



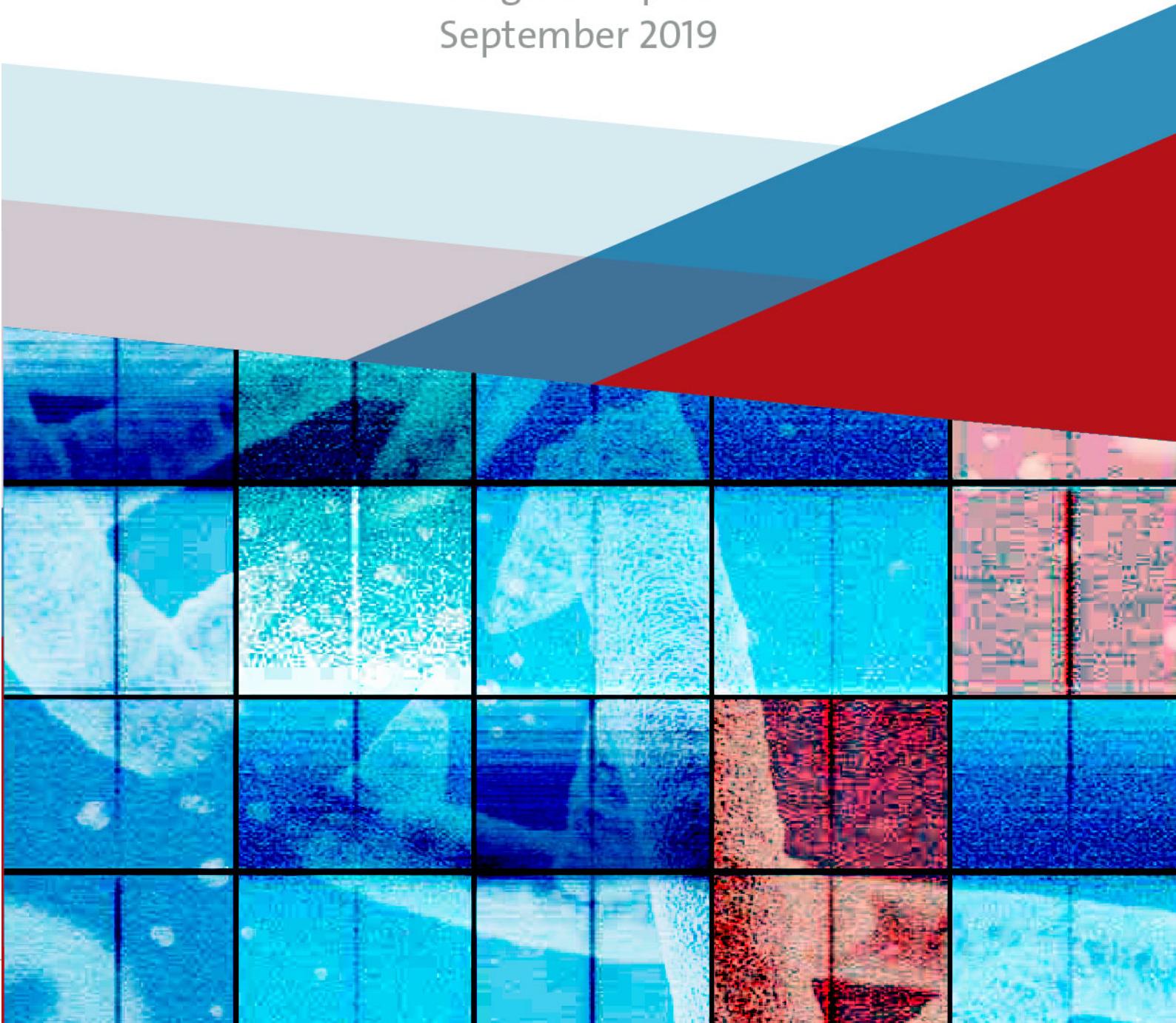
האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM



מרכז לאותנברג לאימונולוגיה ומחקר הסרטן,
מבדות קונצראן
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 2019



This scientific report summarizes one of the best years of our center, if not the best one.

In February, following 50 years in which we were located in an old pharmacy building, we moved to a new brand facility. In our new location, the offices of all the PIs are located next to one another, enabling close interactions. Our new labs are modern and fully equipped. We have a new and large student room where students from different labs can comfortably eat and socialize with one another. Furthermore, we now have a departmental equipment room which contains numerous state-of-the-art instruments. This move was made possible because of our American friends and I would like to take this opportunity and give special thanks to two of them: Michael Kurtz and Derek Alpert from the Concern Foundation. We celebrated our move by holding a scientific symposium where former members of our center, which are now independent researchers in various universities in Israel and abroad, gave scientific talks. This celebratory day ended with a gala dinner which included students and researchers from the center, alumni of the center, friends of the center, our American friends, and the president of the Hebrew University: Prof. Asher Cohen.

Memories and photos of this event and others can be found at our new website:
<https://lautenbergcenter.org/>

I would like to thank Moriah Sapir who is responsible for almost everything mentioned above: our move, the symposium event, the new site, new logo and all other improvements she made in our new facility.

The format of this report was also changed. We now provide a shorter, more comprehensive report which mainly contains lay English summary of each of the researchers' achievements. Additional details can be found at our new website:
<https://lautenbergcenter.org/>.

Our center combines basic and applicable research performed on two major areas: tumor biology and immunology. We are especially proud this year because two anti-cancer medicines that were developed by two members of our center are currently in advanced stages of development. One medicine, aimed at treatment of solid cancer was licensed to Northern Biologics and another medicine for the treatment of AML is in the process of FDA approval.

Additional achievements can be seen in each individual report.

Best wishes,

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 includes 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 it impacts cancer-related genes, both oncogenes and tumor suppressors, and the carcinogenesis process. The link between some of these genes and metabolic diseases (type 2 diabetes) and neuropathies (epilepsy) has been also a focus of our lab in recent years. The ultimate goal of our research is hence to discover the genes (coding and non-coding) and to elucidate the pathways that represent targets for the development of rational, specific and effective therapeutic approaches.

Publications (2016 – 2019):

1. Abu-Odeh, M., Hereema, N. A., and **Aqeilan, R. I.** (2016) WWOX modulates the ATR-mediated DNA damage checkpoint response. *Oncotarget* 7, 4344-4355
2. Del Mare, S., Husanie, H., Iancu, O., Abu-Odeh, M., Evangelou, K., Lovat, F., Volinia, S., Gordon, J., Amir, G., Stein, J., Stein, G. S., Croce, C. M., Gorgoulis, V., Lian, J. B., and **Aqeilan, R. I.** (2016) WWOX and p53 Dysregulation Synergize to Drive the Development of Osteosarcoma. *Cancer Res* 76, 6107-6117
3. Gaudio, E., Paduano, F., Ngankeu, A., Ortuso, F., Lovat, F., Pinton, S., D'Agostino, S., Zanesi, N., **Aqeilan, R. I.**, Campiglia, P., Novellino, E., Alcaro, S., Croce, C. M., and Trapasso, F. (2016) A Fhit-mimetic peptide suppresses annexin A4-mediated chemoresistance to paclitaxel in lung cancer cells. *Oncotarget* 7, 29927-29936
4. Hazan, I., Hofmann, T. G., and **Aqeilan, R. I.** (2016) Tumor Suppressor Genes within Common Fragile Sites Are Active Players in the DNA Damage Response. *PLoS Genet* 12, e1006436
5. Maximov, V. V., and **Aqeilan, R. I.** (2016) Genetic factors conferring metastasis in osteosarcoma. *Future Oncol* 12, 1623-1644
6. Pichiorri, F., Suh, S. S., Rocci, A., De Luca, L., Taccioli, C., Santhanam, R., Zhou, W., Benson, D. M., Jr., Hofmainster, C., Alder, H., Garofalo, M., Di Leva, G., Volinia, S., Lin, H. J., Perrotti, D., Kuehl, M., **Aqeilan, R. I.**, Palumbo, A., and Croce, C. M. (2016) Downregulation of p53-inducible microRNAs 192, 194, and 215 Impairs the p53/MDM2 Autoregulatory Loop in Multiple Myeloma Development. *Cancer Cell* 30, 349-351
7. 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*
8. Khawaled, S., and **Aqeilan, R. I.** (2017) RUNX1, a new regulator of EMT in breast cancer. *Oncotarget* 8, 17407-17408
9. 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
10. 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.

11. 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.
12. 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.
13. 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.
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15. 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.
16. Tanna M, **Aqeilan, R. I.**, Modeling WWOX Loss of Function in vivo: What Have We Learned? *Front Oncol.* 2018 Oct 10;8:420. Review.
17. 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.
18. 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.
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21. 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.
22. 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.

23. 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.
24. 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.

MSc and PhD students that graduated:

PhD

Saleh Khawaled
Muhamnad Abu-Remaileh
Suhaib Abdeen

MSc

Sara Oster
Tirza Bidany
Hazem Safadi
Aya Shwiki

THE INTERRELATION BETWEEN GUT MICROBIOTA AND IMMUNOSUPPRESSIVE ENVIRONMENT IN INTESTINAL CHRONIC INFLAMMATORY DISORDERS

Michal Baniyash



Lay language summary

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing disorders associated with uncontrolled inflammation within the gastrointestinal tract and if persist will develop to colorectal cancer (CRC). These diseases are associated with a disrupted intestinal homeostasis and modifications of the microbiota (gut bacteria) profile towards harmful bacterial species that could invade the normal intestinal tissue thus confronting the local immune system, and later the periphery. Our cumulative data using mouse models for IBD and CRC demonstrate that in late stages of these diseases chronic inflammation induces immunosuppression mediated by myeloid derived suppressor cells (MDSCs) that changes the microbiota profile towards more aggressive strains. We also show that when manipulating the immune system by MDSC depletion tumor regression and recovery from the disease is achieved. Similar results are obtained when using a specific cocktail of antibiotics that eliminates the harmful bacteria, generated during intestinal inflammation. These results are strengthening our hypothesize that a feedback loop from gut inflammation to MDSCs and microbiota profiles and/or vice versa, plays a major role in advanced IBD and transition to CRC. We also demonstrate that the harmful bacteria can directly interact with the MDSCs and activating them to be more suppressive. Currently, we are in the process of identifying combined modalities attacking the harmful immune cells and bacteria to tilt the balance towards beneficial host immunity and intestinal homeostasis, thus blocking severe IBD progression and CRC development. Our work has translational implications to be implemented to IBD and CRC patients towards establishing optimal personalized detection tools for disease staging and the development of novel treatment strategies.

Publications (2016 – 2019):

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., Bocholez, 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.* 22:857-67.
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:

MSc

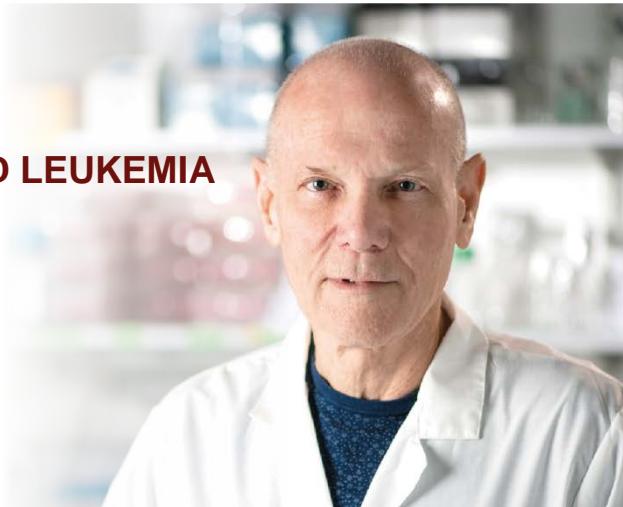
Hadas Ashkenazi

Nira Twaik-Nakav

Kerem Ben-Meir

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 unlike for many other cancer diseases, the standard care of this disease remains the same for the past 50 years. Last year, for the first time in a half decade, four new drugs have been introduced for AML therapy, but they are mostly added on to the old chemotherapy and are prolonging life for only a few months with no cure offer. 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 and TOX study performed by our partner, the US biotech company BioTheryX, we recently received an FDA approval for Phase 1 clinical trial, which may initiate still this year at one of the most important cancer centers in the US.

Publications (2016 – 2019):

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2. Aran D, Lasry A, Zinger A, Biton M, Pikarsky E, Hellman A, Butte AJ and **Ben-Neriah, Y.**, Widespread parainflammation in human cancer. *Genome Biol*, 2016, 2016 Jul 8;17(1):145. doi: 10.1186/s13059-016-0995-z. (highlighted in “The Scientist” magazine)
3. Drayman N, Ben-Nun-Shaul O, Butin-Israeli V, Srivastava R, Rubinstein AM, Mock CS, Elyada E, **Ben-Neriah, Y.**, Lahav G, Oppenheim A. p53 elevation in human cells halt SV40 infection by inhibiting T-ag expression. *Oncotarget*. 2016 Jul 21. doi: 10.18633/oncotarget.10769.
4. 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
5. 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.
6. 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.**, CK1 α 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.
7. Minzel W, Venkatachalam A, Fink A, Hung E, Brachya G, Burstin 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 CK1 α 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.
8. 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.

MSc and PhD students that graduated:

PhD

Upasana Das Adhikari

Audrey Lasry

Waleed Minzel (with distinction and the Hebrew University Viner Prize for best PhD theses)

Awards:

1. Waleed Minzel: Hebrew University Viner Prize for best PhD theses and James Sivarsten Prize for Pediatric Oncology Research
2. Yinon Ben-Neriah: The Emet Prize for Art, Science and Culture

MAINTAINING THE IMMUNE SYSTEM AT CHECK

Michael Berger



Lay language summary

The immune system major role is to defend the human body while maintaining tolerance to self and preventing autoimmunity and immunopathology. A major goal in immunology is to understand how the immune system is positively and negatively regulated so to be able exploiting it for therapeutic purposes.

My research group is interested in understanding what are the processes and factors that control immune response. Specifically we are focusing on three topics: 1) Elucidating key molecular processes maintaining resting state (quiescence) of immune cells. We unraveled a previously unknown functional connection between the T cell quiescence factor, Slfn2, and ER homeostasis. In a follow up study we could demonstrate that chronic ER stress in T cells with a loss-of-function mutation of the T cell quiescence factor, Slfn2, leads to disrupted cholesterol and lipid homeostasis due to increased de novo synthesis and higher levels of the enzyme HMGCR. 2) Exploiting our findings to treat blood cancer. We demonstrated that targeting Slfn2 leads to impaired survival of leukemia initiating cells, suggesting that targeting lymphocytes quiescence could serve as a novel approach for treating leukemia and other type of cancer. 3) Understanding how cellular metabolism controls T cell function and fate. We dissected the energetics of the mitochondrial matrix as a distinct compartment from the cytosol and demonstrated that mitochondrial substrate-based phosphorylation is a major limiting mechanism for hypoxia tolerance in T cells. Moreover, we used our findings regarding T cell metabolism to design a new technology that improves adoptive T cell transfer therapy for treating solid tumors.

Publications (2016 – 2019):

1. 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 Research*. 2019, 79, 2480-2493.
2. Tissue necrosis and its role in cancer progression. Karsch-Bluman A, Feiglin A, Stern T, Shoval H, Arbib E, Schwob O, **Berger, M.**, Benny O. *Oncogene*. 2019, 38, 1920-1935.
3. Germline DNA replication timing shapes mammalian genome composition. Yehuda Y, Blumenfeld B, Mayorek N, Makedonski K, Vardi O, Cohen-Daniel L, Mansour Y, Baror-Sebban S, Masika H, Farago M, **Berger, M.**, Carmi S, Buganim Y, Koren A, Simon I. (2018) *Nucleic Acids Research* 46, 8299-8310.
4. Schlafen2 mutation in mice causes an osteopetrosis 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.
5. Germline DNA replication timing shapes mammalian genome composition. Yehuda Y, Blumenfeld B, Mayorek N, Makedonski K, Vardi O, Cohen-Daniel L, Mansour Y, Baror-Sebban S, Masika H, Farago M, **Berger, M.**, Carmi S, Buganim Y, Koren A, Simon I. *Nucleic Acids Res*. 2018 Sep 19;46(16):8299-8310.
6. Trained Memory of Human Uterine NK Cells Enhances Their Function in Subsequent Pregnancies. Gamliel M, Goldman-Wohl D, Isaacson B, Gur C, Stein N, Yamin R, **Berger, M.**, Grunewald M, Keshet E, Rais Y, Bornstein C, David E, Jelinski A, Eisenberg I, Greenfield C, Ben-David A, Imbar T, Gilad R, Haimov-Kochman R, Mankuta D, Elami-Suzin M, Amit I, Hanna JH, Yagel S, Mandelboim O. *Immunity*. 2018 May 15;48(5):951-962.
7. 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
8. 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.
9. HCFC2 is needed for IRF1- and IRF2-dependent *Tlr3* transcription and for survival during viral infections. Sun L, Jiang Z, Acosta-Rodriguez VA, **Berger, M.**, Du X, Choi JH, Wang J, Wang KW, Kilaru GK, Mohawk JA, Quan J, Scott L, Hildebrand S, Li X, Tang M, Zhan X, Murray AR, La Vine D, Moresco EMY, Takahashi JS, Beutler B. *J Exp Med*. 2017 Nov 6;214(11):3263-3277.
10. Generalized verrucosis and abnormal T cell activation due to homozygous TAOK2 mutation. Molho-Pessach V, Ramot Y, Mogilevsky M, Cohen-Daniel L, Eisenstein EM, Abu-Libdeh A, Siam I, **Berger, M.**, Karni R, Zlotogorski A. *J Dermatol Sci*. 2017 Aug;87(2):123-129.
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.

12. Schlafen2 mutation unravels a role for chronic ER stress in the loss of T cell quiescence. Omar I, Lapenna A, Cohen-Daniel L, Tirosh B, **Berger, M.**, Oncotarget. 2016 Jun 28;7(26):39396-39407.
13. Loss of T-cell quiescence by targeting Slfn2 prevents the development and progression of T-ALL. Goldshtain A, Zerbib SM, Omar I, Cohen-Daniel L, Popkin D, **Berger, M.**, Oncotarget. 2016 Jul 26;7(30):46835-46847.
14. Discovery and Structure-Activity Relationships of the Neoseptins: A New Class of Toll-like Receptor-4 (TLR4) Agonists. Morin MD, Wang Y, Jones BT, Su L, Surakattula MM, **Berger, M.**, Huang H, Beutler EK, Zhang H, Beutler B, Boger DL. J Med Chem. 2016 May 26;59(10):4812-30.
15. TLR4/MD-2 activation by a synthetic agonist with no similarity to LPS. Wang Y, Su L, Morin MD, Jones BT, Whitby LR, Surakattula MM, Huang H, Shi H, Choi JH, Wang KW, Moresco EM, **Berger, M.**, Zhan X, Zhang H, Boger DL, Beutler B. Proc Natl Acad Sci U S A. 2016 Feb 16;113(7):E884-93.

PhD students that graduated:

Ibrahim Omar

Awards:

Michael Berger:

1. The Prof. Yaakov Matzner faculty Award for Outstanding Researcher for 2018.
2. Excellence in Teaching, Faculty of Medicine, The Hebrew University of Jerusalem, Israel 2016-2019.

Ibrahim Omar:

1. The James Sivartsen Prize in Pediatric Cancer Research for 2017.

Patents:

6520-00 US Provisional Application No. 62/821,002; IMPROVING ADOPTIVE CELL TRANSFER THERAPY (ACT) TREATMENT.

THE ROLE OF HUMAN APOBEC3G PROTEIN IN PRESERVING THE GENOME INTEGRITY

Moshe Kotler



Lay Language Summary

Genome integrity and its preservation are critical for the vitality of all organisms. Environmental (irradiation and chemicals) and metabolic events cause DNA damage (DD). DD if not repair or not repair properly, is dangerous to the cells; it may lead to cell death or cancer, respectively. Therefore, several mechanisms, starting with DD recognition to ligation of DNA fragments, have been developed across the evolution. DD repair machinery includes chromatin remodeling complexes, histone-modifying enzymes and a large battery of about 170 enzymes, which participate in several genomic DNA repair pathways.

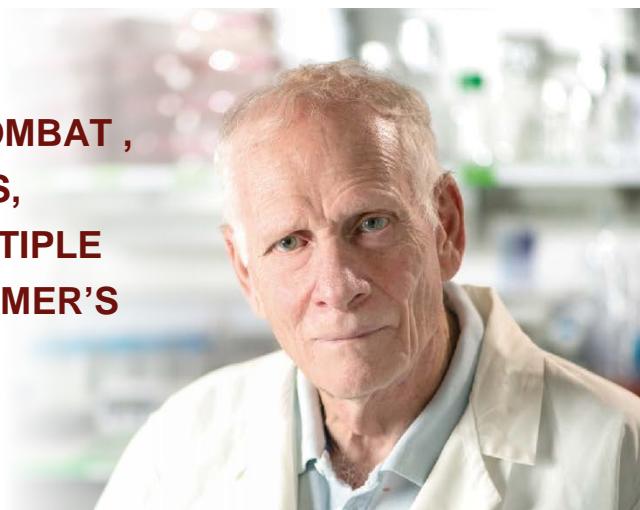
Strikingly, a family of cytosine deaminases (CD) – APOBEC3 (A3), which can modify the genomic DNA, was discovered in invertebrates and all vertebrates. The A3s are up regulated in several human cancers such as breast, ovary, head and neck and others tumors. Modifying the tumor-cells DNA by the A3 leads to tumor promotion, which is evolutionarily advantageous to the tumor, but is deleterious to the host. We discovered that a member of this family, the CD-hA3G plays a pivotal role in DD repair in irradiated cultured cells and in transgenic mice. We demonstrated that hA3G is responsible for the resistance of cells to DD damages induced by irradiation and chemotherapy treatments. We showed that hA3G promotes the repair of double strand breaks induced by radiation and chemotherapies. Hence, our results indicate that hA3G is a novel drug target for circumventing tumor resistance to chemo- and radio-therapies. Our results thus potentially have two important implications: I) Strategies aimed at inhibiting A3G deaminase expression or its catalytic activity may improve the efficacy of genotoxic therapies used to cure malignant tumors. II) Promotion of hA3G may contribute to the reduction of acute radiation syndrome in human exposed to IR either accidentally or due to terror and war activities.

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NOVEL THERAPY TO COMBAT , RHEUMATOID ARTHRITIS, CROHN'S DISEASE, MULTIPLE SCLEROSIS AND ALZHEIMER'S DISEASE.

David Naor



Lay language summary

More than a decade has been spent, researching a peptide of five amino acids (called 5-MER peptide), that neutralizes pathological amyloid proteins, associated with some incurable inflammatory and neurodegenerative diseases, such as Rheumatoid Arthritis, Crohn's disease, Multiples Sclerosis and Alzheimer's Disease. The therapeutic effect of the 5-MER peptide was demonstrated in animal models of these maladies, including an aggressive mouse model of Multiple Sclerosis, which could be a representative of the more progressive phase of this pathology. The four disease that have been explored in connection with 5-MER-peptide share pathological amyloid proteins, which are targeted by this potential peptide drug. This IP-protected peptide is being developed with the support of grants from the Hebrew University's Yissum technology-transfer company, the Israeli government, Spherium Biomed of Spain and the National Multiple Sclerosis Society of the USA.

The two neurodegenerative diseases described here , Multiple Sclerosis and Alzheimer disease, are not very attractive for some drug-developed companies, because human studies are expensive, the potential market is competitive, or they have a lower chance of ending with a successful product .Therefore, efforts must be focused to independently progress toward medical translation of our findings in human patients.

The most important finding, beyond those described in 2018 report, was the discovery that the 5-MER peptide activates protective genes ,that induce resistance to chronic inflammations such as Multiple Sclerosis and Crohn's disease. This finding suggests that the 5-MER peptide not only able to ameliorate the disease ,but it also displays a potential curable element.

To those who are skeptical of our or similar research projects we say : "It is always better to try than to do nothing; if we listen to skepticism rather than vision, medicine could never make any progress."

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DISSECTING THE COMPLEX INTERACTIONS IN THE TUMOR MICROENVIRONMENT AND MODIFYING IMMUNE CELLS TO FIGHT CANCER

Oren Parnas



Lay language summary

Pancreatic ductal adenocarcinoma (PDAC) is a deadly cancer. The five year survival rate is less than 10% with very little improvement over recent decades and only a short delay in disease progression in response to available treatments. PDAC is believed to develop in a gradual manner over many years however, early detection is challenging and late diagnosis is one of the major reasons for the poor prognosis and high mortality of PDAC patients. During the last year we have profiled, in the molecular level, the progress of PDAC from early pre-malignant stage to tumor. Our profile both malignant and non-malignant cells. The main finding includes: (i) unexpected epithelial cell plasticity and heterogeneity, (ii) significant changes in non-malignant cells that may give rise to pro-tumorigenic environment, (iii) novel potential interactions between different cell types in the tumor microenvironment, (iv) set of markers that may be useful for early detection.

This work shed light on the basic initial events that result in this deadly cancer. In addition, we are exploring how the signals that produced by the tumors paralyze the immune cells and restrict the immune cells ability to attack the tumors. Based on this information, we apply genetic methods to find new ways to engineer different immune cells to fight cancer.

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Funding and Awards:

Since I established the lab, I received the following grants and awards:

1. Concern Foundation and Antoinette E. "Mimi" & Herman Boehm Foundation AFHU young professorship award, 2019-2026.
2. Alon Fellowship award for outstanding young scientists, The Israeli Council for Higher Education, 2017-2020.
3. ERC starting grant, "Dissecting Regulatory Networks That Mediate Dendritic Cell Suppression", 2018-2023.
4. ISF personal grant, "Systematic identification of essential genes for latent and lytic infection of Kaposi Sarcoma associated Herpesvirus", 2018-2023.
5. BROAD-ISF, "Heterogeneity in the tumor and its microenvironment as a driving force in pancreatic cancer - the roles of senescent cells", 2018-2021.

HEPATIC INFLAMMATION AND METABOLISM AND THEIR INTRICATE RELATIONSHIP WITH LIVER CANCER

Eli Pikarsky



Lay language summary

The liver is the body's largest metabolic organ, strategically located between the gastrointestinal system and the internal organs. 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 where excess energy is stored in the form of glucose, and upon stress also accumulates 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 form front-line 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.

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. While fatty liver disease is indolent, it 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 are identifying specific regions of p53 which regulate the transition from benign to inflammatory fatty liver disease. This could identify drugs which will prevent fatty liver disease progression.

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MSc and PhD students that graduated:

PhD

Shlomi Finkin

David Knigin

MSc

Yossef Mansour

PREDICTION AND PREVENTION OF CONGENITAL CMV DISEASE: A MULTIFACETED APPROACH

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 a unique ex vivo model of HCMV infection in native human placental tissues maintained as integral 3D multi-cell-type organ cultures. Our studies have uncovered the modes of viral infection and spread from the mother to the fetus, and revealed new innate immune response pathways by which the human placenta protects itself 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.

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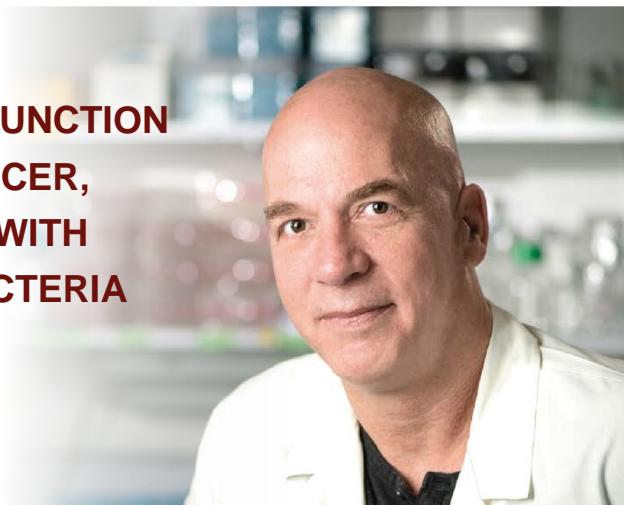
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Students that completed their degree / received prizes

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).
2. Currently – she is a postdoctoral research fellow at the Rockefeller University, NYC.
3. 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.
4. Esther Djian- Completed her PhD studies. Studies new antiviral drugs. She is currently a Post Doctoral student in my lab. Received the prestigious Marie Curie Fellowship of the EU.
5. 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.
6. Ido From- is currently completing his PhD studies in my lab. Has Studied and developed new models of viral entry site and reactivation.

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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MSc

The Rappaport award for BioMedical research 2020.

SLAMF6, A NOVEL TARGET FOR CANCER IMMUNOTHERAPY

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 terminates 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 role of SLAMF6 in the anti-melanoma response.

We generated donors for T cells lacking SLAMF6 which are cognate of melanoma. Lymphocytes from these mice displayed improved polyfunctionality and strong tumor cytotoxicity. T-bet was their dominant transcription factor, and upon activation, they acquired a polarized hyperactive phenotype. Blocking LAG-3 improved the function of SLAMF6 deficient T cells even further. Finally, adoptive transfer of SLAMF6 deficient, melanoma specific T cells into melanoma-bearing mice resulted in lasting tumor regression in contrast to temporary responses achieved with the intact receptor. These results support the notion that SLAMF6 is an inhibitory immune receptor whose absence enables powerful anti-tumor CD8 T cells to eradicate tumors.

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MSc and PhD students that graduated:

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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 sites 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 the DNA and chemical modifications of 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 have 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 drives cancer. I reveled that aberrant DNA methylation of CTCF binding sites perturbs chromosomal topology in IDH-mutant gliomas (Flavahan*, Drier* et al. *Nature* 2016) and SDH-deficient 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, hence promoting the overexpression of the oncogene. This groundbreaking model links metabolic, epigenetic and topological alterations and demonstrates how they can drive cancer. In additional studies we demonstrated how genetic alterations rewire enhancer – promoter interactions to drive adenoid cystic carcinomas (Drier et al. *Nature Genetics* 2016) and B-cell lymphomas (Ryan*, Drier*, et al. *Cancer Discovery* 2015), and how characterization of enhancer elements in pancreatic neuroendocrine tumors reveals clinically relevant developmental subtypes (Cejas*, Drier*, et al. *Nature Medicine* 2019).

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.

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