Sackler Faculty of Medicine

Hospital-Based PhD Research 2022

TEL AVIV UNIVERSITY
Pursuing the Unknown

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.

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

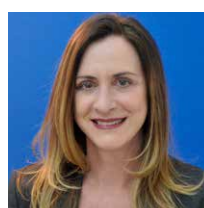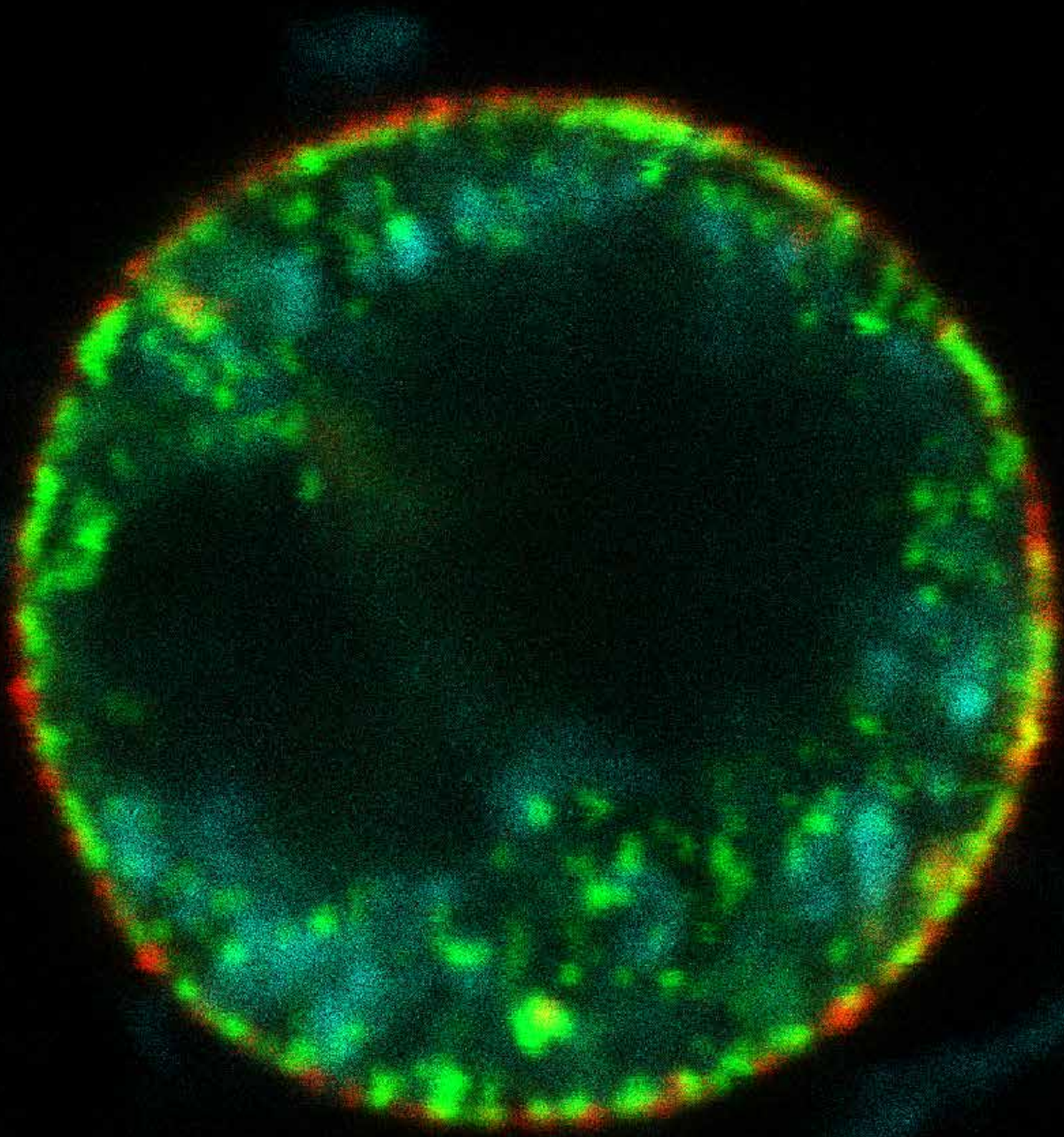Prof. Karen B. Avraham, PhD, Vice Dean (Preclinical)

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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

osnataf@gmail.com

TEL AVIV UNIVERSITY

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

Cohen K, Ellis M, Khoury S, Davis PJ, Hercbergs A and **Ashur-Fabian O.** Thyroid hormone effects on myeloma bone marrow and cell lines: avb3-integrin mediated signaling with relevance to the action of bortezomib. *Leuk & Lymph*, 20:1-8, 2015.

Davis PJ, Glinsky GV, Lin HY, Leith JT, Hercbergs A, Tang HY, **Ashur-Fabian O**, Incerpi S, Mousa SA. Cancer Cell Gene Expression Modulated from Plasma Membrane Integrin $\alpha v\beta 3$ by Thyroid Hormone and Nanoparticulate Tetrac. Front Endocrinol (Lausanne). 5:1-7, 2015.

Hercbergs A, Johnson RE, **Ashur-Fabian O**, Garfield DH, Davis PJ. Medically Induced Euthyroid Hypothyroxinemia May Extend Survival in Compassionate Need Cancer Patients: An Observational Study. The Oncologist, 20(1):72-6, 2015.

Pereg D, Cohen K, Mosseri M, Berlin T, Steinberg DM, Ellis M and **Ashur-Fabian O**. Cell free expression of stress-inducible mRNA in the peripheral blood of acute myocardial infarction patients. Journal of Arteriosclerosis and Thrombosis, 22(9):981-98, 2015.
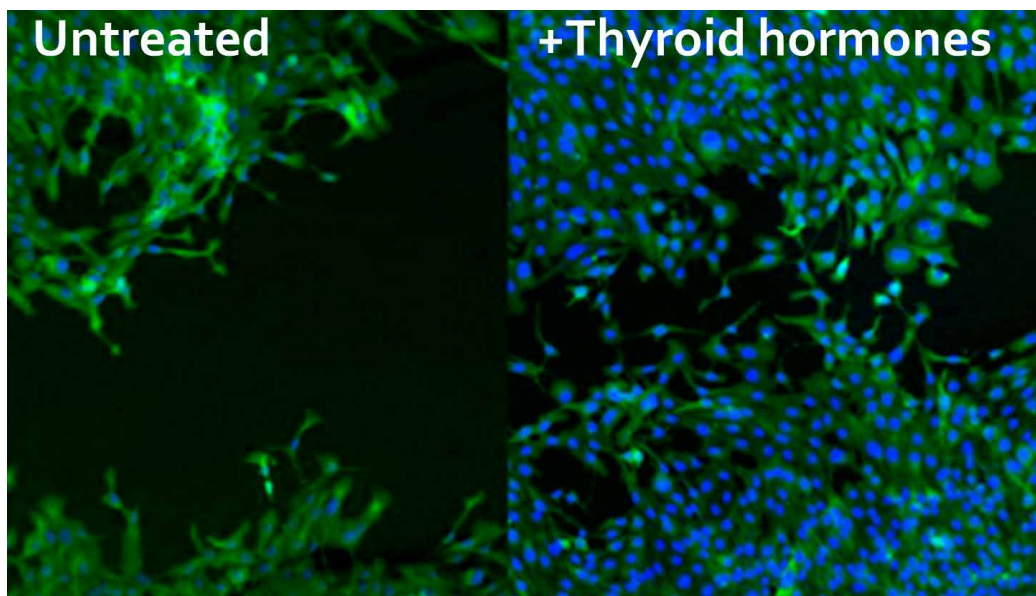
Ovarian cancer cell proliferation and migration is enhanced by thyroid hormones

Fabian ID, Rosner M, Fabian I, Vishnevskia-Dai V, Zloto O, Shinderman E, Cohen K, Ellis M, Hung-Yun Lin, Hercbergs A, Davis PJ and **Ashur-Fabian O**. The Impact of Thyroid Hormone Levels on Survival in a Uveal Melanoma Murine Model. *Oncotarget*, 6(13): 6(13):11038-46, 2015

Shinderman-Maman E, Cohen K, Weingarten C, Nabriski D, Twito O, Baraf L, Hercbergs A, Davis PJ, Werner H, Ellis M and **Ashur-Fabian O**. The thyroid hormone-avb3 integrin axis in ovarian cancer: Regulation of gene transcription and MAPK-dependent proliferation. *Oncogene*,35(15):1977-87, 2016.

Yacobovich S, Tuchinsky L, Kirby M, Kardash T, Agranioni O, Nesher E, Redko B, Gellerman G, Tobi D, Gurova K, Koman I, **Ashur-Fabian O** and Pinhasov A. Novel synthetic cyclic integrin $\alpha v \beta 3$ binding peptide ALOS4: Antitumor activity in mouse melanoma models. *Oncotarget*, 7(39):63549-63560, 2016.

Ellis M, Stern O and **Ashur-Fabian O**. The double benefit of Spalax p53: surviving underground hypoxia while defying lung cancer cells in vitro via autophagy and caspase-dependent cell death. *Oncotarget*, 7(39):63242-63251, 2016.

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.

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.

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

Dr. Liat Drucker, Ph.D.

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

✉ druckerl@clalit.org.il

TEL AVIV UNIVERSITY

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

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

Primary human mesenchymal stem cells (MSCs)
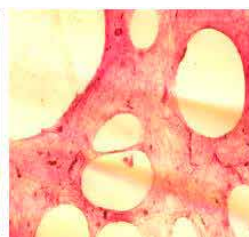
MSCs' extracellular matrix (elastin)
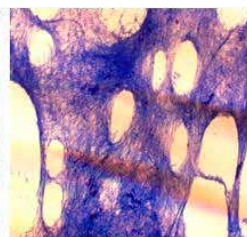
MSCs' extracellular matrix (collagen)
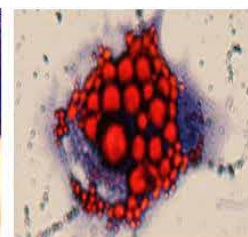
MCS differentiated into adipocyte
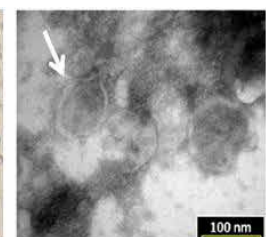
MSCs' microvesicles

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

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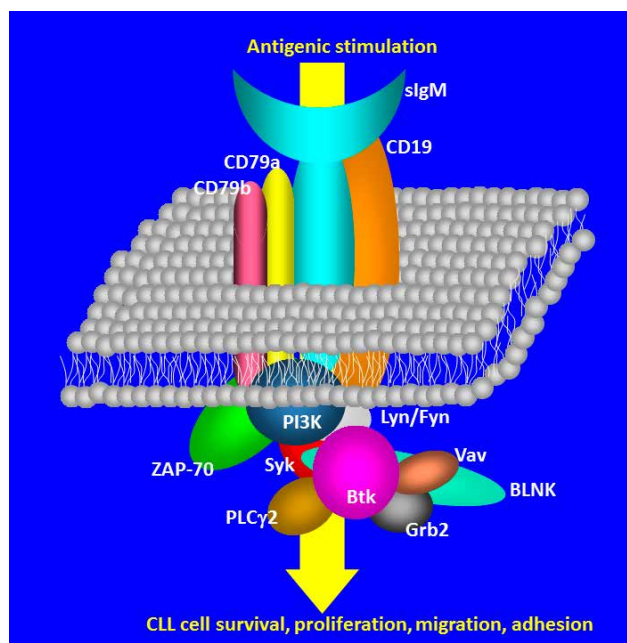
Specific research programs
A) The role of microenvironmental interactions in the pathogenesis of chronic lymphocytic leukemia.
B) The function of CD19 and CD38 in the physiology of malignant B-cells.
D) Development of novel laboratory methodologies to study B-cell malignancies
The complexity of the B-cell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

yael.mardor@sheba.health.gov.il

TEL AVIV UNIVERSITY

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

Zach L, Guez D, Last D, Daniels D, Grober Y, Nissim O, Hoffmann C, Nass D, Talianski A, Spiegelmann R, Tsarfaty G, Salomon S, Hadani M, Kanner A, Blumenthal DT, Bukstein F, Yalon M, Zauberman J, Roth J, Shoshan Y, Fridman E, Wygoda M, Limon D, Tzuk T, Cohen ZR, **Mardor Y**. Delayed contrast extravasation MRI: A new paradigm in neuro-oncology. Neuro Oncol. 2015;17:457-65.

Cooper I, Last D, Guez D, Sharabi S, Elhaik Goldman S, Lubitz I, Daniels D, Salomon S, Tamar G, Tamir T, Mardor R, Fridkin M, Shechter Y, **Mardor Y**. Combined local blood-brain barrier opening and systemic methotrexate for the treatment of brain tumors. J Cereb Blood Flow Metab. 2015;35:967-76.

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

>1 hr post Gd   5 min post Gd   TRAM
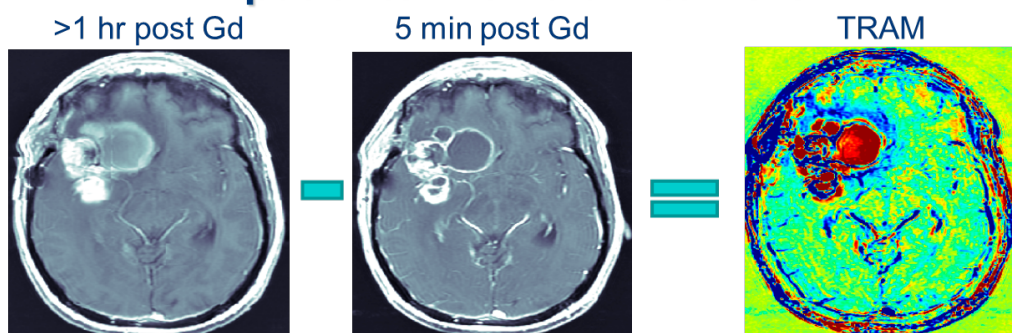
Blue = tumor tissue , efficient Gd clearance at 75 min
Red = non tumor tissue, Gd accumulation at 75 min

3

Itsekson-Hayosh Z, Shavit-Stein E, Last D, Goez D, Daniels D, Bushi D, Gera O, Zibly Z, **Mardor Y**, Chapman J, Harnof S. Thrombin activity and thrombin receptor in rat glioblastoma model: possible markers and targets for intervention? J Mol Neurosci. 2015;56:644-51.

Moisseiev E, Barequet D, Zunz E, Barak A, **Mardor Y**, Segal Z, Loewenstein. A validation of an algorithm for non-metallic intraocular foreign bodies' composition identification based on computed tomography and magnetic resonance imaging. Retina. 2015;35:1898-904

Millet E, Haik J, Ofir E, **Mardor Y**, Winkler E, Harats M, Tessone A. The impact of autologous fat grafting on breast cancer: an experimental model using magnetic resonance imaging. Isr Med Assoc J 2016, 283-285

Sharabi S, Kos B, Last D, Guez D, Daniels D, Harnof S, **Mardor Y**, Miklavcic D. A statistical model describing combined irreversible electroporation and electroporation-induced blood-brain barrier disruption. Radiol Oncol. 2016;50:28-38.

Daniels D, Guez D, Last D, Hoffmann C, Nass D, Talianski A, Tsarfaty G, Salomon S, Kanner AA, Blumenthal DT, Bukstein F, Harnof S, Yekutieli D, Zamir S, Cohen ZR, Zach L, **Mardor Y**. Early biomarkers from conventional and delayed-contrast MRI to predict the response to bevacizumab in recurrent high-grade gliomas. AJNR Am J Neuroradiol. 2016; 37:2003-2009.

Toren A, Pismenyuk T, Yalon M, Freedman S, Simon AJ, Fisher T, Moshe I, Reichardt JK, Constantini S, **Mardor Y**, Last D, Guez D, Daniels D, Assoulin M, Mehrian-Shai R. Zinc enhances temozolomide cytotoxicity in glioblastoma multiforme model systems. Oncotarget. 2016; 7: 74860–74871.

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 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.

Grants

2018-2020   MOH, Application of delayed contrast CT for differentiating tumor/non-tumor tissues in patients with lung cancer, PI with Dr Jair Bar

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

Dr. Ilan Volovitz, Ph.D.

Cancer Immunotherapy Lab
Department of Neurosurgery
Tel Aviv Sourasky Medical Center

TEL AVIV UNIVERSITY

ilanv@tlvmc.gov.il
http://www.tasmc.org.il/sites/
en/Personnel/Pages/Volo-
vitz-Ilan.aspx

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

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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 Neurosci*. 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.

Experimental Hematology Lab
Felsenstein Medical Research Center,
Beilinson Hospital
Rabin Medical Center

galitg@clalit.org.il
URL: http://hospitals.clalit.
co.il/Experimental-hematolo-
gy-lab.aspx

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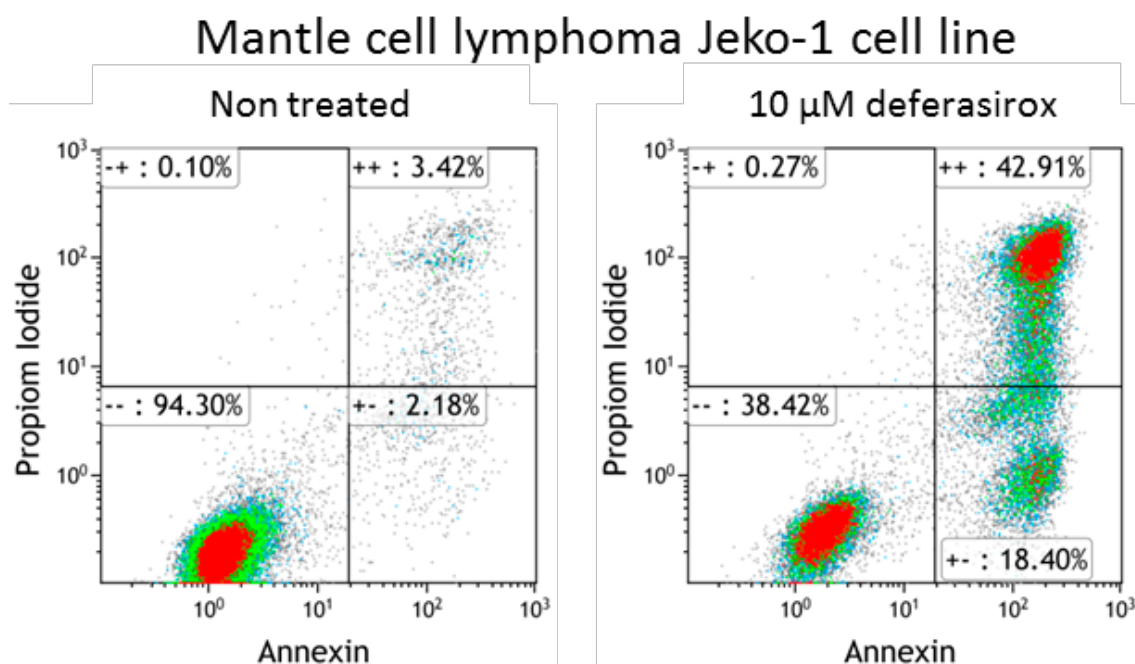
Deferasirox is a rationally-designed oral iron chelator used to reduce chronic iron overload in patients who receive long-term blood transfusions. We showed that this agent can induce apoptosis in mantle cell lymphoma.

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.

Department of Human Molecular Genetics & Biochemistry, Sackler School of Medicine
Laboratory of Molecular Biology – ICPC

TEL AVIV UNIVERSITY

E-mail: shiranshapira@gmail.com, shiransha@tlvmc.gov.il
Tel. 972-3-6974827/4118
Fax: 972-36973132

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 malignances and for other applications as well. CD24 appears to be a promising target for many cancers that currently have limited treatment options. The uniqueness of the suggested antibody is its ability to recognize a specific and unique epitope in the matured core of the protein. The humanized mAbs (unarmed, bi-specific, toxin-conjugated, BiTE and other derivatives) against CD24 are very effective. The antibody was well characterized by means of PK, toxicity, stability, efficacy (xenograft, PDXT and CAM-PDX) etc. Its mechanisms of action include ADCC, ADCP and TGI. The scFv derivative of the mAb was fused to lentiviral particles, in a specific therapeutic setting, and was given as a compensation therapy to five terminal ill patients.

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

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

Publications

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

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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.

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

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

Dr. Orit Uziel, Ph.D.

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

oritu@post.tau.ac.il
oritu@clalit.org.il

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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
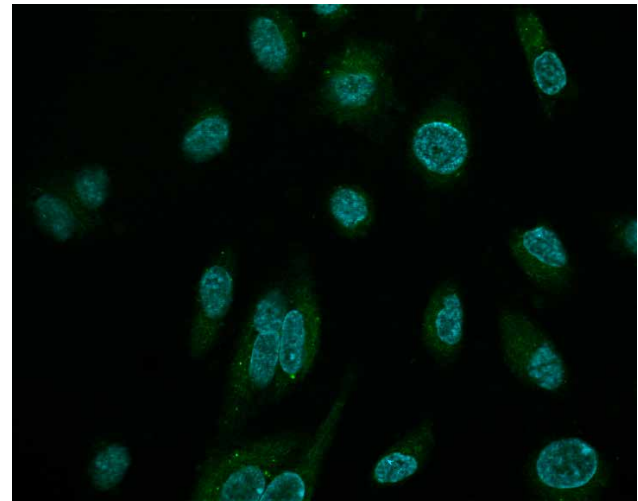

Figure 1. FITC-stained exosomes are taken up by HUVEC cells analyzed by fluoresent microscopy.
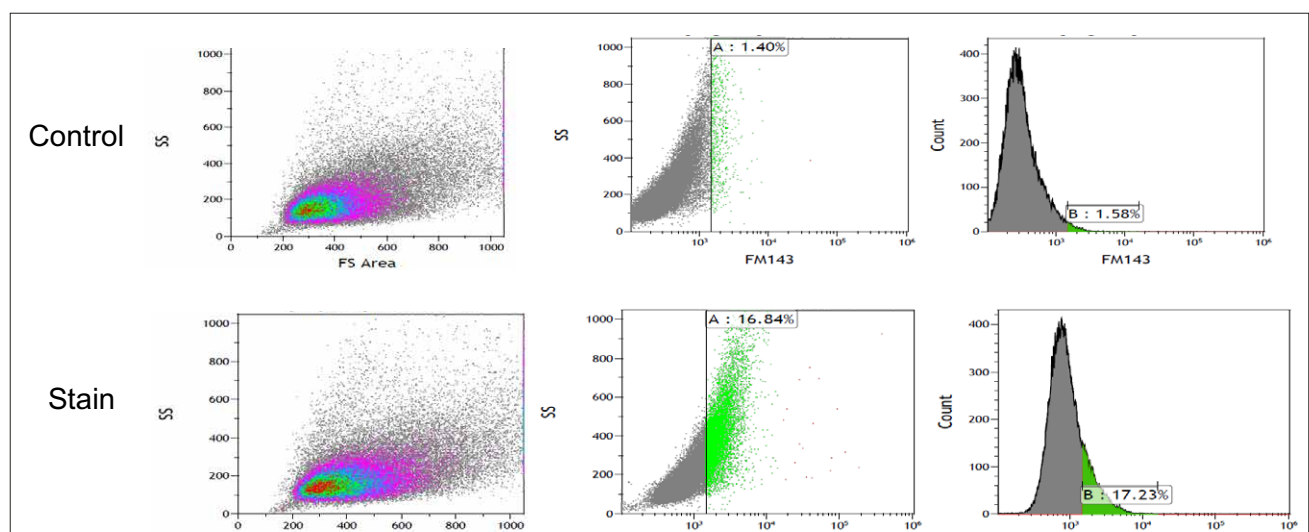

Figure 2. FM-134 stained exosomes are taken up by HUVEC cells analysed by flow cytometry.

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.

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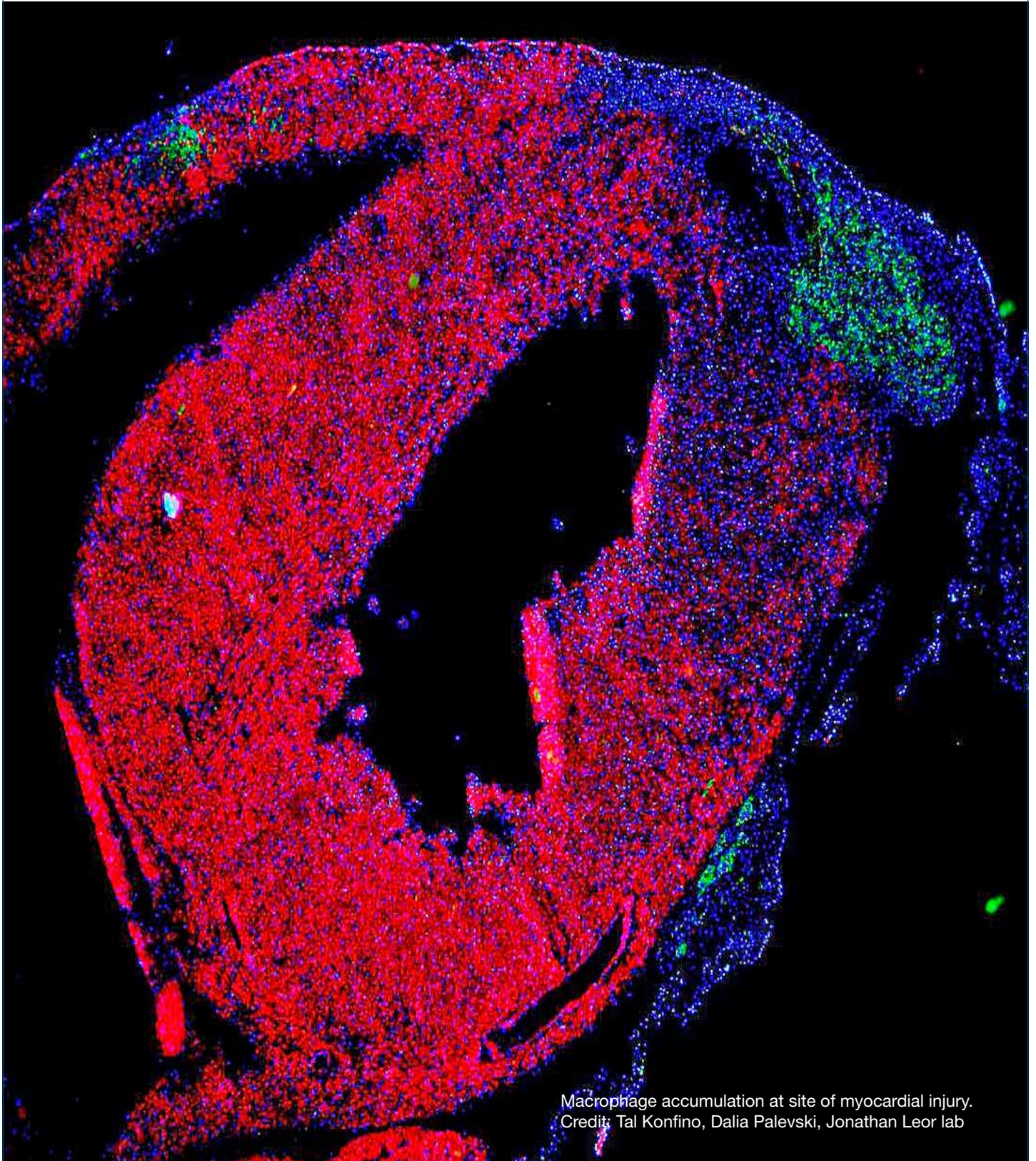
Macrophage accumulation at site of myocardial injury.
Credit: Tal Konfino, Dalia Palevski, Jonathan Leor lab

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

TEL AVIV UNIVERSITY

michale@tlvmc.gov.il
URL: http://www.tasmc.org.
il/sites/en/Personnel/Pages/
Michal-Entin-Meer.aspx

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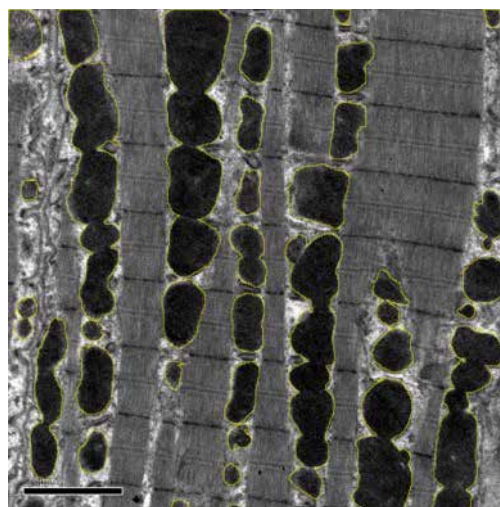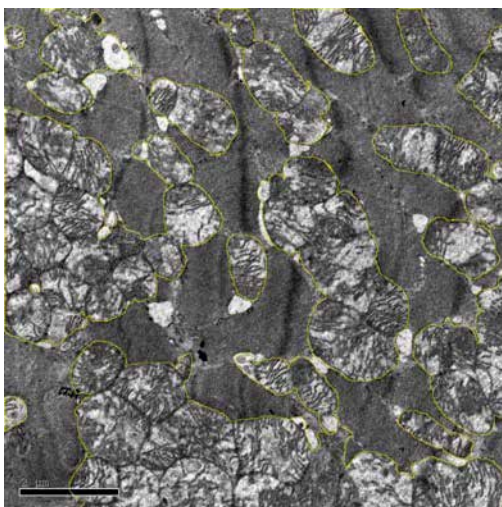
Captures of transmitted electron microscopy demonstrating the organized structure of cardiac mitochondria in sham-operated control rats (A) compared to the swallawed unorganized structure of the mitochondria in the heart tissue of animals with chronic kidney disease (B).

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.

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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.

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Grants

Dr. Joseph Roitelman, Ph.D.

Department of Human Genetics and Biochemistry, Sackler School of Medicine
The Bert W. Strassburger Lipid Center, Sheba Medical Center

TEL AVIV UNIVERSITY

✉ roitelma@post.tau.ac.il
Joseph.roitelman@sheba.health.gov.il

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

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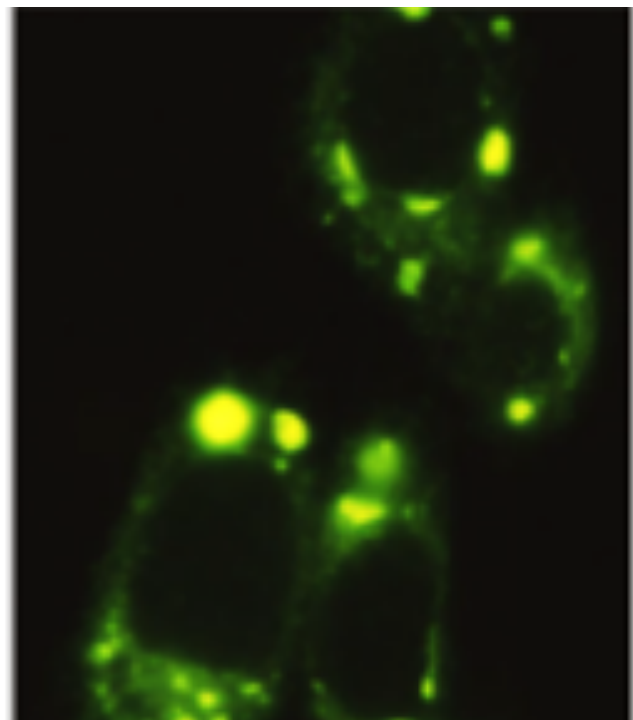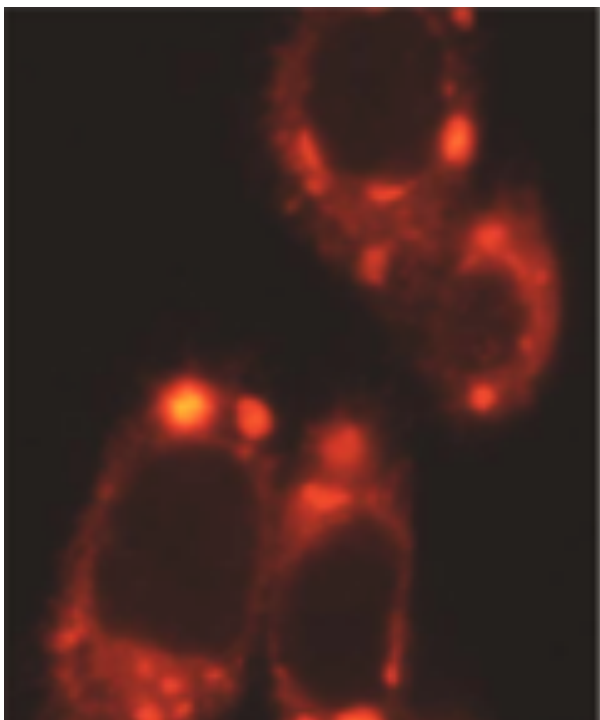
Dr. Shani Shenhar-Tsarfaty, Ph.D.

Department of Internal Medicine "C, "D & "E, and Neurology
Tel Aviv Sourasky Medical Center
Sackler Faculty of Medicine

shanis@tlvmc.gov.il

TEL AVIV UNIVERSITY

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

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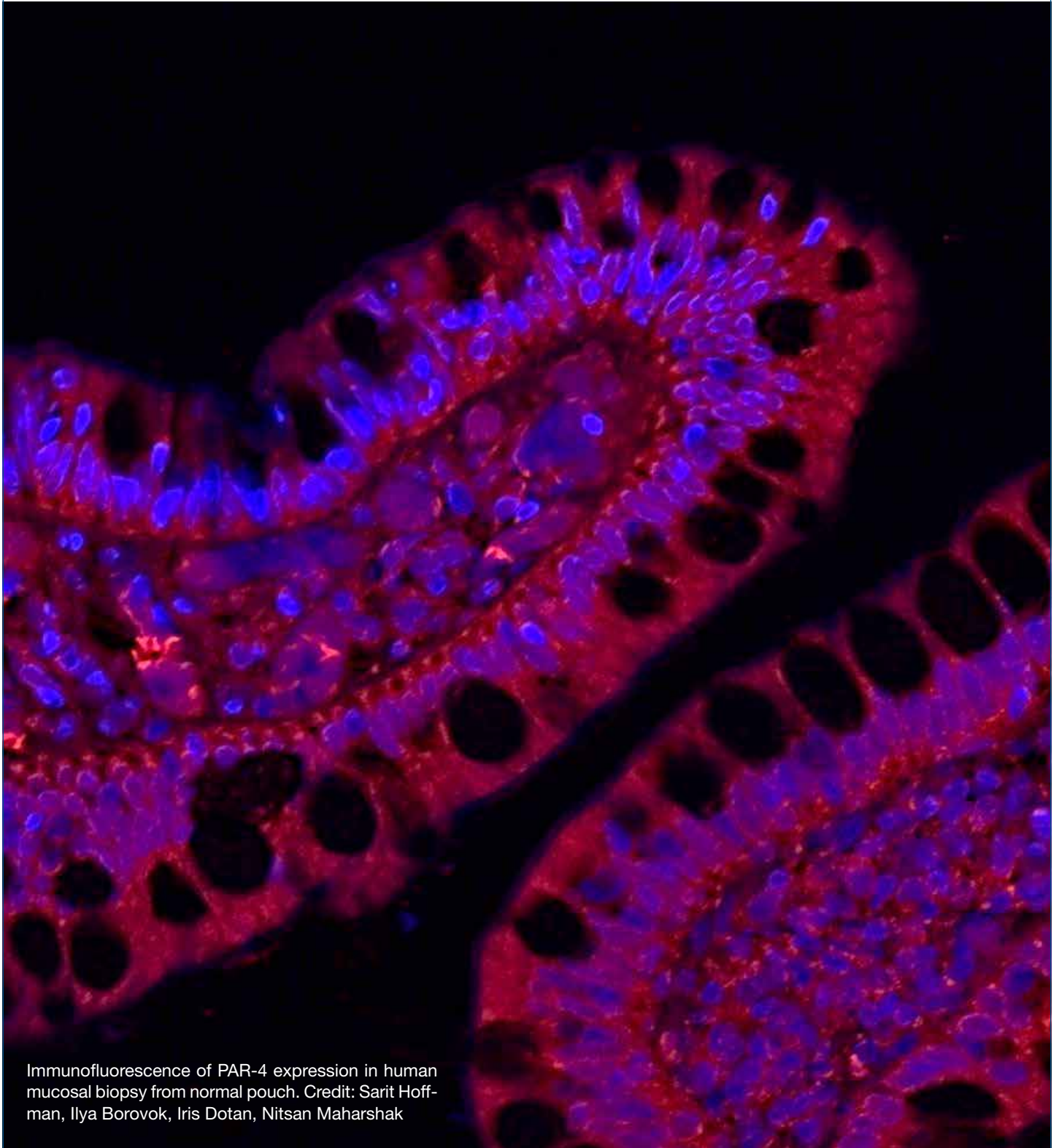
Digestive System

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

Dr. Chen Varol, Ph.D.

Research Center for Digestive Tract & Liver Diseases
Tel Aviv Sourasky Medical Center
Department of Clinical Microbiology & Immunology

chenv@tlvmc.gov.il
http://www.tasmc.org.il/sites/en/Personnel/Pages/Varol-Chen.aspx

TEL AVIV UNIVERSITY

Mononuclear Phagocytes in Digestive Tract Diseases and Metabolic Syndrome

Positions

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

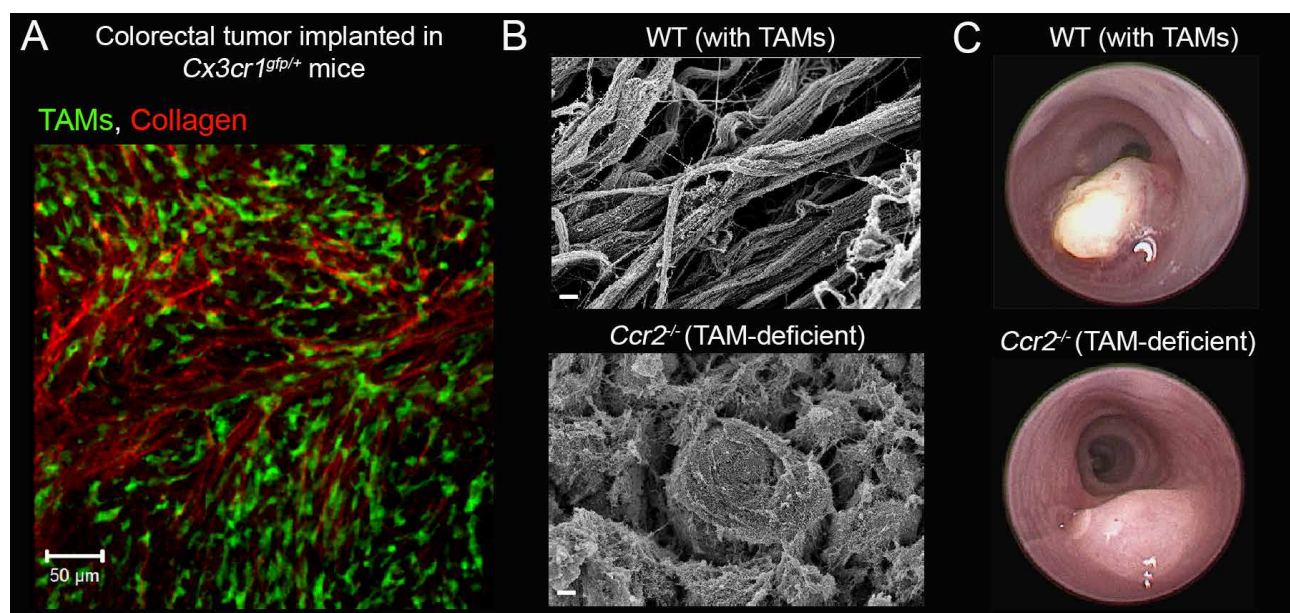Director, Research Center for Digestive Tract & Liver Diseases

Editorial boards: Immunometabolism (Hapres), Frontiers in Immunology

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

Research

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

A Colorectal tumor implanted in *Cx3cr1^gfp/+* mice
TAMs, Collagen
50 μm

B WT (with TAMs)
Ccr2^-/- (TAM-deficient)

C WT (with TAMs)
Ccr2^-/- (TAM-deficient)

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.

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Grants

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

✉ isab@tlvmc.gov.il

TEL AVIV UNIVERSITY

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.
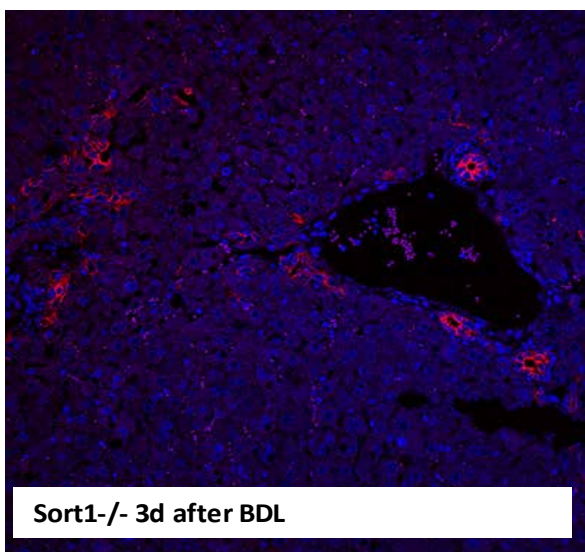
Sort1-/- 3d after BDL
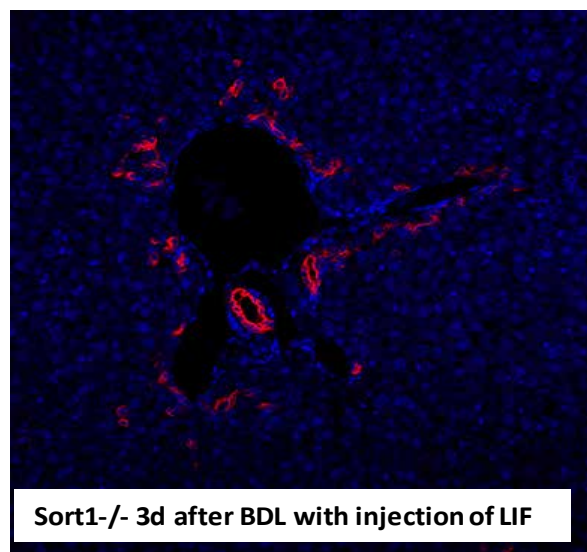
Sort1-/- 3d after BDL with injection of LIF

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

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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

Endocrine Disease

The epiphyseal growth plate.
Credit: Galia Gat-Yablonski

Dr. Galia Gat-Yablonski, Ph.D.

Schneider Children's Medical Center
Sackler Faculty of Medicine

galiagy@post.tau.ac.il

TEL AVIV UNIVERSITY

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
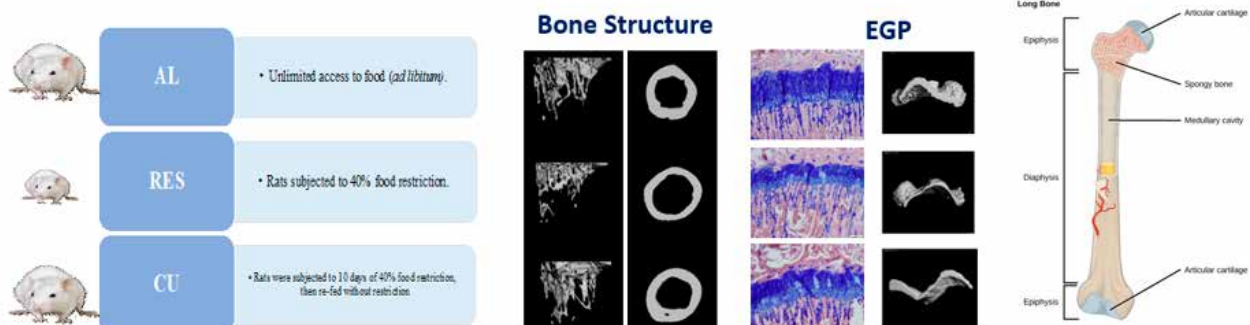
developed in which Sirt1 (an HDAC of family III) was specifically knocked down in the EGP showed that the affected animals had significantly less efficient growth and less efficient response to nutritional manipulation. Surprisingly, a marked effect was identified in bone mineralization and structure 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

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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

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

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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

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Reviews

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Dr. Alicia Leikin-Frenkel, Ph.D.

Sackler Faculty of Medicine
Sheba Medical Center

alicial@post.tau.ac.il
Alicia.leikin@sheba.health.gov.il

TEL AVIV UNIVERSITY

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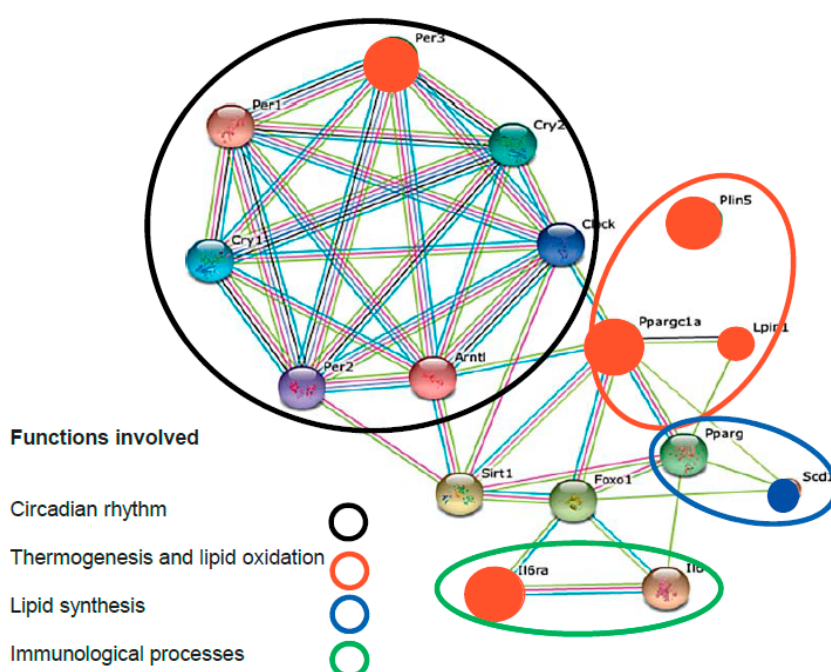
Positions

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.

Functions involved

○ Circadian rhythm
○ Thermogenesis and lipid oxidation
○ Lipid synthesis
○ Immunological processes

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.

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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.

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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

TEL AVIV UNIVERSITY

tali.gal@clalit.org.il

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

A

control   db/db   db/db+ GLP-1   db/db+ GLP-1+ Vit D

B

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.

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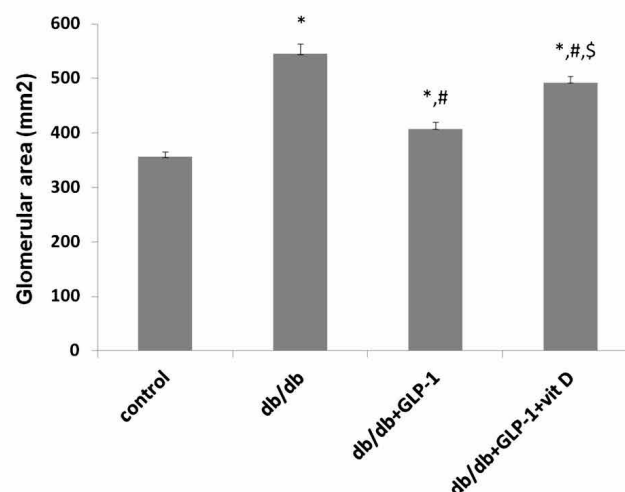Cohen-Hagai K, Rashid G, Einbinder Y, Ohana M, Benchetrit S, **Zitman-Gal T**.(2017) Effect of vitamin D status on Von Willebrand factor and ADAMTS13 in diabetic patients on chronic hemodialysis. Ann Lab Med. 37:155-158.

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.

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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

Dr. Dan Dominissini, Ph.D.

Department of Human Molecular Genetics and Biochemstry, Sackler Faculty of Medicine
Cancer Research Center, Chaim Sheba Medical Center

TEL AVIV UNIVERSITY

Dan.Dominissini@Sheba.health.gov.il

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.

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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.

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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.

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Immunology & Hematology
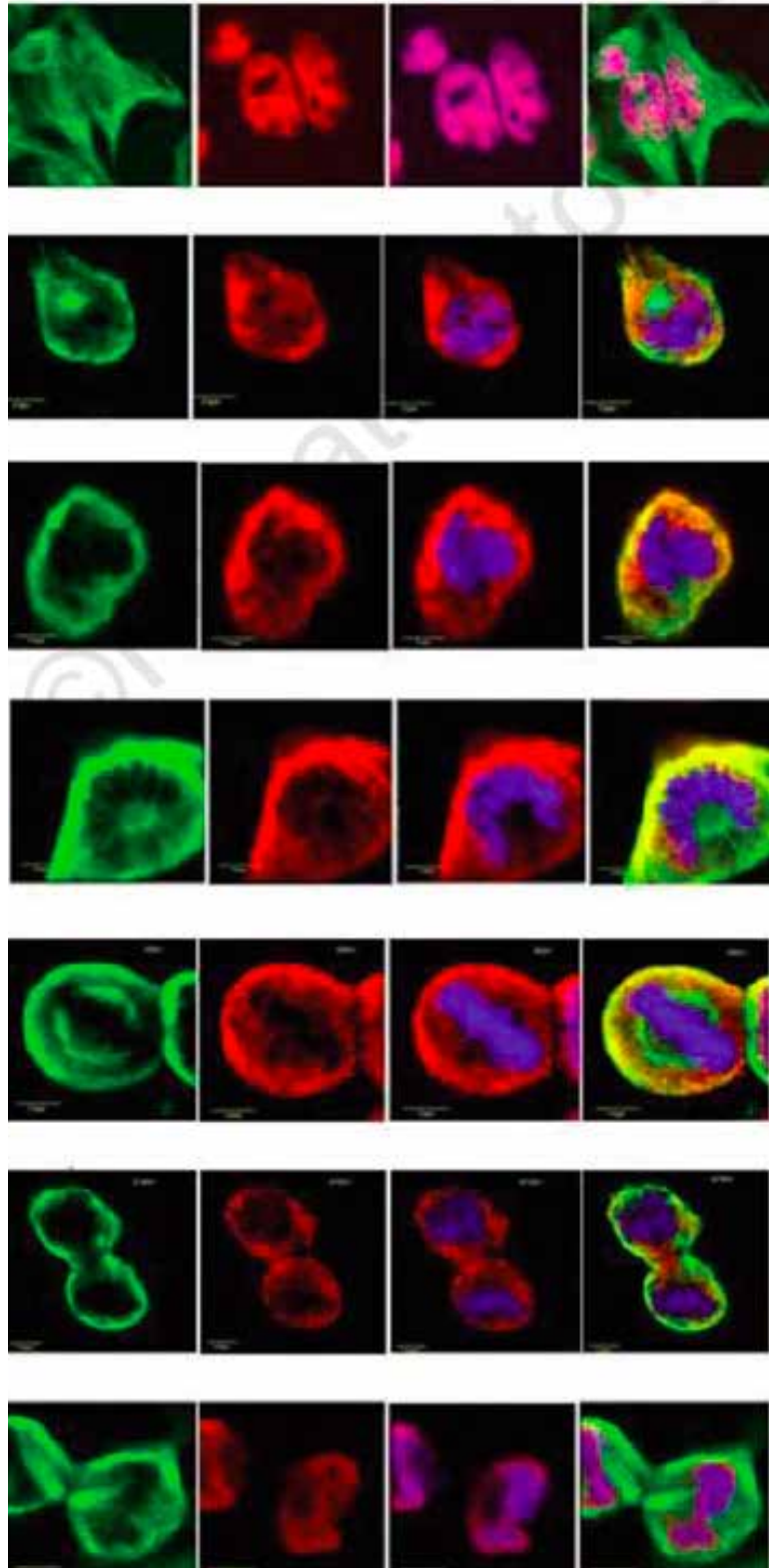
Cell cycle-dependent localization of codanin-1. Credit: Noy-Lotan et al. Haematologica 94:629-37, 2009
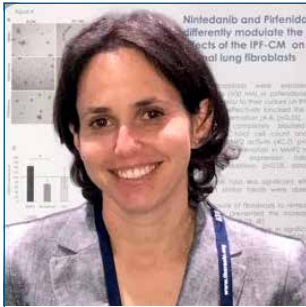
Dr. Gali Epstein Shochet, Ph.D.

Department of Pulmonary Medicine
Meir Medical Center
Sackler Faculty of Medicine

Email: gali.epstein@clalit.org.il
URL: https://galieps.wixsite.com/website

TEL AVIV UNIVERSITY

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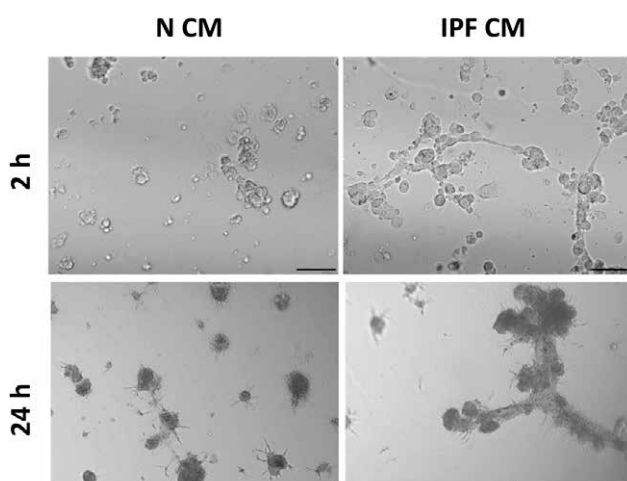
Normal human lung fibroblasts cultured on control (N CM) and IPF CM. As shown on the right side, the normal cells become elongated (2h), migrate and finally cluster into large aggregates (24h) following their culture on the IPF-CM.

Publications

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Grants
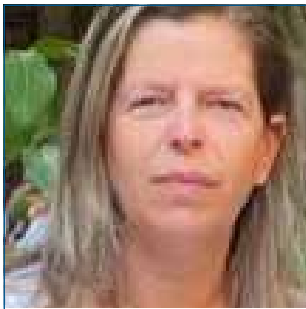
Dr. Smadar Gertel, Ph.D.

The Arthritis Research Laboratory
Department of Rheumatology
Tel Aviv Sourasky Medical Center

TEL AVIV UNIVERSITY

✉ smadarge@tlvmc.gov.il

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

A
Biomarkers for prediction of response to therapeutic agents

B
Differentiate arthritis types by synovial biomarkers
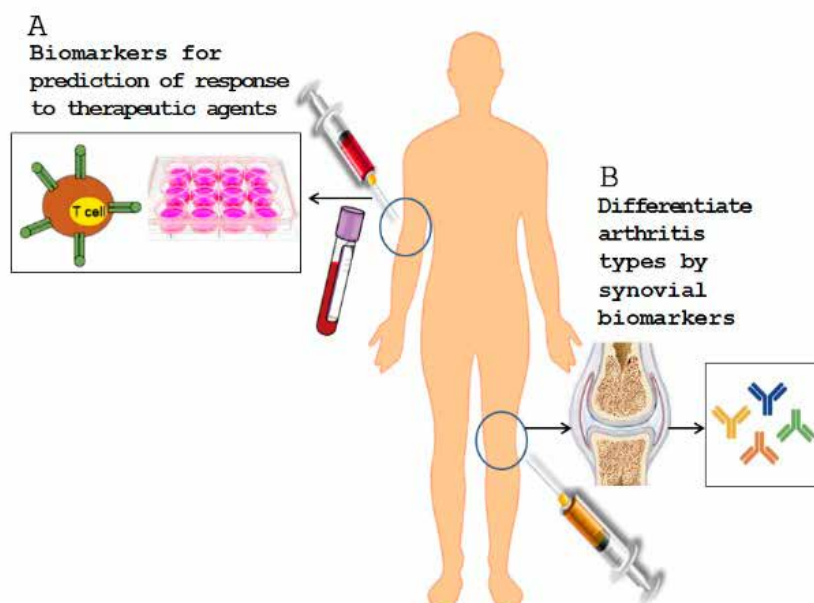
specificity and efficacy of therapies. Moreover, PsA disease diagnosis is based only on clinical evaluation since diagnostic biomarkers are not available yet. Finding of new biomarkers may improve accuracy in the diagnosis of different diseases and may assist in therapy selection. The diagnosis may be 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

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Dr. Gilad Halpert, Ph.D.

Zabludowicz Center for Autoimmune Diseases
Sheba Medical Center

TEL AVIV UNIVERSITY

✉ Gilad.halpert@sheba.health.gov.il

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

A
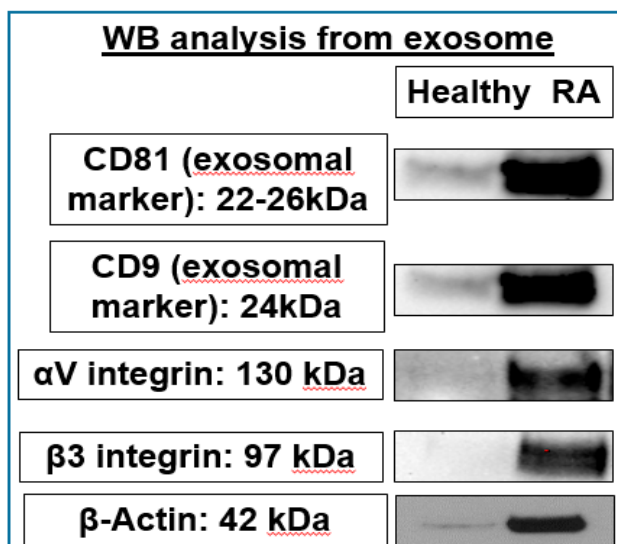
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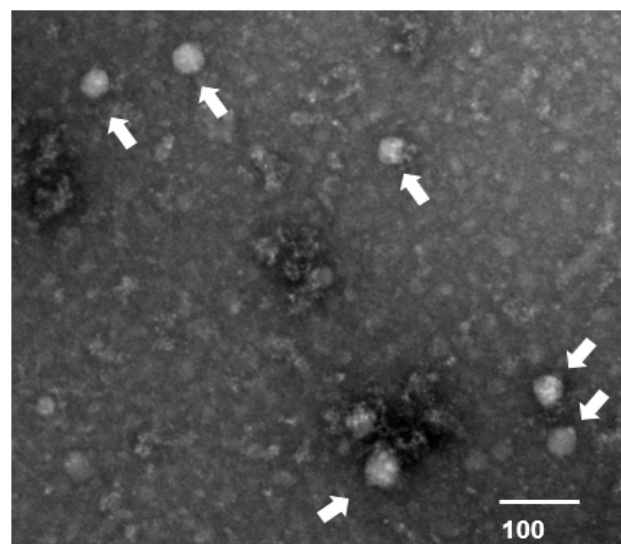
The specific synovial-homing receptor αvβ3 integrin is expressed on serum-derived exosomes (CD9+/CD81+) from rheumatoid arthritis (RA) mice. A. Total exosomes were isolated from pool of serum samples of RA mice (Collagen-induced arthritis model) (n=5) and Sham (n=5) mice. Exosomes homogenates were separated 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

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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.

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Reviews

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

Grants

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

2020-2021   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

Anat Globerson Levin, Ph.D.

Department of Immunology
Sourasky Medical Center, Tel Aviv
Email: anatgl@tlvmc.gov.il
https://www.tasmc.org.il/sites/en/Research/Tech-Transfer/Im-

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munology-Research/Pages/
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

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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.

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

Grants

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

Dr. Tami Livnat, Ph.D.

Department of Hematology
Sackler Faculty of Medicine

tami.livnat@sheba.health.gov.il

TEL AVIV UNIVERSITY

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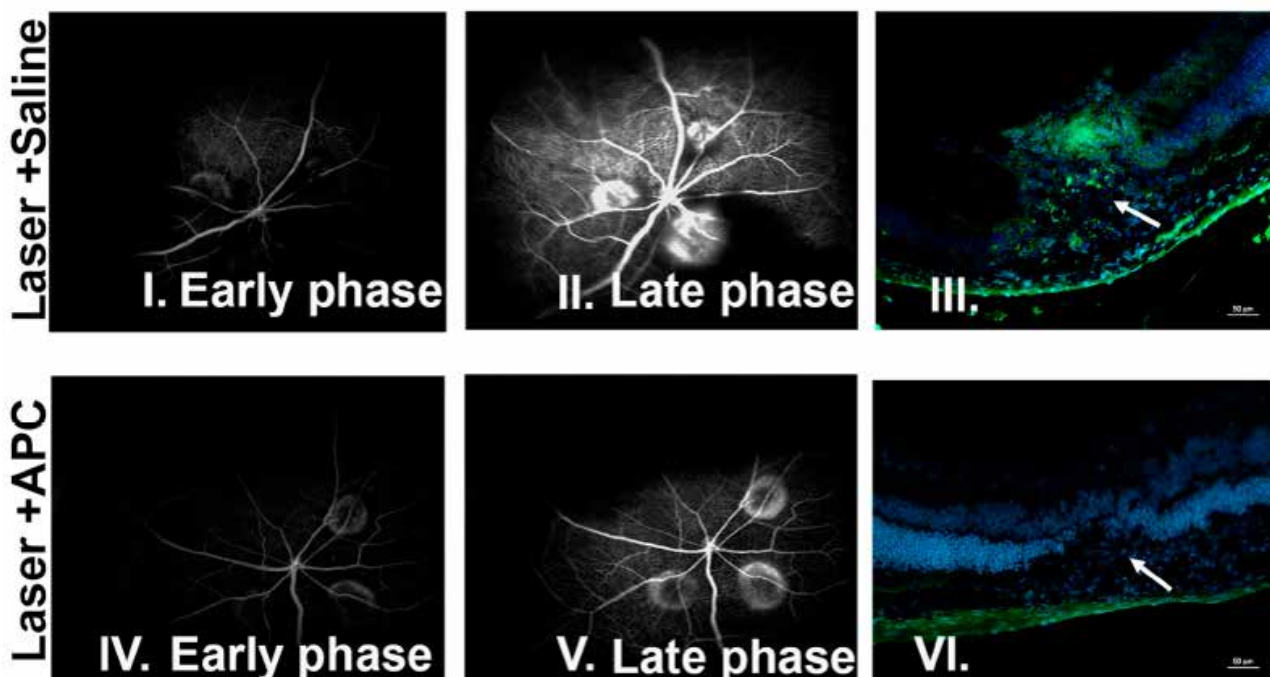
Early and late fluorescein angiograph images of an eye with 3 laser spots treated with saline (I, II) or APC (IV, V) and images of histological sections labeled with FITC-dextran (green) and DAPI (blue) in saline (III) and APC (VI) treated eyes. Arrow indicates the laser spot area.

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

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

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.

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

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.

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Grants

Dr. Shelly Tartakover Matalon, Ph.D.

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

TEL AVIV UNIVERSITY

✉ Matalon.shelly@clalit.org.il

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.

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Infectious Diseases
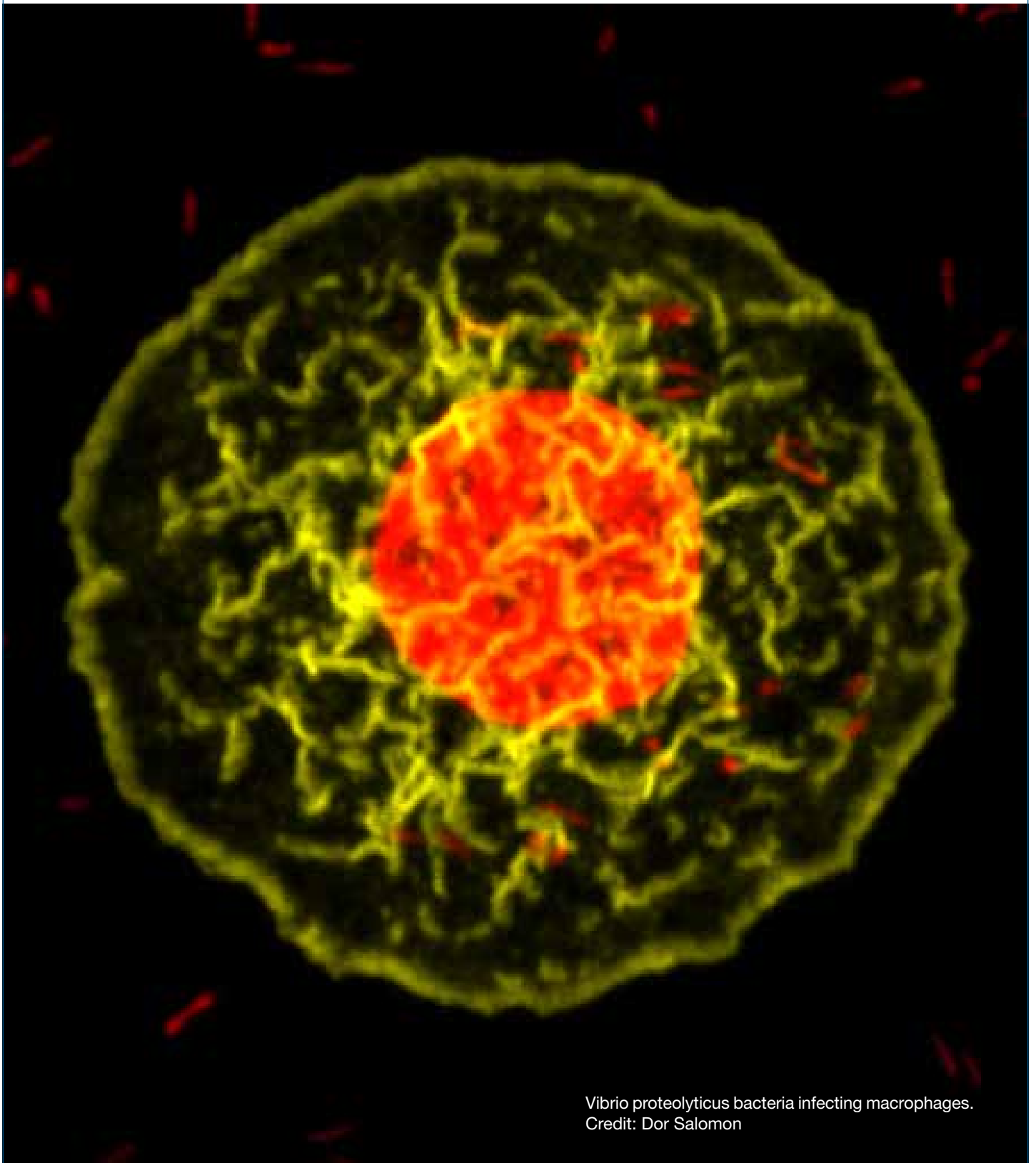
Vibrio proteolyticus bacteria infecting macrophages.
Credit: Dor Salomon
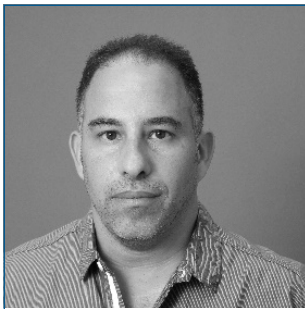
Prof. Ohad Gal-Mor, Ph.D.

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

TEL AVIV UNIVERSITY

Ohad.Gal-Mor@sheba.health.gov.il
http://galmor-lab.com/

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

Positions

Head, Infectious Diseases Research Laboratory, Sheba Medical Center.

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

Secretary, Israel Society for Microbiology.

Section Editor (Bacterial Pathogenesis), Virulence

Research

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

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

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

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

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

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

Publications

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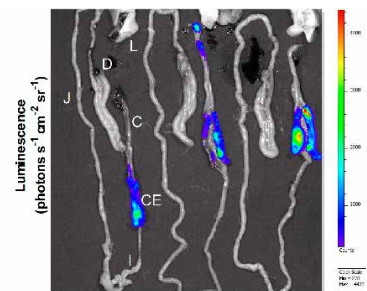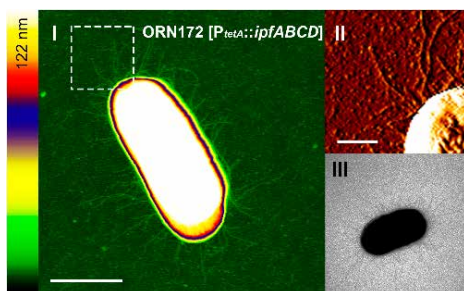
(A) Imaging of the Ipf fimbriae of *Salmonella* Infantis using atomic force microscopy (AFM). (B) Imaging of the type IV secretion system using scanning electron microscopy (SEM). (C) Spatiall expression of *ipf* genes in *S.* Infantis during infection in the chicken model.

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Grants

Dr. Michal Mandelboim, Ph.D.

Central Virology Laboratory, Ministry of Health
Chaim Sheba Medical Center
Department of Epidemiology and Preventive
Medicine, School of Public Health, Sackler
Faculty of Medicine

TEL AVIV UNIVERSITY

✉ michalman@sheba.health.gov.il

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

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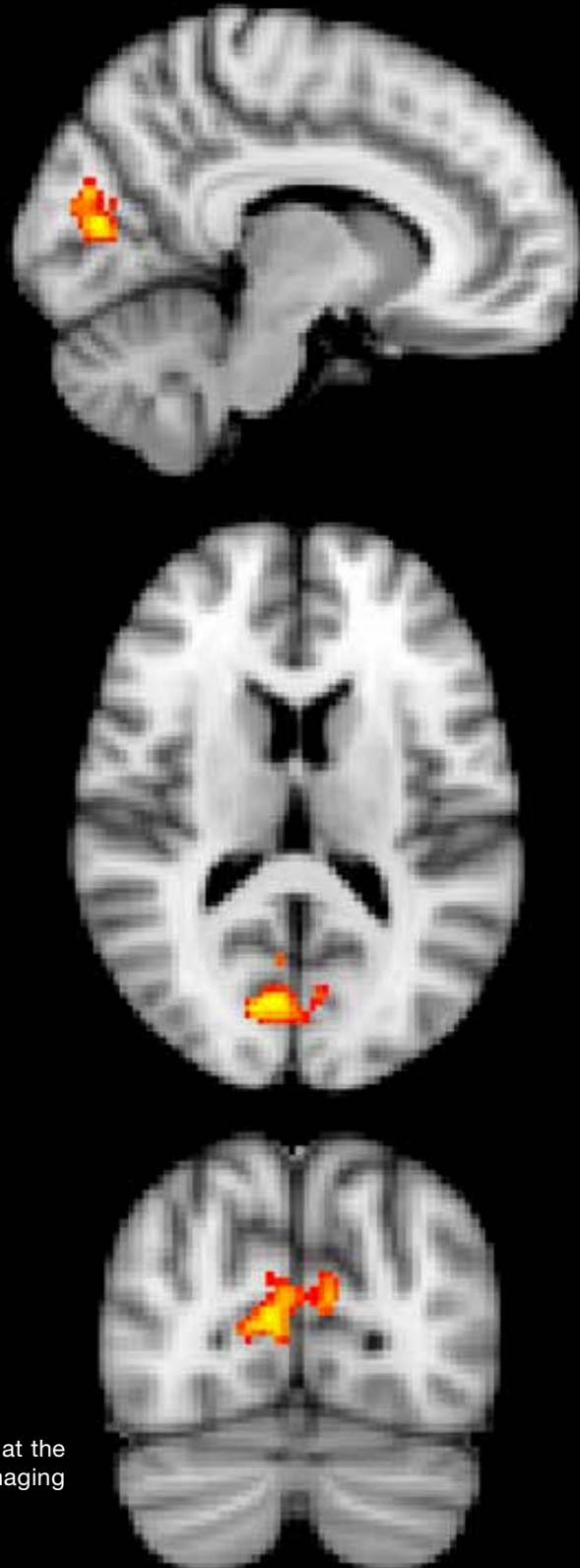
Functional MRI results, scanned at the
Strauss Computational Neuroimaging
Center, TeL Aviv University
Credit: Tom Schonberg

Prof. Jeffrey Hausdorff, Ph.D.

Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center
Department of Physical Therapy, Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

jhausdor@tlvmc.gov.il
URL: tinyurl.com/cmcm-tlvmc
URL: http://www.sagol.tau.ac.il/en/faculty/hausdorff-jeffrey/

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

Positions

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

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

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

Movement Disorders Society Task Force on Technology

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

International Society of Posture and Gait Research Strategic Planning Committee

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

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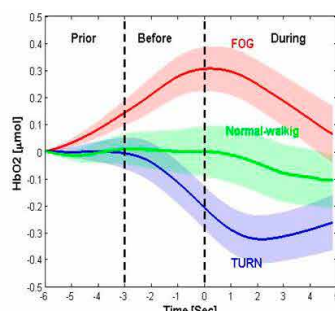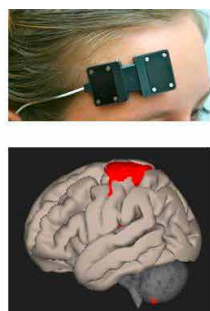
Examples of the modalities that we use to study, assess and treat gait, balance, falls and motor-cognitive interactions.

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

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Grants

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

2016-2019 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)

Dr. Yulia Lerner, Ph.D.

Neurology Department
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

yulia.lerner@gmail.com

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

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

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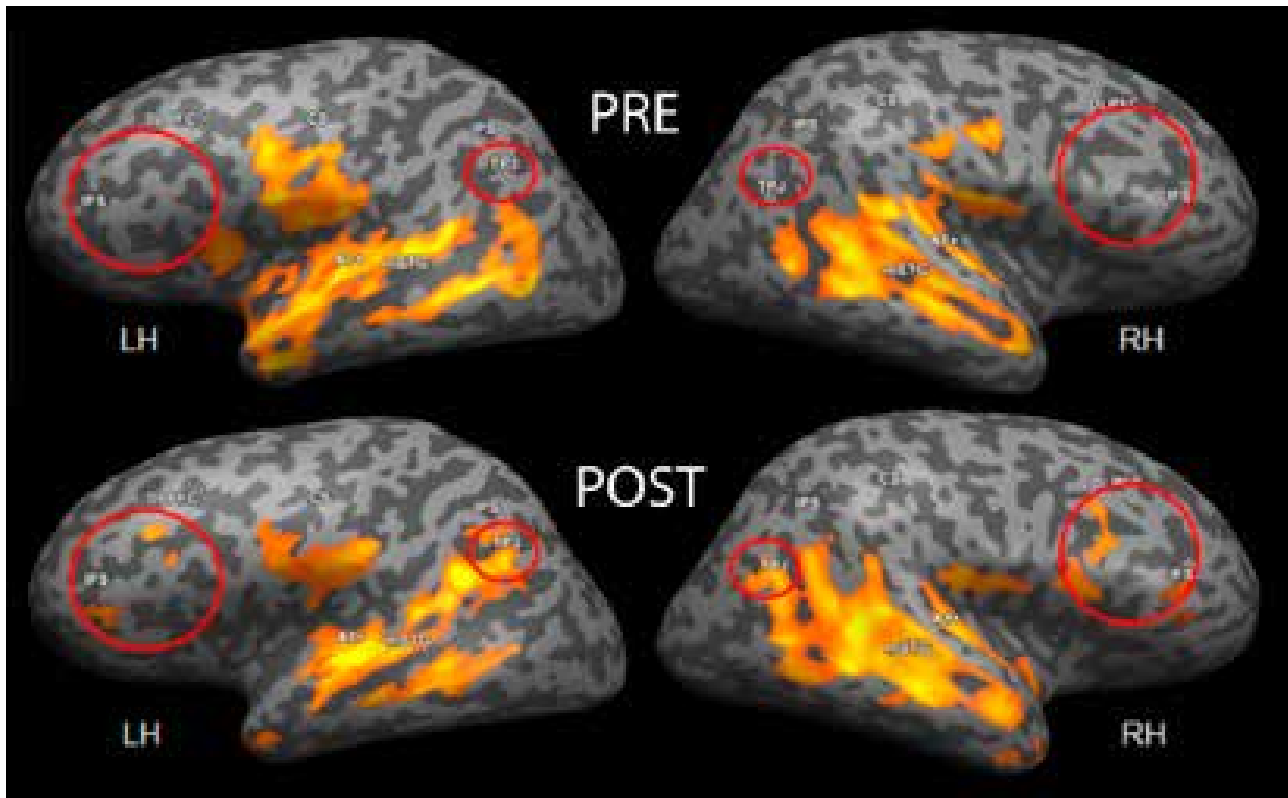
Inter–subject correlations of responses across participants from the aerobic group that listened to the narrated story. After 4 months of aerobic training program, participants demonstrated reliable responses (high inter-SC) to story in the parietal (e.g. temporo-parietal junction) and frontal (e.g.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

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Grants

Dr. Abigail Livny-Ezer, Ph.D.

Department of Diagnostic Imaging
Sheba Medical Center
Affiliated to Sackler Faculty of Medicine

abigail.livnyezer@gmail.com
http://www.livnylab.com

TEL AVIV UNIVERSITY

Functional Neuroimaging Laboratory

Positions

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.

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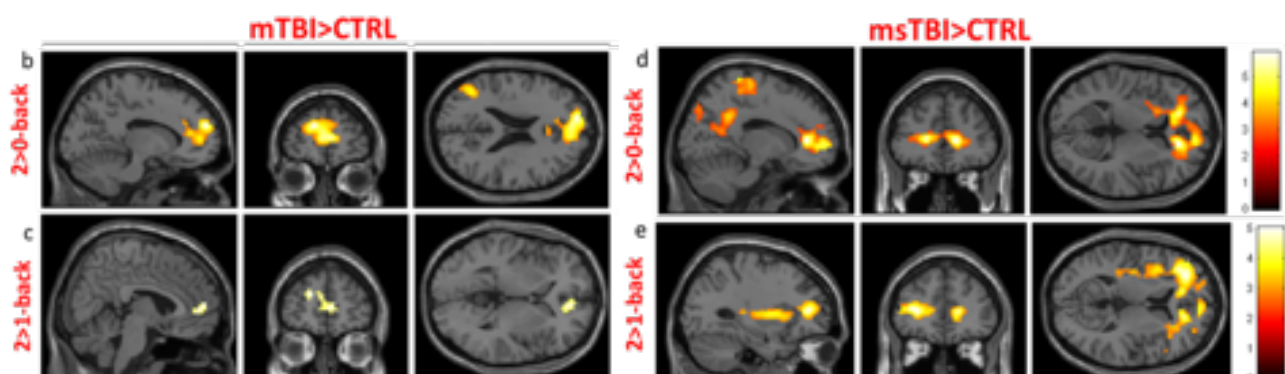
The relation between severity of TBI and working-memory brain activation during an n-back task. Maximum intensity projections in three orthogonal views of the brain (from left to right: sagittal, coronal and axial) depict areas of significant activation (p<0.005, k>100) in a one-tailed-t statistic contrasting 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.

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Reviews

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Grants

Dr. Inbal Maidan, Ph.D.

Neurology and Neurosurgery
Sackler Faculty of Medicine

inbalm@tlvmc.gov.il

TEL AVIV UNIVERSITY

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

Publications

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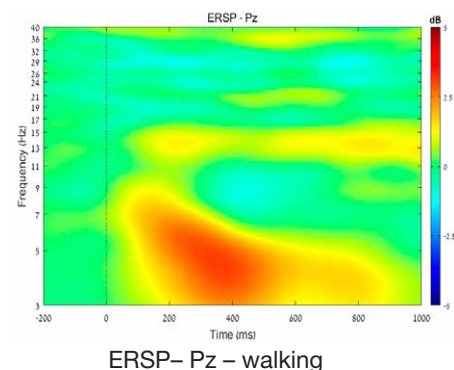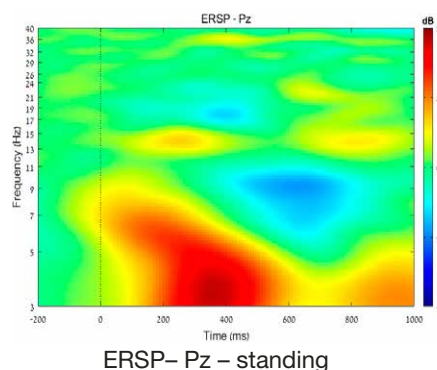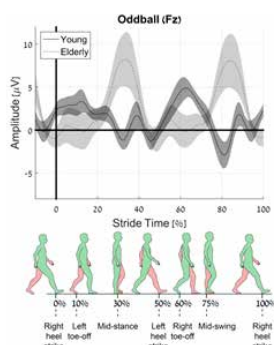
ERSP– Pz – standing

ERSP– Pz – walking

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Grants

Prof. Anat Mirelman, Ph.D.

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

TEL AVIV UNIVERSITY

✉ anatmi@tlvmc.gov.il

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

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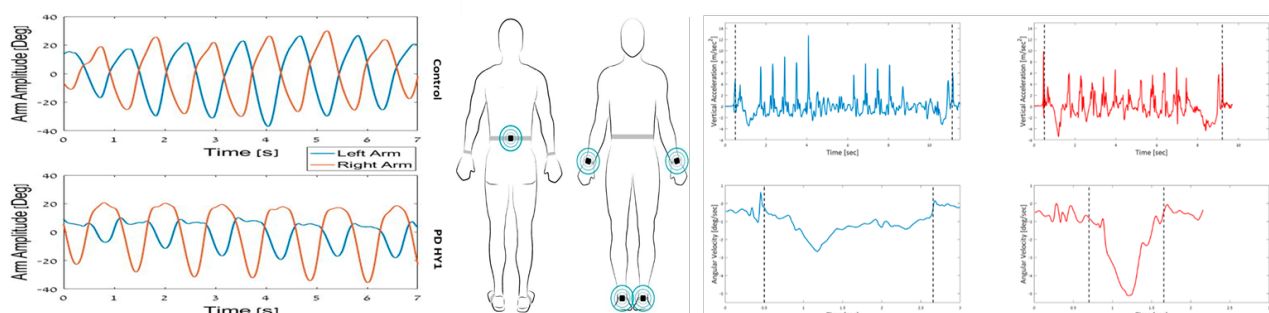
Subtle changes in acceleration as collected by wearable sensors. The signals show different patterns of movement in a person with early stage Parkinson's disease and a healthy subject at risk for developing Parkinson's disease as compared to healthy age matched controls. Features such as these are explored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

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Dr. Michal Taler, Ph.D.

Biological Psychiatry Lab,
Felsenstein Medical Research Center

michalt@tauex.tau.ac.il

TEL AVIV UNIVERSITY

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

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Grants

Dr. Ariel Tankus, Ph.D.

Department of Neurology and Neurosurgery
Sackler Faculty of Medicine

arielta@post.tau.ac.il
https://www.sagol.tau.ac.il/
faculty/tankus-ariel/

TEL AVIV UNIVERSITY

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).
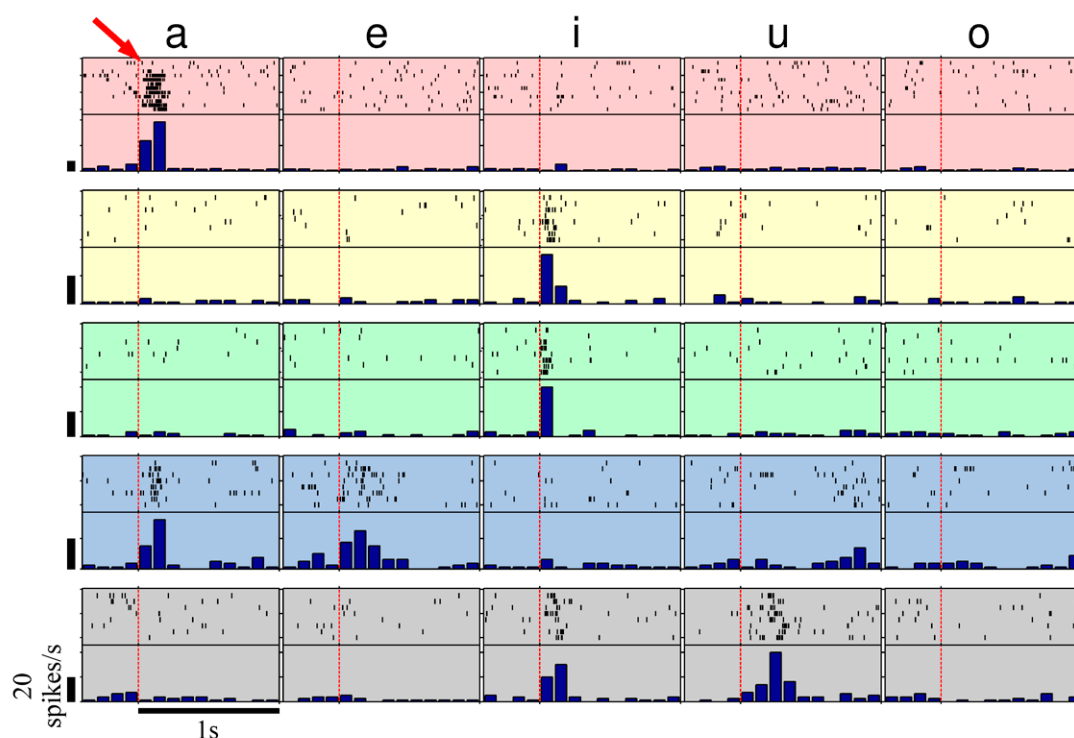
Medial–frontal units that we have discovered, with high specificity to vowels. Raster plots and peri-stimulus time histograms of five units (rows) during the articulation of the five vowels a, e, i, u and o (columns). The response of each unit is specific to one or two vowels only.
Red vertical dashed 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.

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Chapter

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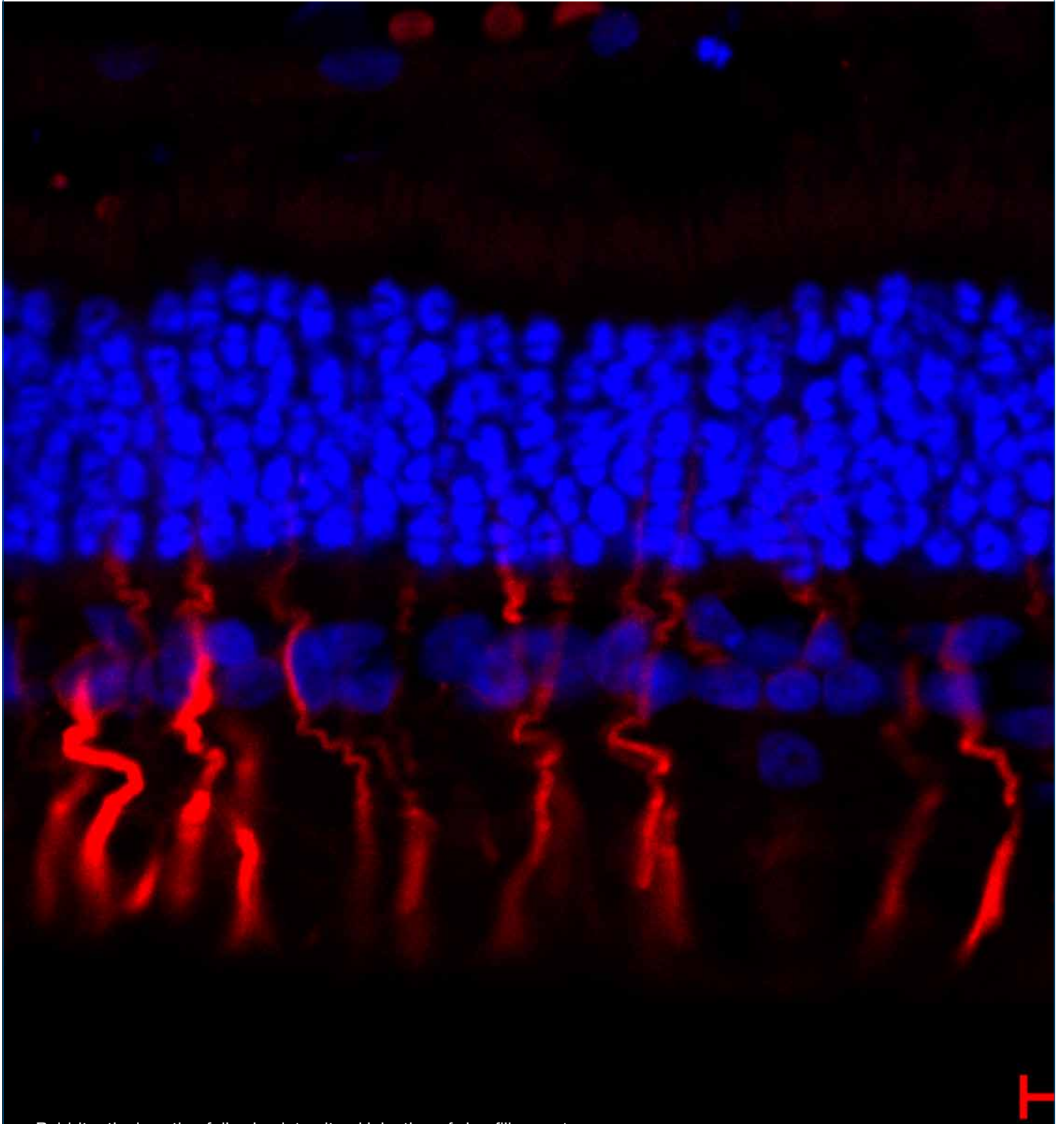
Rabbit retinal section following intravitreal injection of ziv-aflibercept.
Credit: Prof. Anat Lowenstein

Dr. Ifat Sher, Ph.D.

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

Ifat.SherRosenthal@sheba.health.gov.il

TEL AVIV UNIVERSITY

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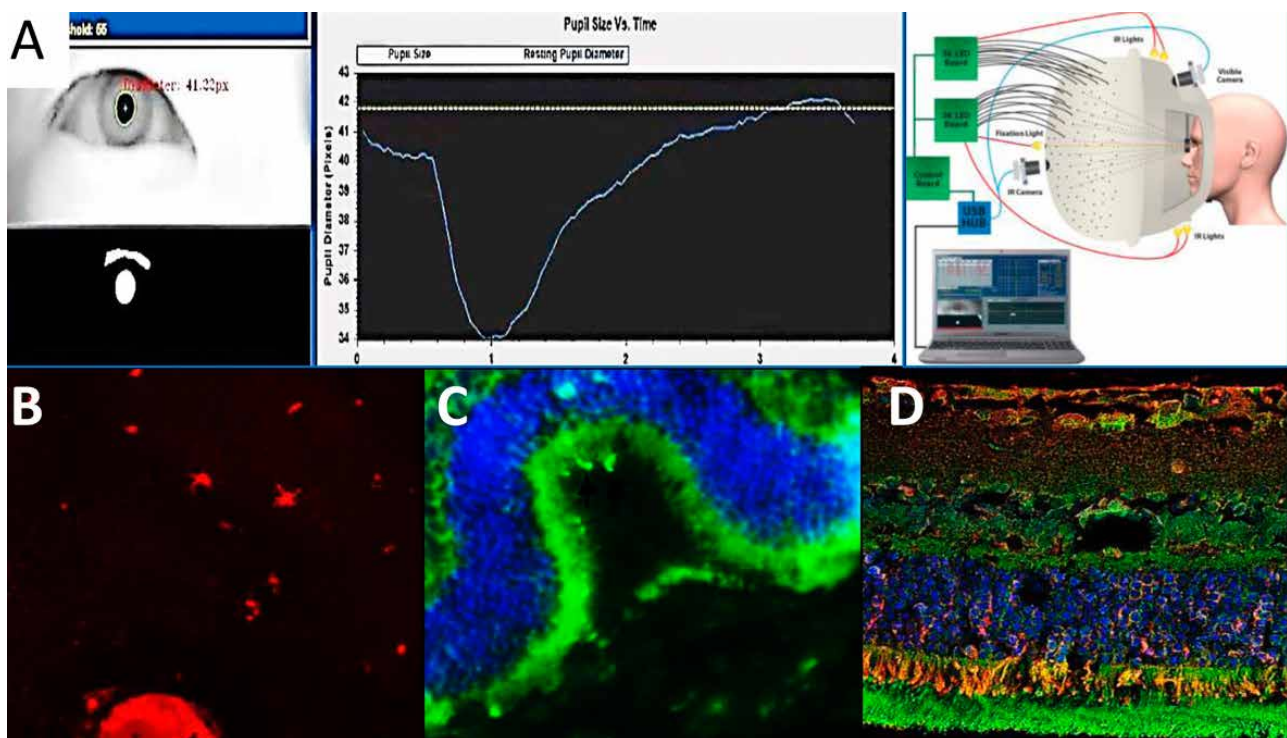
(A) Chromatic pupilloperimetry – an innovative technology for noninvasive measurement of spatial & temporal changes in neuroretinal circuitry (B) Migration of retinal microglial cells into the sub-retina in a retinal degeneration mouse model; (C) Retinal cultures for semi-high throughput drug screening;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

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

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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

Public Health

Prof. Gabriel Chodick, Ph.D., MHA

Epidemiology & Preventive Medicine
School of Public Health

hodik_g@mac.org.il
Website: http://www2.tau.ac.il/
Person/medicine/researcher.
asp?id=adkdighde

TEL AVIV UNIVERSITY

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

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Yu J, Goldshtein I, Shalev V, **Chodick G**, Ish-Shalom S, Sharon O, Modi A. Renal Impairment Among Postmenopausal Women With Osteoporosis From a Large Health Plan in Israel. Archives of Osteoporosis.

Goldshtein I, Karasik A, Melzer-Cohen C, Engel SS, Yu S, Sharon O, Brodovicz K, Gadir N , Katzeff HL, Radican L, **Chodick G**, Shalev V, Tunceli K. Urinary albumin excretion with sitagliptin compared to sulfonylurea as add on to metformin in type 2 diabetes patients with albuminuria: a real-world evidence study. Journal of Diabetes and Its Complications.

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TavorM., Neufeld MY, **Chodick G**, Zack O, SlodownikD, Moshe S. Vocational factors which predict seizure prognosis in young adults during military service. Epilepsy & Behaviour.

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Dankner R, Bachner YG, Ginsberg G, Ziv A, Ben David H, Litmanovitch-Goldstein D, **Chodick G**, Balicer RD, Tanne D, Greenberg D. Correlates of well-being among caregivers of long-term community-dwelling stroke Survivors. International Journal of Rehabilitation Research.

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Grants

Prof. Lizy Fireman, Ph.D.

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

TEL AVIV UNIVERSITY

fireman@tlvmc.gov.il
http://www.tasmc.org.il/In-
ternalmed/Pulmonary/Pages/
allergy-lab.aspx

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

Positions

Head, Laboratory Pulmonary and Allergic Diseases

Chair Department of Environmental and Occupational Health, Tel Aviv University

Research

The "ultrafine hypothesis" suggests that smaller particles are more potent than larger particles at driving inflammation; leading to the initial proposal that respiratory ill health was associated with the number of ambient ultrafine particles. When first introduced in 1994, the "ultrafine hypothesis" met friendly skepticism, with opponents arguing that

NSP (nano-sized particles) are very short-lived and disappear through heterogeneous and homogeneous aggregation within seconds or minutes and therefore are toxicologically irrelevant. This skeptical attitude has changed considerably. Research teams across the world are now working now on NSP, and there are multidisciplinary alliances among atmospheric scientists, epidemiologists, clinicians, and toxicologists, among others. Nonetheless, substantial research gaps continue to prevail. Most of the initial assessments of particulate burden and involvement of inflammatory and structural cells in occupational lung diseases were made in studies using fibreoptic bronchoscopy in conjunction with bronchoalveolar lavage (BAL). The relative invasiveness of this

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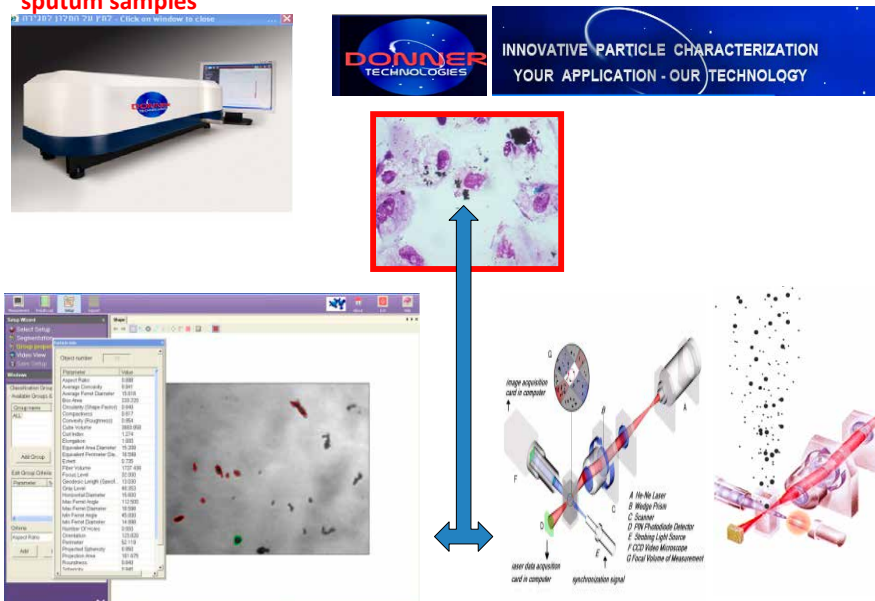

Figure 1

C: Biological monitoring by measuring ultrafine/nano ranged particles in induced sputum samples (MsC thesis of Iris Szwarcfiter)
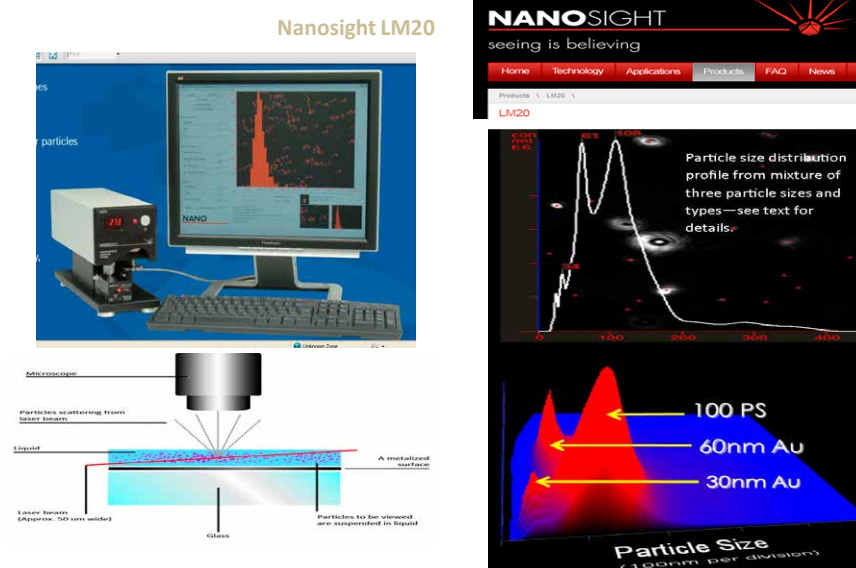
Nanosight LM20

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

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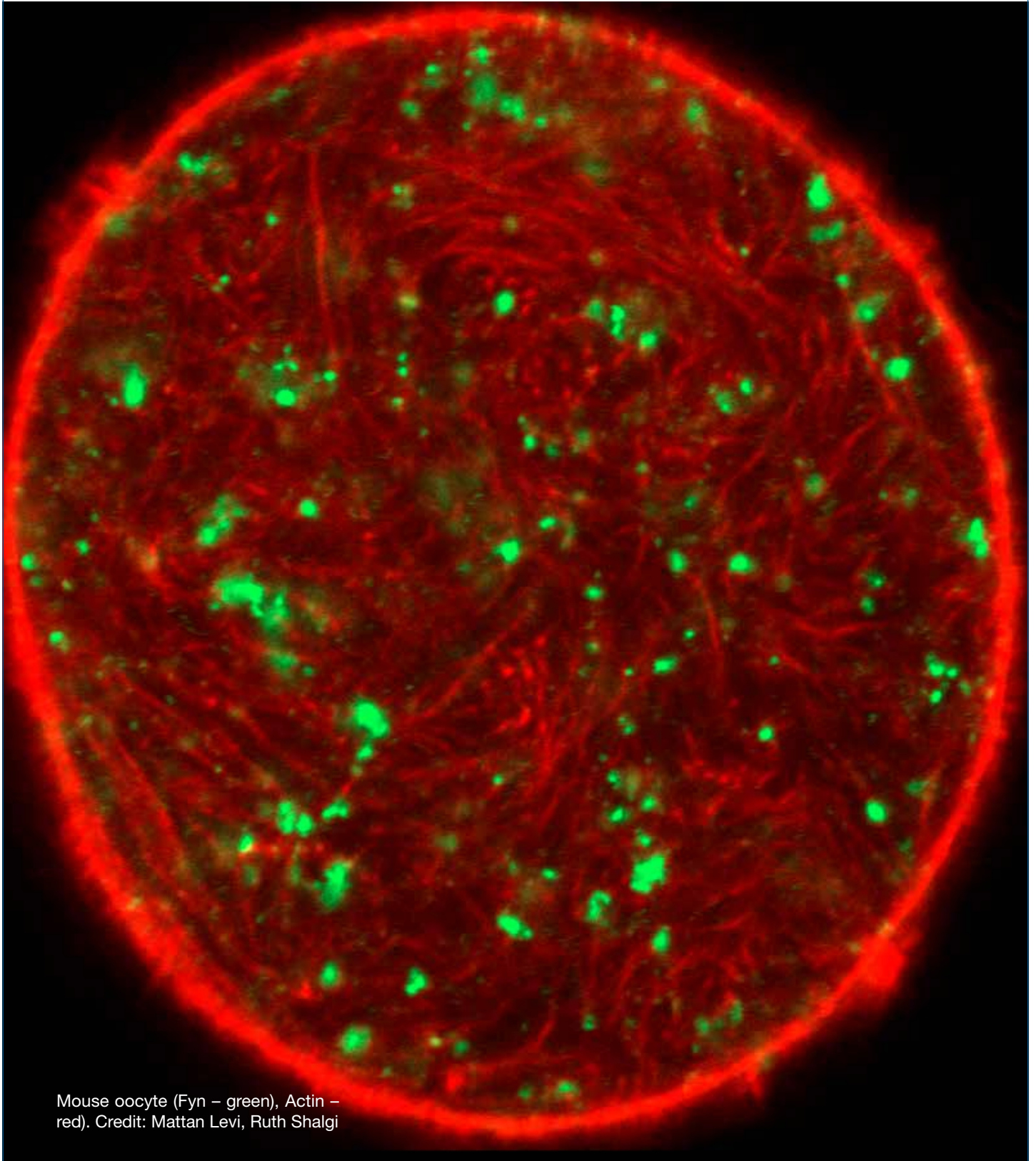
Mouse oocyte (Fyn – green), Actin – red). Credit: Mattan Levi, Ruth Shalgi

Dr. Sandra E. Kleiman, Ph.D.

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

sandrak@tlvmc.gov.il

TEL AVIV UNIVERSITY

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

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our lab works towards uncovering the etiology of male infertility. Our goal is to better understand the spermatogenetic process and improve the diagnosis and the treatment of men with infertility and subfertility. We are applying genetic approaches, combined with endocrinology, histological and cytological approaches in human specimens and mice models. By focusing on the Israeli Jewish and Arab population, our study has identified three new genes, each one playing a pivotal role in different critical processes occurring during spermatogenesis. We are employing deep sequencing to identify additional new genes mutated in infertility and subfertility. Batteries of genes are exclusively expressed at specific stages during spermatogenesis. By studying meiosis, gene expression and gene regulation, we identified testicular molecular markers that predict the presence of sperm in the testis. At present, we are working on detecting markers in semen that can predict testicular sperm cells by studying the seminal
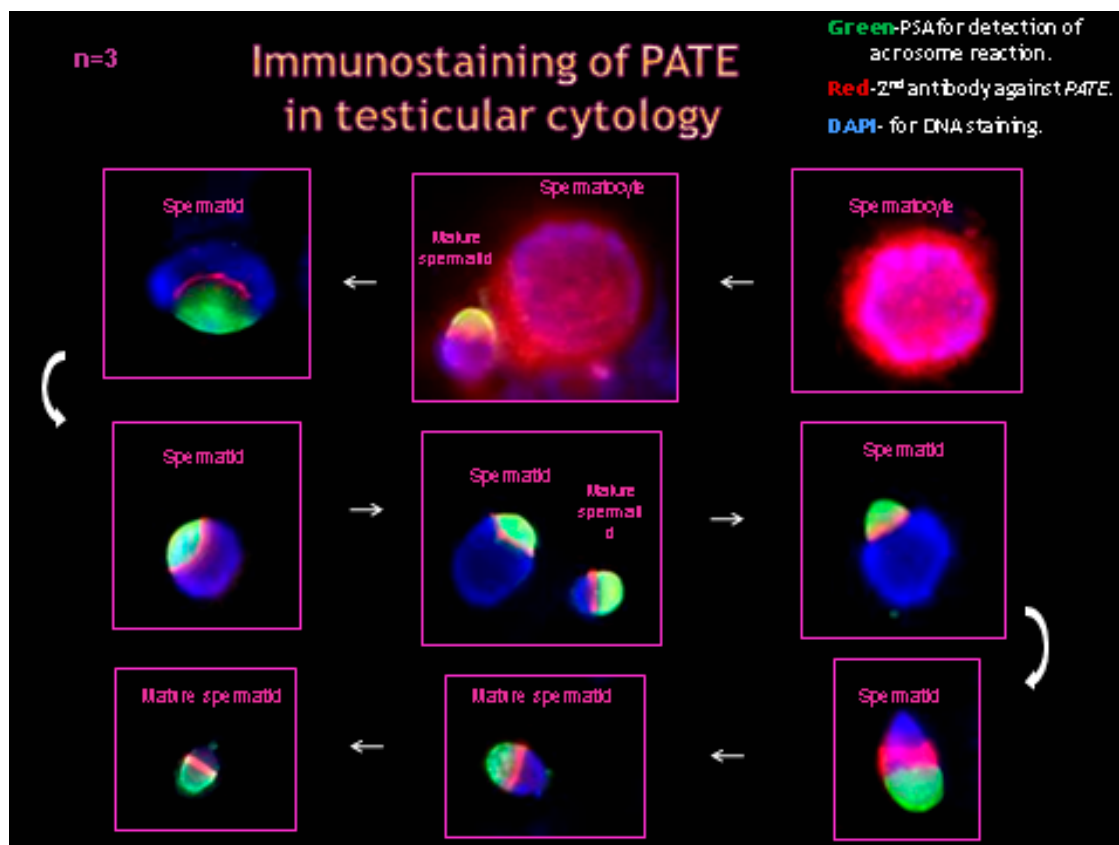
Expression pattern of PATE protein during spermatogenesis. Immunofluorescence analysis reveals the cell stages and the location in which the PATE protein is detected.

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Stem Cells & Regenerative Medicine

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

Prof. Dalit Ben Yosef, Ph.D.

IVF Lab and Wolfe PGD-Stem Cell Lab
Tel Aviv Sourasky Medical Center
Department of Cell and Developmental Biology
Sackler Faculty of Medicine

TEL AVIV UNIVERSITY

✉ dalitb@tlvmc.gov.il

hESCs in Development, Genetic Disorders and Cell Therapy

Positions

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

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

Research

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

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

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

Publications

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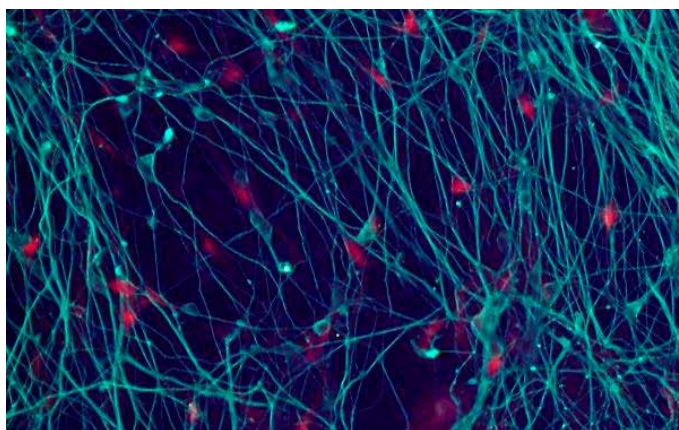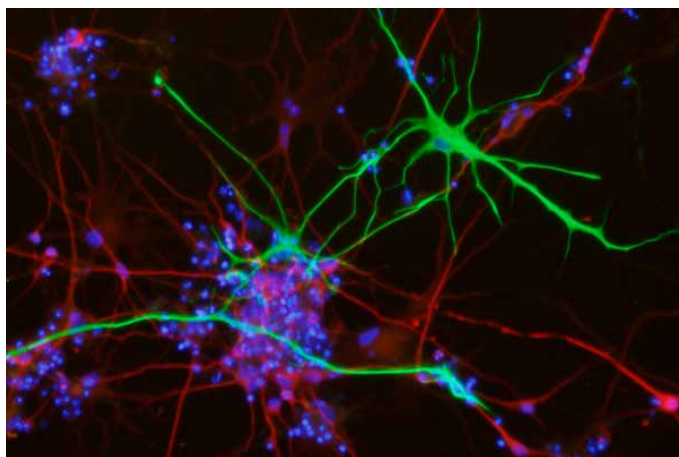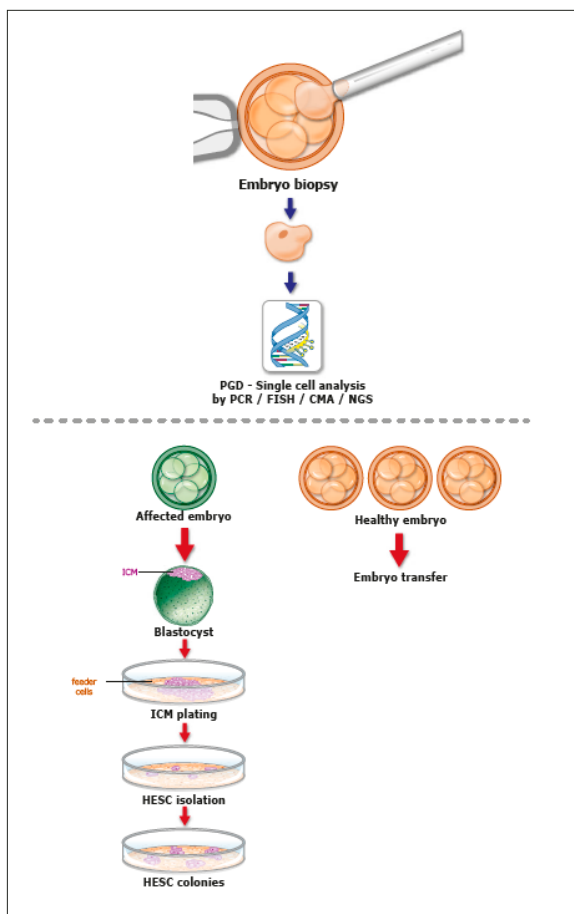
Left: HESCs are derived from PGD embryos affected by genetic disorders. Right: Neurons derived from HESCs: A. Neurons (MAP2, red) and glia (GFAP, green) from fragile X HESCs at day 128 of differentiation. B, C Neurons (Tuj1, green) from normal HESCs express FMRP (red) throughout differentiation (B, C: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

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