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 2018

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, alumi 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,

Ofer Mandelboim

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

ROLE OF TUMOR SUPPRESSOR GENE PRODUCTS OF COMMON FRAGILE SITES IN HUMAN DISEASES

Rami Aqeilan

Lay language summary

Common fragile sites (CFSs) are large genomic regions that are prone to breakage in cells subjected to DNA replication stress. Impairment of CFSs has been shown to be common in cancer. Our work aims to study the consequences of DNA replication stress and how does this impact genes residing in CFSs. Recent observations from our lab clearly suggest that gene products of CFSs play important roles in cancer. Furthermore, accumulating evidence links some of these genes with metabolic diseases and neuropathy. The ultimate goal of our research is hence to discover the genes and to elucidate the pathways that represent targets for the development of rational, specific and effective therapeutic approaches.

Selected Publications (2015-2018)

1. Abu-Remaileh, M., and Aqeilan, R. I. (2015) The tumor suppressor WW domain-containing oxidoreductase modulates cell metabolism. Exp Biol Med (Maywood) 240, 345-350.
2. Abu-Remaileh, M., Joy-Dodson, E., Schueler-Furman, O., and Aqeilan, R. I. (2015) Pleiotropic Functions of Tumor Suppressor WWOX in Normal and Cancer Cells. J Biol Chem 290, 30728-30735.
3. Abu-Remaileh, M., Seewaldt, V. L., and Aqeilan, R. I. (2015) WWOX loss activates aerobic glycolysis. Mol Cell Oncol 2, e965640.
4. Alian, A., and Aqeilan, R. I. (2015) T538 phosphorylation, Pin-ing p63-Itch stability. Cell Cycle 14, 469-470.
5. Del Mare, S., and Aqeilan, R. I. (2015) Tumor Suppressor WWOX inhibits osteosarcoma metastasis by modulating RUNX2 function. Sci Rep 5, 12959.
6. Hazan, I., Abu-Odeh, M., Hofmann, T. G., and Aqeilan, R. I. (2015) WWOX guards genome stability by activating ATM. Mol Cell Oncol 2, e1008288.

7. Hazan, I., and Aqeilan, R. I. (2015) Current questions and controversies in chromosome fragile site research: does WWOX, the gene product of common fragile site FRA16D, have a passive or active role in cancer? Cell Death Discov 1, 15040.

8. Salah, Z., Arafeh, R., Maximov, V., Galasso, M., Khawaled, S., Abou-Sharieha, S., Volinia, S., Jones, K. B., Croce, C. M., and Aqeilan, R. I. (2015) miR-27a and miR-27a* contribute to metastatic properties of osteosarcoma cells. Oncotarget 6, 4920-4935.

9. Abu-Odeh, M., Hereema, N. A., and Aqeilan, R. I. (2016) WWOX modulates the ATR-mediated DNA damage checkpoint response. Oncotarget 7, 4344-4355.

10. 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.

11. 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.

12. 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.

13. Maximov, V. V., and Aqeilan, R. I. (2016) Genetic factors conferring metastasis in osteosarcoma. Future Oncol 12, 1623-1644.

14. 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.

15. 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.

16. Khawaled, S., and Aqeilan, R. I. (2017) RUNX1, a new regulator of EMT in breast cancer. Oncotarget 8, 17407-17408.

17. 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.

18. 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.

19. Peretz, L., Besser, E., Hajbi, R., Casden, N., Ziv, D., Kronenberg, N., Gigi, L. B., Sweetat, S., Khawaled, S., Aqeilan, R., 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.

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

21. 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 RI, 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.

22. Gershkovitz M, Fainsod-Levi T, Khawaled S, Shaul ME, Sionov RV, Cohen-Daniel L, Aqeilan RI, Shaul Y, Fridlender ZG, Granot Z. Microenvironmental Cues Determine Tumor Cell Susceptibility to Neutrophil Cytotoxicity. Cancer Res. 2018 Jul 2, 78(17):5050-5059.

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

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

Awards

Dr. Aqeilan is the recipient of the 2017 Youdim Prize for Excellence in Cancer Research.

MSc and PhD students that graduated:

PhD:

Dr. Sara Del Mare

Dr. Mohammad Abu-Odeh

Dr. Suhaib Abdeen

Dr. Muhannad Abu-Remaileh

MYELOID DERIVED SUPPRESSOR CELLS AS INTRUDERS AND TARGETS: CLINICAL IMPLICATIONS IN CANCER THERAPY

Michal Baniyash

Lay language summary

In pathologies characterized by chronic inflammation such as cancer, inflammatory bowel disease (IBD), rheumatoid arthritis and diabetes, an imbalanced immune system is evident as reflected by the appearance of abnormal populations of immune cells, which suppress the patients' immune functions. During chronic inflammation there is an accumulation of unique immune cells, termed myeloid suppressor cells (MDSCs), which are highly suppressive cells. MDSCs migrate from the bone marrow to the periphery and site of inflammation, where they impair the functions of a variety of immune cells and thus, are major obstacles in the success of a variety of therapies especially those depending on a functional immune system as those that are currently used in various types of cancers. Moreover, MDSCs have the ability to support tumor growth and metastases. When reaching new environments, which exhibit a different array of inflammatory factors, MDSCs sense and adapt to the altered micro-environment by virtue of acquiring different features that involve changing their cell fate, surface receptors, metabolism and intracellular as well as secreted molecules. For example, we recently discovered that MDSCs, which are generated in the bone marrow, can change their features under inflammatory conditions when are in touch with the bone and become osteoclasts (bone destroying cells) thus, inducing bone loss. Indeed, bone loss is evident in many chronic inflammatory diseases such as cancer, rheumatoid arthritis, IBD and diabetes. Moreover, we also show that during chronic inflammation of the gut in IBD cases, MDSCs migrate from the periphery to the damaged intestine, interact with the modified bacteria and perpetuate the disease towards the development of colorectal cancer. Based on the plasticity and biological diversity of MDSCs, they have a dual use: 1) ***As biomarkers*** for the evaluation of the hosts' immune status; while low levels of MDSC indicate a functional immune system, elevated MDSC levels, point at an immunosuppressed system. MDSC as biomarkers could be used as well for the prediction of success rates of immune based therapies; if the patients' immune system is functional, immune based therapies are expected to succeed, and 2) ***As***

targets for treatments aimed at combating them or manipulating their suppressive activity towards achieving a recuperation of a functional immune system and thus, improving therapy success rates in various pathologies characterized by chronic inflammation. We have already developed an optimized system to monitor the hosts' immune status and currently we are in the process of discovering additional new biomarkers for MDSC detection and novel MDSC specific molecules that could serve as targets for treatment.

Publications (2015 – 2018)

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].

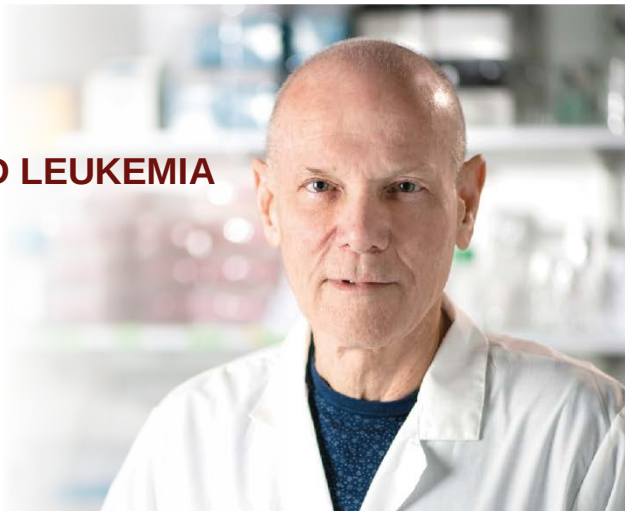
7. Meirow Y, Baniyash M. (2017) Immune biomarkers for chronic inflammation related complications in non-cancerous and cancerous diseases. Cancer Immunol Immunother. 66:1089-1101.

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.

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, there have been no encouraging news to leukemia patients over the past 40 years. Only this year some new therapies have emerged, yet mainly in combination with chemotherapy developed 50-60 years ago and 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 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 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. A US-based company, BioTheryX, bought from the Hebrew University the rights to the drug and is working now with our research team to apply for FDA approval for phase I clinical studies in the US.

Publications (2015 – 2018)

1. Type I Interferons Control Proliferation and Function of the Intestinal Epithelium. Katlinskaya YV, Katlinski KV, Lasri A, Li N, Beiting DP, Durham AC, Yang T, Pikarsky E, Lengner CJ, Johnson FB, **Ben-Neriah Y**, Fuchs SY. ***Mol Cell Biol***. 2016 Jan 25;36(7):1124-35. doi: 10.1128/MCB.00988-15. PMID: 26811327

2. One more wheel for a processing machine. **Ben-Neriah Y**. ***Cell Death Differ***. 2015 Aug;22(8):1235-6. doi: 10.1038/cdd.2015.71.

3. A Systematic Approach to Defining the microRNA Landscape in Metastasis. Mudduluru G, Abba M, Batliner J, Patil N, Scharp M, Lunavat TR, Leupold JH, Oleksiuk O, Juraeva D, Thiele W, Rothley M, Benner A, **Ben-Neriah Y**, Sleeman J, Allgayer H. ***Cancer Res.*** 2015 Aug 1;75(15):3010-9. doi: 10.1158/0008-5472.CAN-15-0997. Epub 2015 Jun 11.

4. Senescence-associated inflammatory responses: aging and cancer perspectives. Lasry A, **Ben-Neriah Y**. ***Trends Immunol***. 2015, 36: 217–228

5. Finkin S, Yuan D, Stein U, Taniguchi K, Weber A, Unger K, Browning JL, Goossens N, Nakagawa S, Gunasekaran G, Schwartz ME, Kobayashi M, Kumada H, Berger M, Pappo O, Rajewsky K, Hoshida Y, Karin M, *Heikenwalder M, ***Ben-Neriah Y** and *Pikarsky E, (*corresponding authors). Ectopic lymphoid structures as microniches for tumor progenitor cells in hepatocellular carcinoma, ***Nature Immunology***, 2015, 16:1235-44

6. Lasry A, Zinger A and **Ben-Neriah Y**, Inflammatory networks underlying colon cancer. ***Nature Immunology***, 2016, 17:230-40

7. 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)

8. 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: 10.18632/oncotarget.10769.

9. 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

10. 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.

11. 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.

12. 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.

MSc and PhD students that graduated:

PhD

Yael Morgenstern

Nir Drayman

Ido burstain

Upasana Das Adhikari

Audrey Lasry

MSc

Nophar Amsalem (Cum Laude)

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 of the bottlenecks and boundaries of T cell hypoxia tolerance. We demonstrated that mitochondrial respiratory-based ATP is not required for T cell activation. In addition, we dissected the energetics of the mitochondrial matrix as a distinct compartment from the cytoplasm. Finally, we pointed to mitochondrial substrate-based phosphorylation as the central limiting mechanism for hypoxia tolerance in T cells.

Publications (2016 – 2018)

1. 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.

2. 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.

3. 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.

4. 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

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. Loss of T-cell quiescence by targeting Slfn2 prevents the development

and progression of T-ALL. Goldshtein A, Zerbib SM, Omar I, Cohen-Daniel L, Popkin D, Berger M. Oncotarget. 2016 Jul 26;7(30):46835-46847.

11. 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.

12. 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 student 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 2016-2017.

Ibrahim Omar:

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

THE FUNCTION OF CELLULAR DEAMINASES IN VIRUS INHIBITION AND CANCER

Moshe Kotler

Lay Language Summary

Modern virology is aimed primarily to reveal strategies to defeat lethal and non-lethal viral diseases mainly by three strategies: i. Search for new vaccines and improvement of existing vaccination procedures. ii. Development of antiviral drugs addressed directly against viral proteins, and iii. Enhancement of the innate immunity, by which hosts protect themselves against viruses. Secondly, modern virology is aimed to elucidate cellular factors essential for virus propagation, or alternatively for virus restriction. Developing of virus based vectors for gene therapy becomes an important challenge.

Our laboratory is studying cellular deaminases, which impede the production of infectious HIV-1 particles, restrict retrotransposition and prevent acquisition of foreign genetic material. Members of this group of cellular deaminases play important roles in antibodies production and in tumor genesis.

Selected Publications (2015-2018)

2. Ponnandy, P., Shandilya, S., Britan-Rosich, E., Nagler,A., Schiffer, C.A. and **Kotler, M.** Inhibition of APOBEC3G Activity Impedes Double-Strand DNA Repair. FEBS J. 2016: 112-29. doi: 10.1111/febs.13556.

3. Fanous, J., Swed A., Joubran, S., Hurevich, M., Britan-Rosich, E., **Kotler, M.,** Gilon, C. and Hoffman, A. Superiority of the S,S conformation in Diverse Pharmacological Processes: Intestinal Transport and Entry Inhibition Activity of Novel Anti-HIV Drug Lead. International Journal of Pharmaceutics, 495: 660–663 (2015).

4. Galilee, M., Britan-Rosich, M., Griner, S.L., Uysal, S., Baumgärtel, V., Lamb, D.C., Kossiakoff, A.A., **Kotler, M.,** Stroud, R.M., Marx, A. and Alian, A. The preserved HTH-docking cleft of HIV-1 integrase is functionally critical.

STRUCTURE journal. In Press (2016). (STRUCTURE-D-16-00178R).

5. Nassar, Taher; Rohald, Ayala ; Naraykin, Natalya; Barasch, Dinora; amsalem, orit; Prabhu, Ponnandy; Kotler, Moshe; Benita, Simone. Nanocapsules embedded in microparticles for enhanced oral bioavailability and efficacy of Lopinavir as an anti-AIDS drug". Submitted (2018).

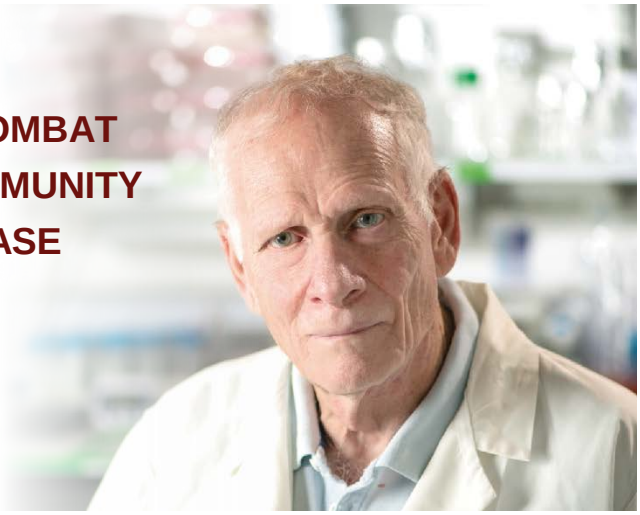
MSc and PhD students that graduated:

MSc

Adi Nagler (Cum Laude)

NOVEL THERAPY TO COMBAT INFLAMMATION, AUTOIMMUNITY AND ALZHEIMER'S DISEASE

David Naor



Lay language summary

Could one drug effectively treat incurable inflammatory diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and multiple sclerosis as well as neurodegenerative maladies such as Alzheimer's disease? The answer is **yes**, but only when all diseases share similar pathological proteins ,which can be recognized and targeted by this drug. Indeed, all these diseases are associated with pathological amyloid proteins (for example, serum amyloid A and Amyloid β) that could be neutralized by the 5-mer peptide (called also pentamer).The pentamer is a synthetic protein snippet that significantly reverses the damaging effects in animal models of inflammatory diseases and Alzheimer's disease, where it restores the learning potential. Once you control the inflammation, you can control the disease, so our target is to reduce as much as possible the inflammatory activity, including in autoimmune diseases.

Rheumatoid arthritis. We began by studying the pentamer effectiveness in rheumatoid arthritis, which affects about one percent of the world population. Currently, about $30 billion worth of biologic drugs (mostly anti-TNF) are sold each year that effectively control, but cannot cure, rheumatoid arthritis and other inflammatory diseases. Furthermore, these drugs don't work in one-third of rheumatoid arthritis patients. Our experiments showed clear results. When mice with collagen-induced arthritis were treated with the pentamer, the severely inflamed tissues in their joints reverted to nearly normal. No harmful side effects were observed.

Inflammatory Bowel Diseases (Crohn's disease and Ulcerative Colitis). Spherium Biomed our collaborators from Barcelona,Spain, assess the pentamer 5-mer peptide in mouse models of inflammatory bowel diseases (IBD), which shares the pathological serum amyloid A with rheumatoid arthritis. They showed it can reduce the gut inflammation in IBD better than the currently prescribed biological medication (for example anti-TNF), which is effective only in half of IBD patients.

Multiple sclerosis. Once the rheumatoid arthritis experiment was repeated successfully in rheumatoid arthritis and IBD, we looked at a different chronic inflammatory disease – multiple sclerosis. In multiple sclerosis the inflammation is not in the joints or the gut, but in the brain, yet share with rheumatoid arthritis and IBD the same pathological amyloid protein-serum amyloid A. Multiple sclerosis (MS) is the most widespread disabling neurological condition of young adults around the world, usually striking between the ages of 20 and 50. There is no cure, but several drugs reduce the frequency of relapses. Five days after MS-like disease was induced in mice, 5-mer peptide injections caused a significant decrease in accumulation of inflammatory cells in the central nervous system and significant reduction in limb paralysis. The effects were weaker when the disease was more progressed, but theoretically the peptide could be introduced during a remission phase of MS. Recently, in collaboration with Prof. Haim Ovadia from Hadassah University Medical Center we achieved another progress by delivering 5-mer peptide (or pentamer) via mouth rather than by injections, with the same therapeutic effect. That means that we may be able to produce pills for oral delivery rather than to provide the drug by injection.

Alzheimer's disease. After a quarter-century of failed efforts to develop a cure for Alzheimer's disease, investment money is dwindling. Yet the number of cases is climbing rapidly along with related costs. About one in nine Americans over 65 has this fatal degenerative neurological disorder affecting 44 million people worldwide. In collaboration with Prof. Hanna Rosenmann from Hadassah, our lab studied the effect of 5- mer peptide (pentamer) in mice with induced Alzheimer's disease. Cognitively normal mice placed inside a watery maze learned quickly how to swim to a safe platform and were able to find it faster with every subsequent attempt. But the Alzheimer's mice took longer finding the platform every time, due to memory/learning difficulties. After treatment with 5-mer peptide, the Alzheimer's mice regained their ability to learn the location of the platform as quickly as cognitively normal mice. The 5-mer peptide appears to prevent the accumulation of amyloid–beta in the brain. Amyloid–beta clumps are believed to attract harmful inflammatory cells from the immune system, thus enhancing Alzheimer's disease.

The mechanism of action of the 5-mer peptide was proven on various harmful amyloid proteins, using sophisticated imaging tools in the lab of Prof. Mary Cowman, our collaborator from New York University. In general terms, we can inject 5-mer peptide even after the disease has started, and it will work. We don't yet know if there is a point of no return when it would no longer work. Because the peptide was derived from human material, it makes sense that it is going to work in humans at least as well as in mice, but the final answer if this statement is correct or incorrect, depends on clinical trials.

Publications (2015-2018)

1. Gesundheit B, Ashwood P, Keating A, Naor D, Melamed M, Rosenzweig J Therapeutic properties of mesenchymal stem cells for autism spectrum disorders. Med Hypotheses. 2015 Mar;84(3):169-77.

1. 2. Nathalie Assayag-Asherie, Dror Sever, Marika Bogdani, Pamela Johnson, Talya Weiss, Ariel Ginzberg, Sharon Perles, Lola Weiss, Lora Eshkar Sebban, Eva A. Turley, Elimelech Okon, Itamar Raz, and David Naor. Can CD44 be a mediator of cell destruction? The challenge of type 1 diabetes. PLoS One. 2015; 10(12): e0143589

2. David Naor .Editorial: Interaction between hyaluronic acid and its receptors (CD44,RHAMM) regulates the activity of inflammation and cancer . Front. Immunol. 7:39.doi: 10.3389/fimmu.2016.00039

3. Barzilay R, Ventorp F, Segal-Gavish H, Aharony I, Bieber A, Dar S, Vescan M, Globus R, Weizman A, Naor D, Lipton J, Janelidze S, Brundin L, Offen D.CD44 Deficiency Is Associated with Increased Susceptibility to Stress-Induced Anxiety-like Behavior in Mice. J Mol Neurosci. 60(4):548-558. 2016

4. Pinner E, Gruper Y, Ben Zimra M, Kristt D, Laudon M, Naor D, Zisapel N CD44 Splice Variants as Potential Players in Alzheimer's Disease Pathology. J Alzheimers Dis. 58(4):1137-1149. 2017

5. Katia B, Naor D, Voevoda V, Ostrovsky O, Bitner H, Rosenberg E, Varda-Bloom N, Canaani J, Danilesko I, Shimoni A, and Nagler A., Dissecting the mechanisms involved in anti-human T-lymphocyteimmunoglobulin (ATG)-induced tolerance in the setting of allogeneic stem cell transplantation - potential implications for Graft versus Host Disease. Oncotarget, 8(53):90748-90765, 2017

SINGLE CELL ANALYSIS TO FOR UNDERSTANDING TUMOR MICROENVIRONMENT AND IMMUNE CELL FUNCTION

Oren Parnas

Lay language summary

Our mission, is to explore how non-malignant cells in the tumor microenvironment contribute to tumor development and find new ways to reprogram immune cells to fight cancer.

The tumor microenvironment evolves to include diverse cell types that adopt a variety of fates, which can dramatically influence disease progression. This heterogeneity raise an urgent need in defining the precise cellular composition in order to understand the roles of such different components in tumor disease and progression. We study the compositional evolution of pancreatic adenocarcinoma (PDAC), among the deadliest tumor types, for which there are no current effective therapies. The disease can initiate from duct or acinar pancreatic cells, most often through Kras activation, and progresses to malignancy through premalignant lesions of several types, including pancreatic intraepithelial neoplasias (PanINs).

In the last year, we focused on exploring the early events that give raise to cellular environment that support PDAC. We have used advance single cell RNA-seq technologies and computational tools to profile premalignant lesions taking in several time points after the induction of Kras activation. We are also using samples from patients to verify the main results found based on our models.

We are currently using this data to investigate: (i) Which cells infiltrate PanINs, (ii) Which genes differentially expressed between cells that infiltrate PanINs and cells in control samples, (iii) How neoplasia form following Kras activation, (iv) How different cell types interact to form immunosuppressive environment.

We have profile the different stages of acinar cell transformation and found potential new regulators of this process. In addition, we characterize the different subpopulations of cells that give raise to premalignant lesions including subpopulations of immune cells, endothelial cells and fibroblast.

Our team that includes, computational and experimental biologists, basic scientists and clinicians, will shed light on the fundamental processes that leads to PDAC and therefore will point on new targets for treatments.

In parallel effort, we are exploring the response of immune cells to suppressive signals that dominate the tumor microenvironment and cause immune cells dysfunction. We hypothesis that targeting the cellular factors that transfer the suppressive signals, can block the effect of the suppressive signals and reverse the dysfunctional phenotype of immune cells.

In the last year we expend the systematic search for genes that play a role in immune response to suppressive signals and include additional immune cell types and additional suppressive signals (cytokines and cancer cells).

The new panel of genes that will be found in these screens, can be targeted using drugs or can be manipulate in immune cells ex-vivo before injecting back to the patients. This strategy will result in prolong immune response to tumors and potentially new therapies.

Grants and awards since 2016

Alon Fellowship

ERC starting grant

ISF- Personal grant

ISF- Equipment grant

Braod-ISF

Israel Cancer Association

CHARACTERIZING INFLAMMATORY LINKS IN LIVER CANCER

Eli Pikarsky

Lay language summary

The past few years yielded an explosion of exciting clinical trials showing remarkable benefit of immune treatments in cancer patients. The link between inflammation and cancer is now established, yet the underlying molecular mechanisms are unresolved. As tumors progress, they modulate the inflammatory cells towards a protumorigenic immunosuppressive phenotype. We have shown that the inflammatory cells reciprocate by sculpting the parenchymal epithelial cells. We hypothesize that these reciprocal interactions lie at the heart of the link between inflammation and cancer. Liver cancer is the second leading cause of cancer death worldwide and is a prototype of inflammation induced cancer.

We employ several strategies to analyze the changes that occur in inflammatory cells before and after liver tumor emergence, based on our preliminary findings showing that changes in inflammatory cells *precede* tumorigenesis. We are comprehensively mapping the changing inflammatory microenvironment in mouse models of inflammation induced Hepatocellular carcinoma (HCC) – the most common form of primary liver cancer. Using genetic manipulation strategies, coupled to cell isolation techniques we are delineating the molecular cues that mediate these changes and are analyzing the functional role of key mediators of these processes in the malignant process. Specifically we noted that: 1. T cell exhaustion often occurs in conglomerates of immune cells termed ELSs. This T cell exhaustion phenotype generates protumorigenic ELSs. Reverting T cell exhaustion with immune-oncology drugs can generate anti tumorigenic ELSs. 2. We identified a specific molecule, that is secreted by hepatocytes to invoke the formation of ELSs in the liver. 3. We have dissected the composition of hepatic ELSs that are associated with increased cancer risk and are delineating the role of several specific cell types in mediating pro and anti tumor effects of the immune system in the liver.

Publications (2015 – 2018)

1. Kravtsova-Ivantsiv Y, Shomer I, Cohen-Kaplan V, Snijder B, Superti-Furga g, Gonen H, Sommer T, Ziv T, Admon A, Naroditsky I, Jbara M, Brik A, Normand R, Shen-Orr SS, Pikarsky E, Kwon YT, Doweck I, and Ciechanover A, KPC1-Mediated Ubiquitination and Proteasomal Processing of NF-κB1 p105 to p50 Restricts Tumor Growth, Cell 161:333-47 (2015).

2. Gilad R, Meir K, Stein I, German L, Pikarsky E & Mabjeesh NJ. High SEPT9_i1 protein expression is associated with high-grade prostate cancers. PLoS ONE, 10:e0124251 (2015).

3. Abu-Remaileh M, Bender S, Raddatz G, Ansari I, Cohen D, Gutekunst J, Musch T, Linhart H, Breiling A, Pikarsky E, Bergman Y & Lyko F. Chronic inflammation induces a novel epigenetic program that is conserved in intestinal adenomas and in colorectal cancer. Cancer Res., 75:2120-30 (2015).

4. Falick Michaeli T, Laufer N, Sagiv JY, Dreazen A, Granot Z, Pikarsky E, Bergman Y & Gielchinsky Y. The rejuvenating effect of pregnancy on muscle regeneration. Aging Cell, 14:698-700 (2015).

5. Lazar CH, Kimchi A, Namburi P, Mutsuddi M, Zelinger L, Beryozkin A, Ben-Simhon S, Obolensky A, Ben-Neriah Z, Argov Z, Pikarsky E, Fellig Y, Marks-Ohana D, Ratnapriya R, Banin E, Sharon D & Swaroop A. Nonsyndromic Early-Onset Cone-Rod Dystrophy and Limb-Girdle Muscular Dystrophy in a Consanguineous Israeli Family are Caused by Two Independent yet Linked Mutations in ALMS1 and DYSF. Hum Mutat., 36:836-41 (2015).

6. Finkin S, Yuan D, Stein I, Taniguchi K, Weber A, Unger K, Browning JL, Goossens N, Nakagawa S, Gunasekaran N, Schwartz ME, Kobayashi M, Kumada H, Berger M, Pappo O, Rajewsky K, Hoshida Y, Karin M, Heikenwalder M#, Ben-Neriah Y# & Pikarsky E#. Ectopic lymphoid structures function as microniches for tumor progenitor cells in hepatocellular carcinoma, Nature Immunology, 16:1235-44 (2015).

7. Horwitz E, Stein I, Ben-Neriah Y & Pikarsky E. Animal model studies indicate a candidate biomarker for sorafenib treatment of hepatocellular carcinoma. Molecular & Cellular Oncology 2:1, e968028 (2015).

8. Hefetz-Sela S, Stein I & Pikarsky E. Restoring inflammatory balance as a potential preventive strategy for inflammation induced cancer. Oncoimmunology, 4:e1039764 (2015).

9. Holt SH, Darash-Yahana M, Sohn YS, Song L, Karmi O, Tamir S, Michaeli D, Luo Y, Paddock ML, Jennings PA, Onuchic JN, Azad RK, Pikarsky E, Cabantchik IZ, Nechushtai R & Mittler R. Activation of apoptosis in NAF-1-deficient human epithelial breast cancer cells, J Cell Sci. 129:155-65 (2016).

10. 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. RNF20 Links Histone H2B Ubiquitylation with Inflammation and Inflammation-Associated Cancer, Cell Rep., 14:1462-76 (2016).

11. Katlinskaya YV, Katlinski KV, Lasri A, Li N, Beiting DP, Durham AC, Yang T, Pikarsky E, Lengner CJ, Johnson FB, Ben-Neriah Y & Fuchs SY. Type I Interferons Control Proliferation and Function of the Intestinal Epithelium, Mol Cell Biol., 36:1124-35 (2016).

12. Samarin J, Laketa V, Malz M, Roessler S, Stein I, Horwitz E, Singer S, Dimou E, Cigliano A, Bissinger M, Falk CS, Chen X, Dooley S, Pikarsky E, Calvisi DF, Schultz C, Schirmacher P & Breuhahn K. PI3K/AKT/mTOR-dependent stabilization of oncogenic far-upstream element binding proteins in hepatocellular carcinoma cells, Hepatology, 63:813-26 (2016).

13. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, Gores G. Hepatocellular carcinoma, Nature Reviews Disease Primers, 2:1-23 (2016).

14. Pikarsky E, Heikenwalder M. Focal and Local: Ectopic Lymphoid Structures and Aggregates of Myeloid and Other Immune Cells in Liver. Gastroenterology. 151:780-783. (2016)

15. Malakar P, Shilo A, Mogilevsky A, Stein I, Pikarsky E, Nevo Y, Benyamini H, Elgavish S, Zong X, Prasanth KV, Karni R .Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation. Cancer Res. 77:1155-1167. (2017)

16. Tarcic O, Granit RZ, Pateras IS, Masury H, Maly B, Zwang Y, Yarden Y, Gorgoulis VG, Pikarsky E, Ben-Porath I, Oren M. RNF20 and histone H2B ubiquitylation exert opposing effects in Basal-Like versus luminal breast cancer. Cell Death Differ. 24:694-704. (2017)

17. Etzioni A, Ciechanover A, Pikarsky E. Immune defects caused by mutations in the ubiquitin system. J Allergy Clin Immunol. 139:743-753. (2017)

18. Hanin G, Yayon N, Tzur Y, Haviv R, Bennett ER, Udi S, Krishnamoorthy YR, Kotsiliti E, Zangen R, Efron B, Tam J, Pappo O, Shteyer E, Pikarsky E, Heikenwalder M, Greenberg DS, Soreq H. miRNA-132 induces hepatic steatosis and hyperlipidaemia by synergistic multitarget suppression. Gut. doi: 10.1136/gutjnl-2016-312869. [Epub ahead of print[(2017)

19. 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 96:e6931. (2017)

20. Yuan D, Huang S, Berger E, Liu L, Gross N, Heinzmann F, Ringelhan M, Connor TO, Stadler M, Meister M, Weber J, Öllinger R, Simonavicius N, Reisinger F, Hartmann D, Meyer R, Reich M, Seehawer M, Leone V, Höchst B, Wohlleber D, Jörs S, Prinz M, Spalding D, Protzer U, Luedde T, Terracciano L, Matter M, Longerich T, Knolle P, Ried T, Keitel V, Geisler F, Unger K, Cinnamon E, Pikarsky E, Hüser N, Davis RJ, Tschaharganeh DF, Rad R, Weber A, Zender L, Haller D, Heikenwalder M. Kupffer Cell-Derived Tnf Triggers Cholangiocellular Tumorigenesis through JNK due to Chronic Mitochondrial Dysfunction and ROS. Cancer Cell. 31:771-789 (2017)

21. Ringelhan M, Pfister D, O'Connor T, Pikarsky E and Heikenwalder M. The immunology of hepatocellular carcinoma. Nature Immunology, doi: 10.1038/s41590-018-0044-z (2018).

22. Roth L, Srivastava S, Lindzen M, Sas-Chen A, Sheffer M, Lauriola M, Enuka Y, Noronha A, Mancini M, Lavi S, Tarcic G, Pines G, Nevo N, Heyman O, Ziv T, Rueda OM, Gnocchi D, Pikarsky E, Admon A, Caldas C, Yarden Y. SILAC identifies LAD1 as a filamin-binding regulator of actin dynamics in response to EGF and a marker of aggressive breast tumors. Sci Signal. doi: 10.1126/scisignal.aan0949. (2018).

23. Abu-Remaileh M, Khalaileh A, Pikarsky E, Aqeilan RI. WWOX controls hepatic HIF1α to suppress hepatocyte proliferation and neoplasia. Cell Death Dis. doi: 10.1038/s41419-018-0510-4. (2018).

24. Grinshpun A, Gavert N, Granit RZ, Masuri H, Ben-Porath I, Breuer S, Zick A, Rosenberg S, Maoz M, Granit A, Pikarsky E, Strausmman R, Peretz T, Sonnenblick A. Ex vivo organ culture as potential prioritization tool for breast cancer targeted therapy. Cancer Biol Ther. doi: 10.1080/15384047.2018.1450114. (2018).

25. Izraely S, Ben-Menachem S, Sagi-Assif O, Telerman A, Zubrilov I, Ashkenazi O, Meshel T, Maman S, Orozco JIJ, Salomon MP, Marzese DM, Pasmanik-Chor M, Pikarsky E, Ehrlich M, Hoon DSB, Witz IP. The Metastatic Microenvironment: Melanoma-Microglia Cross-Talk Promotes the Malignant Phenotype of Melanoma Cells. Int J Cancer. doi: 10.1002/ijc.31745. (2018).

26. Reizel Y, Sabag O, Skversky Y, Spiro A, Steinberg B, Bernstein D, Wang A, Kieckhaefer J, Li C, Pikarsky E, Levin-Klein R, Goren A, Rajewsky K, Kaestner KH, Cedar H. Postnatal DNA demethylation and its role in tissue maturation. Nat Commun. doi: 10.1038/s41467-018-04456-6. (2018).

27. 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 RW, Fung L, Mercurio F, Li D, Vacca J, Kaushansky N, Shlush L, Oren M, Levine R, Pikarsky E, Snir-Alkalay I, Ben-Neriah Y. Small Molecules Co-targeting CKIα and the Transcriptional Kinases CDK7/9 Control AML in Preclinical Models. Cell. doi: 10.1016/j.cell.2018.07.045 (2018)

28. Roy S, Hooiveld GJ, Seehawer M, Caruso S, Heinzmann F, Schneider AT, Frank AK, Cardenas DV, Sonntag R, Luedde M, Trautwein C, Stein I, Pikarsky E, Loosen S, Tacke F, Ringelhan M, Avsaroglu SK, Goga A, Buendia MA, Vucur M, Heikenwalder M, Zucman-Rossi J, Zender L, Roderburg C, Luedde T. microRNA 193a-5p Regulates Levels of Nucleolar- and Spindle-associated Protein 1 to Suppress Hepatocarcinogenesis. Gastroenterology. doi: 10.1053/j.gastro.2018.08.032 (2018)

PhD students that graduated:

Shlomi Finkin, PhD (Cum Laude)

David Knigin, MD PhD

MODELS TO STUDY INFECTION WITH HUMAN VIRUSES

Dana Wolf

Lay language summary

Dana Wolf is a physician scientist in clinical virology and infectious diseases. Her research has focused on the challenge of human cytomegalovirus (HCMV) infection and disease in pregnant women, congenitally-infected infants, and transplant recipients. In view of the need for prenatal prevention of the severe disabilities associated with congenital HCMV infection, she has developed a unique *ex vivo* model of HCMV infection in human placental tissues, uncovering for the first time the early events of viral transmission from the mother to the fetus and the protective innate immune responses, within the native human maternal-fetal interface. Her studies, more recently expanded to reveal the different placental damage pathways exploited by HCMV and Zika virus, pave the way to prenatal prediction and prevention of congenital HCMV disease, and further inform the approach to a growing range of viruses which can adversely impact fetal development.

Together with Ofer Mandelboim (with whom she has had a long-term and highly productive collaboration) and Oren Parnas from the Lautenberg Center she is currently studying how the diverse immune cells in the human placenta respond to HCMV infection and how this critical first-line response protects the fetus from congenital infection. To address the resistance and toxicities associated with the currently available anti-HCMV drugs, she pioneered the discovery of drug resistance mechanisms and the translation of these findings into genotypic diagnostic assays, now routinely employed for patient monitoring and treatment. In line with the growing need for new antiviral drugs with alternative modes of action, she has studied the roles of an essential viral kinase and virus-supportive cellular pathways as new antiviral drug targets. Her studies have recently led to the discovery of a novel artemisinin derivative as a potent inhibitor of HCMV, which is now under development for human clinical studies.

PUBLICATIONS 2016-2018

1. Yamin R, Lecker LSM, Weisblum Y, Vitenshtein A, Le-Trilling VTK, **Wolf DG**, Mandelboim O. HCMV vCXCL1 binds several chemokine receptors and preferentially attracts neutrophils over NK cells by interacting with CXCR2. Cell Rep. 2016; 15:1542-53.

2. Vitenshtein A, Weisblum Y, Hauka S, Halenius A, Oiknine-Djian E, Tsukerman P, Bauman Y, Bar-On Y, Stern-Ginossar N, Enk J, Ortenberg R, Tai J, Markel G, Blumberg RS, Hengel H, Jonjic S, **Wolf DG**, Adler H, Kammerer R, Mandelboim O. Cell Rep. 2016; 15:2331-9.

3. Enk J, Levi A, Weisblum Y, Yamin R, Charpak-Amikam Y, **Wolf DG**, Mandelboim O. HSV1 MicroRNA Modulation of GPI Anchoring and Downstream Immune Evasion. Cell Rep. 2016;17:949-956.

4. Weil M, Mandelboim M, Mendelson E, Manor Y, Shulman L, Ram D, Barkai G, Shemer Y, **Wolf D**, Kra-Oz Z, Weiss L, Pando R, Hindiyeh M, Sofer D. Human enterovirus D68 in clinical and sewage samples in Israel. J Clin Virol. 2017 Jan;86:52-55. doi: 10.1016/j.jcv.2016.11.013. Epub 2016 Nov 30.

5. Weisblum Y, Oiknine-Djian E, Vorontsov OM, Haimov-Kochman R, Zakay-Rones Z, Meir K, Shveiky D, Elgavish S, Nevo Y, Roseman M, Bronstein M, Stockheim D, From I, Eisenberg I, Lewkowicz AA, Yagel S, Panet A, **Wolf DG**. Zika Virus Infects Early- and Midgestation Human Maternal Decidual Tissues, Inducing Distinct Innate Tissue Responses in the Maternal-Fetal Interface. J Virol. 2017 Jan 31;91(4). pii: e01905-16. doi: 10.1128/JVI.01905-16. Print 2017 Feb 15.

6. Almogy G, Stone L, Bernevig BA, **Wolf DG**, Dorozko M, Moses AE, Nir-Paz R. Analysis of Influenza and RSV dynamics in the community using a 'Local Transmission Zone' approach. Sci Rep. 2017 Feb 9;7:42012. doi: 10.1038/srep42012.

7. Dumont TMF, Mouillet JF, Bayer A, Gardner CL, Klimstra WB, **Wolf DG**, Yagel S, Balmir F, Binstock A, Sanfilippo JS, Coyne CB, Larkin JC, Sadovsky Y. The expression level of C19MC miRNAs in early pregnancy and in response to viral infection.. Placenta. 2017;53:23-29.

8. Torgeman A, Mador N, Dorozko M, Lifshitz A, Eschar N, White MD, **Wolf DG**, Epstein E. Efficacy of inactivation of viral contaminants in hyperimmune horse plasma against botulinum toxin by low pH alone and combined with pepsin digestion. Biologicals. 2017;48:24-27.

9. Lustig Y, **Wolf D**, Halutz O, Schwartz E. An outbreak of dengue virus (DENV) type 2 Cosmopolitan genotype in Israeli travellers returning from the Seychelles, April 2017.Euro Surveill. 2017 Jun 29;22(26). pii: 30563. doi:

10.2807/1560-7917.ES.2017.22.26.30563.

10. Charpak-Amikam Y, Kubsch T, Seidel E, Oiknine-Djian E, Cavaletto N, Yamin R, Schmiedel D, **Wolf D**, Gribaudo G, Messerle M, Cicin-Sain L, Mandelboim O. Human cytomegalovirus escapes immune recognition by NK cells through the downregulation of B7-H6 by the viral genes US18 and US20. Sci Rep. 2017 Aug 17;7(1):8661. doi: 10.1038/s41598-017-08866-2.

11. Levin A, Yaari S, Stoff R, Caplan O, **Wolf DG**, Israeli E. Diagnosis of Cytomegalovirus Infection during Exacerbation of Ulcerative Colitis. Digestion. 2017 Aug 26;96(3):142-148. doi: 10.1159/000479865.

12. Glasner A, Oiknine-Djian E, Weisblum Y, Diab M, Panet A, **Wolf DG**, Mandelboim O. Zika virus escapes NK cell detection by upregulating MHC class I molecules.J Virol. 2017 Sep 6. pii: JVI.00785-17. doi: 10.1128/JVI.00785-17. (the last 2 authors contributed equally to the work)

13. Weisblum Y, Oiknine-Djian E, Zakay-Rones Z, Vorontsov O, Haimov-Kochman R, Nevo Y, Stockheim D, Yagel S, Panet A, **Wolf DG**. APOBEC3A is Upregulated by Human Cytomegalovirus in the Maternal-Fetal Interface, Acting as an Innate Anti-HCMV Effector. J Virol. 2017 Sep 27. pii: JVI.01296-17. doi: 10.1128/JVI.01296-17.

14. Fichman Y, Levi A, Hodak E, Halachmi S, Mazor S, **Wolf D**, Caplan O, Lapidoth M. Efficacy of pulsed dye laser treatment for common warts is not influenced by the causative HPV type: a prospective study. Lasers Med Sci. 2017 Dec 7. doi: 10.1007/s10103-017-2413-5

15. Rakovsky A, Gozlan Y, Bassal R, Wax M, Shirazi R, Bakhanashvili M, Kra-Oz Z, Radian-Sade S, Ben-Zvi H, Schreiber L, **Wolf DG**, Shemer-Avni Y, Chemtob D, Mendelson E, Mor O. Diagnosis of HIV-1 infection: Performance of Xpert Qual and Geenius supplemental assays in fourth generation ELISA-reactive samples. J Clin Virol. 2018 Apr;101:7-10. doi: 10.1016/j.jcv.2018.01.007. Epub 2018 Jan 17.

16. Benson AA, **Wolf D**, Lederman N, Safadi R. Direct-acting antivirals response in an acute nosocomial genotype 1b HCV outbreak. Dig Liver Dis. 2018 Mar 15. pii: S1590-8658(18)30229-9. doi: 10.1016/j.dld.2018.03.011.

17. Averbuch D, Safadi R, Dar D, **Wolf D**, Cherniak M, Sorek R, Amit S. Successful Brincidofovir Treatment of Metagenomics-Detected Adenovirus Infection in a Severely Ill STAT1-Deficient Patient. Pediatr Infect Dis J. 2018 May 4. doi: 10.1097/INF.0000000000002090.

18. Oiknine-Djian E, Weisblum Y, Panet A, Wong HN, Haynes RK, **Wolf DG**. The Artemisinin Derivative Artemisone Is a Potent Inhibitor of Human

Cytomegalovirus Replication. Antimicrob Agents Chemother. 2018 Jun 26;62(7). pii: e00288-18. doi: 10.1128/AAC.00288-18.

19. Dassa L, Seidel E, Oiknine-Djian E, Yamin R, **Wolf DG**, Le-Trilling VTK, Mandelboim O. The Human Cytomegalovirus Protein UL148A Downregulates the NK Cell-Activating Ligand MICA To Avoid NK Cell Attack. J Virol. 2018 Aug 16;92(17). pii: e00162-18. doi: 10.1128/JVI.00162-18.

20. Wolday D, Derese M, Gebressellassie S, Tsegaye B, Ergete W, Gebrehiwot Y, Caplan O, **Wolf DG**, Maayan S. HPV genotype distribution among women with normal and abnormal cervical cytology presenting in a tertiary gynecology referral Clinic in Ethiopia. Infect Agent Cancer. 2018 Aug 14;13:28. doi: 10.1186/s13027-018-0201-x.

Students that completed their degree / received prizes

1. Yiska Weisblum- completed her PhD studies. She 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.

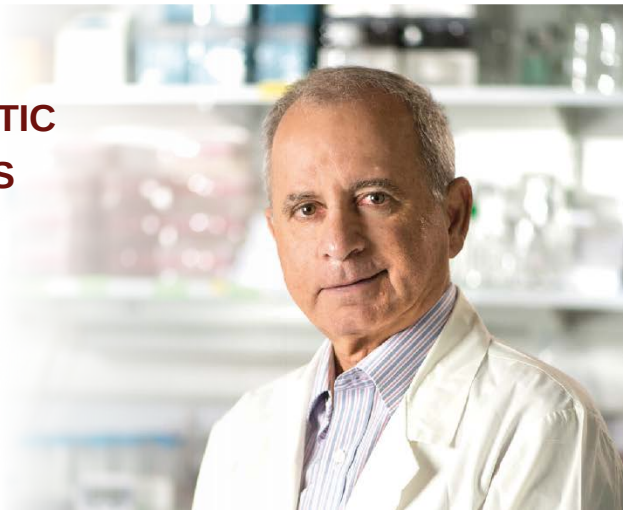
3. Amnon Berger- received MD/PhD degree – has studied viral infection in the developing fetal brain. Has been accepted for a postdoctoral fellowship at NYU Langone Medical Center and plans to specialize in OBGYN.

4. Esther Djian- has studied new antiviral drugs. She is currently a PhD 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.

MICRORNAS AS DIAGNOSTIC AND THERAPEUTIC TOOLS IN LEUKEMIA

Eitan Yefenof



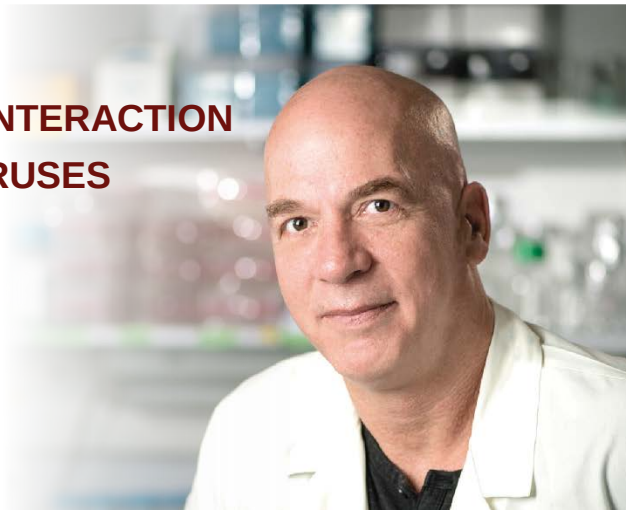
Lay language summary

MicroRNAs(miRs) are a family of small, non-coding RNAs that regulate a wide array of biological processes. They have been implicated in several diseases by virtue of their ability to regulate gene expression. Evidence for miR involvement in Cancer has been first generated by the study of Leukemia, where specific miRs are deregulated due to chromosomal translocations and point mutations. Depending on their target genes, miRs can function as pro-oncogenic (oncomirs) or as tumor suppressors. The discovery that certain oncomirs are clustered in multi-cistrons that are regulated by oncogenes, further illuminated their significance in cancer development and progression. It appears that miR expression profiling provides accurate signatures for different cancer types, which sometimes are superior to genomic profiling. It is expected that specific miRs would become useful biomarkers and drugs in the diagnosis and therapy of various cancers. We studied the role of miRs in the apoptotic response of leukemic cells to glucocorticoid (GC) hormones. Deep-sequencing analysis revealed that miR103 is up-regulated in GC-sensitive but not resistant leukemias upon treatment with GC(Dexamethasone). Upon transfection, miR-103 confers GC apoptotic sensitivity to otherwise GC-resistant cell. miR103 abrogates c-Myc expression and up-regulates Bim, a pro-apoptotic protein crucial for GC-induced death. miR103 mediated, c-Myc ablation is followed by down-regulation of the multi-cistron miR-17~92a (oncomir1), in particular miR18a and miR20a. miR18a targets GR for degradation whereas miR20a targets Bim degradation. Hence, miR103 acts, in concert with Bim and GR, as a "tumor suppressor" that leads to reduced proliferation, cell-cycle arrest and cell death. Our studies indicate that miR103 should be evaluated as a biomarker that predicts the response of leukemia patients to GC based therapy. It may also become a therapeutic tool that sensitizes resistant leukemic cells to GC-induced death.

Publications (2015 – 2018)

1. 1: Liu L, Aleksandrowicz E, Schönsiegel F, Gröner D, Bauer N, Nwaeburu CC, Zhao Z, Gladkich J, Hoppe-Tichy T, Yefenof E, Hackert T, Strobel O, Herr I.
2. Dexamethasone mediates pancreatic cancer progression by glucocorticoid receptor, TGFβ and JNK/AP-1. Cell Death Dis. 2017 Oct 5;8(10):e3064.
3. 2: Kfir-Erenfeld S, Haggiag N, Biton M, Stepensky P, Assayag-Asherie N, Yefenof E. miR-103 inhibits proliferation and sensitizes hemopoietic tumor cells for glucocorticoid-induced apoptosis. Oncotarget. 2017 Jan 3;8(1):472-489
4. 3: Schipp C, Nabhani S, Bienemann K, Simanovsky N, Kfir-Erenfeld S,
5. Assayag-Asherie N, Oommen PT, Revel-Vilk S, Hönscheid A, Gombert M, Ginzel S, Schäfer D, Laws HJ, Yefenof E, Fleckenstein B, Borkhardt A, Stepensky P, Fischer U. Specific antibody deficiency and autoinflammatory disease extend the clinical and immunological spectrum of heterozygous NFKB1 loss-of-function mutations in humans. Haematologica. 2016 Oct;101(10):e392-e396.
6. 4: Uzana R, Eisenberg G, Merims S, Frankenburg S, Pato A, Yefenof E, Engelstein R, Peretz T, Machlenkin A, Lotem M. Human T cell crosstalk is induced by tumor membrane transfer. PLoS One. 2015 Feb 11;10(2):e0118244.

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 established a new startup company named NectinTx which translate our findings in the cancer field into the clinic. I am happy to report that our first anti-cancer agent was recently licensed to Northern Biologics for $85,000,000. In addition, we discovered in the last years that NK cells which are present at very large numbers in the uterus during pregnancy remember the first pregnancy and react better in subsequent pregnancies to better support baby growth.

Publications (2015 – 2018)

1: Isaacson B, Mandelboim O. Sweet Killers: NK Cells Need Glycolysis to Kill Tumors. Cell Metab. 2018 Aug 7;28(2):183-184.

2: Edri A, Shemesh A, Iraqi M, Matalon O, Brusilovsky M, Hadad U, Radinsky O, Gershoni-Yahalom O, Dye JM, Mandelboim O, Barda-Saad M, Lobel L, Porgador A. The Ebola-Glycoprotein Modulates the Function of Natural Killer Cells. Front Immunol. 2018 Jul 2;9:1428.

3: Dassa L, Seidel E, Oiknine-Djian E, Yamin R, Wolf DG, Le-Trilling VTK, Mandelboim O. The Human Cytomegalovirus Protein UL148A Downregulates the NK Cell-Activating Ligand MICA To Avoid NK Cell Attack. J Virol. 2018 Aug 16;92(17).

4: Elias S, Kahlon S, Kotzur R, Kaynan N, Mandelboim O. Obinutuzumab activates FcγRI more potently than other anti-CD20 antibodies in chronic lymphocytic leukemia (CLL). Oncoimmunology. 2018 Feb 12;7(6):e1428158.

5: 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. Trained Memory of Human Uterine NK Cells Enhances Their Function in Subsequent Pregnancies. Immunity. 2018 May 15;48(5):951-962.

6: Isaacson B, Hadad T, Bachrach G, Mandelboim O. Quantification of Bacterial Attachment to Tissue Sections. Bio Protoc. 2018 Mar 5;8(5).

7: Toledano T, Vitenshtein A, Stern-Ginossar N, Seidel E, Mandelboim O. Decay of the Stress-Induced Ligand MICA Is Controlled by the Expression of an Alternative 3' Untranslated Region. J Immunol. 2018 Apr 15;200(8):2819-2825.

8: Glasner A, Levi A, Enk J, Isaacson B, Viukov S, Orlanski S, Scope A, Neuman T, Enk CD, Hanna JH, Sexl V, Jonjic S, Seliger B, Zitvogel L, Mandelboim O. NKp46 Receptor-Mediated Interferon-γ Production by Natural Killer Cells Increases Fibronectin 1 to Alter Tumor Architecture and Control Metastasis. Immunity. 2018 Feb 20;48(2):396-398.

9: Levi-Schaffer F, Mandelboim O. Inhibitory and Coactivating ReceptorsRecognising the Same Ligand: Immune Homeostasis Exploited by Pathogens and Tumours. Trends Immunol. 2018 Feb;39(2):112-122.

10: Glasner A, Isaacson B, Viukov S, Neuman T, Friedman N, Mandelboim M, Sexl V, Hanna JH, Mandelboim O. Increased NK cell immunity in a transgenic mouse model of NKp46 overexpression. Sci Rep. 2017 Oct 12;7(1):13090.

11: Glasner A, Oiknine-Djian E, Weisblum Y, Diab M, Panet A, Wolf DG, Mandelboim O. Zika Virus Escapes NK Cell Detection by Upregulating Major Histocompatibility Complex Class I Molecules. J Virol. 2017 Oct 27;91(22). pii: e00785-17

12: Charpak-Amikam Y, Kubsch T, Seidel E, Oiknine-Djian E, Cavaletto N, Yamin R, Schmiedel D, Wolf D, Gribaudo G, Messerle M, Cicin-Sain L, Mandelboim O. Human cytomegalovirus escapes immune recognition by NK cells through the downregulation of B7-H6 by the viral genes US18 and US20. Sci Rep. 2017 Aug 17;7(1):8661.

13: Bar-On Y, Charpak-Amikam Y, Glasner A, Isaacson B, Duev-Cohen A, Tsukerman P, Varvak A, Mandelboim M, Mandelboim O. NKp46 Recognizes the Sigma1 Protein of Reovirus: Implications for Reovirus-Based Cancer Therapy. J Virol. 2017 Sep12;91(19).

14: Abed J, Maalouf N, Parhi L, Chaushu S, Mandelboim O, Bachrach G. Tumor Targeting by Fusobacterium nucleatum: A Pilot Study and Future Perspectives. Front Cell Infect Microbiol. 2017 Jun 30;7:295.

15: Isaacson B, Hadad T, Glasner A, Gur C, Granot Z, Bachrach G, Mandelboim O. Stromal Cell-Derived Factor 1 Mediates Immune Cell Attraction upon Urinary Tract Infection. Cell Rep. 2017 Jul 5;20(1):40-47.

16: Miletic A, Lenartic M, Popovic B, Brizic I, Trsan T, Miklic K, Mandelboim O, Krmpotic A, Jonjic S. NCR1-deficiency diminishes the generation of protective murine cytomegalovirus antibodies by limiting follicular helper T-cell maturation. Eur J Immunol. 2017 Sep;47(9):1443-1456.

17: Schmiedel D, Mandelboim O. Disarming Cellular Alarm Systems-Manipulation of Stress-Induced NKG2D Ligands by Human Herpesviruses. Front Immunol. 2017 Apr 11;8:390.

18: Eichmüller SB, Osen W, Mandelboim O, Seliger B. Immune Modulatory microRNAs Involved in Tumor Attack and Tumor Immune Escape. J Natl Cancer Inst. 2017 Oct 1;109(10).

19: Berhani O, Nachmani D, Yamin R, Schmiedel D, Bar-On Y, Mandelboim O. Vigilin Regulates the Expression of the Stress-Induced Ligand MICB by Interacting withIts 5' Untranslated Region. J Immunol. 2017 May 1;198(9):3662-3670.

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

21: Glasner A, Isaacson B, Mandelboim O. Expression and function of NKp46 W32R: the human homologous protein of mouse NKp46 W32R (Noé). Sci Rep. 2017 Jan 30;7:40944.

22: Stein N, Tsukerman P, Mandelboim O. The paired receptors TIGIT and DNAM-1 as targets for therapeutic antibodies. Hum Antibodies. 2017;25(3-4):111-119.

23: Enk J, Levi A, Weisblum Y, Yamin R, Charpak-Amikam Y, Wolf DG, Mandelboim O. HSV1 MicroRNA Modulation of GPI Anchoring and Downstream Immune Evasion. Cell Rep. 2016 Oct 18;17(4):949-956.

24: Vitenshtein A, Charpak-Amikam Y, Yamin R, Bauman Y, Isaacson B, Stein N, Berhani O, Dassa L, Gamliel M, Gur C, Glasner A, Gomez C, Ben-Ami R, Osherov N, Cormack BP, Mandelboim O. NK Cell Recognition of Candida glabrata through Binding of NKp46 and NCR1 to Fungal Ligands Epa1, Epa6, and Epa7. Cell Host Microbe. 2016 Oct 12;20(4):527-534.

25: Diab M, Vitenshtein A, Drori Y, Yamin R, Danziger O, Zamostiano R, Mandelboim M, Bacharach E, Mandelboim O. Suppression of human metapneumovirus (HMPV) infection by the innate sensing gene CEACAM1. Oncotarget. 2016 Oct 11;7(41):66468-66479.

26: Schmiedel D, Tai J, Levi-Schaffer F, Dovrat S, Mandelboim O. Human Herpesvirus 6B Downregulates Expression of Activating Ligands during Lytic Infection To Escape Elimination by Natural Killer Cells. J Virol. 2016 Oct 14;90(21):9608-9617.

27: Lenac Rovis T, Kucan Brlic P, Kaynan N, Juranic Lisnic V, Brizic I, Jordan S, Tomic A, Kvestak D, Babic M, Tsukerman P, Colonna M, Koszinowski U, Messerle M, Mandelboim O, Krmpotic A, Jonjic S. Inflammatory monocytes and NK cells play a crucial role in DNAM-1-dependent control of cytomegalovirus infection. J Exp Med. 2016 Aug 22;213(9):1835-50.

28: Vitenshtein A, Weisblum Y, Hauka S, Halenius A, Oiknine-Djian E, Tsukerman P, Bauman Y, Bar-On Y, Stern-Ginossar N, Enk J, Ortenberg R, Tai J, Markel G, Blumberg RS, Hengel H, Jonjic S, Wolf DG, Adler H, Kammerer R, Mandelboim O. CEACAM1-Mediated Inhibition of Virus Production. Cell Rep. 2016 Jun 14;15(11):2331-9.

29: Reches A, Nachmani D, Berhani O, Duev-Cohen A, Shreibman D, Ophir Y, Seliger B, Mandelboim O. HNRNPR Regulates the Expression of Classical and NonclassicalMHC Class I Proteins. J Immunol. 2016 Jun 15;196(12):4967-76.

30: Yamin R, Lecker LSM, Weisblum Y, Vitenshtein A, Le-Trilling VTK, Wolf DG, Mandelboim O. HCMV vCXCL1 Binds Several Chemokine Receptors and Preferentially Attracts Neutrophils over NK Cells by Interacting with CXCR2. Cell

Rep. 2016 May 17;15(7):1542-1553.

31: Baía D, Pou J, Jones D, Mandelboim O, Trowsdale J, Muntasell A, López-BotetM. Interaction of the LILRB1 inhibitory receptor with HLA class Ia dimers. Eur J Immunol. 2016 Jul;46(7):1681-90.

32: Jasinski-Bergner S, Reches A, Stoehr C, Massa C, Gonschorek E, Huettelmaier S, Braun J, Wach S, Wullich B, Spath V, Wang E, Marincola FM, Mandelboim O, Hartmann A, Seliger B. Identification of novel microRNAs regulating HLA-G expression and investigating their clinical relevance in renal cell carcinoma. Oncotarget. 2016 May 3;7(18):26866-78.

33: Ophir Y, Duev-Cohen A, Yamin R, Tsukerman P, Bauman Y, Gamliel M, Mandelboim O. PILRα binds an unknown receptor expressed primarily on CD56bright and decidual-NK cells and activates NK cell functions. Oncotarget. 2016 Jul 5;7(27):40953-40964.

34: Bauman Y, Drayman N, Ben-Nun-Shaul O, Vitenstein A, Yamin R, Ophir Y, Oppenheim A, Mandelboim O. Downregulation of the stress-induced ligand ULBP1 following SV40 infection confers viral evasion from NK cell cytotoxicity. Oncotarget. 2016 Mar 29;7(13):15369-81.

35: Schmiedel D, Tai J, Yamin R, Berhani O, Bauman Y, Mandelboim O. The RNA binding protein IMP3 facilitates tumor immune escape by downregulating the stress-induced ligands ULPB2 and MICB. Elife. 2016 Mar 16;5. pii: e13426.

36: Houston A, Williams JM, Rovis TL, Shanley DK, O'Riordan RT, Kiely PA, Ball M, Barry OP, Kelly J, Fanning A, MacSharry J, Mandelboim O, Singer BB, Jonjic S, Moore T. Pregnancy-specific glycoprotein expression in normal gastrointestinal tract and in tumors detected with novel monoclonal antibodies. MAbs. 2016;8(3):491-500.

37: Duev-Cohen A, Bar-On Y, Glasner A, Berhani O, Ophir Y, Levi-Schaffer F, Mandelboim M, Mandelboim O. The human 2B4 and NTB-A receptors bind the influenza viral hemagglutinin and co-stimulate NK cell cytotoxicity. Oncotarget. 2016 Mar 15;7(11):13093-105.

38: Tsukerman P, Eisenstein EM, Chavkin M, Schmiedel D, Wong E, Werner M, Yaacov B, Averbuch D, Molho-Pessach V, Stepensky P, Kaynan N, Bar-On Y, Seidel E, Yamin R, Sagi I, Elpeleg O, Mandelboim O. Cytokine secretion and NK cell activity in human ADAM17 deficiency. Oncotarget. 2015 Dec 29;6(42):44151-60.

39: Okada K, Sato S, Sato A, Mandelboim O, Yamasoba T, Kiyono H. Identification and Analysis of Natural Killer Cells in Murine Nasal Passages. PLoS One. 2015 Nov 17;10(11):e0142920.

40: Gur C, Mandelboim O, Bachrach G. "Messieurs, c'est les microbes qui auront le dernier mot": Gentlemen, it is the microbes who have the last word (Louis Pasteur)-Fusobacterium nucleatum protect tumors from killing by immune cells. Oncoimmunology. 2015 May 27;4(9):e1038690.

41: Glasner A, Simic H, Miklić K, Roth Z, Berhani O, Khalaila I, Jonjic S,Mandelboim O. Expression, Function, and Molecular Properties of the Killer Receptor Ncr1-Noé. J Immunol. 2015 Oct 15;195(8):3959-69.

42: Weisblum Y, Panet A, Zakay-Rones Z, Vitenshtein A, Haimov-Kochman R, Goldman-Wohl D, Oiknine-Djian E, Yamin R, Meir K, Amsalem H, Imbar T, Mandelboim O, Yagel S, Wolf DG. Human cytomegalovirus induces a distinct innate immune response in the maternal-fetal interface. Virology. 2015 Nov;485:289-96.

43: Levi I, Amsalem H, Nissan A, Darash-Yahana M, Peretz T, Mandelboim O, Rachmilewitz J. Characterization of tumor infiltrating natural killer cell subset. Oncotarget. 2015 May 30;6(15):13835-43.

44: Wensveen FM, Jelenčić V, Valentić S, Šestan M, Wensveen TT, Theurich S, Glasner A, Mendrila D, Štimac D, Wunderlich FT, Brüning JC, Mandelboim O, Polić B. NK cells link obesity-induced adipose stress to inflammation and insulin resistance. Nat Immunol. 2015 Apr;16(4):376-85.

45: Yossef R, Gur C, Shemesh A, Guttman O, Hadad U, Nedvetzki S, Miletić A, Nalbandyan K, Cerwenka A, Jonjic S, Mandelboim O, Porgador A. Targeting natural killer cell reactivity by employing antibody to NKp46: implications for type 1 diabetes. PLoS One. 2015 Feb 26;10(2):e0118936.

46: Seidel E, Le VT, Bar-On Y, Tsukerman P, Enk J, Yamin R, Stein N, Schmiedel D, Oiknine Djian E, Weisblum Y, Tirosh B, Stastny P, Wolf DG, Hengel H, Mandelboim O. Dynamic Co-evolution of Host and Pathogen: HCMV Downregulates the Prevalent Allele MICA∗008 to Escape Elimination by NK Cells. Cell Rep. 2015 Feb 12.

47: Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, Enk J, Bar-On Y, Stanietsky-Kaynan N, Coppenhagen-Glazer S, Shussman N, Almogy G, Cuapio A, Hofer E, Mevorach D, Tabib A, Ortenberg R, Markel G, Miklić K, Jonjic S, Brennan CA, Garrett WS, Bachrach G, Mandelboim O. Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. Immunity. 2015 Feb 17;42(2):344-355.

48: Glasner A, Roth Z, Varvak A, Miletic A, Isaacson B, Bar-On Y, Jonjic S, Khalaila I, Mandelboim O. Identification of putative novel O-glycosylations in the NK killer

receptor Ncr1 essential for its activity. Cell Discov. 2015 Dec 22;1:15036.

49: Brusilovsky M, Radinsky O, Cohen L, Yossef R, Shemesh A, Braiman A, Mandelboim O, Campbell KS, Porgador A. Regulation of natural cytotoxicity eceptors by heparan sulfate proteoglycans in -cis: A lesson from NKp44. Eur J Immunol. 2015 Apr;45(4):1180-91.

MSc and PhD students that graduated:

PhD

Chamutal Gur, PhD (Cum Laude)

Ariella Glasner

Yotam Bar-On

Yoav Bauman

Jonathan Enk

Dominik Schmiedel

Pinhas Tsukerman

Alon Vitenstein (Cum Laude)

Rachel Yamin

MSc

Yael Ophir (Cum Laude)