hyperintensities in APOE4 genotype carriers with type 2 diabetes. Diabetes Care. 2016; 39(6): 1056-9.

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

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

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

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

Livny A., Reichenberg A, Fruchter E., Yoffe R., Goldberg S., Fenchel D., Burshtein S., Bachar E., Davidson M., Weiser M. A population-based longitudinal study of symptoms and signs before the onset of psychosis. American Journal of Psychiatry 2018;175:351-358.

Livny A., Cohen K., Tik N., Tsarfaty G., Rosca P., Weinstein A. The effects of synthetic cannabinoids on brain structure and function. European Neuropsychopharmacology 2018; 28(9):1047-1057.

West R., Ravona-Springer R., **Livny A.**, Heymann A., Shahar D., Leroith D., Preiss R., Zukran R., Silverman J, Schnaider Beeri M. Age modulates the association of caffeine intake with cognition and with gray matter in elderly diabetics. Journal of Gerontology: Medical Sciences ,2018, 74(5), 683-688.

Doniger G., Schnaider Beeri M., Bahar-Fuchs A., Gottlieb A., Tkachov A., Kenan H., **Livny A.**, Bahat Y., Sharon H., Ben-Gal O., Cohen M., Zeilig G., and Plotnik M. Virtual reality-based cognitive-motor training for middle-aged adults at high Alzheimer's disease risk: A randomized controlled trial. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2018, 4:118-129.

Percik R., Cina J., Even B., Gitler A., Geva D., Seluk L., **Livny A.** A Pilot study of a novel therapeutic approach to obesity: CNS modification of food craving by N.I.R. H.E.G. neurofeedback. Clinical Nutrition. 2018. pii: S0261-5614(18)30043-8;

Ganmore I, **Livny A.**, Ravona-Springer R, Cooper I, Alkelai A, Shelly S, Tsarfaty G, Heymann A, Schnaider Beeri M, Greenbaum L. TCF7L2 polymorphisms are associated with amygdalar volume in elderly individuals with Type 2 Diabetes. Sci Rep. 2019;9(1).

Landa J., Bar O., Bord A., Patael SZ., **Livny A.**, Sadeh VT., Tsarfaty G., Ahonniska-Assa J. Growing up with Bilateral parieto-occipital injury: over ten years of clinical observation and neuropsychological follow-up. Neurocase. 2019:1-8.

Krasovsky T., Bar O., Nachshon U., **Livny A.**, Tsarfaty G., Brezner A., Landa J. Despite dystonia: Natural history of delayed-onset pediatric secondary dystonia. Brain Injury. Epub 2019.

Livny A., Schnaider Beeri M., Heymann A., Schmeidler J., Moshier E., Tzukran R., Tsarfaty G., Leroith D., Preiss R., Soleimani L., Guerrero-Berroa E., Silverman JM., Bendlin B., Levy A. and Ravona-Springer R. The association of depressive symptoms with brain volume is stronger among diabetic elderly carriers of the haptoglobin 1-1 genotype compared to non-carriers. Frontiers in Endocrinology. 2019;10:68. eCollection.

Nissim, M., **Livny, A.**, Barmatz, C., Tsarfaty, G., Berner, Y., Sacher, Y., Giron, J., & Ratzon, N. Z. Effects of aquatic physical intervention on fall risk, working memory and hazard-perception as pedestrians in older people: a pilot trial. BMC geriatrics, 2020, 20(1), 74;

BenAri, O., Efrati, S., Sano, M., Bendlin, B. B., Lin, H., Liu, X., Sela, I., Almog, G., **Livny, A.**, Sandler, I., Ben-Haim, S., Sagi, R., LeRoith, D., Schnaider Beeri, M., & Ravona-Springer, R. A double-blind placebo-controlled clinical trial testing the effect of hyperbaric oxygen therapy on brain and cognitive outcomes of mildly cognitively impaired elderly with type 2 diabetes: Study design. Alzheimer's & dementia (New York, N. Y.), 2020;6(1):e12008.

Livny, A., Schnaider Beeri, M., Heymann, A., Moshier, E., Berman, Y., Mamistalov, M., Shahar, D. R., Tsarfaty, G., Leroith, D., Preiss, R., Soleimani, L., Silverman, J. M., Bendlin, B. B., Levy, A., & Ravona-Springer, R. Vitamin E Intake Is Associated with Lower Brain Volume in Haptoglobin 1-1 Elderly with Type 2 Diabetes. Journal of Alzheimer's disease: JAD, 2020;74(2):649-658.

Raizman, Tavor I., Biegon A., Harnof S., Hoffmann C., Tsarfaty G., Fruchter E., Lucian TL., Weiser M., **Livny A.** Traumatic Brain Injury Severity in a Network Perspective: A Diffusion MRI Based Connectome Study. Scientific Reports 10.1 (2020): 1-12.

Dennis EL, Caeyenberghs K, Asarnow RF, Babikian T, Bartnik-Olson B, Bigler ED, Figaji A, Giza CC, Goodrich-Hunsaker NJ, Hodges CB, Hoskinson KR. Königs M, Levin HS, Lindsey HM, Livny A, Max JE, Merkley TL, Newsome MR, Olsen A, Ryan NP, Spruiell MS, Suskauer SJ, Thomopoulos SI, Ware AL, Watson CG, Wheeler AL, Yeates KO, Zielinski BA, Thompson PM, Tate DF, Wilde EA. Challenges and opportunities for neuroimaging in young patients with traumatic brain injury: a coordinated effort towards advancing discovery from the ENIGMA pediatric moderate/severe TBI group. Brain imaging and behavior. 2020, 1-21.

West R., **Livny A.**, Ravona-Springer R., Bendlin BB., Heymann A., Leroith D., Liu X., Lin HM., Hochner H., Friedlander Y., Ganmore I., Tirosh A., Schnaider Beeri M. Higher BMI is associated with smaller regional brain volume in older adults with type 2 diabetes. Diabetologia. 2020;63(11):2446-2451.

Olsen, A., Babikian, T., Bigler, E., Caeyenberghs, K., Conde, V., Dams-O'Connor, K., Dobryakova, E., Genova, H., Grafman, J., Håberg, A. Heggland, I., Hellstrøm T., Cooper BH., Irimia A., Jha RM., Johnson PK., Koliatsos VE., Levin H., Li LM., Lindsey HM., **Livny A.**, Løvstad M., Medaglia J., Menon DK., Mondello S., Monti MM., Newcombe V., Petroni A., Ponsford J., Sharp D., Spitz G., Westlye LT., Thompson PM., Dennis EL., Tate DF., Wilde EA., Hillary FG. Toward a Global and Reproducible Science for Brain Imaging in Neurotrauma: The ENIGMA Adult Moderate/Severe Traumatic Brain Injury Working Group. Brain Imaging and Behavior. 2020, 1-29.

Lotan, Roni, Abigail Livny, Shahar Shelly, Moran Zacharia, Jaime Uribarri, Paul Beisswenger, Weijing Cai, Michal Schnaider Beeri, and Aron M. Troen. Design and Feasibility of A Randomized Controlled Pilot Trial to Reduce Exposure and Cognitive Risk Associated with Advanced Glycation End Products in Older Adults with Type 2 Diabetes. Frontiers in Nutrition 8: 5.

Ravona-Springer, R., Sharvit-Ginon, I., Ganmore, I., Greenbaum, L., Bendlin, B. B., Sternberg, S. A., ... & Beeri, M. S. (2020). The Israel Registry for Alzheimer's Prevention (IRAP) Study: Design and Baseline Characteristics. Journal of Alzheimer's Disease, 78, 777-788, 2020.

Borodkin, K., **Livny, A.**, Kushnir, T., Tsarfaty, G., Maliniak, O., & Faust, M. (2021). Linking L2 proficiency and patterns of functional connectivity during L1 word retrieval. Brain and Language, 216, 104931.

Tik, N., **Livny, A.**, Gal, S., Gigi, K., Tsarfaty, G., Weiser, M., & Tavor, I. (2020). Predicting Individual Variability in Task-Evoked Brain Activity in Schizophrenia. Human Brain Mapping. 2021.

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
Sackler Faculty of Medicine

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Investigating the Underlying Neural Mechanisms that Contribute to Changes in Function

Positions

Lecturer, Sackler 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 focuse 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

Nieuwhof F, Bloem BR, Reelick MF, Aarts E, **Maidan I**, Mirelman A, Hausdorff JM, Toni I, Helmich RC. Impaired dual tasking in Parkinson's disease is associated with reduced focusing of cortico-striatal activity. *Brain* 2017; 140:1384-1398.

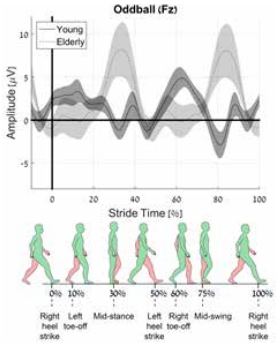
Maidan I, Bernad-Elazari H, Giladi N, Hausdorff JM, Mirelman A. When is higher level cognitive control needed for locomotor tasks among patients with Parkinson's disease? *Brain Topography* 2017; 30:531-538.

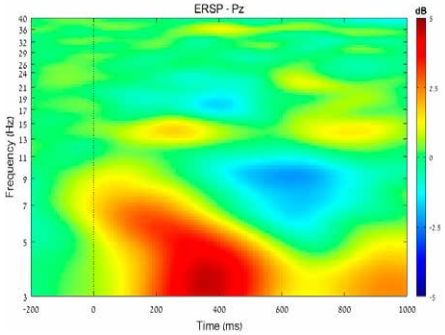
Mirelman A, **Maidan I**, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. *Brain and Cognition* 2017; 115:41-46.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Hausdorff JM, Mirelman A. Disparate effects of training on brain activation in Parkinson disease. *Neurology* 2017; 89:1804-1810.

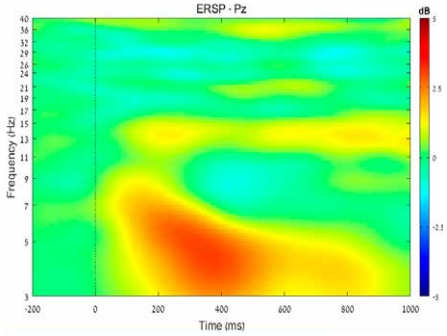
Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, Giladi N, Mirelman A, Hausdorff JM. Age-associated changes in obstacle negotiation strategies: Does size and timing matter? *Gait Posture* 2017; 59:242-247.

Maidan I, Shustak S, Sharon T, Bernad-Elazari H, Geffen N, Giladi N, Hausdorff JM, Mirelman





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.

Thaler A, Kliper E, **Maidan I**, Herman T, Rosenberg-Katz K, Bregman N, Gurevich T, Shiner T, Hausdorff JM, Orr-Urtreger A, Giladi N, Mirelman A. Cerebral imaging markers of GBA and LRRK2 related Parkinson's disease and their first-degree unaffected relatives. *Brain Topography* 2018; 31:1029-1036.

Thumm PC, **Maidan I**, Brozgol M, Shustak S, Gazit E, Shema Shiratzki S, Bernad-Elazari H, Beck Y, Giladi N, Hausdorff JM, Mirelman A. Treadmill walking reduces pre-frontal activation in patients with Parkinson's disease. *Gait Posture* 2018; 62:384-387.

Li KZH, Bherer L, Mirelman A, **Maidan I**, Hausdorff JM. Cognitive involvement in balance, gait and dual-tasking in aging: a focused review from a neuroscience of aging perspective. *Front Neurol* 2018; 29;9:913.

Maidan I, Jacob Y, Giladi N, Hausdorff JM, Mirelman A. Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease. *Parkinsonism Relat Disord* 2019; 63:77-82.

Sunderaraman P, **Maidan I**, Kozlovski T, Apa Z, Mirelman A, Hausdorff JM, Stern Y. Differential associations between distinct components of cognitive function and mobility: Implications for understanding aging, turning and dual-task walking. *Front Aging Neurosci* 2019; 11:166.

Eyal S, Kurz I, Mirelman A, **Maidan I**, Giladi N, Hausdorff JM. Successful negotiation of anticipated and unanticipated obstacles in young and older adults: Not all is as expected. *Gerontology* 2019; 28:1-10.

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.

Maidan I, Patashov D, Shustak S, Fahoum F, Gazit E, Shapiro B, Levy A, Sosnik R, Giladi N, Hausdorff JM, Mirelman A. A new approach to quantifying the EEG during walking: Initial evidence of gait related potentials and their changes with aging and dual tasking. *Exp Gerontol* 2019; 126:110709.

Patashov D, Menahem Y, Ben-Haim O, Gazit E, **Maidan I**, Mirelman A, Sosnik R, Goldstein D, Hausdorff JM. Methods for gait analysis during obstacle avoidance task. *Ann Biomed Eng* 2020; 48:634-643.

Maidan I, Droby A, Jacob Y, Giladi N, Hausdorff JM, Mirelman A. The neural correlates of falls: Alterations in large-scale resting-state networks in elderly fallers. *Gait Posture*; 2020; 80:56-61.

Sharon T, Kurz I, Bernad-Elazari H, Shustak S, Galperin I, Giladi N, Mirelman A, Hausdorff JM, **Maidan I**. Which obstacle attributes place additional demands on higher-level cognitive function in patients with Parkinson's disease? *Parkinsonism Relat Disord;* 2020;78:178-183.

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.

Maidan I, Mirelman A, Hausdorff JM, Stern Y, Habeck CG. Distinct cortical thickness patterns link disparate cerebral cortex regions to select mobility domains. *Sci Rep*. 2021;11(1):6600.

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.

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

Prof. Anat Mirelman, Ph.D.

Laboratory for Early Markers of Neurodegeneration (LEMON)
Neurological Institute, Tel Aviv Sourasky Medical Center
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Investigating Early Markers of Neurodegeneration

Positions

Associate Professor, Neurological Department, Sackler School of Medicine

Faculty Member, Sagol School of Neuroscience

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

Research

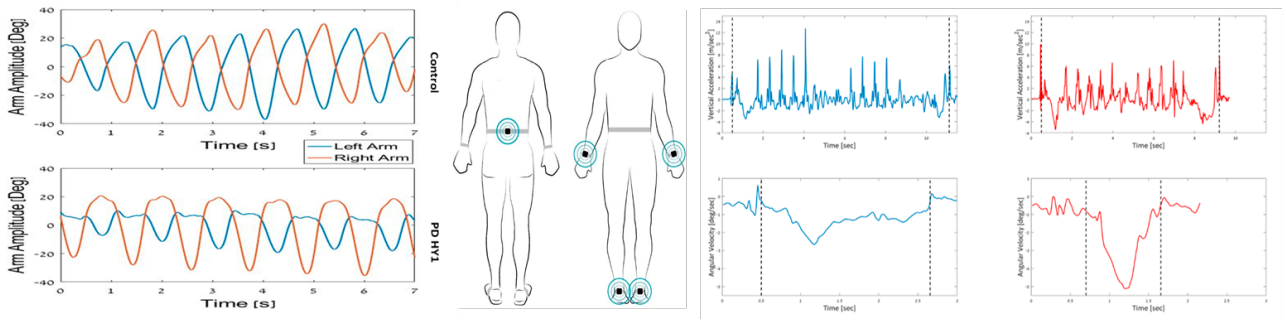
Research in the LEMON lab is performed in a clinical setting. Our mission is to identify new markers of ageing and neurodegeneration. More specifically, we aim to better understand the pathological process of neurodegeneration and its progression. We investigate clinical, biological and neuronal markers 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

Gan-Or Z, **Mirelman A**, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y, Desautels A, Gagnon JF, Leblond CS, Frauscher B, Alcalay RN, Saunders-Pullman R, Bressman SB, Marder K, Monaca C, Hogl B, Orr-Urtreger A, Dion PA, Montplaisir JY, Giladi N, Rouleau GA. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol 2015;2:941-945.

Helmich RC, Thaler A, van Nuenen BF, Gurevich T, **Mirelman A**, Marder KS, Bressman S, Orr-Urtreger A, Giladi N, Bloem BR, Toni I. Reorganization of corticostriatal circuits in healthy G2019S LRRK2 carriers. Neurology 2015;84:399-406.

Mirelman A, Alcalay RN, Saunders-Pullman R, Yasinovsky K, Thaler A, Gurevich T, Mejia-Santana H, Raymond D, Gana-Weisz M, Bar-Shira A, Ozelius L, Clark L, Orr-Urtreger A, Bressman S, Marder K, Giladi N. Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene. Mov Disord 2015;30:981-986.



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.

Mirelman A, Giladi N, Hausdorff JM. Body-Fixed Sensors for Parkinson Disease. JAMA 2015;314:873-874.

Mirelman A, Bernad-Elazari H, Nobel T, Thaler A, Peruzzi A, Plotnik M, Giladi N, Hausdorff JM. Effects of aging on arm swing during gait: The role of gait speed and dual tasking. PLoS One 2015;10:e0136043.

Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, Rikkert MO, Bloem BR, Pelosin E, Avanzino L, Abbruzzese G, Dockx K, Bekkers E, Giladi N, Nieuwboer A, Hausdorff JM. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomized controlled trial. Lancet. 2016;388:1170-82.

Giladi N, **Mirelman A**, Thaler A, Orr-Urtreger A. A personalized approach to Parkinson's Disease patients based on founder mutation analysis. Front Neurol 2016;7:71.

Maidan I, Rosenberg-Katz K, Jacob Y, Giladi N, Deutsch JE, Hausdorff JM, **Mirelman A**. Altered brain activation in complex walking conditions in patients with Parkinson's disease. Parkinsonism Relat Disord 2016;25:91-96.

Maidan I, Nieuwhof F, Bernad-Elazari H, Reelick MF, Bloem BR, Giladi N, Deutsch JE, Hausdorff JM, Claassen JA, **Mirelman A**. The Role of the frontal lobe in complex walking among patients with Parkinson's Disease and healthy older adults: An fNIRS study. Neurorehabil Neural Repair 2016;30:963-971.

Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, Saunders-Pullman R, Raymond D, Doan N, Bressman SB, Marder KS, Alcalay RN, Rao AK, Berg D, Brockmann K, Aasly J, Waro BJ, Tolosa E, Vilas D, Pont-Sunyer C, Orr-Urtreger A, Hausdorff JM, Giladi N. Arm swing as a potential new prodromal marker of Parkinson's disease. Mov Disord 2016;31:1527-1534.

Thaler A, Helmich RC, Or-Borichev A, van Nuenen BF, Shapira-Lichter I, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, Giladi N, Hendler T, **Mirelman A**. Intact working memory in non-manifesting LRRK2 carriers--an fMRI study. Eur J Neurosci 2016;43:106-112.

Artzi M, Even-Sapir E, Lerman SH, Thaler A, Urterger AO, Bressman S, Marder K, Hendler T, Giladi N, Ben BD, **Mirelman A**. DaT-SPECT assessment depicts dopamine depletion among asymptomatic G2019S LRRK2 mutation carriers. PLoS One 2017;12:e0175424.

Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. Brain Cogn 2017;115:41-46.

Thaler A, Gurevich T, Bar SA, Gana WM, Ash E, Shiner T, Orr-Urtreger A, Giladi N, **Mirelman A**. A "dose" effect of mutations in the GBA gene on Parkinson's disease phenotype. Parkinsonism Relat Disord 2017;36:47-51.

Maidan I, Shustak S, Sharon T, Bernad-Elazari H, Geffen N, Giladi N, Hausdorff JM, **Mirelman A**. Prefrontal cortex activation during obstacle negotiation: What's the effect size and timing? Brain Cogn 2018;122:45-51.

Mirelman A, Saunders-Pullman R, Alcalay RN, Shustak S, Thaler A, Gurevich T, Raymond D, Mejia-Santana H, Orbe RM, Ozelius L, Clark L, Gana-Weisz M, Bar-Shira A, Orr-Utreger A, Bressman SB, Marder K, Giladi N. Application of the Movement Disorder Society prodromal criteria in healthy G2019S-LRRK2 carriers. Mov Disord 2018;33:966-973.

Thaler A, Kliper E, Maidan I, Herman T, Rosenberg-Katz K, Bregman N, Gurevich T, Shiner T, Hausdorff JM, Orr-Urtreger A, Giladi N, **Mirelman A**. Cerebral imaging markers of GBA and LRRK2 related Parkinson's Disease and Their first-degree unaffected relatives. Brain Topogr 2018;31:1029-1036.

Thaler A, Bregman N, Gurevich T, Shiner T, Dror Y, Zmira O, Gan-Or Z, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, Giladi N, **Mirelman A**. Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA gene. Parkinsonism Relat Disord 2018;55:45-49.

Thaler A, Kozlovski T, Gurevich T, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, Giladi N, **Mirelman A**. Survival rates among Parkinson's disease patients who carry mutations in the LRRK2 and GBA genes. Mov Disord 2018;33:1656-1660.

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.

Kozlovski T, Mitelpunkt A, Thaler A, Gurevich T, Orr-Urtreger A, Gana-Weisz M, Shachar N, Galili T, Marcus-Kalish M, Bressman S, Marder K, Giladi N, Benjamini Y, **Mirelman A**. Hierarchical data-driven analysis of clinical symptoms among patients with Parkinson's Disease. Front Neurol. 2019;10:531.

Maidan I, Jacob Y, Giladi N, Hausdorff JM, **Mirelman A**. Altered organization of the dorsal attention network

is associated with freezing of gait in Parkinson's disease. Parkinsonism Relat Disord 2019;63:77-82.

Sunderaraman P, Maidan I, Kozlovski T, Apa Z, **Mirelman A**, Hausdorff JM, Stern Y. Differential associations between distinct components of cognitive function and mobility: implications for understanding aging, turning and dual-task walking. Front Aging Neurosci. 2019;11:166.

Mirelman A, Bonato P, Camicioli R, Ellis TD, Giladi N, Hamilton JL, Hass CJ, Hausdorff JM, Pelosin E, Almeida QJ. Gait impairments in Parkinson's disease. Lancet Neurol 2019;18:697-708

Grants

2016-2019 Ministry of Science and Technology

2018-2020 Michael J Fox Foundation

2019-2021 Biogen Biotechnologies Research Grant

2019-2024 European Commision- H2020 Program

Dr. Michal Taler, Ph.D.

Biological Psychiatry Lab,
Felsenstein Medical Research Center

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

Positions

Head, Biological Psychiatry Lab, Felsenstein Medical Research Center, Sackler Faculty of Medicine

Research

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

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

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

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

Our lab is located at the heart of the intersection between basic science and clinical practice. It is physically located at the Belinson campus, in close proximity to the Geha Mental Health Center. The staff is composed of senior clinical researchers, as well as senior neuroscientists, working in collaboration. We aim to bring together clinical information with animal model data to eventually take back as therapeutic interventions for a population with severe illness and urgent unmet needs.

Publicationsr

Gil-Ad I, Amit BH, Hayardeni L, Tarasenko I, **Taler M**, Gueta RU, Weizman A. Effects of the anti-multiple sclerosis immunomodulator laquinimod on anxiety and depression in rodent behavioral models. *J Mol Neurosci*. 2015, 55:552-60

Bloch K, Gil-Ad I, Tarasenko I, Vanichkin A, **Taler M**, Hornfeld SH, Vardi P, Weizman A. Intracranial pancreatic islet transplantation increases islet hormone expression in the rat brain and attenuates behavioral dysfunctions induced by MK-801 (dizocilpine). *Horm Behav*. 2015, 72:1-11

Taler M, Vered I, Globus R, Shbiro L, Weizman A, Weller A, Gil-Ad I. Attenuated Weight Gain with the Novel Analog of Olanzapine Linked to Sarcosinyl Moiety (PGW5) Compared to Olanzapine. *J Mol Neurosci*. 2016, 58:66-73

Amitai M, **Taler M**, Carmel M, Michaelovsky E, Eilat T, Yablonski M, Orpaz N, Chen A, Apter A, Weizman A, Fennig S. The Relationship Between Plasma Cytokine Levels and Response to Selective Serotonin Reuptake Inhibitor Treatment in Children and Adolescents with Depression and/or Anxiety Disorders. *J Child Adolesc Psychopharmacol*. 2016, 26:727-732.

Hollander S, Hochman E, Shoval G, **Taler M**, Trommer S, Hermesh H, Weizman A, Krivoy A. The association between serum creatine kinase, mood and psychosis in inpatients with schizophrenia, bipolar and schizoaffective disorders. *Psychiatry Res*. 2016, 30;238:333-337

Krivoy A, Gil-Ad I, Tarasenko I, Weizman A, **Taler M**. Trans-generation enrichment of clozapine-responsiveness trait in mice using a subchronic hypo-glutamatergic model of schizophrenia:A preliminary study. *Behav Brain Res*. 2017, 14;323:141-145

Segal-Gavish H, Gazit N, Barhum Y, Ben-Zur T, **Taler M**, Hornfeld SH, Gil-Ad I, Weizman A, Slutsky I, Niwa M, Kamiya A, Sawa A, Offen D, Barzilay R. BDNF overexpression prevents cognitive deficit elicited by adolescent cannabis exposure and host susceptibility interaction. *Hum Mol Genet*. 2017, 26:2462-2471

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

Zohar AH, Eilat T, Amitai M, **Taler M**, Bari R, Chen A, Apter A, Weizman A, Fennig S. An exploratory study of adolescent response to fluoxetine using psychological and biological predictors. PeerJ. 2018, 10;6:e4240.

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.

Grants

National Institute of Psychobiology in Israel

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The Neuronal Encoding of Human Speech

Positions

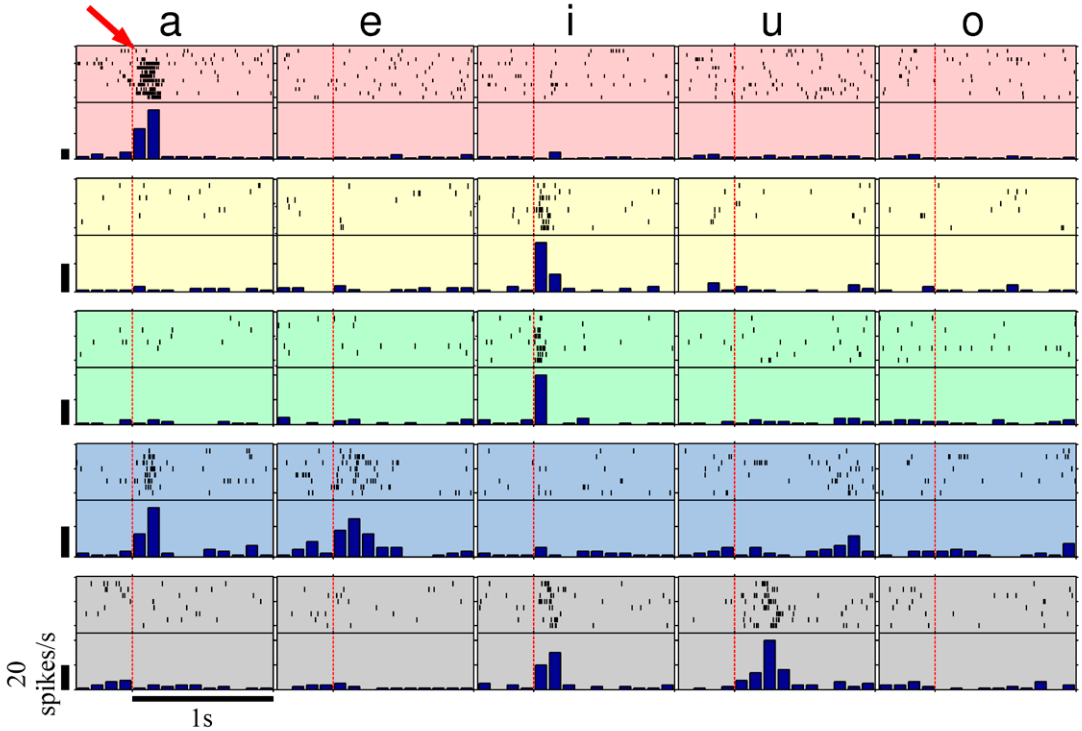
Senior Lecturer, Sackler Faculty of Medicine and Sagol School of Neuroscience

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

Research

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



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).

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. Brozgol, 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

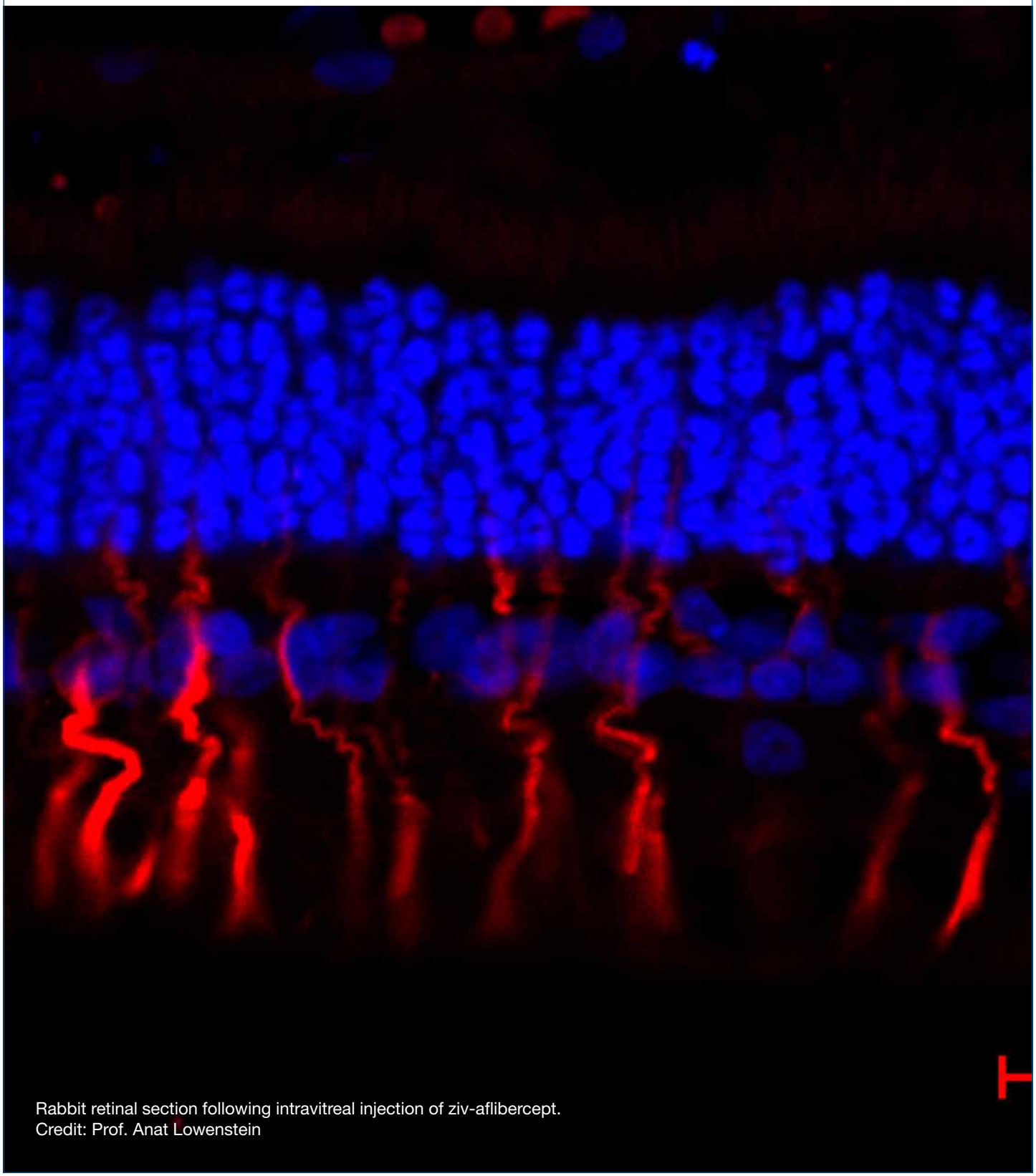
A. Tankus and J.M. Hausdorff. Deep brain stimulation in Parkinson's disease: effects on gait and postural control. In F.A. Barbieri and R. Vitório, editors, Locomotion and Posture in Older Adults – The Role of Aging and Movement Disorders, Springer, Chapter 25, pages 385–396, 2017.

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
Sackler Faculty of Medicine
Sheba Medical Center
Tel Hashomer

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Neurodegeneration in the Eye and Brain

Positions

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

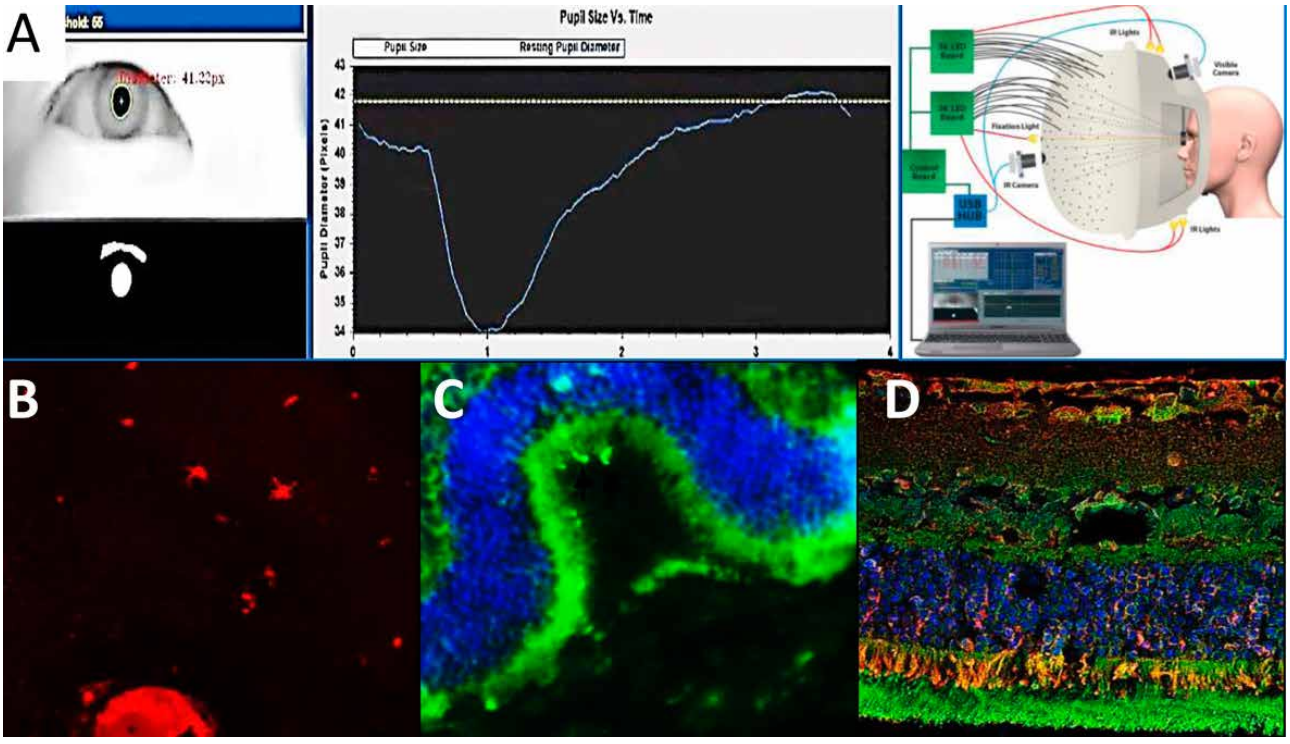
Member, Animals in Research Committee (ARC) of Association for Research in Vision and Ophthalmology (ARVO)

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.

Sher I, Tzameret A, Peri-Chen S, Edelshtain V, Ioffe M, Sayer A, Buzhansky L, Gazit E, Rotenstreich Y. Synthetic 9-cis-beta-carotene inhibits photoreceptor degeneration in cultures of eye cups from Rpe65rd12 mouse model of retinoid cycle defect. *Sci Rep*. 2018;8(1):6130.

Haj Yahia S, Hamburg A, **Sher I**, Ben Ner D, Yassin S, Chibel R, Mimouni M, Derazne E, Belkin M, Rotenstreich Y. Effect of stimulus intensity and visual field location on rod- and cone-mediated pupil response to focal light stimuli. *Invest Ophthalmol Vis Sci*. 2018;59(15):6027-6035.

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**, Edelstain 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.

Tzameret A, Ketter-Katz H, Edelshtain V, **Sher I**, Corem-Salkmon E, Levy I, Last D, Guez D, Mardor Y, Margel S**,** Rotenstriech Y. In vivo MRI assessment of bioactive magnetic iron oxide/human serum albumin nanoparticle delivery into the posterior segment of the eye in a rat model of retinal degeneration. *J Nanobiotechnology*. 2019; 17(1):3.

Edelshtain V., Peled A., Tzameret A, Pri-Chen S., Ziv H., Derazne, E., Harats D., Greenberg R., Harari A., Shaish A, **Sher I**, Rotenstreich, Y. Long-term treatment with 9-cis-β-carotene rich alga dunaliella bardawil ameliorates photoreceptor degeneration in a mouse model of retinoid cycle defect. *Algal Research*. 2019; 101607.

Cohen S, Tucker Y, Guttman S, Bubis E, Rubinstein Y, Skaat A, **Sher I**, Rotenstreich Y. Anterior-segment optical coherence tomography-guided measurement of a melting ulcer for follow-up of corneoscleral thinning progression. *Int Med Case Rep J*. 2019;12:335-338.

Rubinstein Y, Fogel-Levin M, Singer R, Levkovitch-Verbin H, Moros I, **Sher I,** Rotenstreich Y, Skaat A. Microarchitecture of schlemm canal before and

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 607 862 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.

Mangel L, Morag S, Mandel D, Marom R, Moran-Lev H, Lubetzky R. The effect of infant's sex on human milk macronutrients content: An observational study. *Breastfeed Med.* 2020;15(9):568-571.

Palnizky Soffer G, Siri M, **Mangel L**, Mandel D, Lubetzky R. Impact of maternal anxiety on human milk macronutrients content: A prospective observational study. *Breastfeed Med.* 2020;15(9):572-575.

Be'er M, Mandel D, Yelak A, Gal DL, **Mangel L**, Lubetzky R. The effect of physical activity on human milk macronutrient content and its volume. *Breastfeed Med.* 2020;15(6):357-361.

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.

Yelak A, Marom R, Mandel D, **Mangel L**, Grisaru-Soen G, Adler A. Retrospective study showed that bacterial gastroenteritis was an important cause of bloody stools in newborn infants. *Acta Paediatr.* 2019 Oct;108(10):1781-1785.

Mangel L, Mimouni FB, Mandel D, Mordechaev N, Marom R. Breastfeeding difficulties, breastfeeding duration, maternal body mass index, and breast anatomy: Are they related? *Breastfeed Med*. 2019;14(5):342-346.

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

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Epidemiology & Preventive Medicine
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Real-World Evidence Pharmacoepidemiology

Positions

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

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

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

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

Research

Our research interests include large-scale clinical epidemiology, drug safety and effectiveness analytics using Maccabi's electronic medical records databases. Our research team is aimed at investigating multiple dimensions of healthcare quality, including safety (e.g. adverse effects of IVF, renal effects of chronic medications), efficacy and effectiveness of medical technologies (e.g. glycemic control and outcomes in patients treated with new generation therapies for diabetes), clinical and economic burden of diseases and health events (e.g. congestive heart failure, hepatitis C infections), as well as pharmacoepidemiology studies on medication adherence and pleiotropic effects of drugs. Our other interests include health effects of low dose ionizing radiation and specifically cancer and cataract. As the founding head of the Epidemiology & Database Research Department at Maccabi, I have the overall responsibility for the direction of the scientific database research team of KSM Institute for Research & Innovation.

Publications

Moshe S, Cinamon T, Zack O, Segal N**, Chodick G**, Krakov A, Tal M.The need for social work services in occupational medicine.Occupational Medicine 2017.

Shalev H, Solt I, **Chodick G**. Month of birth and risk of autism spectrum disorder: a retrospective cohort of male children born in Israel. BMJ Open. 2017;7:e014606.

Lerman S, Amichai B, Weinstein G, Shalev V, **Chodick G**. Parkinson's Disease, Melanoma, and Keratinocyte Carcinoma: A Population-Based Study. Neuroepidemiology. 2018;50:168-173.

Goldshtein I, **Chodick G**, Kochba I, Gal N, Webb M, Shibolet O. Nonalcoholic Fatty Liver Identification and Characterization Using Big Data. Clin Gastroenterol Hepatol. 2019; pii: S1542-3565(19)30863-8.

Yelin I, Snitser O, Novich G, Katz R, Tal O, Parizade M, **Chodick G**, Koren G, Shalev V, Kishony R. Personal clinical history predicts antibiotic resistance of urinary tract infections. Nat Med. 2019;25:1143-1152.

Chodick G, Tenne Y, Barer Y, Shalev V, Elchalal U. Gestational diabetes and long term risk for dyslipidemia: a population-based historical-cohort study. BMJ Open Diabetes & Care. 2020;**8:**e000870.

Fishman B, Zloof Y, Orr O, Tsur AM, Furer A, Omer Gilon M, **Chodick G**, Leiba A, Derazne E, Tzur D, Afek A, Grossman E, Twig G. The opposing trends of body mass index and blood pressure during 1977-2020; nationwide registry of 2.8 million male and female adolescents. Cardiovasc Diabetol. 2021;20(1):242.

Ram S, Ram HS, Rosenthal YS, Attali E, Warshaviak M, Gamzu R, Yogev Y, **Chodick G**. The impact of breast augmentation on breast feeding in primigravida women - A cohort study. Eur J Obstet Gynecol Reprod Biol. 2021;268:116-120.

Rosenberg V, Bareket-Samish A, **Chodick G**, Siegelmann-Danieli N. Hormone-replacement therapy and its association with breast cancer subtypes:

A large retrospective cohort study. Int J Womens Health. 2021;13:1207-1216.

Machtinger R, Fallach N, Goldstein I, **Chodick G**, Schiff E, Orvieto R, Mashiach R. Ovarian stimulation for fertility treatments and risk of breast cancer: a matched cohort study. Hum Reprod. 2021:deab270.

Chodick G, Omer-Gilon M, Derazne E, Puris G, Rotem R, Tzur D, Pinhas-Hamiel O, Cukierman-Yaffe T, Shina A, Zucker I, Tirosh A, Afek A, Shalev V, Twig G. Adolescent body mass index and changes in pre-pregnancy body mass index in relation to risk of gestational diabetes. EClinicalMedicine. 2021;42:101211.

Levine-Tiefenbrun M, Yelin I, Uriel H, Kuint J, Schreiber L, Herzel E, Katz R, Ben-Tov A, Gazit S, Patalon T, **Chodick G**, Kishony R. SARS-CoV-2 RT-qPCR test detection rates are associated with patient age, sex, and time since diagnosis. J Mol Diagn. 2021:S1525-1578(21)00386-X.

Zhuo X, Melzer Cohen C, Chen J, **Chodick G**, Alsumali A, Cook J. Validating the UK prospective diabetes study outcome model 2 using data of 94,946 Israeli patients with type 2 diabetes. J Diabetes Complications. 2022;36(1):108086.

Rotem RS, **Chodick G**, Davidovitch M, Bellavia A, Weisskopf MG. Maternal thyroid anomalies and attention-deficit hyperactivity disorders in progeny. Am J Epidemiol. 2021:kwab272.

Netanel C, Ben-Aharon O, Ben-Ari Z, **Chodick G**, Anis E, Magnezi R. Evaluation of a universal hepatitis B vaccination program and antenatal screening for hepatitis B surface antigen: Results from a real-world study 2015-2016. Vaccine. 2021;39(48):7101-7107.

Gamus A, Keren E, Kaufman H, Brandin G, Peles D, **Chodick G**. Telemedicine versus face-to-face care for treatment of patients with lower extremity ulcers. J Wound Care. 2021;30(11):916-921.

Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, **Chodick G**, Gazit S, Patalon T. Correlation of SARS-CoV-2-breakthrough infections to time-from-vaccine. Nat Commun. 2021;12(1):6379.

Levine-Tiefenbrun M, Yelin I, Alapi H, Katz R, Herzel E, Kuint J, **Chodick G**, Gazit S, Patalon T, Kishony R. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. Nat Med. 2021;27(12):2108-2110.

Chodick G, Teper GR, Levi S, Kopel H, Kleinbort A, Khen E, Schejter E, Shalev V, Stein M, Lewis N. The impact of a Facebook campaign among mothers on HPV vaccine uptake among their daughters: A randomized field study. Gynecol Oncol. 2021;160(1):106-111.

Weil C, Bilavsky E, Sinha A, **Chodick G**, Goodman E, Wang WV, Calhoun SR, Marks MA. Epidemiology of cytomegalovirus infection in pregnancy in Israel: Real-world data from a large healthcare organization. J Med Virol. 2022;94(2):713-719.

Mizrahi B, Bivas-Benita M, Kalkstein N, Akiva P, Yanover C, Yehezkelli Y, Kessler Y, Alon SH, Rubin E, **Chodick G**. Results of an early second PCR test performed on SARS-CoV-2 positive patients may support risk assessment for severe COVID-19. Sci Rep. 2021;11(1):20463.

Shiyovich A, Shalev V, **Chodick G**, Tirosh M, Katz A, Klar MM, Shuvy M, Pereg D, Minha S. Shifting from vitamin K antagonists to non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: predictors, patterns and temporal trends. BMC Cardiovasc Disord. 2021;21(1):493.

Reiner-Benaim A, Neuberger A, **Chodick G,** Henig O. Use of antibiotics and factors associated with treatment failure among 152,245 patients with pneumonia treated in the community - a retrospective cohort study. Eur J Clin Microbiol Infect Dis. 2021.

Hamood R, Tirosh M, Fallach N, **Chodick G**, Eisenberg E, Lubovsky O. Prevalence and incidence of Osteoarthritis: A population-based retrospective cohort study. J Clin Med. 2021;10(18):4282.

Sharman Moser S, **Chodick G**, Ni YG, Chalothorn D, Wang MD, Shuldiner AR, Morton L, Salomon O, Jalbert JJ. The association between Factor XI deficiency and the risk of bleeding, cardiovascular, and venous thromboembolic events. Thromb Haemost. 2021.

Ben-Ari T, **Chodick G**, Shalev V, Goldstein D, Gomez R, Landau Z. Real-World treatment patterns and outcomes of growth hormone treatment among children in israel over the past decade (2004-2015). Front Pediatr. 2021;9:711979.

Weil C, **Chodick G**, Shalev V, Kan I, Afik R, Cohen R, Sail K, Herishanu Y. Epidemiology, longitudinal treatment patterns and outcomes of chronic lymphocytic leukemia in Israel. Leuk Lymphoma. 2021;62(5):1136-1145.

Shalev Ram H, Ram S, Wiser I, Tchernin N, **Chodick G**, Cohen Y, Rofe G. Associations between breast implants and postpartum lactational mastitis in breastfeeding women: retrospective study. BJOG. 2022;129(2):267-272.

Rosenberg V, Tzadok R, **Chodick G**, Kariv R. Proton pump inhibitors long term use-trends and

patterns over 15 years of a large health maintenance organization. Pharmacoepidemiol Drug Saf. 2021;30(11):1576-1587.

Parikh R, Sorek E, Parikh S, Michael K, Bikovski L, Tshori S, Shefer G, Mingelgreen S, Zornitzki T, Knobler H, **Chodick G**, Mardamshina M, Boonman A, Kronfeld-Schor N, Bar-Joseph H, Ben-Yosef D, Amir H, Pavlovsky M, Matz H, Ben-Dov T, Golan T, Nizri E, Liber D, Liel Y, Brenner R, Gepner Y, Karnieli-Miller O, Hemi R, Shalgi R, Kimchi T, Percik R, Weller A, Levy C. Skin exposure to UVB light induces a skin-brain-gonad axis and sexual behavior. Cell Rep. 2021;36(8):109579.

Banon T, Wortsman J, Ben Moshe S, Gazit S, Peretz A, Ben Tov A, **Chodick G**, Perez G, Patalon T. Evaluating red blood cell distribution width from community blood tests as a predictor of hospitalization and mortality in adults with SARS-CoV-2: a cohort study. Ann Med. 2021;53(1):1410-1418.

Schechter M, Melzer-Cohen C, Rozenberg A, Yanuv I, **Chodick G**, Karasik A, Kosiborod M, Mosenzon O. Cardiorenal outcomes with sodium/glucose cotransporter-2 inhibitors in patients with type 2 diabetes and low kidney risk: real world evidence. Cardiovasc Diabetol. 2021;20(1):169.

Grupel D, Gazit S, Schreiber L, Nadler V, Wolf T, Lazar R, Supino-Rosin L, Perez G, Peretz A, Ben Tov A, Mizrahi-Reuveni M, **Chodick G,** Patalon T. Kinetics of SARS-CoV-2 anti-S IgG after BNT162b2 vaccination. Vaccine. 2021;39(38):5337-5340.

Shin JI, Chang AR, Grams ME, Coresh J, Ballew SH, Surapaneni A, Matsushita K, Bilo HJG, Carrero JJ, **Chodick G**, Daratha KB, Jassal SK, Nadkarni GN, Nelson RG, Nowak C, Stempniewicz N, Sumida K, Traynor JP, Woodward M, Sang Y, Gansevoort RT; CKD Prognosis Consortium. Albuminuria testing in hypertension and diabetes: An individual-participant data meta-analysis in a global consortium. Hypertension. 2021;78(4):1042-1052.

Shapiro M, Arbel C, Zucker I, Balmor GR, Lutski M, Derazne E, Beer Z, Pinhas-Hamiel O, Mosenzon O, Tzur D, Afek A, Tirosh A, Cukierman-Yaffe T, Gerstein HC, Rosenberg V, **Chodick G**, Raz I, Twig G. Asthma in youth and early-onset type 2 diabetes: A nationwide study of 1.72 million Israeli adolescents. J Clin Endocrinol Metab. 2021;106(12):e5043-e5053.

Goldshtein I, Nevo D, Steinberg DM, Rotem RS, Gorfine M, **Chodick G**, Segal Y. Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection in pregnant women. AMA. 2021;326(8):728-735.

Ben-Tov A, Banon T, **Chodick G**, Kariv R, Assa A, Gazit S; Collaborators of the Maccabi Institute for Research & Innovation COVID-19 Task Force. BNT162b2 messenger RNA COVID-19 vaccine effectiveness in patients with inflammatory bowel disease: Preliminary real-world data during mass vaccination campaign. Gastroenterology. 2021;161(5):1715-1717.e1.

Milman O, Yelin I, Aharony N, Katz R, Herzel E, Ben-Tov A, Kuint J, Gazit S, **Chodick G**, Patalon T, Kishony R. Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. Nat Med. 2021;27(8):1367-1369.

Muhsen K, Na'aminh W, Lapidot Y, Goren S, Amir Y, Perlman S, Green MS, **Chodick G**, Cohen D. A nationwide analysis of population group differences in the COVID-19 epidemic in Israel, February 2020-February 2021. Lancet Reg Health Eur. 2021;7:100130.

Fallach N, **Chodick G**, Tirosh M, Eisenberg E, Lubovsky O. Pain pharmacotherapy in a large cohort of patients with osteoarthritis: A real-world data analysis. Rheumatol Ther. 2021;8(3):1129-1141.

Avivi I, Yekutiel N, Cohen I, Cohen YC, **Chodick G**, Weil C. Diabetes, but not pre-diabetes, is associated with shorter time to second-line therapy and worse outcomes in patients with multiple myeloma. Leuk Lymphoma. 2021;62(11):2785-2792.

Chodick G, Tene L, Patalon T, Gazit S, Ben Tov A, Cohen D, Muhsen K. Assessment of effectiveness of 1 dose of BNT162b2 vaccine for SARS-CoV-2 infection 13 to 24 days after immunization. JAMA Netw Open. 2021;4(6):e2115985.

Moser SS, Apter L, Arunachalam A, Burke T, Shalev V, **Chodick G**, Siegelmann-Danieli N. Real-world study of PD-L1 testing patterns and treatment distribution in patients with metastatic non-small-cell lung cancer in Israel. Immunotherapy. 2021;13(10):851-861.

Rosenthal YS, Rosenthal A, Shalev Ram H, Ram S, **Chodick G**, Koren G. Association between oral contraceptives and serious infections: A population-based cohort study. Br J Clin Pharmacol. 2021;87(11):4241-4251.

Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, Weil C, Goldshtein I, Twig G, Cohen D, Muhsen K. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. Clin Infect Dis. 2021:ciab438.

Bardugo A, Fishman B, Libruder C, Tanne D, Ram A, Hershkovitz Y, Zucker I, Furer A, Gilon R, **Chodick G**, Tiosano S, Derazne E, Tzur D, Afek A, Pinhas-Hamiel

O, Bendor CD, Yaniv G, Rotem RS, Twig G. Body mass index in 1.9 million adolescents and stroke in young adulthood. Stroke. 2021;52(6):2043-2052.

Melzer Cohen C, Hallén N, **Chodick G**, Bourvine L, Waner T, Karasik A. Short-term excess healthcare costs associated with cardiovascular events among adults with type 2 diabetes in Israel: A retrospective cohort study. Pharmacoecon Open. 2021;5(3):533-544.

Haj S, **Chodick G**, Goren S, Na'amnih W, Shalev V, Muhsen K. Differences in glycated hemoglobin levels and cholesterol levels in individuals with diabetes according to Helicobacter pylori infection. Sci Rep. 2021;11(1):8416.

Moser SS, Bar J, Kan I, Ofek K, Cohen R, Khandelwal N, Shalev V, **Chodick G**, Siegelmann-Danieli N. Real world analysis of small cell lung cancer patients: Prognostic factors and treatment outcomes. Curr Oncol. 2021;28(1):317-331.

Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, Wolf T, Nadler V, Ben-Tov A, Kuint J, Gazit S, Patalon T, **Chodick G**, Kishony R. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. Nat Med. 2021;27(5):790-792.

Chodick G, Leader AE, Larson S. Catch-up HPV vaccination and subsequent uptake of papanicolaou testing in a state-mandated health system. Cancer Prev Res (Phila). 2021 Apr;14(4):415-420.

Benderly M, Buber J, Kalter-Leibovici O, Blieden L, Dadashev A, Lorber A, Nir A, Yalonetsky S, **Chodick G**, Weitzman D, Balicer R, Mazor Dray E, Murad H, Razon Y, Hirsch R; Israeli Adult Congenital Heart Disease Research Group. Health service utilization patterns among adults with congenital heart disease: A population-based study. J Am Heart Assoc. 2021;10(2):e018037.

Shiyovich A, **Chodick G**, Azani L, Tirosh M, Shuvy M, Pereg D, Katz A, Minha S. Sex-specific contemporary trends in incidence, prevalence and survival of patients with non-valvular atrial fibrillation: A long-term real-world data analysis. PLoS One. 2021;16(2):e0247097.

Lechtman N, Shamir R, Cohen S, **Chodick G**, Kariv R, Supino-Rosin L, Weintraub Y, Yerushalmy-Feler A, Ben Tov A. Increased incidence of coeliac disease autoimmunity rate in Israel: a 9-year analysis of population-based data. Aliment Pharmacol Ther. 2021;53(6):696-703.

Rotem RS, Nguyen VT, **Chodick G**, Davidovitch M, Shalev V, Hauser R, Coull BA, Bellavia A, Weisskopf MG. Associations of maternal androgen-related conditions with risk of autism spectrum disorder in progeny and mediation by cardiovascular, metabolic, and fertility factors. Am J Epidemiol. 2021;190(4):600-610.

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

Positions

Head, Laboratory Pulmonary and Allergic Diseases

Chair Department of Environmental and Occupational Health, Tel Aviv University

Research

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

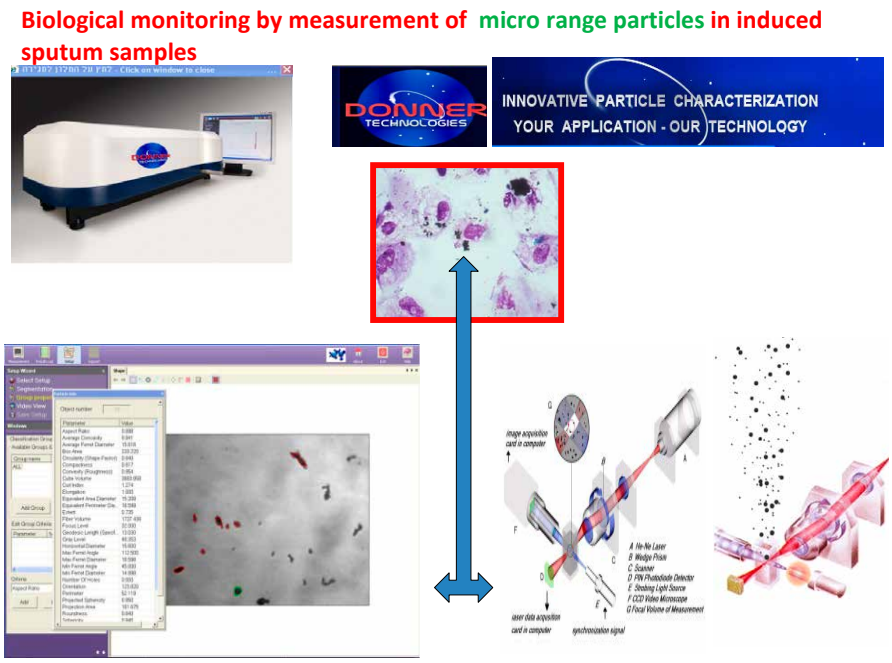


Figure 1

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

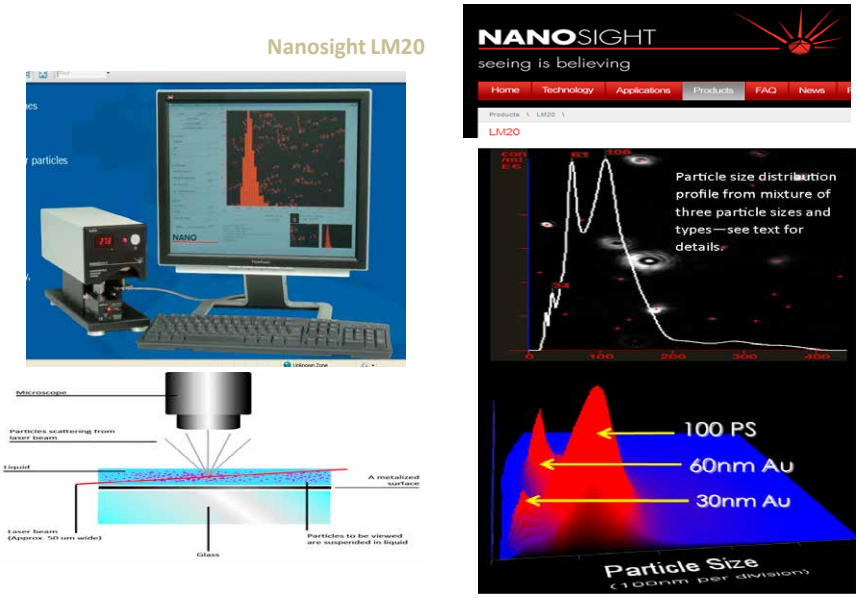


Figure 2

technique, however, has restricted the use of bronchoscopy to a limited number of specialised centres, and hampered its development into a practical and suitable tool for screening programmes, exposure evaluation or repeated follow-up of workers exposed to hazardous dust in large populations.

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

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

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

Publications

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

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.

Grubstein A, Shtraichman O, **Fireman E**, Bachar GN, Noach-Ophir N, Kramer MR. Radiological evaluation of artificial stone silicosis outbreak: emphasizing findings in lung transplant recipients. J Comput Assist Tomogr. 2016;40(6):923-927

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.

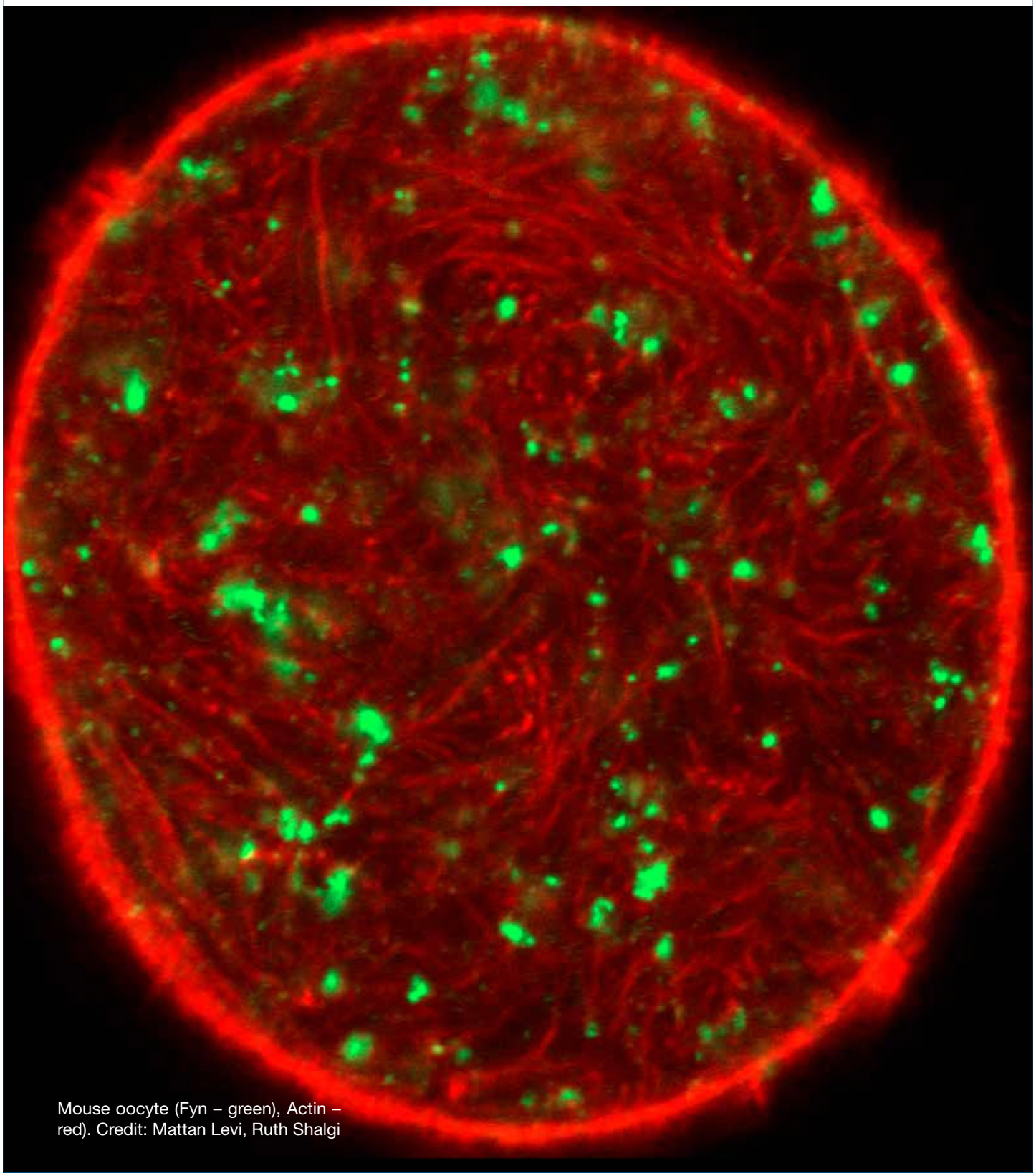
Ophir N, Bar Shai A, Korenstein R, Kramer M, **Fireman E**. Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure. *Occup Environ Med* 2019; 76: 875-879.

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

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

Position

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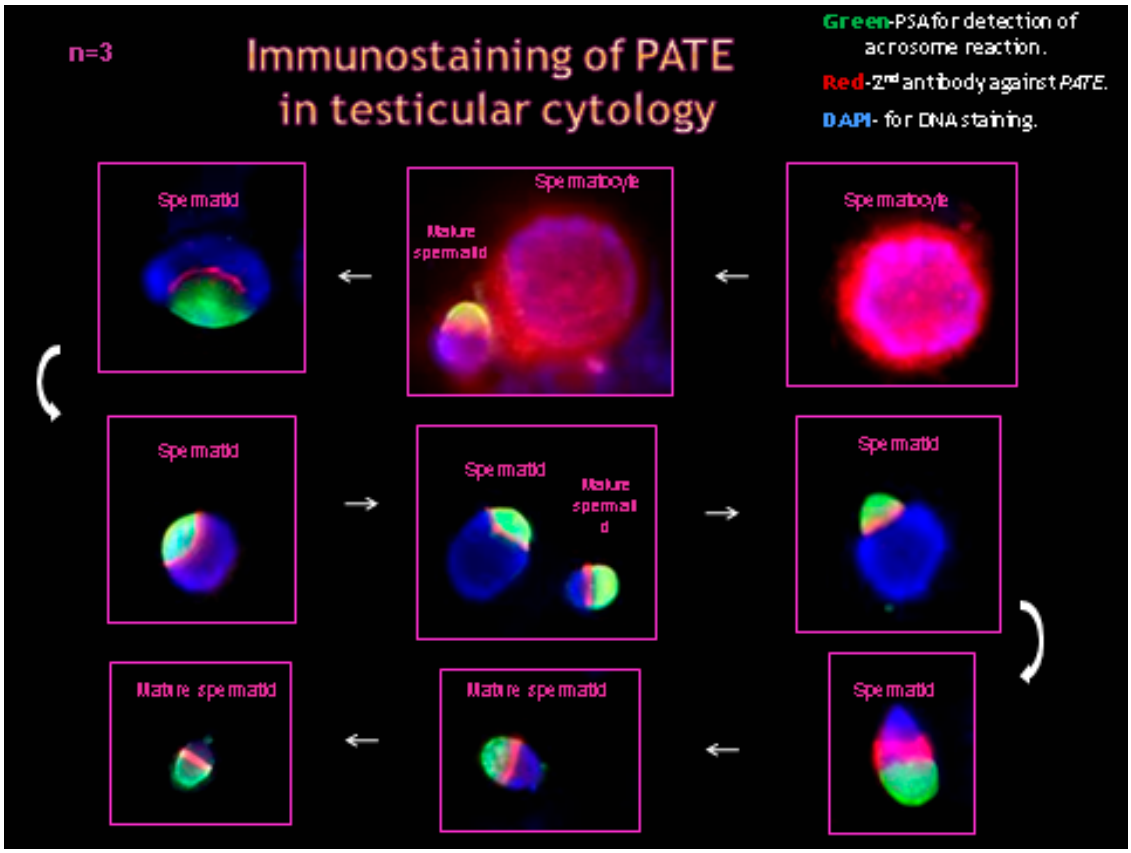
Research

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



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

small RNA transcriptome and unravelling insights into small RNA regulation in spermatogenesis.

Publications

Gershoni M, Hauser R, Yogev L, Lehavi O, Azem F, Yavetz H, Pietrokovski S, **Kleiman SE**. A familial study of azoospermic men identifies three novel causative mutations in three new human azoospermia genes. *Genet Med*. 2017; 19:998-1006.

Malcov M, Gold V, Peleg S, Frumkin T, Azem F, Amit A, Ben-Yosef D, Yaron Y, Reches A, Barda S, **Kleiman SE**, Yogev L, Hauser R. Improving preimplantation genetic diagnosis (PGD) reliability by selection of sperm donor with the most informative haplotype. *Reprod Biol Endocrinol*. 2017; 15:31.

Gershoni M, Hauser R, Shimi Barda, Lehavi O, Eli Arama, Pietrokovski S, **Kleiman SE**. A new MEIOB mutation is a recurrent cause for azoospermia and testicular meiotic arrest. *Hum Reprod*. 2019; 34:666.

Zaghi B, Barda S, **Kleiman SE**, Hauser R. Impact of time between repeated sperm freezing cycles on sperm quality. *Reprod Biol*. 2020;20(1):75-80.

Barda S, Mano R, Lehavi O, **Kleiman SE**, Yossepowitch O, Azem F, Hauser R, Dekalo S. Questioning the utility of round spermatid injections in men with non-obstructive azoospermia. *Andrology*. 2021;9(4):1145-1150.

Arafat M, **Kleiman SE**, AbuMadighem A, Zeadna A, Levitas E, Vardi IH, Barda S, Lehavi O, Hauser R, Lunenfeld E, Huleihel M, Gershoni M, Parvari R. Pathogenic variations in Germ Cell Nuclear Acidic Peptidase (GCNA) are associated with human male infertility. *Eur J Hum Genet*. 2021;29(12):1781-1788.

Barda S, Hauser R, Mano R, Savin Z, Molad-Hayo Y, Lehavi O, **Kleiman SE**, Azem F, Yossepowitch O, Dekalo S. Testicular microlithiasis defines a subgroup of azoospermic men with low rates of sperm retrieval. *Int J Urol*. 2022;29(1):65-68.

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

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Research

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

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

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

Publications

Shpiz, A., **Ben-Yosef, D**., and Kalma, Y. (2016). Impaired function of trophoblast cells derived from translocated hESCs may explain pregnancy loss in women with balanced translocation (11;22). J Assist Reprod Genet *33*, 1493-1499.

Bar-El, L., Kalma, Y., Malcov, M., Schwartz, T., Raviv, S., Cohen, T., Amir, H., Cohen, Y., Reches, A., Amit, A., and **Ben-Yosef, D**. (2016). Blastomere biopsy for PGD delays embryo compaction and blastulation: a time-lapse microscopic analysis. J Assist Reprod Genet *33*, 1449-1457.

Telias, M., Segal, M., and **Ben-Yosef, D**. (2016). Immature Responses to GABA in Fragile X Neurons Derived from Human Embryonic Stem Cells. Front Cell Neurosci *10*, 121.

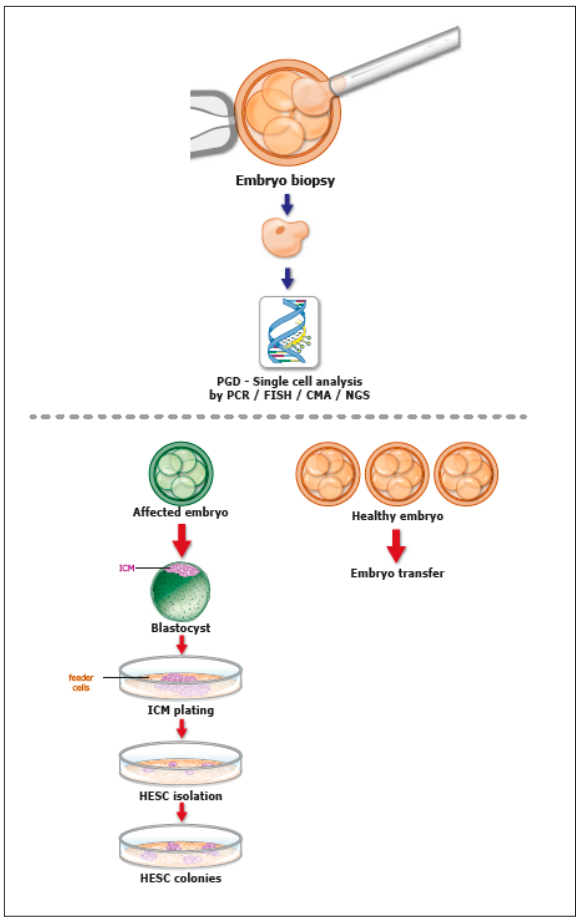
Yedid, N., Kalma, Y., Malcov, M., Amit, A., Kariv, R., Caspi, M., Rosin-Arbesfeld, R., and **Ben-Yosef, D**. (2016). The effect of a germline mutation in the APC gene on beta-catenin in human embryonic stem cells. BMC Cancer *16*, 952.

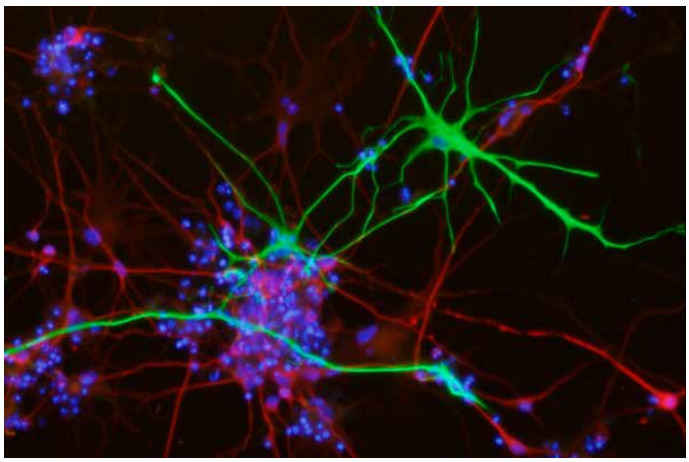
Malcov M, Gold V, Peleg S, Frumkin T, Azem F, Amit A, **Ben-Yosef D**, Yaron Y, Reches A, Barda S, Kleiman SE, Yogev L, Hauser R. Improving preimplantation genetic diagnosis (PGD) reliability by selection of sperm donor with the most informative haplotype. Reproductive Biology and Endocrinology; 15(1):31 2017.

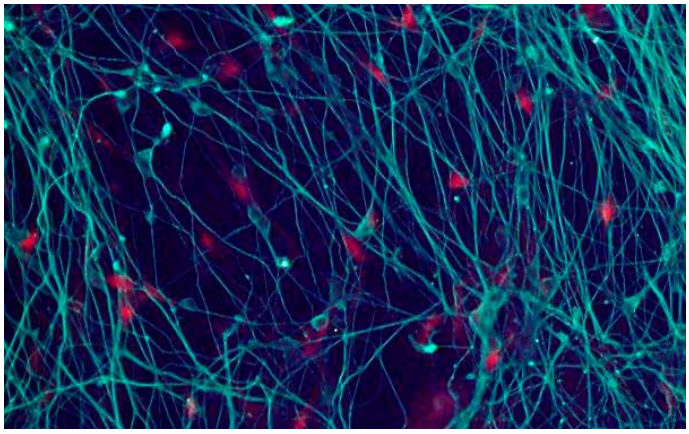
Frumkin T, Peleg S, Gold V, Reches A, Asaf S, Azem F, **Ben-Yosef D**, Malcov M. Complex chromosomal rearrangement-a lesson learned from PGS. J. Assisted Reproduction and Genetics, 2017

Kalma Y, Bar-El L, Asaf-Tisser S, Malcov M, Reches A, Hasson J, Amir Azem F, **Ben-Yosef D**. Optimal timing for blastomere biopsy of 8-cell embryos for preimplantation genetic diagnosis. Hum. Reprod. 2017

Frumkin T, Peleg S, Gold V, Reches A, Asaf S, Azem F, **Ben-Yosef D**, Malcov M. Complex chromosomal







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).

rearrangement-a lesson learned from PGS. J Assist Reprod Genet. 2017

Preisler L, **Ben-Yosef D**†, Mayshar Y†. Adenomatous Polyposis Coli as a major regulator of human embryonic stem cells self-renewal. *Stem Cells.* 2019; 37:1505-1515. †Co-senior authors.

Warshaviak M, Kalma Y, Carmon A, Samara N, Dviri M, Azem F, **Ben-Yosef D**. The effect of advanced maternal age on embryo morphokinetics. *Front. Endocrinol*. 2019; 10:686.

Amir A, Barbash-Hazan S, Kalma Y, Frumkin T, Malcov M, Samara N, Hasson J, Reches A, Azem F, **Ben-Yosef D.** Time-lapse imaging reveals delayed development of embryos carrying unbalanced chromosomal translocations. *J Assist Reprod Genet* 2019.

Leahy B. D, Jang W. G, Yang H. Y, Struyven R, Wei1 D, Sun Z, Lee K. R, Royston C, Cam L, Kalma Y, Azem F, **Ben-Yosef D**, Pfister H, Needleman D. Automated measurement of key morphological features of human embryos for IVF. *Med Image Comput Comput Assist Interv* (MICCAI) 2020.

Preisler L, Habib A, Shapira G, Kuznitsov-Yanovsky L, Mayshar Y, Carmel Gross I, Malcov M, Azem F, Shomron N, Kariv R, Hershkovitz D, **Ben-Yosef D**. Heterozygous APC germline mutations impart predisposition to colorectal cancer. *Sci Rep.* 2021;11(1):5113.

Bayerl J, Ayyash M, Shani T, Manor YS, Gafni O, Massarwa R, Kalma Y, Aguilera-Castrejon A, Zerbib M, Amir H, Sheban D, Geula S, Mor N, Weinberger L, Naveh Tassa S, Krupalnik V, Oldak B, Livnat N, Tarazi S, Tawil S, Wildschutz E, Ashouokhi S, Lasman L, Rotter V, Hanna S, **Ben-Yosef D**, Novershtern N, Viukov S, Hanna JH. Principles of signaling pathway modulation for enhancing human naive pluripotency induction. *Cell Stem Cell*. 2021.

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