האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

מרכז לאוטנברג לאימונולוגיה וחקר הסרטן,
מעבדות קונצרן
The Concern Foundation Laboratories
at the Lautenberg Center for Immunology
and Cancer Research

The Concern Foundation Laboratories at the Lautenberg Center for Immunology and Cancer Research

Progress Report
September 2021

LRC MEDICINE IN CLINICAL TRAILS

Program	Description	Preclinical	IND Enabling	Phase 1	Phase 2: Combination Therapy	Cancer Indications	Milestones
BTX-A51 Triple-kinase inhibitor (CKIa-CDK7-CDK9)	A first in class Human Study NTC04243785	→	→	Memorial Sloan Kettering Cancer Center MD Anderson Cancer Center City of Hope	Memorial Sloan Kettering Cancer Center City of Hope	Acute Myeloid Leukemia & High risk MDS	Demonstrated acceptable safety profile and promising monotherapy antileukemic activity in heavily pretreated refractory patients Ball et al, JCO, 2022

Program	Description	Preclinical	IND Enabling	Phase 1	Cancer Indications	Milestones
Anti-PVR mAb (NTX1088)	First-in-class ICI Triple MoA	→	→	MD Anderson Cancer Center	Solid Tumors	• IND Cleared • FPI 2Q 2022 • MDACC

Dear friends, colleagues, and supporters,

2022 hopefully marks the end of the COVID-19 pandemic. It was a productive year for our center.

With the help of our loving friends we have started planning for an additional new floor, consisting of around 500 square meters, that will accommodate new PIs that will join our center. This expansion will allow us to recruit 4 new faculty members towards the end of 2023. We are highly grateful to Michael Kurtz and Derek Alpert from the Concern Foundation for their immense effort in raising the needed construction funds in nearly no time, and to Moriah Sapir, our devoted LRC administrative manager, for her huge efforts, and for managing the expansion project.

This expansion includes a secured position for Dr. Matan Hofree. Matan is a computational biologist working on cancer and the immune system. His will be a joint position with the school of computational sciences, and will also be part of the new computational medicine program of the medical school. With that regard, I am happy to report that the head of the computational medicine program, Prof. Nir Fridman, has also joined our center. You can read about Nir's extraordinary work in this report.

We also gave out two awards this year: the Sivartsen award, which is the largest (money-wise) PhD award, was given to Dr. Batya Isaacson, and the Shacknai award was given to Elaine Fuchs of Rockefeller University for her outstanding discoveries in studying skin and skin diseases.

Despite pandemic-related challenges, we had a very productive academic year in 2021. 19 new students started working this year at the LRC and the overall student number surpassed 100. The LRC published dozens of publications this year, in highly rated scientific journals.

The LRC is proud not only of its academic achievements but also of its contribution to cancer therapy. Two new medicines were developed at our Center: one for refractory AML, and the other for immunotherapy of cancer. The AML experimental drug is already being tested in three leading cancer centers in the US, and the immunotherapy drug's clinical trial is being conducted at MD Anderson and is funded by the hospital itself.

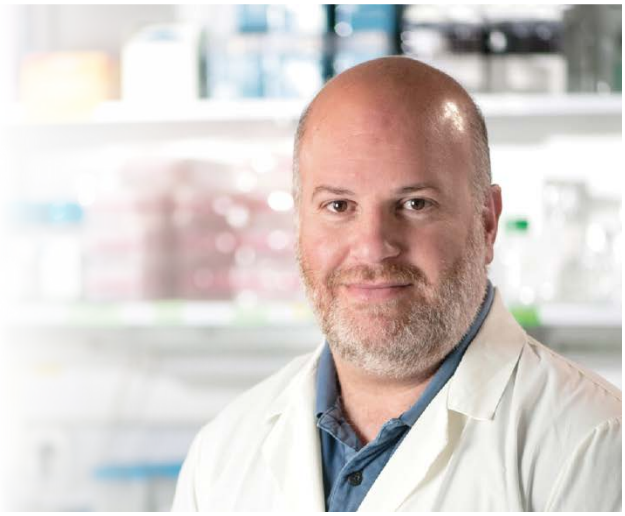
Based on the Center's achievements last year, and despite the pandemic difficulties, we trust that 2022-2023 will be at least as productive and rewarding as 2021, if not better.

Ofer Mandelboim

Head of the Concern Foundation Laboratories at Lautenberg Center for Immunology.

MOLECULAR BASIS OF CARCINOGENESIS AND TUMOR SUPPRESSION

Rami Aqeilan



Lay language summary

Cancer is a genetic disease. Detailed analyses of several cancer types have led to the identification of a heterogeneous repertoire of hundreds of cancer-causing genes resulting from various underlying mutational processes. This include age-related mutagenesis, DNA repair deficiency and enzymatic mutagenesis. These processes could result in various genetic alterations leading to the unique mutational landscape of each of the human cancer types. Our work aims to study the consequences of failed DNA repair and how does this impact cancer-related genes, both oncogenes and tumor suppressors, and the carcinogenesis process. The link between some of these genes and neurological disorders (epilepsy and multiple sclerosis) has been also the foucs of our recent lab interest. The ultimate goal of our research is hence to discover the genes (coding and non-coding) and to elucidate the mechanisms that lead to alteration in these genes with focus to identify vulnaribilities that can be therapeutically targeted.

Publications (2019– 2022)

1. Khawaled S., Suh S-S, Abdeen SK, Monin J, Distefano R, Nigita G, Croce CM and **Aqeilan R. I**. (2019) WWOX inhibits metastasis of triple-negative breast cancer cells via modulation of microRNAs. Cancer Res, 79(8):1784-1798.
2. Abu-Remaileh M., Akkawi R., Pacold M, Tam, Y. **Aqeilan R. I.** (2019) Somatic ablation of WWOX in skeletal muscles alters glucose metabolism. Molecular Metabolism, 22:132-140.
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5. Abdeen SK, **Aqeilan RI**. Decoding the link between WWOX and p53 in aggressive breast cancer. Cell Cycle. 2019 May 10; 18(11):1177-1186.

6. Chang NS, Lin R, Sze CI, **Aqeilan RI**. Editorial: WW Domain Proteins in Signaling, Cancer Growth, Neural Diseases, and Metabolic Disorders. Front Oncol. 2019 Aug 2;9:719.
7. Soudah T, Khawaled S, **Aqeilan RI**, Yavin E. AntimiR-155 Cyclic Peptide-PNA Conjugate: Synthesis, Cellular Uptake, and Biological Activity. ACS Omega. 2019 Aug 12;4(9):13954-13961.
8. Hazan I, Monin J, Bouwman BAM, Crosetto N, **Aqeilan RI**. Activation of Oncogenic Super-Enhancers Is Coupled with DNA Repair by RAD51. Cell Rep. 2019 Oct 15;29(3):560-572.e4.
9. Oster S, **Aqeilan RI**. Mapping the breakome reveals tight regulation on oncogenic super-enhancers. Mol. Cell. Oncology. 2020 Feb 11;7(3):1698933.
10. Khawaled S., Nigita G, Distefano R, Oster S, Suh S-S, Smith Y, Khalaileh A, Peng Y, Croce CM Geiger T, Seewaldt VL, **Aqeilan RI**. Pleiotropic tumor suppressor functions of WWOX antagonize metastasis. Signal Transduct Target Ther. 2020 Apr 17;5(1):43.
11. Yang X, Ma L, Wei R, Ye T, Zhou J, Wen M, Men R, **Aqeilan RI**, Peng Y, Yang L. Twist1-induced miR-199a-3p promotes liver fibrosis by suppressing caveolin-2 and activating TGF-β pathway. Signal Transduct Target Ther. 2020 Jun 5;5(1):75.
12. Oster S, **Aqeilan RI**. Programmed DNA Damage and Physiological DSBs: Mapping, Biological Significance and Perturbations in Disease States. Cells. 2020 Aug 10;9(8):1870.
13. **Aqeilan RI**. Engineering organoids: a promising platform to understand biology and treat diseases. Cell Death Differ. 2021 Jan;28(1):1-4.
14. Liebl MC, Moehlenbrink J, Becker H, Raddatz G, Abdeen SK, **Aqeilan RI**, Lyko F, Hofmann TG. DAZAP2 acts as specifier of the p53 response to DNA damage. Nucleic Acids Res. 2021 Mar 49(5):2759-2776.
15. Repudi S, Steinberg DJ, Elazar N, Breton VL, Aquilino MS, Saleem A, Abu-Swai S, Vainshtein A, Eshed-Eisenbach Y, Vijayaragavan B, Behar O, Hanna JJ, Peles E, Carlen PL, **Aqeilan RI**. Neuronal deletion of Wwox, associated with WOREE syndrome, causes epilepsy and myelin defects. Brain. 2021 April;144(10):3061-3077.
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17. Steinberg DJ, Repudi S, Saleem A, Kustanovich I, Viukov S, Abudiab B, Banne E, Mahajnah M, Hanna JJ, Stern S, Carlen PL, **Aqeilan RI**. Modeling Genetic Epileptic Encephalopathies using Brain Organoids. EMBO Mol. Med. 2021 Aug 9;13(8):e13610.
18. Sapir G, Steinberg DJ, **Aqeilan RI**, Katz-Brull R. Real-Time Non-Invasive and Direct Determination of Lactate Dehydrogenase Activity in Cerebral Organoids-A New Method to Characterize the Metabolism of Brain Organoids? Pharmaceuticals (Basel). 2021 Aug 30;14(9):878.
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20. Machour FE, Abu-Zhayia ER, Awwad SW, Bidany-Mizrahi T, Meinke S, Bishara LA, Heyd F, **Aqeilan RI**, Ayoub N. RBM6 splicing factor promotes homologous recombination repair of double-strand breaks and modulates sensitivity to chemotherapeutic drugs. Nucleic Acids Res. 2021 Nov 18;49(20):11708-11727.
21. Repudi S, Kustanovich I, Abu-Swai S, Stern S, **Aqeilan RI**. Neonatal neuronal WWOX gene therapy rescues Wwox null phenotypes. EMBO Mol Med. 2021 Dec 7;13(12):e14599. *Invited to be featured on cover page of the Journal in Dec 2021*
22. Steinberg DJ, **Aqeilan RI**. WWOX-Related Neurodevelopmental Disorders: Models and Future Perspectives. Cells. 2021 Nov 9;10(11):3082.

PhD and MSc students that graduated 2019 - 2022

PhD

1. Aya Shweiki, Msc
2. Hazem Safadi, MSc
3. Houssam Hussieni, PhD
4. Sara Abu-Swai, MSc
5. Tirza Bidani, MSc
6. Sara Oster, MSc
7. Saleh Khawaled, PhD

UNCOVERING THE LINK BETWEEN CHRONIC INFLAMMATION AND BONE LOSS

Michal Baniyash

Lay language summary

Chronic inflammatory responses lead to rapid and systemic bone loss, as evident in numerous chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, multiple myeloma, and bone metastasis in various types of cancer. It is still unclear how the ambient inflammation tilts bone homeostasis towards bone resorption. In the course of our studies, we discovered novel osteoclast precursors (inflammatory osteoclast precursors), possessing enhanced differentiation towards highly active osteoclasts during chronic inflammation, that are central contributors to the observed bone loss. We show unique underlying mechanisms controlling specifically the inflammatory osteoclast precursors, making these cells ideal for targeting and serving as biomarkers for the detection of bone loss in various inflammatory diseases. Our findings offer scientific insight on the close relation between the skeletal and immune systems, highlighting an immune-cell-based cause as being responsible for the bone loss observed during chronic inflammation. The obtained results deepen our understanding of the mechanisms underlying the changes in bone marrow homeostasis during chronic inflammation, which lead to a shift in the differentiation of a unique myeloid cell population towards active osteoclasts. Our work proposes a new approach toward bone loss during chronic inflammation, one that focuses on dealing with the osteoclast precursors rather than inhibiting mature osteoclasts. Our work holds clinical implications for the diagnosis, treatment, and prevention of bone loss in chronic inflammatory diseases.

Publications (2017 – 2022)

1. Meirow Y, Baniyash M. (2017) Immune biomarkers for chronic inflammation related complications in non-cancerous and cancerous diseases. Cancer Immunol Immunother. 66:1089-1101.
2. Jacquelot N, Roberti MP, Enot DP, Rusakiewicz S, Ternès N, Jegou S, Woods DM, Sodré AL, Hansen M, Meirow Y, Sade-Feldman M, Burra A, Kwek SS, Flament C, Messaoudene M, Duong CPM, Chen L, Kwon BS, Anderson AC, Kuchroo VK, Weide B, Aubin F, Borg C, Dalle S, Beatrix O, Ayyoub M, Balme B, Tomasic G, Di Giacomo AM, Maio M, Schadendorf D, Melero I, Dréno B, Khammari A, Dummer R, Levesque M, Koguchi Y, Fong L, Lotem M, Baniyash M, Schmidt H, Svane IM, Kroemer G, Marabelle A, Michiels S, Cavalcanti A, Smyth MJ, Weber JS, Eggermont AM, Zitvogel L. (2017) Predictors of responses to immune checkpoint blockade in advanced melanoma. Nat. Commun. 2017 8:592-605.
3. Mizrahi O., Ish Shalom E., Baniyash M., Klieger Y. (2018) Quantitative flow cytometry: Concerns and recommendations in clinic and research. Cytometry B Clin Cytom., 94:211-218.
4. Ben-Meir K, Twaik N, Baniyash M. (2018) Plasticity and biological diversity of myeloid derived suppressor cells. Curr Opin Immunol. 51:154-161.
5. Maimon A, Levi-Yahid V, Ben-Meir K, Halpern A, Talmi Z, Priya S, Mizraji G, Mistriel-Zerbib S, Berger M, Baniyash M, Loges S, Burstyn-Cohen T. (2021) Myeloid cell-derived PROS1 inhibits tumor metastasis by regulating inflammatory and immune responses via IL-10. J Clin Invest. 131(10):e126089.
6. Ashkenazi-Preiser H, Mikula I Jr, Baniyash M. (2021) The diverse roles of myeloid derived suppressor cells in mucosal immunity. Cell Immunol. Jul;365:104361.
7. Luo L, Liang W, Pang J, Xu G, Chen Y, Guo X, Wang X, Zhao Y, Lai Y, Liu Y, Li B, Su B, Zhang S, Baniyash M, Shen L, Chen L, Ling Y, Wang Y, Liang Q, Lu H, Zhang Z, Wang F. (2021) Dynamics of TCR repertoire and T cell function in COVID-19 convalescent individuals. Cell Discov. Sep 28;7(1):89.
8. Meirow Y, Jovanovic M, Zur Y, Habib J, Colombo DF, Twaik N, Ashkenazi-Preiser H, Ben-Meir K, Mikula I Jr, Reuven O, Kariv G, Daniel L, Baraghithy S, Klein Y, Krijgsveld J, Levaot N, Baniyash M. (2022) Specific inflammatory osteoclast precursors induced during chronic inflammation give rise to highly active osteoclasts associated with inflammatory bone loss. Bone Res. Apr 8;10(1):36.

MSc and PhD students that graduated:

PhD students

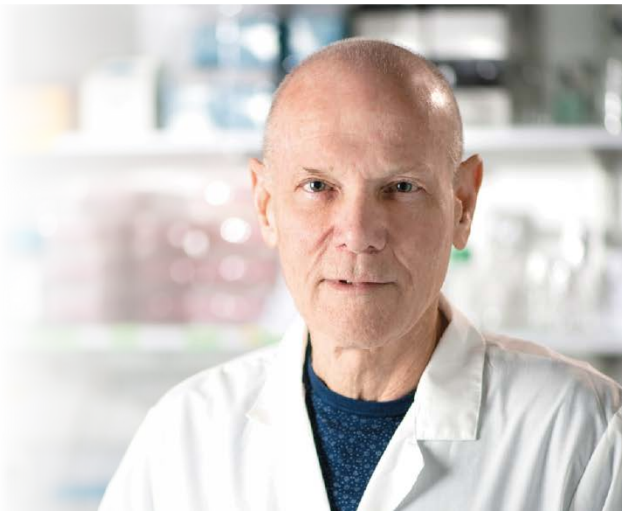
1. Yaron Meirow; Graduated October 2021.
2. Hadas Preiser; Completed her studies July 2022, not yet graduated.
3. Kerem Ben-Meir; 2015-
4. Nira Twaik; 2015-
5. Or Reuven; 2020-

MSc students:

1. Guy Kariv; 2021-
2. Mahdi Kurd; 2021-

NEW PROTOTYPE DRUG DEVELOPED TO BEAT ACUTE MYELOID LEUKEMIA

Yinon Ben-Neriah



Lay language summary

Acute myeloid leukemia is one of the most aggressive, yet also one of the most interesting types of cancer. Despite a lot of progress in its treatment, it is still considered a disease with unmet therapy needs and the 5-year survival of the patient is only 20%. Following an intensive research and development effort our research team succeeded in developing a biological drug, which was found to cure up to 50% of model mice of poor risk human leukemia and eradicate human leukemia transplanted to model mice.

Leukemia cells produce many proteins which are barely made in normal blood cells, working in concert to provide the leukemic cell growth advantage and death protection even upon chemotherapy. Biological cancer drugs developed so far, mostly attack a single leukemic protein and the leukemic cells quickly find a way to avoid the drug effect through alternative proteins. Unlike most modern cancer drugs, our newly developed drug works like a cluster bomb that attacks simultaneously many leukemic proteins and thus makes it difficult for the leukemia cell to evade the therapy. Another important advantage of the new drug is its capacity to eradicate leukemia stem cells, which is a big challenge in cancer therapy and one of the main reasons for failing to cure cancer. Based on our preclinical studies at the Lautenberg Center, our drug received an FDA approval for Phase 1 clinical trial, which has just been successfully completed at three of the most important cancer centers in the US. A significant fraction of AML patients, who are refractory to all treatments benefited from treatment with our drug. Based on the results of phase 1, our clinical trial will soon expand to phase 2 and possibly to other cancer diseases.

Publications (2017 – 2022)

1. Lasry A, Aran D, Butte A, **Ben-Neriah Y**. Cancer Cell–Autonomous Parainflammation Mimics Immune Cell Infiltration. *Cancer Res*, OnlineFirst June 30, 2017; DOI: 10.1158/0008-5472.CAN-16-3383
2. Morgenstern M, Das Adhikari U, Ayyash M, Elyada E, Tóth B, Moor A, Itzkovitz S, **Ben-Neriah Y.** Casein kinase 1-epsilon or 1-delta required for Wnt-mediated intestinal stem cell maintenance *EMBO J,* 2017, Oct 16;36(20):3046-3061. doi: 10.15252/embj.201696253.
3. Chang CH, Kuo CJ, Ito T, Su YY, Jiang ST, Chiu MH, Lin YH, Nist A, Mernberger M, Stiewe T, Ito S, Wakamatsu K, Hsueh YA, Shieh SY, Snir-Alkalay I, **Ben-Neriah Y**. CK1α ablation in keratinocytes induces p53-dependent, sunburn-protective skin hyperpigmentation. *Proc Natl Acad Sci U S A*. 2017 Sep 6. pii: 201702763. doi: 10.1073/pnas.1702763114.
4. Minzel W, Venkatachalam A, Fink A, Hung E, Brachya G, Burstain I, Shaham M,, Rivlin A, Omer I, Zinger A, Elias S, Winter E, Erdman PE, Sullivan RS, Fung L, Mercurio F, Li D, Vacca J, Kaushansky N, Shlush L, Oren M, Levine L, Pikarsky E, Snir-Alkalay I, and **Ben-Neriah Y**. Small molecules co-targeting CKIα and the transcriptional kinases CDK7/9 control acute myeloid leukemia in preclinical models. *Cell*. 2018 Sep 20;175(1):171-185.e25. doi: 10.1016/j.cell.2018.07.045.
5. β-TrCP upregulates HIF-1 in prostate cancer cells. Cohen M, Amir S, Golan M, **Ben-Neriah Y**, Mabjeesh NJ. *Prostate*. 2019 Mar;79(4):403-413. doi: 10.1002/pros.23746. Epub 2018 Nov 28.
6. Kadosh E, Snir-Alkalay I, Venkatachalam A, May S, Lasry A, Elyada E, Zinger A, Shaham M, Vaalani G, Mernberger M, Stiewe T, Pikarsky E, Oren M & **Ben-Neriah Y**. Gut microbiota switches mutant p53 from tumor-suppressive to oncogenic. *Nature* 2020 (Oct 1st), 538: 133-138
7. Venkatachalam A, Pikarsky E and **Ben-Neriah Y**. Putative homeostatic role of cancer driver mutations. *Trends in cell biology*, 2021, https://doi.org/10.1016/j.tcb.2021.07.002
8. Fink A, Hung E, Sing I and **Ben-Neriah Y**. Immunity in acute myeloid leukemia: where the immune response and targeted therapy meet. *European J. Immunol*. 2021, DOI:10.1002/eji.202048945

MSc and PhD students that graduated:

MSc

1. Bar Lossos
2. Hodaya Furman
3. Amitai Rivlin

PhD

1. Adar Zinger

Awards:

1. Yinon Ben-Neriah: The EMET Prize for Art, Science and Culture, provided by the PM of Israel
2. Elected Member of the Israeli Academy of Sciences and Humanities

UTILIZING T CELL METABOLISM TO TREAT CANCER AND TO IMPROVE ANTI-VIRAL VACCINATIONS

Michael Berger

Lay language summary

CD8 Cytotoxic T cells (CTLs) are the main anti-cancer and anti-virus immune cells in our body. These cells have the ability to recognize and kill cells that express foreign or altered components.

My research group is interested in finding molecular checkpoints that regulate T cell transition from naïve, to effector, or memory state. In addition, we are interested in finding ways to exploit our findings to develop new anti-cancer therapies and to improve anti-viral vaccinations.

In the past year, we focused on water metabolism in T cells. We developed a novel method, Cold Aqua Trap-Isotope Ratio Mass Spectrometry (CAT-IRMS), based on the intracellular water isotope composition, to directly measure both the source of and the rate by which cells gain water mass. We then applied CAT-IRMS to study water mass build-up in T cells. We identified for the first time that T cells use three different dominant cellular water gain mechanisms. In addition, we focused on finding ways to improve adoptive T cell transfer therapy (ACT) against solid tumors. We could show that by manipulating T cell metabolism we able to “train” effector T cells to function under hypoxic conditions by limiting mitochondrial-derived ATP transfer to the cytosol. Moreover, we manage to develop a groundbreaking technology to generate metaboliclly supirior T cells. Our study is expected to provide both a novel approach and practical tools for precision therapy for different solid tumors. Therefore, it is crucial to transitioning of ACT from merely a promising treatment to an effective one.

Publications (2019 – 2022)

1. Analysis of cellular water content in T cells reveals a switch from slow metabolic water gain to rapid water influx prior to cell division. A Saragovi, T Zilberman, G Yasur, K Turjeman, I Abramovich, M Kuchersky, E Gottlieb, Y Barenholz, **M Berger**. Journal of Biological Chemistry 2022; 298.
2. Myeloid cell-derived PROS1 inhibits tumor metastasis by regulating inflammatory and immune responses via IL-10. Maimon A, Levi-Yahid V, Ben-Meir K, Halpern A, Talmi Z, Priya S, Mizraji G, Mistriel-Zerbib S, **Berger M**, Baniyash M, Loges S, Burstyn-Cohen T. J Clin Invest 2021; 131.
3. Systemic hypoxia inhibits T cell response by limiting mitobiogenesis via matrix substrate-level phosphorylation arrest. Saragovi A, Abramovich I, Omar I, Arbib E, Toker O, Gottlieb E, **Berger M**. *Elife*. 2020 ;9:e56612.
4. Exogenous interleukin-2 can rescue in-vitro T cell activation and proliferation in patients with a novel capping protein regulator and myosin 1 linker 2 mutation. Shamriz O, Simon AJ, Lev A, Megged O, Ledder O, Picard E, Joseph L, Molho-Pessach V, Tal Y, Millman P, Slae M, Somech R, Toker O, **Berger M**. *Clin Exp Immunol*. 2020; 200
5. IL-17+ CD8+ T cell suppression by dimethyl fumarate associates with clinical response in multiple sclerosis. Lückel C, Picard F, Raifer H, Campos Carrascosa L, Guralnik A, Zhang Y, Klein M, Bittner S, Steffen F, Moos S, Marini F, Gloury R, Kurschus FC, Chao YY, Bertrams W, Sexl V, Schmeck B, Bonetti L, Grusdat M, Lohoff M, Zielinski CE, Zipp F, Kallies A, Brenner D, **Berger M**, Bopp T, Tackenberg B, Huber M. Nat Commun. 2019; 10.
6. Long Noncoding RNA MALAT1 Regulates Cancer Glucose Metabolism by Enhancing mTOR-Mediated Translation of TCF7L2. Malakar P, Stein I, Saragovi A, Winkler R, Stern-Ginossar N, **Berger M**, Pikarsky E, Karni R. Cancer Res. 2019; 79
7. Tissue necrosis and its role in cancer progression. Karsch-Bluman A, Feiglin A, Arbib E, Stern T, Shoval H, Schwob O, **Berger M**, Benny O. Oncogene. 2019; 38

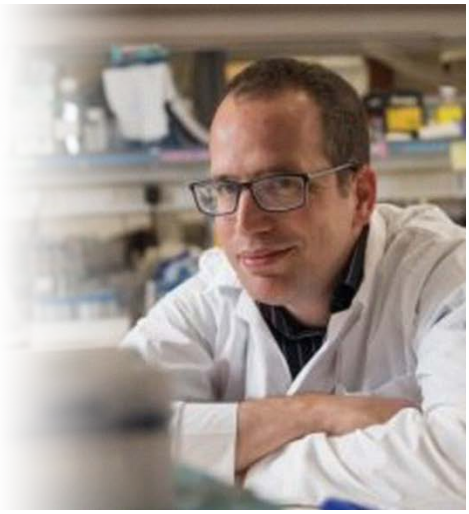
MSc and PhD and Postdoc students that graduated:

PhD

1. Ibrahim Omar
2. Amijai Saragovi
3. Eliran Arbib

EPIGENETIC AND TOPOLOGICAL DYSREGULATION AS A DRIVING FORCE IN CANCER

Yotam Drier



Lay language summary

In recent years extensive efforts revealed how changes in the DNA sequence of genes drive cancer. However most of our DNA does not code for genes. One key function of this "noncoding" DNA is to regulate DNA related processes such as replication of the DNA, transcription (reading the DNA and producing RNA), and the 3-dimensional structure of the DNA (*chromosomal topology*). Unlike genetic alterations of genes, we still do not understand the role of alterations of the regulatory DNA elements in cancer. Transcription is regulated by regulatory DNA elements known as *promoters* (just upstream of the gene) and *enhancers* (that can be found away from the genes they regulate). Chromosomal topology is governed by topological boundaries and binding of a protein known as *CTCF*. In addition to information encoded in the DNA sequence, there is an additional layer of chemical modifications "on top" the DNA sequence, known as *epigenetic* information. This includes mostly methylation of DNA and chemical modifications to the tails of the histones around which the DNA is wrapped. In addition to the genetic changes of the DNA sequence in cancer, there are also many epigenetic changes that contribute to the disease. The scope and function of epigenetic changes of regulatory DNA is even less well understood.

We are studying how genetic and epigenetic changes of regulatory DNA elements such as enhancers and CTCF binding sites are involved in cancer initiation, progression and response to therapy. We combine cutting edge experimental techniques to characterize epigenomes and topology of primary tumors, advanced computational models to integrate these data and predict oncogenic events, and experimental validation of these predictions in cancer models. At present we are applying these approaches to study the epigenetic and topologic effects of:

1. EBV infection and its role in gastric cancer.
2. Liver chronic inflammation and its role in hepatocellular carcinoma oncogenesis.
3. CTCFL overexpression and its role in melanoma progression
4. IDH1 mutation and its role in altering splicing and promoting gliomagenesis.

In addition, we demonstrated how the characterization of enhancer elements in pancreatic neuroendocrine tumors reveals clinically relevant developmental subtypes (Cejas*, Drier*, et al. Nature Medicine 2019), and are now working to expanding these observations to lung neuroendocrine tumors.

COVID-19 related activities

During the COVID-19 outbreak, we have teamed up with the Clinical Virology Unit of the Hadassah Medical Center, led by Prof. Dana Wolf, to improve the efficiency and throughput of COVID-19 tests by implementing pooling of several samples to allow testing all these samples in one test, while retaining the high sensitivity of the test (Ben-Ami at el. Microbiol Infect. 2020). In addition, we are studying the regulatory networks that govern SARS-CoV-2 entry to human cells.

Publications (2019 - 2021)

1. Antman I*, Davis E*, Abu-Kamel S*, Hecht M, **Drier Y**: *Simultaneous mapping of enhancers and enhancer rearrangements with paired-end H3K27ac ChIP-seq*. Methods in molecular biology 2022, in print.
2. Dahan S, Sharma A, Cohen K, Baker M, Taqatqa N, Bentata M, Engal E, Siam A, Kay G, **Drier Y**, Elias S, Salton M: *VEGFA's distal enhancer regulates its alternative splicing in CML*. NAR Cancer. 2021 Jul 13;3(3):zcab029.
3. Anand P*, Guillaumet-Adkins A*, Dimitrova V*, Yun H*, **Drier Y***, Sotudeh N, Rogers A, Ouseph MM, Nair M, Potdar S, Isenhart R, Kloeber JA, Vijaykumar T, Niu L, Vincent T, Guo G, Frede J, Harris MH, Place AE, Silverman LB, Teachey DT, Lane AA, DeAngelo D, Aster JC, Bernstein BE, Loh JG, Knoechel B: *Single cell RNA-seq reveals developmental plasticity with coexisting oncogenic states and immune evasion programs in ETP-ALL*. Blood, 2021 May 6;137(18):2463-2480. * Equal Authorship
4. Ben-Ami R, Klochendler A, Seidel M, Sido T, Gurel-Gurevich O, Yassour M, Meshorer E, Benedek G, Fogel I, Oiknine-Djian E, Gertler A, Rotstein Z, Lavi B, Dor Y, Wolf DG, Salton M, **Drier Y**: *Large-scale implementation of pooled RNA extraction and RT-PCR for SARS-CoV-2 detection*. Clinical Microbiology and Infection 2020, 26(9):1248-1253.
5. **Drier Y**: *Enhancer and super-enhancer regulation and its disruption in cancer.* Current Opinion in Systems Biology 2020, 19:24-30.
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Funding and Awards

1. Concern Foundation and Antoinette E. "Mimi" & Herman Boehm Foundation AFHU young professorship award, 2019-2026, $280,000
2. Alon Fellowship award for outstanding young scientists, The Israeli Council for Higher Education, 2019-2021, 170,000 NIS.
3. ERC starting grant, Elucidating the mechanisms, heterogeneity and role of epigenetic topological alterations in cancer, 2021-2026, 1,500,000 Euro.
4. ISF personal research grant, Uncover how epigenetic alterations of chromosome topology drive liver cancers, 2020-2025, 1,400,000 NIS.
5. ISF Curbing Coronavirus (SARS-CoV-2) Research program, Uncovering regulatory networks governing SARS-CoV-2 entry to human cells, 2020-2021, 606,900 NIS (with Dr. Oren Parnas).
6. NETRF investigator award, Elucidate the Developmental and Regulatory Heterogeneity of Lung Carcinoids, 2020-2021, $300,000.

MSc and PhD and Postdoc students that graduated:

1. Dana Rimini
2. Shahd Abu-Kamel

EPIGENOMICS LIQUID BIOPSY

Nir Freidman

Lay Language Summary

We are all familiar with the analogy of DNA as the “blue print” of life. One of the greatest challenges in biology is in understanding how living cells read these complex instructions. In particular, how do cells turn the proper genes to “ON” or “OFF” at the right timing? Such transcriptional regulation is critical to all forms of life from microorganisms to humans, and is established by multiple cascades of regulatory mechanisms. During the last two decades we learned the importance of mechanisms that involve chromatin, the packaging of DNA inside the cells, as a substrate. This packing could be marked at individual DNA locations by a wide range of different marks (chemical modifications). These marks can be recognized by other proteins, which in turn can affect how other regulatory proteins access the DNA at the specific location. Thus, similar to the way marking on boxes can influence where and how they are shipped, the marking on chromatin can influence how the DNA at that particular location is accessed and used within the cell. The discovery of multiple different marks and numerous “writer” and “reader” proteins, suggest that cells can use *epigenetic* annotations over the immutable DNA sequence as local memory of past decisions.

My lab traditionally focused on understanding the mechanisms, logic, and function of chromatin marks in establishing and maintaining transcriptional regulation. We have studied the chromatin-transcription system in a systematic manner. In the last few years we shifted our focus to a somewhat surprising aspect of these epigenetic modifications and their use in medicine.

Briefly, cells dying (or being replaced) in the body are broken down to smaller molecules that can be removed for recycling. This process also involves the DNA within the cell. Decades ago, researchers reported on the presence of cell-free DNA in the blood. This observation became relevant with the advance of technology that enabled sequencing this cell-free DNA. Based on sequence we can tell whether the DNA is from “normal” cells or cells with a different sequence, due for examples to mutations in cancer or to different donor in the case of organ transplants. These differences are already being used in the clinic for monitoring cancer recurrence, organ failure, and non-invasive pre-natal diagnosis. However, most of the cell-free DNA comes from cells in the body has the same sequence, and thus sequence alone cannot tell us about the difference between say liver cells and lung cells.

Our eureka moment was when we realized that this cell-free DNA is actually packaged as fragments of chromatin. We reasoned that if chromatin modifications were retained on these fragments we could read from each molecule two aspects – its role in the cell (e.g., active gene) and its sequence, which would tell us which gene it is. We developed technology to do this, and from a single blood sample (one tube) we can report on the activity status of all the genes in the genome in the cells that died and contributed to the cell-free DNA. This information allowed to deduce what type of cells are dying (due to cell-type specific gene activity) and what is their state (e.g., hypoxia or inflammation). This new technology opened up a large range of medical applications from diagnosis of disease, monitoring disease progress, and predicting treatment efficacy. It also provides new window to under basic questions about human biology that are not accessible today.

We are able to do so through our interdisciplinary capabilities that combine extensive experience in modeling and data analysis with innovative unique experimental systems and state-of-the-art high-throughput technologies. Our overall aim is to uncover basic principles of transcriptional regulation and understanding the molecular mechanisms that implement these principles to achieve highly regulated cellular behavior.

Publications (2019-2022)

1. A Chappleboim, D Joseph-Strauss, O Gershon, **N Friedman**. “Transcription feedback dynamics in the wake of cytoplasmic mRNA degradation shutdown” *Nucleic Acids Research* **50** (10), 5864-5880, 2022
2. A Chappleboim, D Joseph-Strauss, ..., N. Friedman “Early sample tagging and pooling enables simultaneous SARS-CoV-2 detection and variant sequencing” *Science Translational Medicine* **13** (618), eabj2266, 2021
3. N Moriel, E Senel, N Friedman, N Rajewsky, N Karaiskos, M Nitzan. “NovoSpaRc: flexible spatial reconstruction of single-cell gene expression with optimal transport” *Nature Protocols* **16** (9), 4177-4200, 2021
4. R Sadeh, I Sharkia, ..., N. Friedman. “ChIP-seq of plasma cell-free nucleosomes identifies gene expression programs of the cells of origin” *Nature Biotechnology,* 2021
5. I Haralampiev, S Prisner, ..., N. Friedman, …, A Hermann. “Selective flexible packaging pathways of the segmented genome of influenza A virus” *Nature communications* **11** (1), 1-13, 2020
6. CG de Boer, ED Vaishnav, R Sadeh, EL Abeyta, N Friedman, A Regev. “Deciphering eukaryotic gene-regulatory logic with 100 million random promoters” *Nature Biotechnology* **38** (1), 56-65, 2020
7. M Nitzan, N Karaiskos, N Friedman, N Rajewsky. “Gene expression cartography” *Nature* **576** (7785), 132-137, 2019
8. J Gutin, D Joseph-Strauss, A Sadeh, E Shalom, N Friedman. “Genetic screen of the yeast environmental stress response dynamics uncovers distinct regulatory phases” *Molecular Systems Biology* **15** (8), e8939, 2019

9. A Klein-Brill, D Joseph-Strauss, A Appleboim, N Friedman. “Dynamics of chromatin and transcription during transient depletion of the RSC chromatin remodeling complex” *Cell Reports* **26** (1), 279-292. e5, 2019

MSc and PhD and Postdoc students that graduated:

Phd:

1. Jenia Gutin, currently CTO at Senseera Inc
2. Alon Chappleboim, about to start a postdoc at Harvard

Msc:

1. Matan Lotem
2. Ela Fallik

APOBEC3G IS A RADIO-PROTECTIVE AGENT THAT RESCUES HUMAN CULTURED CELLS AND MICE FROM RADIATION-INDUCED DAMAGE

Moshe Kotler

Lay language summary

Cytosine deaminases AID/APOBEC proteins act as potent nucleic-acid editors, playing important roles in innate and adaptive immunity. However, the mutagenic effects of some of these proteins compromise genomic integrity and may promote tumorigenesis. Human APOBEC3G (A3G), in addition to its role in innate immunity, promotes double-strand breaks (DSBs) repair *in vitro* and *in vivo*. Transgenic mice expressing human A3G successfully survived lethal irradiation, whereas wild-type controls quickly succumbed to radiation syndrome. We discovered the mechanism by which A3G protein penetrates the nuclei where it repairs DSBs induced by radiation. Importantly, we found that A3G not only accelerates break repair but also promotes deamination-dependent error-free rejoining. These findings have two implications: (i) strategies aimed at inhibiting A3G may improve the efficacy of genotoxic therapies used to cure malignant tumors; and (ii) enhancing A3G activity may reduce acute radiation syndrome in individuals exposed to ionizing radiation.

Publications (2019 – 2022)

1. Aravind Ramanathana, A., Weintraubb, M., Orlovetskiea, N., Serruyaa,R., Mania, D., Marcua , M., Stepenskyc , P., Weisblumd , Y., Djiand, E., Shaage, A,. Revel-Vilkf, S., Fried, I., **Kotler, M**., Rouvinskia, A., Wolfe, Elpelegh,I., and Jarrousa, N. A mutation in POLR3E impairs antiviral immune response and RNA polymerase III PNAS, 117: 22113-22121 (2020). https://doi.org/10.1073/pnas.2009947117
2. Botvinnik, A., Shivam, P., Smith, Y., Sharma, G., Olshevsky, U., Moshel, O., Manevitch, Z., Climent, N., Oliva, H., Britan-Rosich, E. and **Kolter, M**. APOBEC3G rescues cells from the deleterious effects of DNA damage. FEBS J. 288 (20): 6063-6077 (2021) doi:10.1111/febs.16025
3. Yelena Britan-Rosich, Jing Ma, Eran Kotler, Faizan Hassan, Alexander Botvinnik, Yoav Smith, Ofra Moshel, Abed Nasereddin, Gunjan Sharma, Eli Pikarsky, Susan Ross* and Moshe Kotler. APOBEC3G protects the genome of human cultured cells and mice from radiation-induced damage. FEBS J. 2022 (under revision).

REGULATORY SPLICING OF IMMUNE CHECKPOINTS AND NEW APPROACHES TO IMMUNOTHERAPY

Michal Lotem

Lay language summary

Alternative splicing is a post-transcriptional process that results in multiple proteins (isoforms) produced from the same gene. This mechanism plays a vital role in the normal function of human cells, and its dysregulation can lead to many severe diseases. We have shown that in a checkpoint molecule termed SLAMF6, as a result of alternative splicing, one isoform leads to inhibition while the other leads to activation of lymphocytes. We are now focusing our efforts on elucidating this regulatory mechanism and exploiting it to develop novel immunotherapies.

After a long process, an exciting advance last year was launching a Phase I clinical trial of adoptive cell therapy using T lymphocytes from the patient engineered to express an antigen termed NY-ESO-1, which is present in many cancers. The cells are then reinjected to the patient. After approval by the Ministry of Health, we started last month and successfully treated two patients.

With eyes to the future: The consortium project “RNA Processing For Anti-Cancer Immunotherapy,” which I coordinate, has been approved for funding by HORIZON-HLTH-2021 from the European Commission. Twelve scientific entities will research next-generation advanced therapies to treat highly prevalent and high-burden diseases with unmet medical needs.

Publications since 2016:

1. Weinstein-Marom, H, Pato, A, Levin, N, Susid, K, Margalit, A, Peretz, T, **Lotem M**, and Gross, G. Membrane-attached cytokines expressed by mRNA electroporation act as potent T cell adjuvants. J Immunother. 2016 Feb-Mar;39(2):60-70
2. Moshe Sade-Feldman, Julia Kanterman, Amijai Saragovi, Hani Steinberg, **Michal Lotem** & Michal Baniyash*. Clinical significance of circulating CD33+CD11b+HLA-DR- myeloid cells in Stage IV melanoma patients treated with ipilimumab. Clin Cancer Res, 2016 Dec 1;22(23):5661-5672
3. **Lotem M**, Merims S, Frank S; Hamburger T; Nissan A; Kadouri L; Cohen J; Straussman R; Eisenberg G; Frankenburg S; Peretz T. Autologous melanoma vaccine for macroscopic stage III disease: adjuvant role, biomarkers and improved response to CTLA-4 blockade. J Immunol Res. 2016;2016:8121985
4. Engelstein R, Merims S, Eisenberg G, Cohen JE, Frank S, Hamburger T, Frankenburg S, Ron I, Isacson R, Grenader T, Steinberg H, Cohen CJ, Peretz T, **Lotem M**. Immune monitoring of patients treated with a whole-cell melanoma vaccine engineered to express 4-1BBL. J Immunother. 2016 Oct;39(8):321-8.
5. Cohen JE, Merims S, Frank S, Engelstein R, Peretz T, **Lotem M**. Adoptive cell therapy: past, present and future. Immunotherapy. 2017 Jan;9(2):183-196.
6. Levin N, Pato A, Cafri G, Eisenberg G, Peretz T, Margalit A, **Lotem M**, Gross G. Spontaneous Activation of Antigen-presenting Cells by Genes Encoding Truncated Homo-Oligomerizing Derivatives of CD40. J Immunother. 2017 Feb/Mar;40(2):39-50.
7. Zick A, Peretz T, **Lotem M**, Hubert A, Katz D, Temper M, Rottenberg Y, Uziely B, Nechushtan H, Meirovitz A, Sonnenblick A, Sapir E, Edelman D, Goldberg Y, Lossos A, Rosenberg S, Fried I, Finklstein R, Pikarsky E, Goldshmidt H. Treatment inferred from mutations identified using massive parallel sequencing leads to clinical benefit in some heavily pretreated cancer patients. Medicine (Baltimore). 2017 May;96(20):e6931
8. Senses KM, Ghasemi M, Akbar MW, Isbilen M, Fallacara AL, Frankenburg S, Schenone S, **Lotem M**, Botta M, Gure AO. Phenotype-based variation as a biomarker of sensitivity to molecularly targeted therapy in melanoma. Medchemcomm. 2017 Jan 1;8(1):88-95
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10. Jacquelot N, Roberti MP, Enot DP, Rusakiewicz S, Ternès N, Jegou S, Woods DM, Sodré AL, Hansen M, Meirow Y, Sade-Feldman M, Burra A, Kwek SS, Flament C, Messaoudene M, Duong CPM, Chen L, Kwon BS, Anderson AC, Kuchroo VK, Weide B, Aubin F, Borg C, Dalle S, Beatrix O, Ayyoub M, Balme B, Tomasic G, Di Giacomo AM, Maio M, Schadendorf D, Melero I, Dréno B, Khammari A, Dummer R, Levesque M, Koguchi Y, Fong L, **Lotem M**, Baniyash M, Schmidt H, Svane IM, Kroemer G, Marabelle A, Michiels S, Cavalcanti A, Smyth MJ, Weber JS, Eggermont AM, Zitvogel L. Predictors of responses to immune checkpoint blockade in advanced melanoma. Nat Commun. 2017 Sep 19;8(1):592

11. Fellner A, Makranz C, **Lotem M**, Bokstein F, Taliansky A, Rosenberg S, Blumenthal BT, Mandel J, Fichman S, Kogan E, Steiner I, Siegal T, Lossos A, Yust-Katz S. Neurologic complications of immune checkpoint inhibitors. Journal of Neuro-Oncology January 2018

12. Eisenberg G, Engelstein R, Geiger A, Hajaj E, Merims S, Frankenburg S, Uzana R, Rutenberg A, Machlenkin A, Frei G, Peretz T, **Lotem M**. Targeting SLAMF6 receptor induces strong anti-melanoma activity of adoptively transferred T cells. Cancer Immunol Res, 2018 Feb;6(2):127-138.

13. Filippou PS, Ren AH, Korbakis D, Dimitrakopoulos L, Soosaipillai A, Barak V, Frenkel S, Pe'er J, **Lotem M**, Merims S, Molina R, Blasutig I, Bogdanos DP, Diamandis EP. Exploring the potential of mucin 13 (MUC13) as a biomarker for carcinomas and other diseases. Clin Chem Lab Med. 2018 Oct 25;56(11):1945-1953

14. Kalaora S, Wolf Y, Feferman T, Barnea E, Greenstein E, Reshef D, Tirosh I, Reuben A, Patkar S, Levy R, Quinkhardt J, Omokoko T, Qutob N, Golani O, Zhang J, Mao X, Song X, Bernatchez C, Haymaker C, Forget MA, Creasy C, Greenberg P, Carter BW, Cooper ZA, Rosenberg SA, **Lotem M**, Sahin U, Shakhar G, Ruppin E, Wargo JA, Friedman N, Admon A, Samuels Y. Combined Analysis of Antigen Presentation and T-cell Recognition Reveals Restricted Immune Responses in Melanoma. Cancer Discov. 2018 Nov;8(11):1366-1375

15. Levin N, Weinstein-Marom H, Pato A, Itzhaki O, Besser MJ, Eisenberg G, Peretz T, **Lotem M**, Gross G. Potent Activation of Human T Cells by mRNA Encoding Constitutively Active CD40. J Immunol. 2018 Nov 15;201(10):2959-2968

16. Weinstein-Marom H, Levin N, Pato A, Shmuel N, Sharabi-Nov A, Peretz T, Eisenberg G, **Lotem M**, Itzhaki O, Besser MJ, Gross G. Combined Expression of Genetic Adjuvants Via mRNA Electroporation Exerts Multiple Immunostimulatory Effects on Antitumor T Cells. J Immunother. 2019 Feb/Mar;42(2):43-50.

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19. Ascierto PA, Ferrucci PF, Fisher R, Del Vecchio M, Atkinson V, Schmidt H, Schachter J, Queirolo P, Long GV, Di Giacomo AM, Svane IM, **Lotem M**, Bar-Sela G, Couture F, Mookerjee B, Ghori R, Ibrahim N, Moreno BH, Ribas A. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med. 2019 Jun;25(6):941-946.

20. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil CM, **Lotem M**, Larkin JMG, Lorigan P, Neyns B, Blank CU, Petrella TM, Hamid O, Su SC, Krepler C, Ibrahim N, Long GV. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019 Jul 22.

21. Emma Hajaj, Galit Eisenberg, Shiri Klein, Shoshana Frankenburg, Sharon Merims, Inna Ben David, Thomas Eisenhaure, Sarah E. Henrickson, Alexandra-Chloé Villani, Nir Hacohen, Nathalie Abudi, Rinat Abramovich, Jonathan E. Cohen, Tamar Peretz, Andre Veillette, **Michal Lotem**. SLAMF6 is an inhibitory immune checkpoint of anti-tumor CD8 T cells. Elife. 2020 Mar 3;9. pii: e52539. doi: 10.7554/eLife.52539.

22. Reut Hadash-Bengad, Emma Hajaj, Shiri Klein, Sharon Merims, Stephen Frank, Galit Eisenberg, Alexander Yakobson, Marina Orevi, Nadia Caplan, Tamar Peretz, **Michal LotemPI**, Jonathan E. Cohen. Immunotherapy Potentiates the Effect of Chemotherapy in Metastatic Melanoma-A Retrospective Study. Front Oncol. 2020 Feb 14;10:70. doi: 10.3389/fonc.2020.00070. eCollection 2020.

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25. Kucukkaraduman B, Turk C, Fallacara AL, Isbilen M, Senses KM, Ayyildiz ZO, Akbar MW, **Lotem M**, Botta M, Gure AO. Predictive Gene Signature for Pyrazolopyrimidine Derivative c-Src Inhibitor 10a Sensitivity in Melanoma Cells. ACS Med Chem Lett. 2020 Feb 18;11(5):928-932. doi: 10.1021/acsmedchemlett.9b00679

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MSc and PhD and Postdoc students that graduated:

1. Emma Hajaj, MD/PhD program (2016-2019)
2. Anat Geiger, post doctorate (2015-2018)
3. Reut Koren, MsC (2019-2020)
4. Shay Tzaban, MD/PhD program (2019-)
5. Ori Stern, MD/PhD program (2020-)
6. Elad Zisman, MD/PhD Marom (2019-)
7. Liat Zoran, MD/PhD Marom (2019-)
8. Amit Schwarz, MD/PhD Marom (2020-)
9. Reyut Lewis, MSc student (2022-)
10. Emile Abdallah, MsC student (2022-)

NATURAL KILLER CELL INTERACTION WITH CANCER, FUNGI VIRUSES AND BACTERIA

Ofer Mandelboim

Lay language summary

Natural Killer (NK) cells belong to the innate immunity system. They were initially described as cells able to kill cancer cells immediately without any prior activation.

Today we know that NK cells can kill many enemies which include not only cancer cells but also viruses, fungi and bacteria and that NK cells also has a certain type of memory. In the last years we studied the activity of NK cells against all of these enemies. We discovered new mechanisms through which NK cells recognize and kill cancer cells, viruses, fungi and bacteria and based on these discoveries we developed new medicine against cancer. We have 5 new drugs against various types of cancer which are now at various stages of clinical development by a startup company named NectinTx (https://www.nectintx.com/). Our first drug received an NDA approval and Phase I clinical trials are planned to start in August 2022. The trails will be performed at MD Anderson and is funded by the hospital. In addition, we licensed another antibody of us to Cytovia. The company is planning to use this antibody for the recruitment of NK cells to the tumors, especially for the treatment of liver cancer.

Publications (2019 – 2022)

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MSc and PhD students that graduated:

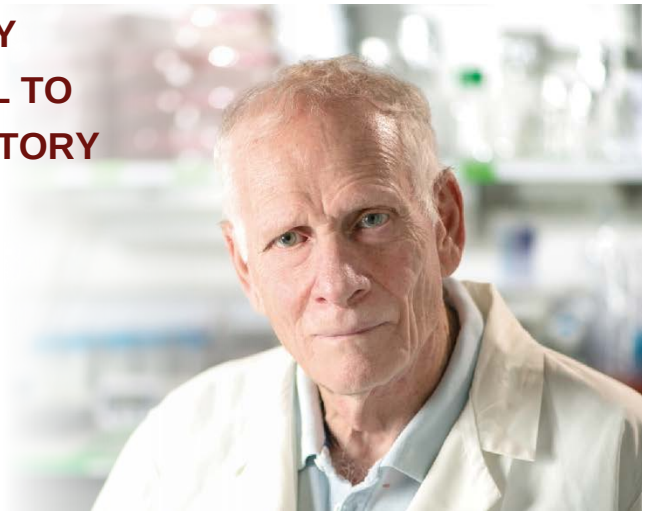
PhD

1. Einat Seidel
2. Liat Dassa
3. Tirtsa Toledano
4. Alex Cohen
5. Orit Berhani
6. Adi Reches
7. Natan Stein

MSc

1. Lea Asulin
2. Afek Elnekave

A NOVEL ANTI-INFLAMMATORY PEPTIDE WITH THE POTENTIAL TO COMBAT CHRONIC INFLAMMATORY DISEASES



David Naor

Lay language summary

The 5-MER peptide (abbreviated 5MP) is a 5 amino acids (Methionine, Threonine, Alanine, Aspartic acid, Valine) synthetic anti-inflammatory peptide. The peptide sequence was derived from a protein (called CD44 variant), that fuels the divisions of inflammatory cells. The peptide shows therapeutic activity in animal models of chronic inflammation diseases (Rheumatoid Arthritis, Crohn's disease/Ulcerative Colitis, Multiple Sclerosis) Interestingly, recently we found, in a preliminary study, inhibition effect, mediated by the peptide, on tumor growth in a mouse model of human breast cancer. The human cancer cells were transplanted in mice lacking immune system to avoid rejection of human cells. All the disease models challenged by the 5MP share a protein called Serum Amyloid A(SAA), that fuel s chronic inflammation and cancer growth in several malignant diseases. We suggest that 5MP neutralizes (or targets) this protein, thus preventing its pathological effects. Chronic inflammation, supported by SAA causes, damage to the joints in Rheumatoid Arthritis, to intestine in Crohn's disease/ Ulcerative Colitis and to brain neurons in Multiple Sclerosis. We found that the binding of 5-MP to SAA interferes with pathological aggregation (generation of huge particles) of SAA. SAA in it aggregated form is responsible for its pathological activity by stimulating release of proteins called pro-inflammatory cytokines, that support also cancer growth. Pro-inflammatory Cytokines at high concentrations (phenomenon known known as "cytokine storm") generate the tissue damage. Therefore, neutralizing SAA by 5MP can suppress the "cytokine storm". SAA is an acute phase reactant, whose concentration in serum rises rapidly in response to acute stimuli such as infection or trauma. An elevated concentration of SAA was identified in sera of patients with multiple autoimmune diseases and more recently, in COVID19 infected patients. In vitro study to investigate the effect of 5-MP on SAA-stimulated human peripheral blood mononuclear cells (PBMCs) from healthy volunteers revealed significant reduction of pro-inflammatory cytokines release from these cells after treatment with the peptide, suggesting a potential tool for controlling "cytokine storm" in patients. When we scrambled the order of the 5 amino acids, the peptide lost its anti-inflammatory inhibition effect. Recently, the peptide 5-MP was first time tested in a human phase 1-study. It was injected into human volunteers at doses far above the required therapeutic dose, but side effect or any biological damage were not detected, making the peptide ready for clinical studies. Finally, we recently received a grant from Ines Mandl Foundation to explore the effect of 5-MP on connective

tissue diseases., including Rheumatic Arthritis, in which joint fibroblasts play a major role in pathology (builting the pannus, a destructive tissue in the joint). Indeed, we found that 5-MP inhibits the release of pro-inflammatory cytokines (for example IL-6) and the growth of Rheumatoid Arthritis joint fibroblasts.

Recent publications

1. **David Naor**, Mary Cowman, Jin Kim, Maayan Hemed-Shaked. MTADV 5-MER PEPTIDE SUPPRESSES IBD PATHOLOGY AND UNVEILS A NEW POTENTIAL TARGET-SERUM AMYLOID A. Gastroenterology Vol. 162, No. 3S(2019).Recent Publications
2. Toshiyuki Murai, Hiroto Kawashim a and **David Naor**. Editorial: Cell-Cell and Cell- Matrix Adhesion in Immunobiology and Cancer. Front. Immunol. 10:3126. doi: 10.3389/fimmu.2019.03126
3. **D. Naor**, M. Hemed-Shaked, M. Cowman, J Kim, J. Armengol, J. Alemany, D.Kanduc, A human-derived 5-mer peptide (MTADV), which restrictively alleviates the pro-inflammatory activity of serum amyloid a (SAA), substantially ameliorates IBD pathology: new potential drug (MTADV) and therapeutic target candidate (SAA) for IBD. Inflamm. Bowel Dis. 6:S3–4 (2020)
4. Maayan Hemed-Shaked , Mary K Cowman , Jin Ryoun Kim , Xiayun Huang , Edward Chau, Haim Ovadia, Keren-Or Amar , Lora Eshkar-Sebban , Michal Melamed , Libat Bar Lev , Eli Kedar , Jordi Armengol , Jorge Alemany , Shaul Beyth, Eli Okon, Darja Kanduc, Sharona Elgavish , Shulamit B Wallach-Dayan , Shmuel Jaffe Cohen , **David Naor**, MTADV 5-MER peptide suppresses chronic inflammations as well as autoimmune pathologies and unveils a new potential target-Serum Amyloid A . J Autoimmun . 2021 Nov; 124:102713

Prizes

1. Award from Johnson & Johnson, Focused Giving Program "In recognition of outstanding research toward the advances of science and technology in health care." 1994
2. Award from Hebrew University of Jerusalem for his “outstanding achievements in research and teaching” 2018
3. Hebrew University Kaye prize for scientific innovation 2021

Grants

1. A pilot grant USA National Multiple Sclerosis Society (NMSS). 2018-2019 ($40,000)
2. Ines Mandl Foundation 2022-2023 ($80,000)
3. Ministry of Regional Cooperation for collaboration with United Arabs Emirates University 2022-2023 (100,000 INS)

Stuff (post docs)

1. Dr. Hassan Elssana
2. Dr. Rawan Atiq

PANCREATIC CANCER DEVELOPMENT AND MODIFICATIONS OF IMMUNE CELLS TO RESTRICT TUMOR GROWTH

Oren Parnas

Lay language summary

Pancreatic cancer is one of the deadliest cancer types with 10% five years survival, and minor improvements in treatments. Our lab investigates how pancreatic cancer develops aiming the reveal: (i) What are the changes that the epithelial cells undergo during the malignant process, (ii) how the different cell types that associate with the pancreas contribute to the malignant process, (iii) how the immunosuppressive tumor microenvironment is formed. We have profiled the very early changes in the pancreas at the beginning of tissue transformation and in the last-years investigate key regulators that accelerate the malignancy process and the contribution of inflammation (pancreatitis), one of the major risk factors of pancreatic cancer. We are using mice models and human samples and published human data. Investigating different types of lesions including Pancreatic Intraepithelial Neoplasia (PanINs) and Intraductal Papillary Mucinous Neoplasm (IPMN), we expect that in addition to improving basic understanding of cancer development, we will be able to find new markers for early detection and new treatments. Toward this end, we make a systematic effort to reveal the critical transcription factors that control the transformation of the epithelial cells and the formation of tumors.

The atlas of pancreatic cancer development that we generate reveals potential cellular interactions and signaling that support cancer development, including signals that dampen the immune response. We have recently developed a systematic method that allows the finding of a combination of genes to target to optimize a cellular phenotype. We applied it to modulate innate immune cells and find a combination of genetic perturbations that support the mounting of immune responses against tumors. We are currently implementing this method to improve immune cell function in the hostile environment of pancreatic cancer.

Publications:

1. Placental colonization by Fusobacterium nucleatum is mediated by binding of the Fap2 lectin to placentally displayed Gal-GalNAc. Parhi L, Abed J, Shhadeh A, Alon-Maimon T, Udi S, Ben-Arye SL, Tam J, **Parnas O**, Padler-Karavani V, Goldman-Wohl D, Yagel S, Mandelboim O, Bachrach G. *Cell Rep. 2022 Mar 22;38(12):110537.*
2. An instructive role for Interleukin-7 receptor α in the development of human B-cell precursor leukemia. Geron I, Savino AM, Fishman H, Tal N, Brown J, Turati VA, James C, Sarno J, Hameiri-Grossman M, Lee YN, Rein A, Maniriho H, Birger Y, Zemlyansky A, Muler I, Davis KL, Marcu-Malina V, Mattson N, **Parnas O**, Wagener R, Fischer U, Barata JT, Jamieson CHM, Müschen M, Chen CW, Borkhardt A, Kirsch IR, Nagler A, Enver T, Izraeli S. *Nat Commun. 2022 Feb 3;13(1):659.*
3. Senolytic elimination of Cox2-expressing senescent cells inhibits the growth of premalignant pancreatic lesions. Kolodkin-Gal D, Roitman L, Ovadya Y, Azazmeh N, Assouline B, Schlesinger Y, Kalifa R, Horwitz S, Khalatnik Y, Hochner-Ger A, Imam A, Demma JA, Winter E, Benyamini H, Elgavish S, Khatib AA, Meir K, Atlan K, Pikarsky E, **Parnas O**, Dor Y, Zamir G, Ben-Porath I, Krizhanovsky V. *Gut. 2022 Feb;71(2):345-355.*
4. Targeting the Kaposi's sarcoma-associated herpesvirus genome with the CRISPR-Cas9 platform in latently infected cells. Haddad CO, Kalt I, Shovman Y, Xia L, Schlesinger Y, Sarid R, **Parnas O**. *Virol J. 2021 Mar 17;18(1):56.*
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9. Adamson B, Norman TM, Jost M, Cho MY, Nuñez JK, Chen Y, Villalta JE, Gilbert LA, Horlbeck MA, Hein MY, Pak RA, Gray AN, Gross CA, Dixit A, **Parnas O**, Regev A, Weissman JS. A Multiplexed Single-Cell CRISPR Screening Platform Enables Systematic Dissection of the Unfolded Protein Response. *Cell. 2016 Dec 15;167(7):1867-1882.*
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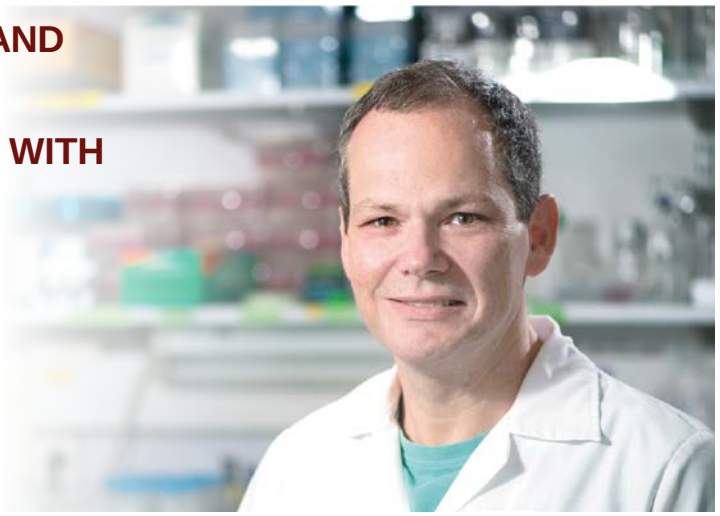
Students that graduated

1. Lei Xia
2. Yehuda Schlesinger
3. Re'ee Yifa
4. Loreano Peters
5. Arielle Jacover

HEPATIC INFLAMMATION AND METABOLISM AND THEIR INTRICATE RELATIONSHIP WITH LIVER CANCER



Eli Pikarsky

Lay language summary

The liver coordinates our body's response to metabolic stress and governs metabolic availability to other organs. In addition, it coordinates multiple immunological functions, and is the organ that harbors the largest numbers of immune cells in our body. Thus the liver is the first organ exposed to all nutrients, drugs, toxins and chemicals that are introduced into the body by ingestion. It is also the place were excess energy is stored in the form of glucose, and upon stress also accumulated fatty acids.

In recent years we are studying a very common form of liver inflammation – formation of immune cell aggregated termed Tertiary Lymphoid Like structures (TLSs). It was known that TLSs form frontal command posts that fight tumors, but we discovered that in specific settings, which are very common in certain diseases such as Hepatitis C inflammation, TLSs can be protumorigenic. We have identified specific forms of T cell dysfunction as well as B cells as mediators of these protumorigenic functions.

Fat accumulation in the liver is caused by excess energy intake, or by deranged ability of the liver to metabolize and export fatty acids. Accumulation of fatty acids in the liver is one of the most common causes of liver inflammation and liver cancer: fatty liver disease. This has become an epidemic, affecting nearly 25% of the population and is now also seen in obese adolescents and even children. Fatty liver disease often progresses to a more severe form denoted steatohepatitis – due to the appearance of an inflammatory component. Yet the mechanisms that induce such progression are not known. We have discovered that the tumor suppressor gene p53, which is highly important in liver cancer, has a "moonlighting job" in the liver – it regulates multiple metabolic pathways. We discovered that a specific region of p53 – which mostly works as a tumor suppressor – is active in the liver, and also other organs including muscle and pancreas, in regulating glucose and fat homeostasis. This could identify drugs which will prevent fatty liver disease progression.

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For full list https://orcid.org/0000-0003-4186-7105

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MSc and PhD students that graduated:

PhD

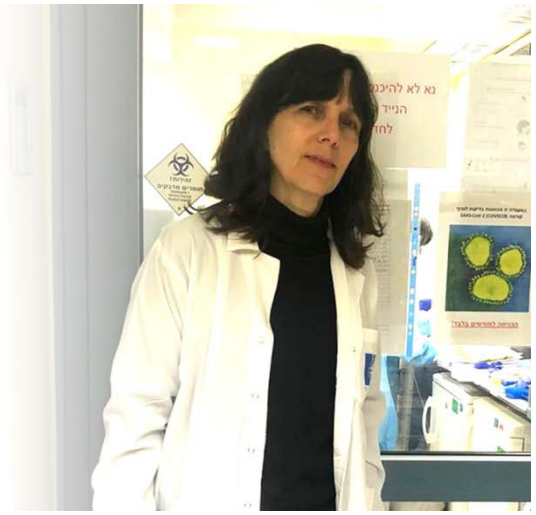
1. Ela Nazirov

2. Yoganathan Ramia Krishnamoorthy

MSc

1. Nasrallah Nasrallah

PREDICTION AND PREVENTION OF CONGENITAL CMV DISEASE: A MULTIFACETED APPROACH FACILITATED THE DISCOVERY OF NOVEL BIOMARKERS WHICH PREDICT THE SEVERITY OF CONGENITAL CMV INFECTION



Establishment of a new SARS-CoV-2 research lab and high-throughput COVID-19 PCR and antibody testing facility

Optimizing maternal immunization: new insights on transplacental antibody transfer define vaccination strategies to protect both the mother and the neonate

Dana Wolf

Lay language summary

Cytomegalovirus (CMV) is the leading cause of congenital infections, affecting ~1% of all newborns worldwide, and leading to hearing loss, brain anomalies, and a wide range of neurodevelopmental disabilities. Despite the immense health burden associated with CMV there is no vaccine available to prevent the infection, and systematic screening of pregnant women and newborn babies for CMV infection is not officially utilized, mainly due to the lack of early biomarkers of fetal/neonatal disease. The development of biomarkers has been hampered thus far by the lack of biological understanding of the mechanism of congenital CMV brain injury, and by the small numbers of affected pregnancies with known clinical outcome. The latter, stems mainly from the fact that many women diagnosed with CMV infection unfortunately choose to terminate the pregnancy – a decision driven (as we often see in the clinic) by the lack of prognostic biomarkers of disease progression.

As a physician scientist, I employ a multi-faceted translational research approach to facilitate the understanding and prevention of CMV infection and disease. We have established unique *ex vivo* models of CMV infection in native human placental (mother-to-fetus transmission site) and nasal mucosa (initial viral entry site) tissues, maintained as integral 3D multi-cell-type organ cultures. Our studies have uncovered the modes of viral transmission to the mother and the fetus, and revealed new immune response pathways mediating protection and injury of the developing fetus. We have combined these *ex vivo* studies with development and analysis of new antibodies and antiviral drug interventions - conducted within the frame of an EU consortium and in collaboration with leading vaccine companies. On the clinical front - we have developed advanced neonatal screening tools for the early identification of newborns with congenital CMV infection**. More recently, addressing the pressing clinical-diagnostic need, we have discovered novel amniotic fluid biomarkers, which predict the severity of congenital CMV disease with unprecedented accuracy**. This discovery, defined as

“groundbreaking” in the international CMV-2022 conference, will provide pregnant women, parents, and consulting physicians with a long-awaited diagnostic tool which could be employed **to profoundly improve the prognostic assessment of CMV-infected fetuses and newborns and guide personalized decisions and treatment.**

The findings provide insights for further mechanistic studies of inflammatory pathways and treatable targets involved in the progression of CMV-related fetal brain damage.

Since the onset of the COVID-19 pandemic, we have converted into a high-throughput COVID-19 testing facility. We have developed and pioneered a new sample-pooling diagnostic methodology, which has significantly improved testing efficiency and throughput. Following our findings, this approach has been widely adopted in Israel and globally, to enhance continued surveillance, control, and community openings during the continued circulation of SARS-CoV-2. Expanding our interest in the maternal-fetal interface, we have now defined for the first time the kinetics of anti- SARS-CoV-2 antibodies in mothers and infants following maternal immunization and determined the efficiency of transplacental antibody transmission in relation to the timing of antenatal vaccination of pregnant women. The findings have a broad relevance toward developing general strategies for maternal immunization. In parallel, we have developed unique ex vivo models of SARS-C0V-2 infection in human respiratory target tissues, to understand the different severity of newly evolving variants, and evaluate new therapeutic measures against SARS-CoV-2 and other respiratory viruses.

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Students that completed their degree / received prizes

1. Yiska Weisblum- completed her PhD studies. Studied viral transmission in the maternal-fetal interface. Graduated with distinction and received 2 excellence prizes (Hebrew University & Faculty of Medicine).

   Currently – she is a postdoctoral research fellow at the Rockefeller University, NYC.

2. Amnon Berger- received MD/PhD degree – has studied viral infection in the developing fetal brain. Currently he is participating in a distinguished physician- researcher residency program at Harvard.

3. Esther Djian- Completed her PhD studies. Studies new antiviral drugs. She is currently a Post Doctoral student in my lab and the supervisor of the SARS-CoV-2 Diagnostic lab. Received the prestigious Marie Curie Fellowship of the EU.

4. Olesya Vorontsov- completed her MSc degree. She is currently a PhD student in my lab, studying local immune control of human viruses in human target tissues.

5. Ido From completed his PhD studies. Studied and developed new models of viral entry site and reactivation. Currently he heads a major Poultry Health Viral Diagnostic Lab.

THE JAMES SIVARTSEN PRIZE IN PEDIATRIC CANCER RESEARCH

The 11th James Sivartsen Prize in Pediatric Cancer Research was awarded at a special ceremony on July 5, 2022 during the annual Lautenberg Center's retreat at the Botanical Gardens in Jerusalem, attended by researchers and students from the Lautenberg Center.

The James Sivartsen Prize in Pediatric Cancer Research is awarded each year to a Hebrew University graduate student who is doing the most innovative work with application to the field of pediatric cancer research.

The Densen Family from Summit, New Jersey, longstanding supporters of the Lautenberg Research Center, established the prize in honor of their friend James Sivartsen who passed away in August 2003 at the age of 20, after a valiant struggle with rhabdomyosarcoma.

This year's recipient was Batya Isaacson. During her PhD in the lab of Professor Ofer Mandelboim, Batya published 3 research papers and 2 scientific reviews, studying Urinary Tract Infection biology and treatment modalities.