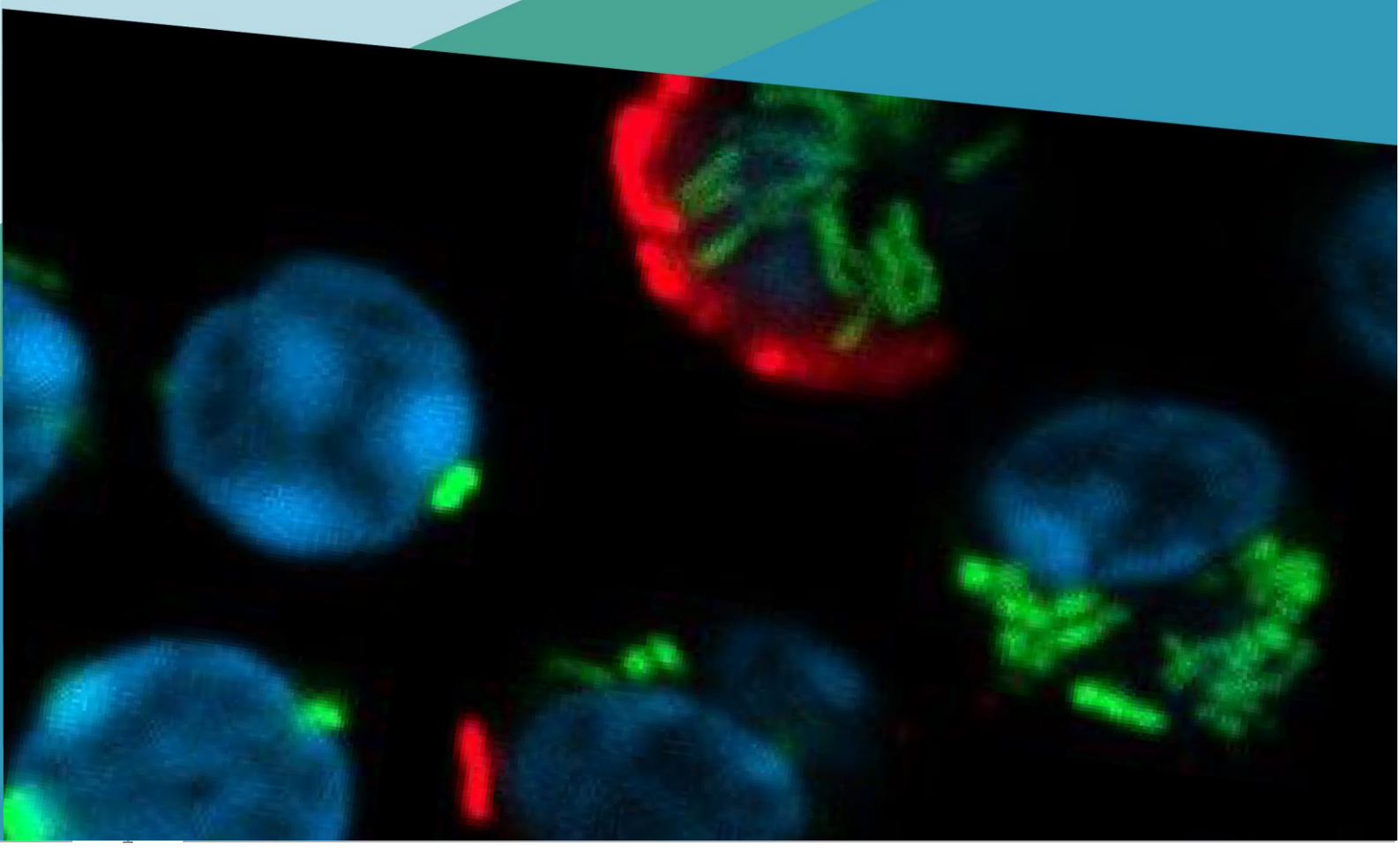
האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

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 2020



Dear friends and supporters,

2020 was challenging anywhere, not sparing the Lautenberg Research Center. The corona pandemic hit us on February and we had to adapt to a different way of living and doing science. Nevertheless, research at the LRC has not stopped here even for an hour. On the contrary, our student and staff realized they must continue working on their projects by all means and additionally, volunteered in many ways to combat the pandemic. We gave a hand in building the coronavirus testing system at the Medical School and Hadassah Medical Center, took a major part in running the tests and many of the LRC groups proposed and carried out studies aiming to fight the disease, from better diagnosis to developing COVID-19 therapeutics. You may read about some of these activities in the group reports. All this was done under the harsh work limitations of the pandemic. Students walked or cycled long hours to get to work with no public transportation, adapted their lab schedule to two-three shifts, both day and night, and with all that, did their best to avoid unnecessary contacts, both at home and at work to escape the disease and home isolation due to sick people contacts. In fact, only a handful of LRC members contracted the disease, or had to leave work for isolation.

Despite of the pandemic challenge, we had a very productive academic year in 2020. **17** new students started working this year at the LRC and the overall student number mounted to **84**. **45** LRC publications appeared during this year, in highly rated scientific journals, including *Nature, Nature Communication, eLife* and *PNAS*. Two LRC members won the most prestigious and rewarding ERC grants this year, turning us to the most successful department in Israel and perhaps in Europe in winning ERC grants - three quarters of all our members have or recently had it. Likewise, all LRC members held this year Israel Science Foundation grants, the premier Israeli research grants. Two members of the LRC won top Israeli prizes, The Rappaport Award for Excellence in Biomedical Research and the Art Science and Culture EMET prize by the PM of Israel. One member was elected to the Israel Young Academy, the most prestigious organization of young scientists in Israel. LRC is proud not only for its academic achievements, but also for contribution to cancer therapy and two new medicines developed at our Center, one for refractory AML and the other for immunotherapy of cancer, have already, or will soon reach clinical studies. The AML experimental drug is already being tested in three leading cancer centers in the US.

With the help our devoted American friends, primarily Michael Kurtz and Derek Alpert from Concern Foundation, we have secured this year outstanding funds for the expansion of the Lautenberg Center venue. This will allow us to recruit 3 new faculty members in a new 500 sqm wing of the Center, to be built in a floor above us. A floor program has already been designed and the architectural and engineering plans will soon follow. We are highly grateful to Michael and Derek for the immense effort they did in raising the needed construction funds in nearly no time and to Moria Sapir, our devoted LRC administrating manager for mobilizing our expansion project.

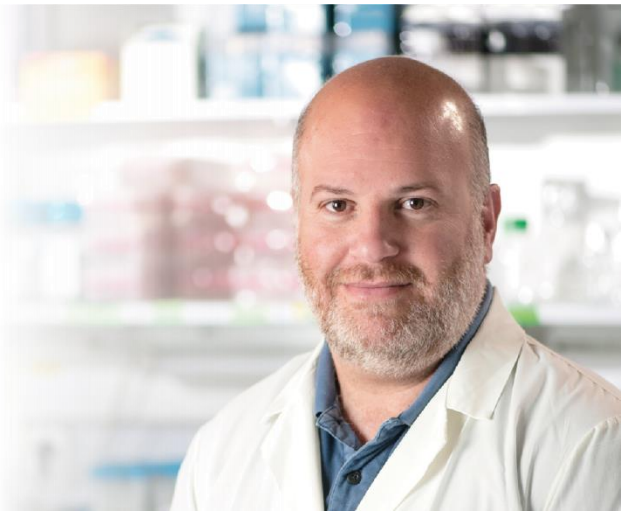
Based on the Center achievements last year, despite the pandemic difficulties, we trust that 2021, even upon on-going health challenges, will be at least as productive and rewarding as 2020.

Yinon Ben-Neriah

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 other metabolic diseases (type 2 diabetes) and neurological disorders (epilepsy) has been also a 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 (2017 – 2020):

1. Gaudio, E., Paduano, F., Pinton, S., D'Agostino, S., Rocca, R., Costa, G., Ngankeu, A., **Aqeilan, R.I**., Croce, C. M., Bertoni, F., Alcaro, S., and Trapasso, F. (2017) TCL1A interacts with TP63 and enhances the survival of Raji Burkitt lymphoma cell line. Br J Haematol
2. Khawaled, S., and **Aqeilan, R.I**. (2017) RUNX1, a new regulator of EMT in breast cancer. Oncotarget 8, 17407-17408
3. Trapasso, F., Pichiorri, F., Gaspari, M., Palumbo, T., **Aqeilan, R.I**., Gaudio, E., Okumura, H., Iuliano, R., Di Leva, G., Fabbri, M., Birk, D. E., Raso, C., Green-Church, K., Spagnoli, L. G., Venuta, S., Huebner, K., and Croce, C. M. (2017) Fhit interaction with ferredoxin reductase triggers generation of reactive oxygen species and apoptosis of cancer cells. J Biol Chem 292, 14279
4. Gershkovitz, M., Caspi, Y., Fainsod-Levi, T., Katz, B., Michaeli, J., Khawaled, S., Lev, S., Polyansky, L., Shaul, M. E., Sionov, R. V., Cohen-Daniel, L., **Aqeilan, R.I.**, Shaul, Y., Mori, Y., Karni, R., Fridlender, Z. G., and Binshtok, A. M., Granot, Z. (2018) TRPM2 mediates neutrophil killing of disseminated tumor cells. Cancer Res 78(10):2680-2690.

5. Peretz, L., Besser, E., Hajbi, R., Casden, N., Ziv, D., Kronenberg, N., Gigi, L. B., Sweetat, S., Khawaled, S., **Aqeilan, R.I.**, and Behar, O. (2018) Combined shRNA over CRISPR/cas9 as a methodology to detect off-target effects and a potential compensatory mechanism. Sci Rep 8(1):93.

6. Abu-Remaileh M, Khalaileh A, Pikarsky E, **Aqeilan R.I.**, WWOX controls hepatic HIF1α to suppress hepatocyte proliferation and neoplasia. Cell Death Dis. 2018 May 1;9(5):511.

7. Ma L, Yang X, Wei R, Ye T, Zhou JK, Wen M, Men R, Li P, Dong B, Liu L, Fu X, Xu H, **Aqeilan R.I.**, Wei YQ, Yang L, Peng Y. MicroRNA-214 promotes hepatic stellate cell activation and liver fibrosis by suppressing Sufu expression. Cell Death Dis. 2018 Jun 18;9(7):718.

8. Gershkovitz M, Fainsod-Levi T, Khawaled S, Shaul ME, Sionov RV, Cohen-Daniel L, **Aqeilan R.I.**, Shaul Y, Fridlender ZG, Granot Z. Microenvironmental Cues Determine Tumor Cell Susceptibility to Neutrophil Cytotoxicity. Cancer Res. 2018 Jul 2.

9. Abdeen SK, Ben-David U, Shweiki A, Maly B, **Aqeilan R.I.**, Somatic loss of WWOX is associated with TP53 perturbation in basal-like breast cancer. Cell Death Dis. 2018 Aug 6;9(8):832.

10. Tanna M, **Aqeilan R.I.**, Modeling WWOX Loss of Function in vivo: What Have We Learned? Front Oncol. 2018 Oct 10;8:420. Review.

11. 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.

12. Abu-Remaileh M., 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.

13. Druck T, Cheung DG, Park D, Trapasso F, Pichiorri F, Gaspari M, Palumbo T, **Aqeilan R.I.**, Gaudio E, Okumura H, Iuliano R, Raso C, Green K, Huebner K, Croce CM. Fhit-Fdxr interaction in the mitochondria: modulation of reactive oxygen species generation and apoptosis in cancer cells. Cell Death Dis. 2019 Feb 15;10(3):147.

14. Maximov VV, Akkawi R, Khawaled S, Salah Z, Jaber L, Barhoum A, Or O, Galasso M, Kurek KC, Yavin E, **Aqeilan R.I.** MiR-16-1-3p and miR-16-2-3p possess strong tumor suppressive and antimetastatic properties in osteosarcoma. Int J Cancer. 2019 Apr 24.

15. Abdeen SK, **Aqeilan R.I.**, Decoding the link between WWOX and p53 in aggressive breast cancer. Cell Cycle. 2019 May 10; 18(11):1177-1186.

16. Chang NS, Lin R, Sze CI, **Aqeilan R.I.** Editorial: WW Domain Proteins in Signaling, Cancer Growth, Neural Diseases, and Metabolic Disorders. Front Oncol. 2019 Aug 2;9:719.

17. Soudah T, Khawaled S, **Aqeilan R.I.**, Yavin E. AntimiR-155 Cyclic Peptide-PNA Conjugate: Synthesis, Cellular Uptake, and Biological Activity. ACS Omega. 2019 Aug 12;4(9):13954-13961.

18. Hazan I, Monin J, Bouwman BAM, Crosetto N, **Aqeilan R.I.** Activation of Oncogenic Super-Enhancers Is Coupled with DNA Repair by RAD51. Cell Rep. 2019 Oct 15;29(3):560-572.e4.

19. Oster S, **Aqeilan R.I.** Mapping the breakome reveals tight regulation on oncogenic super-enhancers. Mol. Cell. Oncology. 2020 Feb 11;7(3):1698933.

20. Khawaled S., Nigita G, Distefano R, Oster S, Suh S-S, Smith Y, Khalaileh A, Peng Y, Croce CM Geiger T, Seewaldt VL, **Aqeilan R.I.** Pleiotropic tumor suppressor functions of WWOX antagonize metastasis. Signal Transduct Target Ther. 2020 Apr 17;5(1):43.

21. Yang X, Ma L, Wei R, Ye T, Zhou J, Wen M, Men R, **Aqeilan R.I.**, 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.

22. Oster S, **Aqeilan R.I.**, Programmed DNA Damage and Physiological DSBs: Mapping, Biological Significance and Perturbations in Disease States. Cells. 2020 Aug 10;9(8):1870.

PhD and MSc students that graduated:

PhD

Suhaib Abdeen, currently a post-doc at Weizmann Institute of Science

Muhannad Abu-Remaileh, currently a post-doc at Dana Farber

Saleh Khawaled, currently a post-doc at MIT

MSc

Sara Oster

Tirza Bidany

Hazem Safadi

Aya Shwiki

COMPLICATIONS ASSOCIATED WITH CHRONIC INFLAMMATION: THE ROLE OF MYELOID DERIVED SUPPRESSOR CELLS (MDSCs).

MDSCs as multi-tasking sensors and orchestrators of divers clinical outcomes

Michal Baniyash

Lay language summary

In pathologies characterized by chronic inflammation altered formation of various blood cells originating in the bone marrow is evident, in association with the accumulation of myeloid derived suppressor cells (MDSCs). MDSCs are heterogenous cells featured by highly immune suppressive activities. These cells are found in sites of inflammation as in various tumors, in inflammatory organs as the intestine, during inflammatory bowel disease (IBD) and the stomach, during Helicobacter Pillory infection. In most cases, when the disease is severe, inflammation is also evident in the periphery. MDSCs have the capacity to impair immune functions of different lymphocytes required for the execution of an optimal immune response and exacerbate the body's inflammatory state. These ensue in a variety of complications as tissue damage, susceptibility to infections and high risk to develop cancer. In the course of our studies, we discovered that MDSCs are diverse and plastic; when reaching a new environment, which exhibits a unique array of pro-inflammatory mediators/growth factors, they can sense and adapt to the altered micro-environment by virtue of acquiring different features that involve changing their cell fate, surface molecules, metabolism and intracellular as well as secreted compounds. For example, we discovered that during chronic inflammation a subpopulation of MDSCs localized in the bone marrow can differentiate to highly active osteoclasts, which are cells that resorb the bone, and lead to inflammatory bone loss and osteoporosis. We also discovered that MDSCs can communicate with bacteria in the damaged intestine during IBD. This results in the enhancement of MDSC suppressive and inflammatory functions, thus supporting the process of colon cancer development. As MDSCs have harmful immune suppressive effects under chronic inflammatory conditions, they are the major obstacles for the success of various anti-cancer treatments based on the immune system. Therefore, major efforts are now gathered in using MDSCs as: 1) Biomarkers for the evaluation of chronic inflammation-induced complications, 2) As predictors of success rates of immune-based therapies, and 3) As targets for treatments aimed at combating them towards achieving recuperated immune responses and thus, improving therapies in various pathologies characterized by chronic inflammation including cancer.

Publications (2016 – 2020):

1. Ish-Shalom, E., Meirow, Y., Sade-Feldman, M., Kanterman, J., Wang, L., Mizrahi, O., Klieger, Y., and **Baniyash, M.** (2016) Impaired SNX9 Expression in Immune Cells during Chronic Inflammation: Prognostic and Diagnostic Implications. J Immunol. 196:156-67.
2. Tarcic, O., Pateras, IS., Cooks, T., Shema, E., Kanterman, J., Ashkenazi, H., Boocholez, H., Hubert, A., Rotkopf, R., **Baniyash, M.**, Pikarsky, E., Gorgoulis, VG., Oren, M. (2016) RNF20 Links Histone H2B Ubiquitylation with Inflammation and Inflammation-Associated Cancer. Cell Rep. 14:1462-76.
3. Sade-Feldman, M., Kanterman, J., Keliger, Y., Ish-Shalom, E., Mizrahi, O., Saragovi, A., Shtainberg, H., Lotem, M., and **Baniyash, M.** (2016) Clinical significance of circulating CD33+CD11b+HLA-DR- myeloid cells in Stage**-**IV melanoma patients treated with ipilimumab. Clin Cancer Res, 65:857-67.
4. Meirow, Y., Vaknin, I. and **Baniyash M.** (2011-2016) Inflammatory response and immunity. Encyclopedia of Cancer. Editors: Manfred Schwab, Springer publication.
5. **Baniyash, M.** (2016) Myeloid derived suppressor cells as intruders and targets: Clinical implications in cancer therapy. Invited review. Cancer Immunol Immunother, 65:857-67.
6. Mizrahi O., Ish Shalom E., **Baniyash M.**, Klieger Y . (2017) Quantitative flow cytometry: Concerns and recommendations in clinic and research. Cytometry B Clin Cytom. Feb 11. doi: 10.1002/cyto.b.21515. [Epub ahead of print].
7. Meirow Y, **Baniyash M.** (2017) Immune biomarkers for chronic inflammation related complications in non-cancerous and cancerous diseases. Cancer Immunol Immunother. 66:1089-1101.
8. 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. 8:592-605.
9. Ben-Meir K, Twaik N, **Baniyash M.** (2018) Plasticity and biological diversity of myeloid derived suppressor cells. Curr Opin Immunol. 51:154-161.

MSc and PhD students that graduated:

PhD
Julia kanterman

Yaron Meirow

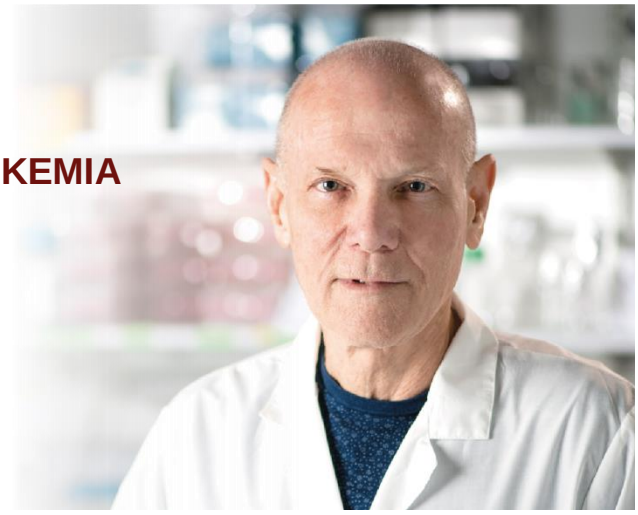
MSc
Kerem Ben-Meir

Nira Twaik-Nakav

Hadas Ashkenazi

Or Reuven

NEW THERAPEUTICS TO COMBAT ACUTE MYELOID LEUKEMIA



Yinon Ben-Neriah

Lay language summary

Acute myeloid leukemia is one of the most aggressive types of cancer and despite the progress made in its treatment lately, the 5-year survival rate for people 20 and older with AML is only about 25% and seldom there is a cure to the disease. 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 experimental drug, which is the first of its kind, received an FDA approval for clinical trial, and a phase 1 trial was initiated this year at the Memorial Sloan Kettering Cancer Center and soon at two other major centers in the US.

Publications (2017 – 2020):

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, 1 October, 586: 133-138, https://doi.org/10.1038/s41586-020-2541-0

PhD students recently graduated:

Upasana Das Adhikari

Audrey Lasry

Waleed Minzel, with distinction and the Hebrew University Viner Prize for best PhD theses (top 3% of all graduates)

Eliran Kadosh, Hebrew University Prize for best PhD theses and the International Birnstiel Award for Doctoral Research in Molecular Life Sciences (one of 6 – worldwide).

Major grants & Awards:

ERC-advanced grant, by the European Research Council

Israel Science Foundation, Center of Excellence

Israel Precision Medicine Partnership grant

The **Emet** Prize for Art, Science and Culture -2019

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, and to find ways to exploit our findings to develop new anti-cancer therapies and to improve anti-viral vaccinations. In the last years we studied how cellular metabolism shapes T cells immunity.

We revealed the detrimental effect of hypoxia on T cells, and points at a new approach for improving viral resistance in patients with respiratory diseases. In addition, we discovered how T cells use cellular metabolism to maturate and to better fight viruses. Finally, we utilized our deep understanding in T cell metabolism to generate metabolically superior T cells to improve efficacy of Adoptive Cell Transfer Therapy (ACT) against solid tumors. 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 transition T cell ACT from merely a promising treatment to an effective one. Based on these findings we issued a patent.

Publications (2017 – 2020):

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2. 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 Jun; 200(3):215-227. doi: 10.1111/cei.13432. PMID: 32201938

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5. 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 Mar;38(11):1920-1935. doi: 10.1038/s41388-018-0555-y. PMID: 30390074.
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7. Schlafen2 mutation in mice causes an osteopetrotic phenotype due to a decrease in the number of osteoclast progenitors. Omar I, Guterman-Ram G, Rahat D, Tabach Y**, Berger M**., Levaot N. Sci Rep. 2018 Aug 29;8(1):13005. doi: 10.1038/s41598-018-31428-z. PMID: 30158544.
8. Post-transcriptional 3´-UTR cleavage of mRNA transcripts generates thousands of stable uncapped autonomous RNA fragments. Malka Y, Steiman-Shimony A, Rosenthal E, Argaman L, Cohen-Daniel L, Arbib E, Margalit H, Kaplan T, **Berger M.** Nat Commun. 2017 Dec 11;8(1):2029. doi: 10.1038/s41467-017-02099-7. PMID: 29229900.
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10. Slfn2 mutation-induced loss of T-cell quiescence leads to elevated de novo sterol synthesis. Omar I, Rom O, Aviram M, Cohen-Daniel L, Gebre AK, Parks JS, **Berger M.** Immunology. 2017 Nov;152(3):484-493. doi: 10.1111/imm.12785. PMID: 28672048.
11. A novel spontaneous mutation in the TAP2 gene unravels its role in macrophage survival. Lapenna A, Omar I, **Berger M.** Immunology. 2017 Apr;150(4):432-443. doi: 10.1111/imm.12694. PMID: 27861817.

MSc, PhD and Postdoc students that graduated:

Postdoc
Yuval Malka

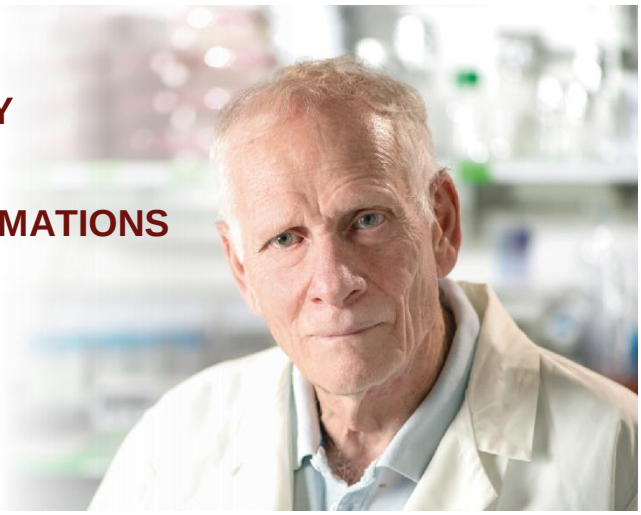
PhD
Ibrahim Omar

Amijai Saragovi

MSc
Miriam Kuchersky

A NOVEL ANTI-INFLAMMATORY PEPTIDE WITH A POTENTIAL TO COMBAT CHRONIC INFLAMMATIONS

David Naor



Lay language summary

We present here a 5-MER peptide (abbreviated 5MP) ,a 5 amino acid synthetic peptide MTADV (Methionine, Threonine, Alanine, Aspartic acid, Valine), which shows therapeutic activity in animal models of chronic inflammation diseases (Rheumatoid Arthritis, Crohn's disease/ Ulcerative Colitis, Multiple Sclerosis).The 5 amino acids sequence of 5MP is Identical to a specific MTADV sequence in the human CD44 variant found in synovial fluid cells from joints of rheumatoid arthritis (RA) patients. The 5-MER peptide neutralizes the supportive activity of Serum Amyloid A (SAA), which accelerates chronic inflammations. 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 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. 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. An *ex-vivo* 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 . **Relevance to COVID 19.** This data suggests that 5-MP may also have a therapeutic role not only in chronic inflammations ,including autoimmune diseases ,but also in the treatment of patients with severe COVID-19 infection, characterized by significantly high levels of SAA and pro-inflammatory cytokines , which are the main cause for the "cytokine storm" damage (for instance in lungs) in these patients. Therefore 5MP displays a potential therapeutic effect in COVID 19 patients.

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4. **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. 26:S3–4 ,2020

Staff (post docs):

Dr. Ma’ayan Hemed-Shaked

Dr. Libat Bar Lev

PROFILING PANCREATIC PREINVASIVE LESIONS AND CANCER TO EXPLORE TUMOR DEVELOPMENT AND FIND NEW WAYS TO TREAT CANCER

Oren Parnas

Lay language summary

Pancreatic cancer is one of the most aggressive cancers, with five-year survival rates of less than 10%. Two related phenomena contribute to the high mortality: late detection and lack of efficient treatments. In more than 80% of the cases, pancreatic cancer is diagnosed after cancer has already spread to other parts of the body. In addition, the primary tumor is stiff, difficult to resect, and irresponsive to chemotherapy and other treatments.

Although pancreatic cancer is generally diagnosed at late stages, microscopic changes and tissue abnormality can be detected years before the tumor is formed. The lesions that develop over many years can theoretically, be used to estimate the risk of developing cancer. To find new molecules that can assist in diagnosis, we performed an extensive single-cell expression profile of lesion development over time and recently published the lab's first paper in Nature Communications (2020 Sep 9;11(1):4516). In this work, we describe surprising cellular heterogeneity in the early pancreatic lesions. We are currently continuing to investigate how the lesions' different cell types and states are formed, which of the cell types and states can develop into cancer, and how the other cell types in the tissue contribute to the malignant process.

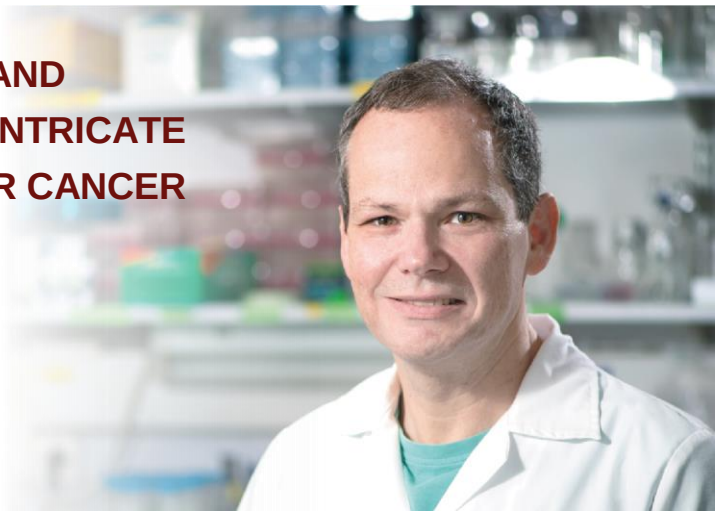
In a parallel effort, we aim to find new treatments for pancreatic cancer. We take advantage of the findings that immune cells can be detected in early lesions and tumors and that various treatments that induce the immune system to fight cancer, restrict tumor growth of other types of cancer. Toward this end, we perform CRISPR/CAS genetic screens to find new genes that play a role in immune suppression, one of the major mechanisms that reduce the effectiveness of immune cells. We found targeted genes that can induce immune activation and we are currently investigating the mechanism and function of these genes and in addition, explore the effect of targeted immune cells on the growth of different cancer types including pancreatic cancer. The new methodology that we are establishing is expected to reveal how cancer manipulates the immune system and how the negative effects can be reversed.

The Parnas lab includes seven Ph.D. students, three master students, a post-doc, and a lab manager. We received several grants in the last year: ICRF, MOST-DKFZ, CRISPRIL, and the Israel Precision Medicine Program. **Together with the generous support of Concern Foundation**, the Parnas lab can develop and apply cutting edge genetic and genomic research, that should lead to new discoveries in cancer and immunology.

Publications (2020):

Schlesinger Y, Yosefov-Levi O, Kolodkin-Gal D, Granit RZ, Peters L, Kalifa R, Xia L, Nasereddin A, Shiff I, Amran O, Nevo Y, Elgavish S, Atlan K, Zamir G, **Parnas O**. Single-cell transcriptomes of pancreatic preinvasive lesions and cancer reveal acinar metaplastic cells' heterogeneity. *Nature Communication. 2020 Sep 9;11(1):4516.*

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 Ectopic Lymphoid Like structures (ELSs). It was known that ELSs can for 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, ELSs can be protumorigenic. We are now deciphering the mechanisms that underlie the transition from anti-tumor to pro-tumor immunity.

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 homostasis. 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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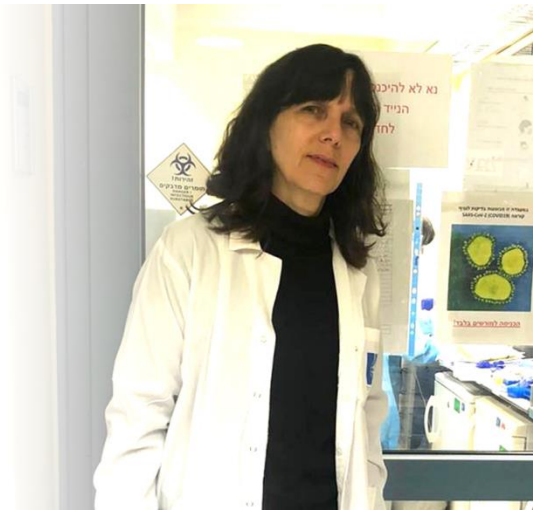
MSc and PhD students that graduated:

PhD
David Knigin

Ela Nazirov

MSc
Youssef Mansour (cum Laude)

PREDICTION AND PREVENTION OF CONGENITAL CMV DISEASE: A MULTIFACETED APPROACH



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

Dana Wolf

Lay language summary

Human cytomegalovirus (HCMV) 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. HCMV is also a major cause of severe disease and death in the growing population of immunocompromised individuals, including cancer patients and transplant recipients. Despite the immense health burden associated with HCMV there is no vaccine available to prevent the infection, and the use of currently-approved antiviral drugs has been limited by toxicity and drug resistance. Our current understanding of the mechanisms modulating HCMV immune protection has remained poor, largely due to the lack of relevant animal models for this human-specific virus – thus hampering vaccine and drug development.

As a physician scientist, I employ a multi-faceted translational research approach to facilitate the understanding and prevention of HCMV infection and disease. We have established unique *ex vivo* models of HCMV infection in native human placental (maternal-fetal transmission site) and nasal mucosa (viral entry site) tissues maintained as integral 3D multi-cell-type organ cultures. Our studies have uncovered the modes of viral infection and spread between individuals and from the mother to the fetus, and revealed new innate immune response pathways by which the human nasal mucosa and placenta protect the mother and the fetus from the virus. We are currently combining 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. Finally- on the clinical front- we have developed advanced neonatal screening tools for the early identification of newborns with congenital HCMV infection.

In the last year, we have converted into a high-throughput COVID-19 testing facility. We have developed and pioneered a new sample-pooling method, which has improved testing efficiency, pace and throughput. In a recent big-data analysis of our findings, we observed pooling efficiency and sensitivity that have exceeded theoretical predictions and support the use of pooling for large-scale SARS-CoV-2 testing, to enhance continued surveillance, control, and community re-openings. In parallel, we have developed unique ex vivo models of SARS-C0V-2 infection in human respiratory target tissues, to evaluate new therapeutic and preventive measures against SARS-CoV-2.

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students that graduated / 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.

NATURAL KILLER CELL FUNCTION IN PREGNANCY AND CANCER, AND DURING INFECTION WITH 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 established a new startup company named NectinTx which develops new, antibody-based treatment for cancer and another startup company named BacoCure which develops bacteria-based therapy for cancer. In addition, we studied the function of NK cells during pregnancy. One of our major last discovery was that NK cells in the uterus, remember first pregnancy and function better in subsequent pregnancies to support baby growth.

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Awards:

The Rappaport Award for BioMecical Rsearch

MSc and PhD students that graduated:

students that graduated:

PhD

Ariella Glasner

Yotam Bar-On

Einat Seidel

Natan Stein

Dominik Schmiedel

Pinhas Tsukerman

Adi Reches

Orit Berhani

SLAMF6, A NOVEL TARGET FOR CANCER IMMUNOTHERAPY AND A REPRESENTATIVE CASE OF REGULATORY SPLICING OF IMMUNE CHECKPOINTS

Michal Lotem

Lay language summary

SLAMF6 is a homotypic receptor of the Ig-superfamily whose exact role in immune modulation has remained elusive. Its constitutive expression on resting and activated T cells precludes it from being a *bona fide* exhaustion marker.

We attribute a negative effect to this receptor, which takes effect in various situations, including high-density cellular environments and vigorous activation of lymphocytes, which then revert into a suppressive state to terminate the immune response.

Since this role is undesirable in the cancer situation, we have generated mice that reproduce a cancer-specific model to test the part of SLAMF6 in the anti-melanoma response.

We generated mice donors for T cells lacking SLAMF6, which recognize melanoma. Lymphocytes from these mice were strong tumor killers. In contrast to the transient responses achieved with the intact receptor, the adoptive transfer of SLAMF6-deficient, melanoma-specific T cells into melanoma-bearing mice resulted in lasting tumor regression. These results support the notion that SLAMF6 is an inhibitory immune receptor whose absence enables powerful anti-tumor CD8 T cells to eradicate tumors.

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 SLAMF6 has two main isoforms. The longer isoform, which is the dominant one in natural conditions, leads to the inhibition of T lymphocytes, while the shorter isoform leads to their activation. Our ongoing research focuses on the molecular aspects of this two-sided phenomenon to elucidate the bifunctional capacity of SLAMF6 and PD-1. Another exciting project is **analyzing and perturbing the molecular splicing landscape** of in-vitro activated T-lymphocytes to link the splicing program with the function of T-lymphocytes. These analyses are critical to elucidate the role of alternative splicing in T-cell regulation and develop new immunotherapy drugs.

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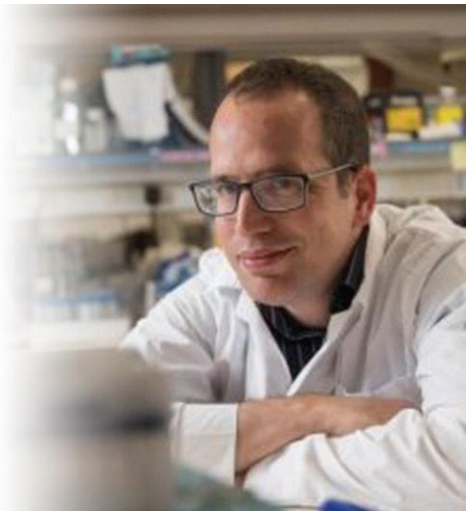
EPIGENETIC AND TOPOLOGICAL DYSREGULATION AS A DRIVING FORCE IN CANCER



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.

I joined the Lautenberg Center for Immunology and Cancer Research at the Hebrew University in early 2019, after a postdoctoral research at the Harvard Medical School, Massachusetts General Hospital and Broad Institute. In my postdoctoral research I focused on epigenetic changes that drive cancer. I revealed that aberrant DNA methylation perturbs chromosomal structure in brain tumors (Flavahan*, Drier* et al. Nature 2016) and gastrointestinal stromal tumors (Flavahan*, Drier* et al. Nature 2019). In these tumors, accumulation of DNA methylation at the boundary between two topological domains inhibited CTCF binding and disrupted the insulation between the domains. This led to aberrant interactions between an oncogene in one domain and enhancers in the other, leading to over-expression of the oncogene. This groundbreaking model links metabolic, epigenetic and topological alterations and demonstrates how they can drive cancer.

Based on these breakthroughs, I am establishing a laboratory and team at the Lautenberg Center to systematically uncover 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 gastric cancer, melanoma, liver cancers and brain tumors.

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 other 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 in collaboration with Dr. Oren Parnas.

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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.