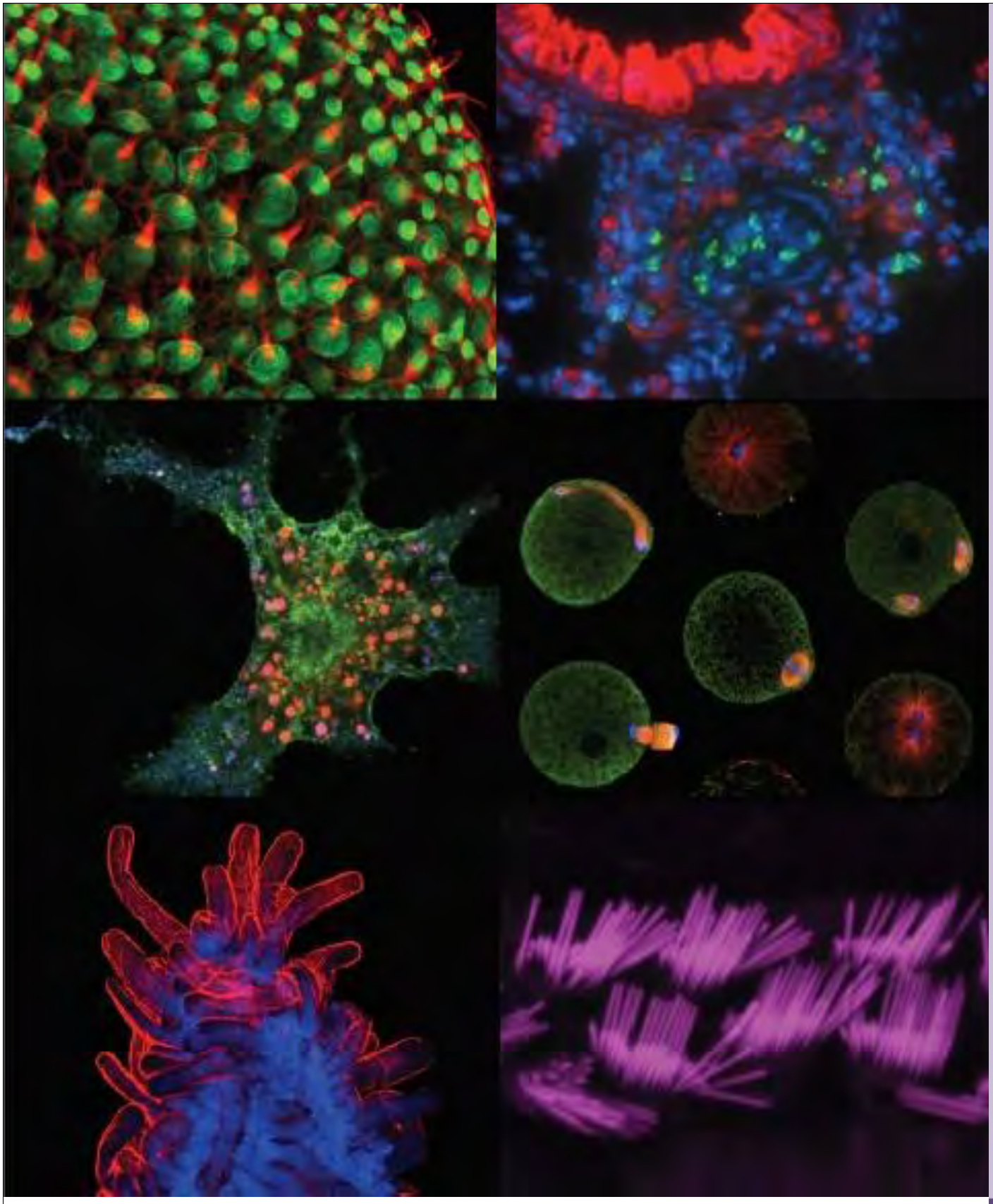

Sackler Faculty of Medicine

Research 2014

TEL AVIV UNIVERSITY

The Sackler Faculty of Medicine

The Sackler Faculty of Medicine is Israel's largest medical research and training complex. The Sackler Faculty of Medicine of Tel Aviv University was founded in 1964 following the generous contributions of renowned U.S. doctors and philanthropists Raymond, and the late Mortimer and Arthur Sackler. Research at the Sackler Faculty of Medicine is multidisciplinary, as scientists and clinicians combine efforts in basic and translational research. Research is conducted in the laboratories on the TAU campus, and in the clinical facilities affiliated to the Faculty. This network of preclinical and clinical teams helps realize the ultimate goals of the research: the basic understanding of human pathophysiology and the improvement of prevention, diagnosis and treatment of disease. The research of most of the 120 Preclinical faculty members, from four schools of the Sackler Faculty of Medicine, are featured in this research brochure. These schools are the Sackler School of Medicine, the School of Health Professions, the School of Public Health, and the School of Dental Medicine. Education takes place in all these schools and in the Graduate School of Medicine, School of Continuing Medical Education, the New York State American Program and the B.Sc. Program in Medical Life Sciences.

The Faculty of Medicine engages in joint teaching and research programs with nearly every faculty at Tel Aviv University and multi-nationally with schools, hospitals and research centers throughout the world. The Sackler faculty is known for research in the following areas: cancer biology, stem cells, diabetes, neurodegenerative diseases, infectious diseases and genetic diseases, including but not imited to Alzheimer's disease, Parkinson's disease and HIV/AIDS. Physicians in 181 Sacker affiliated departments and institutes in 17 hospitals hold academic appointments at Tel Aviv University. The Gitter-Smolarz Life Sciences and Medicine Library serves students and staff and is the center of a consortium of 15 hospital libraries.

The student body is made up of 750 Israeli students enrolled in the regular 6-year M.D. degree program, 300 American and Canadian students enrolled in a 4-year M.D. program chartered by the State of New York and accredited by the State of Israel, and a 4-year program for Israeli students for the M.D. degree, with 62 students. Approximately 200 students study dental medicine in a six-year program where they are awarded the D.M.D. degree and another 2,000 students are enrolled in the health professions programs where they will earn degrees in Communications Disorders, Nursing, Physical Therapy and Occupational Therapy. Sackler's Graduate School for Advanced Studies trains approximately 800 masters and doctoral level students in the biomedical disciplines, with a special emphasis on a multidisciplinary approach and application of fundamental knowledge to important biomedical problems.

The Sackler Faculty of Medicine is led by the Dean, Professor Yosef Mekori; Vice Deans Prof. Karen Avraham, Prof. Leonard Leibovici, Prof. Moshe Phillip, Prof. Anat Lowenstein, and Prof. Ehud Grossman; and Assistant to the Dean, Ms. Yael Keilin.

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Tel Aviv University Sackler Cellular and Molecular Imaging Center (SCMIC)

Preclinical Faculty (by School and Principal Investigator)

School of Medicine

School of Health Professions

School of Public Health

School of Dental Medicine

Prof. Ruth Ashery-Padan, Ph.D.

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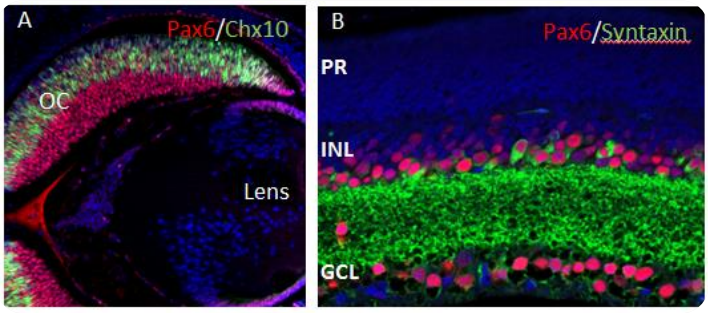
Investigating the Molecular Basis of Visual System Development

Positions

Associate Professor, Sackler Faculty of Medicine
Committee Member, Israel Society of Developmental Biology

Research

We study the gene networks that transform the embryonic cells into a complex, differentiated organ. We focus on exploring this question by studying the process of eye development as a model for organogenesis. We apply cutting-edge technologies including mouse genetic tools (Cre/loxP), molecular biology, and microarray analysis to identify and functionally characterize genes that regulate the development of the eye in mammals. Understanding the normal developmental regulation of the different eye structures is essential for understanding visual disorders and designing treatments for ocular phenotypes including retinal degeneration, glaucoma and cataracts, all of which are leading causes of blindness.



Developmental genes play role in adult neurons. Immunofluorescence analysis reveals the expression pattern of developmental transcription factors (A) in the retinal progenitor cells located in the embryonic mouse optic cup (OC). (C) In the adult retina the developmental gene Pax6 is expressed in subtypes of retinal interneurons that co-express the synaptic protein syntaxin.

Publications

Raviv, S., K. Bharti, S. Rencus-Lazar, Y. Cohen, R. Schyr, N. Evantal, E. Meshorer, A. Zilberberg, M. Idelson, B. Reubinoff, R. Grebe, R. Rosin-Arbesfeld, B.E. Lauderdale, G. Lutty, H. Arnheiter, and **R. Ashery-Padan,** PAX6 Regulates Melanogenesis in the Retinal Pigmented Epithelium through Feed-Forward Regulatory Interactions with MITF. Accepted., PLoS Genet, 2014.

Wolf, L., W. Harrison, J. Huang, Q. Xie, N. Xiao, J. Sun, L. Kong, S.A. Lachke, M.R. Kuracha, V. Govindarajan, P.K. Brindle, **R. Ashery-Padan**, D.C. Beebe, P.A. Overbeek, and A. Cvekl,

Histone posttranslational modifications and cell fate determination: lens induction requires the lysine acetyltransferases CBP and p300. Nucleic Acids Res, 2013. 41(22):10199-214

Wolf, L., C.S. Gao, K. Gueta, Q. Xie, T. Chevallier, N.R. Podduturi, J. Sun, I. Conte, P.S. Zelenka, **R. Ashery-Padan**, J. Zavadil, and A. Cvekl, Identification and characterization of fgf2-dependent mrna:microrna networks during lens fiber cell differentiation. G3: Genes, Genomes, Genetics, 2013. 3:2239-2255.

Farhy, C., M. Elgart, Z. Shapira, V. Oron-Karni, O. Yaron, Y. Menuchin, G. Rechavi, and **R. Ashery-Padan**, Pax6 is required for normal cell-cycle exit and the differentiation kinetics of retinal progenitor cells. PLoS One, 2013. **8**(9): p. e76489.

Zembrzycki A, Chou SJ, **Ashery-Padan R**, Stoykova A, O'Leary DD. Sensory cortex limits cortical maps and drives top-down plasticity in thalamocortical circuits. *Nat Neurosci*. 2013, 16:1060-7.

Shaham O, Gueta K, Mor E, Oren-Giladi P, Grinberg D, Xie Q, Cvekl A, Shomron N, Davis N, Keydar- Prizant M, Raviv S, Pasmanik-Chor M, Bell R, **Levy C**, Avellino R, Banfi S, Conte I, Ashery-Padan R. Pax6 regulates gene expression in the vertebrate lens through miR-204. *PLoS Genet,* 2013, 9:e1003357.

Bochner R, Ziv Y, Zeevi D, Donyo M, Abraham L, Ashery-Padan R, **Ast G**. Phosphatidylserine increases IKBKAP levels in a humanized knock-in IKBKAP mouse model. *Hum Molec Genet*. 2013, 22: 2785-2794

Shaham, O., Y. Menuchin, C. Farhy, and **R. Ashery-Padan**, Pax6: a multi-level regulator of ocular development. Prog Retin Eye Res, 2012. **31**(5): p. 351-76.

Magenheim J, Klein AM, Stanger BZ, **Ashery-Padan R,** Sosa-Pineda B, Gu G, Dor Y. Ngn3(+) endocrine progenitor cells control the fate and morphogenesis of pancreatic ductal epithelium. *Dev Biol* 2011, 359:26-36.

Huang J, Rajagopal R, Liu Y, Dattilo LK, Shaham O, **Ashery-Padan R**, Beebe DC. The mechanism of lens placode formation: A case of matrix-mediated morphogenesis. *Dev Biol* 2011, 355:32-42.

Davis N, Mor E, **Ashery-Padan R**. Roles for Dicer1 in the patterning and differentiation of the optic cup neuroepithelium. *Development* 2011, 138:127-138.

Kroeber M, Davis N, Holzmann S, Kritzenberger M, Shelah-Goraly M, Ofri R, **Ashery-Padan R**, Tamm ER. Reduced expression of Pax6 in lens and cornea of mutant mice leads to failure of chamber angle development and juvenile glaucoma. *Hum Mol Genet* 2010, 19:3332-3342.

He S, Pirity MK, Wang WL, Wolf L, Chauhan BK, Cveklova K, Tamm ER, **Ashery-Padan R**, Metzger D, Nakai A, Chambon P, Zavadil J, Cvekl A. Chromatin remodeling enzyme Brg1 is required for mouse lens fiber cell terminal differentiation and its denucleation. *Epigenetics Chromatin* 2010, 3:21.

Bandah-Rozenfeld D, Mizrahi-Meissonnier L, Farhy C, Obolensky A, Chowers I, Pe'er J, Merin S, Ben-Yosef T, **Ashery-Padan R**, Banin E, Sharon D. Homozygosity mapping reveals null mutations in FAM161A as a cause of autosomal-recessive retinitis pigmentosa. *Am J Hum Genet* 2010, 87:382-391.

Review

Shaham O, Menuchin Y, Farhy C, **Ashery-Padan R**: Pax6: A multi-level regulator of ocular development. *Prog Retin Eye Res* 2012, 31:351-76.

Grants

2010-2014, Roles of Pax6 in retinal development, Israel Science Foundation

2012-2015, Roles for microRNA in RPE differentiation, Morasha, Israel Science Foundation

2012-2015, Roles for Pax6 in neurons of the olfactory bulb, midbrain and retina, German Israeli Foundation (Co-PI with Magdalena Goetz).

Prof. Gil Ast, Ph.D.

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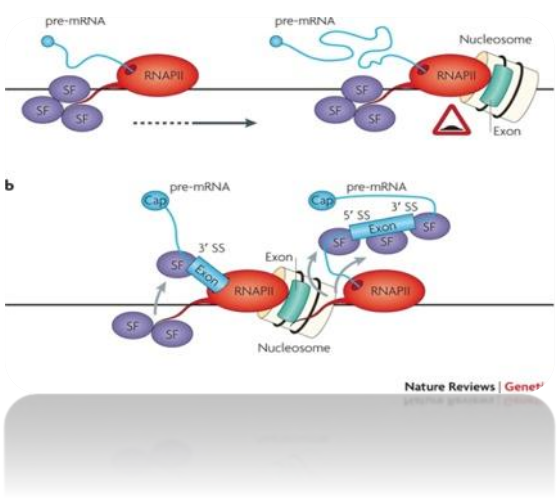
Alternative Splicing Generates Transcriptomic Diversity in Genetic Disorders and Cancer

Positions

Professor, Sackler Faculty of Medicine
Chair, Adelson Graduate School of Medicine

Research

By utilizing the unique strengths of our research group in bioinformatic analyses as well as in genomic and advanced molecular biology methodologies, we are able to make groundbreaking discoveries in the field of alternative splicing. We study how alternative splicing generates higher level of organism complexity, especially in human. However, this comes with a price, and alternative splicing also inflicts many genetic disorders and cancer. Our research involves these two facets of alternative splicing. On one hand, we found how new functions evolved via the generation of new exons (mostly in human). We have also showed how different layers of gene expression affect each other, and found that chromatin organization and epigenetic markers (DNA methylation) mark the exon-intron structure. We also found that during the evolution of warm-blooded organisms two exon-intron gene architectures developed, and these also reflect the different effects of mutations on splicing in cancer and other genetic disorders. On the other hand, we study the impact of splicing abnormalities on colon and lung cancer, and we have recently discovered a new therapy for Familial Dysautonomia, a neurodegenerative disease caused by a splicing defect in the nervous system.



Nucleosome occupancy marks exons and is coupled to transcription. **a** | RNA polymerase II (RNAPII), associated with different splicing factors (SFs), travels along the gene and transcribes it. When RNAPII reaches an area with high nucleosome occupancy and encounters specific histone modifications that mark an exon, it is slowed down. **b** | This panel shows RNAPII and the nucleosome at the point at which their coupling marks the exon boundaries for the splicing machinery. RNAPII transcribes the exon and SFs detach from the carboxy-terminal domain of RNAPII and bind to the 3′ splice site (3′ SS) region of the precursor mRNA (pre-mRNA). During transcription elongation, additional SFs bind intronic and exonic splicing regulatory elements and the 5′ SS.

Publications

Gelfman S, **Ast G**. When epigenetics meets alternative splicing. (2013) The roles of DNA methylation and GC architecture. *Epigenomics*. 2013:351-353.

Melamed Z, Levy A, Ashwal-Fluss R, Lev-Maor G, Mekahel K, Atias N, Gilad S, Sharan R, Levy C, Kadener S, **Ast G**. Alternative splicing regulates biogenesis of miRNAs located across exon-intron junctions. (2013). *Molecular Cell*, 50:869-881.

Bochner R, Ziv Y, Zeevi D, Donyo M, Abraham L, Ashery-Padan R, **Ast G**. Phosphatidylserine increases IKBKAP levels in a humanized knock-in IKBKAP mouse model. (2013) *Human Molecular Genetics*. 22: 2785-2794

Gelfman S, Cohen N, Yearim A, **Ast G**. DNA-methylation effect on cotranscriptional splicing is dependent on GC architecture of the exon-intron structure. (2013) *Genome Research*. 23:789-799.

Amit M, Donyo M, Hollander D, Goren A, Kim E, Gelfman S, Lev-Maor G, Burstein D, Schwartz S, Postolsky B, Pupko P, **Ast G.** (2012) Differential GC content between exons and introns establishes distinct strategies of splice site recognition. *Cell Reports*, 1:543-556.

Gelfman S, Burstein D, Penn O, Savchenko A, Amit M, Schwartz S, Pupko T, **Ast G**. (2012) Changes in exon-intron structure during vertebrate evolution affect the splicing pattern of exons. *Genome Research* 22:35-50.

Cheishvili D, Maayan C, Cohen-Kupiec R, Lefler S, Weil M, **Ast G**, Razin A. (2011) IKAP/Elp1 involvement in cytoskeleton regulation and implication for familial dysautonomia. *Hum Mol Genet*. 20:1585-1594.

Keren H., Donyo M., Zeevi D., Maayan, C., Pupko, T. and **Ast G**. (2010) Phosphatidylserine increases IKBKAP levels in Familial Dysautonomia Cells. *PloS One*, 5:e15884.

Llorian, M., Schwartz, S., Clark, T. A., Hollander, D., Tan, L., Spellman, R., Gordon, A., Schweitzer, A. C., de la Grange, P., **Ast ,G**., and Smith, C. (2010) Position-dependent alternative splicing activity revealed by global profiling of alternative splicing events regulated by PTB. *Nature Struct Mol Biol.* 17:1114-23.

Sela N, Mersch B, Hotz-Wagenblatt A, **Ast G**. (2010) Characteristics of transposable element exonization within human and mouse. *PLoS One*. 2010 ;5:e10907.

Sela N, Kim E, **Ast G**. (2010) The role of transposable elements in the evolution of non-mammalian vertebrates and invertebrates. *Genome Biol*. 11:R59.

Goren A, Kim E, Amit M, Vaknin K, Kfir N, Ram O, **Ast G**. (2010) Overlapping splicing regulatory motifs--combinatorial effects on splicing. *Nucleic Acids Res*. 38:3318-3327.

Asaf Levy, Schraga Schwartz and **Ast G**. (2010) Insertion hotspots and nepotism of DNA parasites: large-scale analysis of human nested transposed elements. *Nucleic Acids Research*, 38:1515-1530.

Reviews

Schraga Schwartz and **Ast G**. (2010) Chromatin density and splicing destiny: on the cross-talk between chromatin structure and splicing. *EMBO J*. 29:1629–1636.

Keren H, Lev-Maor G, **Ast G**. (2010) Alternative splicing and evolution: diversification, exon definition and function. *Nature Rev Genet.* 11:345-355.

Grants

2012-2014 Dysautonomia Foundation, Understanding the role of IKAP gene in Neurodegeneration

2012-2015 ISF- Morasha for Neurodegenerative Diseases, Tissue-specific alternative splicing disease

2013-2015 Teva – Neuroscience, Evaluation of therapeutic agents in a mouse model for Familial Dysotonomia

2013-2018 Israel Science Foundation, Identification of novel determinants of splicing regulation

June 1, 2014

Prof. Bernard Attali, Ph.D.

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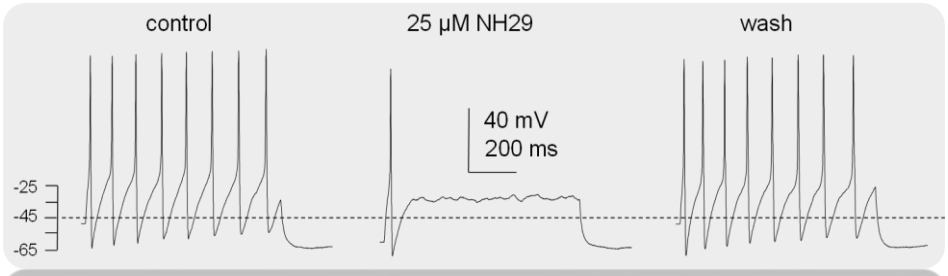
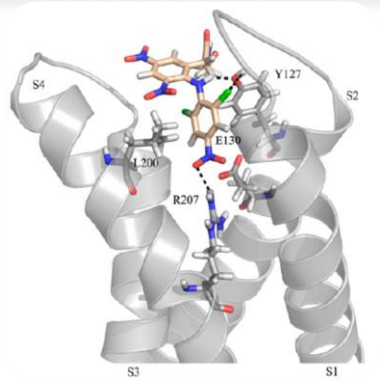
Normal and Diseased Potassium Channels in Human Brain and Heart

Position
Professor, Sackler Faculty of Medicine

Research
Reaching an understanding in molecular terms of the mechanisms by which changes in membrane potential regulate cellular events is the main concern of our research. We focus our interest on potassium channels because they play crucial roles in many cellular functions such as shaping cardiac and neuronal action potentials, tuning neuronal firing patterns, synaptic integration or modulating neurotransmitter release. Using the powerful combination of molecular biology, biophysics, biochemistry and electrophysiology, our research aims at elucidating the structural, biophysical and physiological attributes of potassium channels in human brain and heart and whose mutations lead to major neurological and cardiovascular disorders like epilepsy, myokymia, atrial or ventricular fibrillation.



Activation of M-type potassium channels by our homemade NH29 opener inhibits evoked spike discharge in dorsal root ganglion sensory neurons.



Docking of the NH29 gating-modifier molecule onto the voltage sensor domain of the Kv7.2 potassium channel.

Publications

Manuscripts

Peretz A, Pell L, Gofman Y, Haitin Y, Shamgar L, Patrich E, Kornilov P, Gourgy-Hacohen O, Ben-Tal N, **Attali B**. (2010) Targeting the voltage sensor of Kv7.2 channels with a new gating-modifier. *Proc Natl Acad Sci USA*.107:15637-15642.

Strutz-Seebohm N, Pusch M, Wolf S, Stoll R, Tapken D, Gerwert K, **Attali B**, Seebohm G. (2011) Structural basis of slow activation gating in the cardiac I Ks channel complex. *Cell Physiol Biochem.* 27:443-452.

Ebner-Bennatan S, Patrich E, Peretz A, Kornilov P, Tiran Z, Elson A, **Attali B**. (2012) Multi-faceted modulation of K+ channels by protein tyrosine phosphatase epsilon tunes neuronal excitability. *J Biol Chem.* 287:27614-27628.

Weisbrod D, Peretz A, Ziskind A, Menaker N, Oz S, Barad L, Eliyahu S, Itskovitz-Eldor J, Dascal N, Khananshvili D, Binah O, **Attali B**. (2013) SK4 Ca2+ activated K+ channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA*. 110:E1685-94.

Kornilov P, Peretz A, Lee Y, Son K, Lee JH, Refaeli B, Roz N, Rehavi M, Choi S, **Attali B**. (2014) Promiscuous gating modifiers target the voltage sensor of Kv7.2, TRPV1, and Hv1 cation channels.FASEB J. 2014 Mar 5. [Epub ahead of print].

Reviews

Kornilov P, Peretz A, **Attali B.** (2013) Channel gating pore: a new therapeutic target. *Cell Res.* 2013 23:1067-8.

Dvir M, Peretz A, Haitin Y, **Attali B**. (2013) Recent molecular insights from mutated I_{KS} channels in cardiac arrhythmia. *Curr. Opin. Pharmacol*. In press.

Grants

2013-2017: Israel Academy of Science, (ISF:1215/13). Role of SK4 Ca2+-activated K+ channels in the developing human cardiac pacemaker using
embryonic stem cell-derived cardiomyocytes as a model. (PI).

2013-2017: Fields Fund for Cardiovascular Research (Co-PI).

May 24, 2014

Prof. Karen B. Avraham, Ph.D.

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Sackler Faculty of Medicine
Sagol School of Neuroscience

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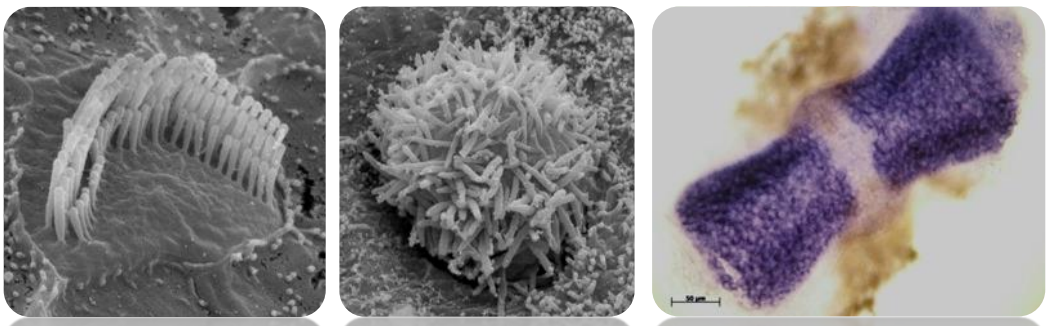
Genomic Analysis of Hereditary Hearing Loss

Positions

Professor, Sackler Faculty of Medicine
Vice Dean for Preclinical Affairs, Sackler Faculty of Medicine
Board Member, I-CORE for Gene Regulation in Complex Human Disease
President, Israel Society of Auditory Research

Research

Our primary interest is the genetic basis of hereditary hearing loss or deafness. Our group is working towards the identification, characterization and regulation of genes associated with hereditary hearing loss. For gene discovery, we focus on the Israeli Jewish and Palestinian Arab populations in the Middle East. Our studies have encompassed the prevalence of connexin 26 mutations in these populations, the most common form of deafness, to the identification of mutations in over 30 genes, since this is a genetically heterogeneous disease. We are employing deep sequencing, also known as massively parallel sequencing, to identify mutations using the latest genomic technology. Our work has provided the link between gene discovery and clinical diagnosis in genetic clinics in medical centers throughout Israel. In addition, we have studied the auditory and vestibular systems of a dozen mouse mutants, focusing on mutation identification, morphological and functional analysis of the organ of Corti and its cells, and behavioral analysis of hearing and balance disorders. This has allowed us to define the pathways leading to deafness in mouse models for human deafness. Most recently, we have demonstrated that microRNAs are essential for development and function of inner ear hair cells in vertebrates through microRNA expression, mouse mutants and target identification.



Wild type and mutant hair cell bundles in the PCKO mouse, lacking microRNAs in the inner ear, demonstrated by scanning electron microscopy (2 left panels). *In situ* hybridization reveals expression of the microRNA-182 in the inner ear crista (right).

Publications
Manuscripts

Shefer, S., Gordon, C.R., **Avraham, K.B**. and Mintz, M. (2010) Progressive vestibular mutation leads to elevated anxiety. *Brain Res*. 1317: 157–164.

Shahin, H., Rahil, M., Abu Rayan, A., **Avraham, K.B**., King, M.-C., Kanaan, M. and Walsh, T. (2010) Nonsense mutation of the stereociliar membrane protein gene PTPRQ in human hearing loss DFNB84. *J. Med. Gen*. 47: 643-645.

Wainreb, G., Ashkenazy, H., Bromberg, Y., Starovolsky-Shitrit, A., Haliloglu, T., Ruppin, E., **Avraham, K.B**., Rost, B. and Ben-Tal, N. (2010) MuD: an interactive web server for the prediction of non-neutral substitutions using protein structural data. *Nucleic Acids Res*. 38: W523-528.

Walsh, T., Shahin, H., Elkan-Miller, T., Lee, M.K., Thornton, A.M., Roeb, W., Abu Rayyan, A., Loulus, S., **Avraham, K.B.**, King, M.-C. and Kanaan, M. (2010) Whole exome sequencing and homozygosity mapping identify mutation in the cell polarity protein GPSM2 as the cause of non-syndromic hearing loss DFNB82. Am. J. Hum. Genet. 87: 1-5.

Walsh, T., Pierce, S.B., Lenz, D.R., Brownstein, Z., Dagan-Rosenfeld, O., Shahin, H., Roeb, W., McCarthy, S., Nord, A.S., Gordon, C.R., Ben-Neriah, Z., Sebat, J., Kanaan, M., Lee, M.K., Frydman, M., King, M.-C. and **Avraham, K.B**. (2010) Genomic duplication and over-expression of *TJP2/ZO-2* leads to altered expression of apoptosis genes in progressive non-syndromic hearing loss DFNA51. *Am. J. Hum. Genet*. 87: 101-109.

Dror, A.A., Politi, Y., Shahin, H., Lenz, D.R., Dossena, S., Nofziger, C., Fuchs, H., Hrabé de Angelis, M., Paulmichl, M., Weiner, S. and **Avraham, K.B**. (2010). Calcium oxalate stone formation in the inner ear as a result of an *Slc26a4* mutation. *J. Biol. Chem*. 285: 21724-21735.

Atar, O. and **Avraham, K.B**. (2010) Anti-apoptotic factor z-val-ala-asp-fluoromethylketone promotes the survival of cochlear hair cells in a mouse model for human deafness. *Neurosci.* 168: 851–857.

Lenz, D.R., Dror, A.A., Wekselman, G. Fuchs, H., Hrabé de Angelis, M. and **Avraham, K.B**. (2010) The inner ear phenotype of Volchok (*Vlk*): an ENU-induced mouse model for CHARGE syndrome. *Audiol. Med*. 8: 110-119.

Walsh, V.L., Raviv, D., Dror, A.A., Shahin, H., Walsh, T., Kanaan, M.N., **Avraham, K.B**. and King, M.-C. (2010) A mouse model for human hearing loss DFNB30 due to loss of function of myosin IIIA. *Mamm. Genome* 22: 170-177.

Wainreb, G., Ashkenazy, H., Bromberg, Y., Starovolsky-Shitrit, A., Haliloglu, T., Ruppin, E., **Avraham, K.B**., Rost, B. and Ben-Tal, N. (2010) MuD: an interactive web server for the prediction of non-neutral substitutions using protein structural data. *Nucleic Acids Res.* 38: W523-528.

Paz, A., Brownstein, Z., Ber, Y., Bialik, S., David, E., Sagir, D., Ulitsky, I., Elkon, R., Kimchi, A., **Avraham, K.B.,** Shiloh, Y. and Shamir, R. (2011) SPIKE: a database of highly curated human signaling pathways. *Nucleic Acids Res*. 39: D793-793.

Elkan-Miller, T., Ulitsky, I., Hertzano, R., Rudnicki, A., Dror, A.A., Lenz, D.R., Elkon, R., Irmler, M., Beckers, J., Shamir, R. and **Avraham, K.B**. (2011) Integration of transcriptomics, proteomics, and microRNA analyses reveals novel microRNA regulation of targets in the mammalian inner ear. *PLoS One* 6: e18195.

Brownstein, Z.*, Friedman, L.M.*, Shahin, H., Oron-Karni, V., Kol, N., Abu Rayyan, A., Parzefall, T., Lev, D., Shalev, S., Frydman, M., Davidov, B., Shohat, M., Rahile, M., Lieberman, S., Levy-Lahad, E., Lee, M., Shomron, N., King, M.-C., Walsh, T., Kanaan, M. and **Avraham, K.B.** (2011) Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families. *Genome Biol*. 12: R89.

Rosengauer, E., Hartwich, H., Hartmann, A.M., Rudnicki, A., Satheesh, S.V., **Avraham, K.B.** and Nothwang, H.G. (2012) Egr2::Cre mediated conditional ablation of Dicer disrupts histogenesis of mammalian central auditory nuclei. *PLoS One*. 7:e49503.

Horn, H.F.*, Brownstein, Z.*, Lenz, D.R., Shivatzki, S., Dror, A.A., Dagan-Rosenfeld, O., Friedman, L.M., Roux, K.J., Kozlov, S., Jeang, K.-T., Frydman, M., Burke, B., Stewart, C.L., and **Avraham, K.B.** (2013) The LINC complex is essential for hearing. *J. Clin. Invest.* 123:740-750

Parzefall T.*, Shivatzki, S.*, Lenz, D.R., Rathkolb, B., Ushakov, K., Karfunkel, D., Shapira, Y., Wolf, M., Mohr, M., Wolf, E., Sabrautzki, S.,Hrabé de Angelis, M., Frydman, M., Brownstein, Z., and **Avraham, K.B.** (2013) Cytoplasmic mislocalization of POU3F4 due to novel mutations leads to deafness in humans and mice. *Hum. Mut*. 34:1102-1110.

Ehmann, H., Hartwich, H., Salzig, C., Hartmann, N., Clément-Ziza, M., Ushakov, K., **Avraham, K.B**., Bininda-Emonds, O.R.P., Hartmann, A.K., Lang, P., Friauf, E., and Gerd Nothwang, H. (2013) Time-dependent gene expression analysis of the developing superior olivary complex. *J. Biol. Chem.* 288:25865-25879.

Brownstein, Z.*, Abu-Rayyan, A.*, Karfunkel-Doron, D., Sirigu, S., Davidov, B., Shohat, M., Frydman, M., Houdusse, A., Kanaan, M., **Avraham, K.B.** (2013) Novel myosin mutations for hereditary hearing loss revealed by targeted genomic capture and massively parallel sequencing. *Eur J Hum Genet*., 22:768-75.

Takada, Y., Beyer, L.A., Swiderski, D.L., O'Neal, A.L., Prieskorn, D.M., Shivatzki, S., **Avraham, K.B.**, and Raphael, Y. (2013) Connexin 26 null mice exhibit spiral ganglion degeneration that can be blocked by BDNF gene therapy. *Hear. Res*. 309C:124-135.

Behar, D.M., Davidov, B., Brownstein, Z., Ben-Yosef, T., **Avraham, K.B.**, and Shohat, M. (2014) The many faces of sensorineural hearing loss: one founder and two novel mutations affecting one family of mixed Jewish ancestry. *Genet. Test. Mol. Biomarkers*. 18:123-126.

Rudnicki, A., Shivatzki, S., Beyer, L.A., Takada, Y., Raphael, Y. and **Avraham, K.B**. (2014) microRNA-224 regulates Pentraxin 3, a component of the humoral arm of innate immunity, in inner ear inflammation. *Hum. Molec. Genet*. 23:3138-46.

Dror A.A., Lenz, D.R., Shivatzki, S., Cohen, K., Ashur-Fabian, O. and **Avraham, K.B.** (2014) Atrophic thyroid follicles and inner ear defects reminiscent of cochlear hypothyroidism in *Slc26a4*-related deafness. *Mamm. Genome*. DOI 10.1007/s00335-014-9515-1 [Epub ahead of print

Reviews and Chapters

Raviv, D., Dror, A.A. and **Avraham, K.B**. (2010) Hearing loss: a common disorder caused by many rare alleles. *Ann. N.Y. Acad. Sci*. 1214: 168-179.

Dror, A.A. and **Avraham, K.B**. (2010) Hearing impairment: a panoply of genes and functions. *Neuron* 68: 293-308.

Ozçelik, T., Kanaan, M., **Avraham, K.B.**, Yannoukakos, D., Mégarbané, A., Tadmouri, G.O., Middleton, L., Romeo, G., King, M.C. and Levy-Lahad, E. (2010) Collaborative genomics for human health and cooperation in the Mediterranean region. *Nat. Genet*. 42: 641-645.

Lenz, D.R. and **Avraham, K.B**. (2011) Hereditary hearing loss: From human mutation to mechanism. *Hear. Res.* 281: 3-10.

Dror, A., Brownstein, Z. and **Avraham, K.B**. (2011) Integration of human and mouse genetics reveals pendrin function in hearing and deafness. *Cell. Physiol. Biochem*. 28: 535-544.

Brownstein, Z., Bhonker, Y. and **Avraham, K.B**. High-throughput sequencing and the genetic heterogeneity of deafness. *Genome Biol*. 13:245.

Rudnicki, A. and **Avraham, K.B.** (2012) microRNAs: the art of silencing in the ear. *EMBO Mol Med.* 4:849-859.

Avraham, K.B. and Kanaan, M. (2012) Genomic advances for gene discovery in hereditary hearing loss. *J Basic Clin Physiol Pharmacol*. 23:93-97.

Friedman, L.M., Elkan-Miller, T., Rudnicki, A., Dror, A.A. and **Avraham, K.B.** (2011) MicroRNAs in the inner ear: implications for hearing loss. *In*: Usher Syndrome: Pathogenesis, Diagnosis and Therapy. (A. Satpel, ed). Nova Publishers. Chapter 9.

Brownstein, Z., Shivatzki, S. and **Avraham, K.B.** (2013) Molecular Etiology of Deafness and Cochlear Consequences. *In*: Deafness. (A. Kral, A.N. Popper, R.R. Fay, eds). Springer-Verlag, NY. 47:17-39.

Higashi, T., Lenz, D.R., Furuse, M. and **Avraham, K.B.** (2013) A "*Tric*" to tighten cell-cell junctions in the cochlea for hearing. *J. Clin. Invest*. 123:3712-3715.

Idan, N., Brownstein, Z., Shivatzki, S., and **Avraham, K.B.** (2013) Advances in genetic diagnosis for hereditary hearing loss. *J Basic Clin Physiol Pharmacol.* 24:165-170.

Avraham, K.B. (2013) Rescue from hearing loss in Usher's syndrome. *N Engl J Med.* 369:1758-1760.

Ushakov, K., Rudnicki, A., **Avraham, K.B**. (2013) MicroRNAs in sensorineural diseases of the ear. *Front Molec Neurosci*. 6:52.

Bhonker, Y., Ushakov, K., **Avraham, K.B**. (2014) Human Gene Discovery for Understanding Development of the Inner Ear and Hearing Loss. *In:* Development of Auditory and Vestibular Systems. Fourth Edition. (R. Romand, I. Varela, eds). Elsevier.

Grants

2011 – 2015 Gene Expression and microRNA Regulation in Hair and Supporting Cells of Mouse, Israel Science Foundation

2011 – 2016 Gene Discovery for Hearing Loss in Middle East by Massively Parallel Sequencing, National Institutes of Health, Co-PI: Moien Kanaan

2012 – 2016 Morphodynamics of Mammalian Planar Cell Polarity - a Quantitative Approach, Human Frontier Science Program, Co-PIs: Ping Chen, David Sprinzak, Fumio Matsuzaki

2012 – 2016 The Regulation and Cellular Activities of the Arl2 GTPase, National Institutes of Health – R01, Co-PIs: Richard Kahn, Saima Riazuddin

May 25 2013

Prof. Yechiel Michael Barilan, M.D., M.A.

Department of Medical Education
Sackler Faculty of Medicine

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Bioethics, Biolaw and Medical Humanities

Position

Associate Professor, Sackler Faculty of Medicine

Research

The research area of our group is Medical Humanities, relying on theoretical methods with the occasional excrusion to qualitative research.

My own personal interests encompass moral theory and the intersections among bioethics, social history and related normative domains, such as law and religion, especially Halakhah (Jewish religious law). I explore human rights law and international humanitarian law in the light of the contemporary ethical and meta-ethical discourse. Another aspect of my work aims at developing better understanding and tools of deliberation in bioethics as a psycho-moral process and as socially constructed events of legitimization and education. I am intrigued by the incorporation of the history and philosophy of ideas such as conscience, responsibility, hope and doubt in clinical reality and medical education.

Another branch of research is the socio-historical and moral ideas in the representation of illness and medicine in Western visual art, since the late middle ages through contemporary and experimental art.

Ongoing research projects are:

1. Moral psychology and the notion of ethical expertise in medical education.
2. The history of karyotyping exams in questions of gender (e.g. gender verification in sport).
3. Ethics and law of military, humanitarian and disaster medicine.
4. The regulation of cloning in international law.
5. New born screening and the regulation of large, public-health data banks.
6. Human rights and international humanitarian law.

Our group's chief aim is to integrate deep theoretical knowledge and creativity with applied problems, contextualizing their ethical dimensions historically and socially. Efforts are made in the direction of cross-disciplinary work, especially through participation in the activities of the new **Edmund J. Safra Center for Ethics**, Tel Aviv University.

Monographs

Barilan, YM. Human dignity, human rights and responsibility: the new language of global bioethics ad biolaw. Cambridge (MA): MIT Press. 2012.

Barilan, YM. Jewish bioethics: rabbinic law and theology in their social and historical contexts. Cambridge University Press. *In press*.

Publications

Barilan YM. Bedside rationing or rational planning: in search for perspective on medical need and safety. In: Masin M, Fleck L, Hurst S. (eds.) Towards fair rationing at the bedside. Oxford: Oxford University Press, 2013. (Forthcoming)

Barilain YM, Barnea R. Routine medical care in the military. In: Siegal G, Kasher A. (eds.) Bioethics blue and white. Ha'kibbutz Ha'Me'uhad Press, 2013. [Hebrew] (Forthcoming)

Barilan YM. From hope in palliative care to hope as a virtue and a life skill. (An original keynote article with a response to commentators) Philosophy, Psychiatry and Psychology. 2012; 19:165-181.

Barilan YM. Hope and friendship: being and Having. Philosophy, Psychiatry and Psychology. 2012; 19:191-195.

Barilan YM. When inmates are silent, walls bear witness. In Hanging: Aya Ben Ron. S. Malik (ed.) Berlin: Jatje Cantz, 2012; pp. 177-181.

Barilan YM, Brusa M, Halperin P. Triage in disaster medicine: ethical strategies in various scenarios. In: Gordijn B, O'mathuna D, Macklin R. (eds.) Ethics in disaster medicine. Dordrecht: Springer, 2012. (Forthcoming)

Shani R, **Barilan YM.** Excellence, deviance and gender: lessons from the XYY episode. American Journal of Bioethics 2012; 12:27-30.

Barilan YM. Anatomy. 2nd edition of the Encyclopedia of Applied Ethics. R. Chadwick, ed. San Diego: Academic Press. 2012, pp. 117-126.

Barilan YM. Ulysses contracts and the nocebo effect. Am J Bioethics 2012; 12:37-39.

Barilan YM, Brusa M. Deliberation at the hub of medical ed ucation: beyond virtue ethics and code of practice. Medicine, Health Care and Philosophy 2012 (Published online first)

Barilan YM. The biomedical uses of the body: lessons from the history of human rights and dignity. In: Lenk C, Hoppe N, Beier K. (eds.) Human tissue research: A European perspective on the ethical and legal challenges. Oxford: Oxford University Press, 2011; pp. 3-14.

Barilan YM, Brusa M. Triangular reflective equilibrium: A consciences based method for bioethical deliberation. Bioethics 2011; 25:304-319.

Barilan YM. Abortion. In: Chadwick R, Ten Have H, Meslin E. (eds.) Healthcare ethics in the era of globalization. New York, Sage, 2011; pp. 127-144.

Barilan YM. Respect for personal autonomy and the problem of botched autonomy. Journal of Medicine and Philosophy 2011; 36:496-515. **Barilan YM.** Her pain prevails and her judgment respected: abortion in Jewish law and in the laws of the state of Israel. Journal of Law and Religion 2010; 25:97-186.

Shani R, Gross S, **Barilan YM**. Exploring Kuhn's concept of a "scientific paradigm": the case of the "XYY hypothesis". International Journal of Technology, Knowledge and Society 2010; 6:47-56.

Barilan YM. The dilemma of good clinical practice in the study of compromised standards of care. Editorial Critical Care 2010; 14:176.

Barilan YM. Informed consent: between waiver and excellence in responsible deliberation. Medicine, Health Care and Philosophy 2010; 13:89-95.

Brusa M, **Barilan YM.** Cultural circumcision in EU public hospitals: an ethical discussion.

Grants

2010-2014, ISF, Responsibility in medical education.
2012-2015 COST (EU join collaborative grant), Ethics in Disaster Medicine.

Prof. Dafna Benayahu, Ph.D.

Department of Cell and Developmental Biology
Sackler Faculty of Medicine

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Musculoskeletal – Stem cells and Nanotechnology

Position

Professor, Sackler Faculty of Medicine

Chair, Department of Cell and Developmental Biology

Research

Our interest is to follow the differentiation of skeletal stem cells and their lineage fate. The balance between skeletal stem cells and the adipose lineage is studied at the cellular and molecular biology levels. In sillico characterization using bioinformatics of genes profiling and identification of biomarkers networks to identify markers for stem cells. Recent projects we gave shown that biomechanics play a role in the stem cells activation and function under normal physiology and along aging. The ultimate goal of the research is to study how to improve the stem cells functionality. Such knowledge will provide novel approaches to combat skeletal changes due to aging or metabolic disease. The use of stem cell is also developed towards tissue regeneration along with development of novel collagen-based-scaffold.

Research methods used include bioinformatics, gene cloning, qRT-PCR, cell biology analysis including immunofluorescence, scanning electron microscopy and biochemistry. Nanotechnology combines the cell fate differentiation with multidisciplinary approaches for the development new plat formed for cell analysis.

Publications

Ron A, Shur I, Singh RR, Daniel R, Fishelson N, Croitoriu N, **Benayahu D**, Shacham-Diamand Y 2010. Dielectric screening of early differentiation patterns in mesenchymal stem cells induced by steroid hormones. Bioelectrochem 78:161-172

Ron A, Fishelson N, Croitoriu N, Shur I, **Benayahu D**. 2010. Shacham-Diamand Y. 2010. Examination of the induced potential gradients across inner and outer cellular interfaces in a realistic 3d cytoplasmic-embedded mitochondrion model. *J Electro-analyt Chem*. 638:59-69

Shefer G, Rauner G., Yablonka-Reuveni, Z**, Benayahu D,** 2010. Reduced satellite cell numbers and myogenic capacity in aging can be alleviated by endurance exercise. *PloS One* 5:e13307

Shefer G and **Benayahu D**. 2010. SVEP1 is a novel marker of activated pre-determined skeletal muscle satellite cells. *Stem Cell Rev*. 6:42-49

Binderman I, Yaffe A, Zohar R, **Benayahu D**, Bahar H. 2011. Tissue Engineering of bone: an ectopic rat *Model Front Biosci* S3, 61-68,

Shefer G, **Benayahu D**. 2011. The effect of exercise on IGF-I on muscle fibers and satellite cells. *Front Biosci* 4, 230-239

Akavia UD, Socher R, **Benayahu D.** 2011. Tracking the molecular signature of developing skeletal tissues. *Front Biosci* 4:1941-1950

Glait-Santar C, **Benayahu D**. 2011. SVEP1 promoter regulation by methylation of CpG sites. Gene 490 (1-2): 6-14.

Shefer G, **Benayahu D.** 2012. The effect of exercise on IGF-I on muscle fibers and satellite cells. Front. Biosci 4:230-9

Akavia UD, Socher R, **Benayahu D**. 2012. Tracking the Molecular Signature of Developing Skeletal Tissues. Front. Biosci 4:1941-50.

Shoham N, Gottlieb R, Shaharabani-Yosef O, Zaretsky U, **Benayahu D,** Gefen A. 2012 Mechanical Stretching Accelerates Lipid Production in 3T3-L1 Adipocytes by Activating the MEK Signaling Pathway. American Journal of Physiology – Cell Physiology 302(2):C429-41**.**

Glait-Santar C, **Benayahu D**. 2012. Regulation of SVEP1 gene expression by 17beta-estradiol and TNFalpha in pre-osteoblastic and mammary adenocarcinoma cells. Journal of Steroid Biochemistry and Molecular Biology 130:36-44.

Reizel Y, Itzkovitz S, Adar R, Elbaz J, Jinich A, Chapal-Ilani N1, Maruvka YE, Nevo N, Marx Z, Horovitz I, Wasserstrom A, Mayo A, Shur I, **Benayahu D**, Skorecki K, Segal E, Dekel N, Shapiro E. 2012. Cell lineage analysis of the mammalian female germline. Plos Genetics 8(2):e1002477.

Glait-Santar C, Pasmanik-Chor M, Oron-Karni V, **Benayahu D,** 2012. Molecular profiling of functional interactions between pre-osteoblastic and breast carcinoma cells. Genes Cells 17(4):302-15

Glait-Santar C, Pasmanik-Chor M, **Benayahu D**. 2012. Expression pattern of SVEP1 alternatively-spliced forms. Gene 15; 505(1):137-145.

Marcus Y, Shefer G, Sasson K, Kohen F, Limor R, Pappo O, Nevo N, Biton I, Bach M, Berkutzki T, Fridkin M, **Benayahu D**, Shechter Y, Stern N. 2013. Angiotensin 1-7 as a novel means to prevent the metabolic syndrome: lessons from the fructose-fed rat model. Diabetic 62(4):1121-1130

Shefer G, Rauner G, Stuelsatz P, **Benayahu D**, Yablonka-Reuveni Z. 2013 Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. FEBS J. 280(17): 4063-4073

Shoham N, Sasson A, Lin FH, **Benayahu D,** HAj-Ali R, Gefen A. 2013. Mechanics of hyaluronic acid/adipic acid dihydrazide hydrogel: towards developing a vessel for delivery of preadipocytes to native tissues Journal of the Mechanical Behavior of Biomedical Materials. J Mech Behav Biomed Mater. 22; 28C:320-331

Shoham N, Girshovitz P, Katzengold R, Shaked NT, **Benayahu D**, Gefen A. 2014. Adipocyte Stiffness Increases with Accumulation of Lipid Droplets. Biophysical J 106: 1-11.

Ben-Or Frank M, Shoham N, **Benayahu D**, Gefen A. 2014 Effects of accumulation of Lipid Droplets on load transfer between and within Adipocytes. Biomechanics and Modeling in Mechanobiology (Accepted)

Sharabi M, Mandelberg Y, **Benayahu D**, Benayahu Y, Azem A, Haj-Ali R. A new class of bio-composite materials of unique collagen fibers. 2014. Journal of the Mechanical Behavior of Biomedical Materials 36:71-81

Grants

2012 -2016	Israel Science Foundation Jointly with A. Gefen
2013	Stem Cell Core Facility - "MAGNET" Project, Ministry of Industry

Dr. Limor Broday, Ph.D.

Department of Cell and Developmental Biology
Sackler Faculty of Medicine

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Molecular Analysis of Ubiquitin and SUMO Pathways in the C. elegans *Model*

Position

Senior Lecturer, Sackler Faculty of Medicine

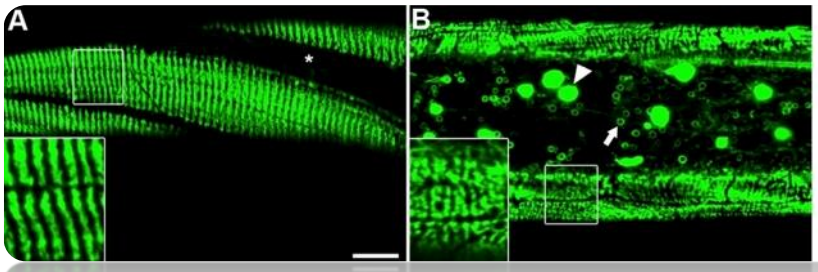
Research

Protein modifications by ubiquitin and ubiquitin-like proteins are essential for many cellular regulatory mechanisms. De-regulation of such processes are a cause for many human diseases. The main objective of our research is to understand, at a mechanistic and molecular level, how these processes are regulated. We use the nematode *C. elegans* as a model system to analyze various elements of the ubiquitin and ubiquitin-like system

Current lab projects:

Regulation of morphogenetic processes by SUMO (small ubiquitin-like modifier)

The role of E3 ubiquitin ligases in normal development and under cellular stress conditions



(A) Organization of the *C. elegans* epidermal intermediate filament protein IFB-1 in circumferential bands in wild-type animal. (B) Abnormal filaments and formation of inclusions in *smo-1* deleted worms.

Publications

Darom, A., Bening-Abu-Shach, U., **Broday L**. 2010. RNF-121 is an ER-membrane E3 ubiquitin ligase required for ER homeostasis and regulation of PAT-3/β-integrin levels. *Mol Biol Cell* 21:1788-1798.

Zaidel-Bar, R., Miller, S., Kaminsky, R., **Broday, L**. 2010. Regulation of integrin adhesion complexes' dynamics by RNF-5 E3-ligase during molting in *C. elegans*. *Biochem Biophys Res Commun*. 395:509-514.

Pichinuk E, **Broday L**, Wreschner DH. 2011. Endogenous RNA cleavages at the ribosomal SRL site likely reflect miRNA (miR) mediated translational suppression. *Biochem Biophys Res Commun*. 414:706-11.

Linhart, E Halperin, Y. Darom, A. Kidron, S. **Broday, L**. and Shamir. R. 2012. A novel cis-regulatory motif pair in the promoters of germline and oogenesis genes in *C. elegans. Genome Res*. 22:76-83.

Kuang E, Okumura CY, Sheffy-Levin S, Varsano T, Shu VC, Qi J, Niesman IR, Yang HJ, López-Otín C, Yang WY, Reed JC, **Broday L**, Nizet V, Ronai ZA. 2012. Regulation of ATG4B stability by RNF5 limits basal levels of autophagy and influences susceptibility to bacterial infection. *PLoS Genet*. 8:e1003007.

Grants

2011 – 2015, The role of SUMO in the assembly of cytoskeletal intermediate filaments, The Israel Science Foundation (ISF).

May 25, 2014

Prof. Malka Cohen-Armon, D.Sc.

Dept. of Physiology & Pharmacology
and the Neufeld Cardiac Research Institute
Sackler Faculty of Medicine

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PARP Proteins in Health and Disease

Position

Associate Professor, Sackler Faculty of Medicine

Research

The general focus of our research is on signal transduction mechanisms implicating PARP (polyADP-ribose polymerase) proteins. PARPs are highly conserved proteins that are involved in a variety of processes, including epigenetic mechanisms, DNA repair, cell cycle and gene expression. PARP-1, the most abundant PARP protein, is activated by binding to single strand DNA breaks. Activated PARP-1 recruits ligazes to the lesion, promoting DNA repair.

One of our contributions to this field was the discovery of alternative mechanisms activating PARP-1 in the absence of DNA breaks. This unveiled a variety of extra-nuclear signals activating PARP proteins in a variety of processes regulating gene expression.

We found that PARP-1 is a target of signal transduction mechanisms activated by intracellular Ca^{2+} mobilizition or by the MEK-ERK phosphorylation cascade. Moreover, we found that ERK activity in the nucleus is highly up-regulated by activated PARP-1, implicating PARP-1 in ERK-dependent gene expression. Up-regulation of immediate early genes underlying long-term memory formation may underlie the pivotal role of PARP-1 in long-term memory formation during learning. Regulation of gene expression, controlling cell growth and development, may underlie the role of PARP-1 in neuronal remodeling and cardiomyocytes growth.

Recently, we found that a phenanthrene derived PARP inhibitor acts as an extra-centrosomes de-clustering agent, exclusively and efficiently eradicating human cancer cells by 'mitotic catastrophe' cell death, without impairing normal cells. Since many human cancer cells depend on extra-centrosomes clustering for their survival, this molecule is now used for developing a novel cancer targeting therapy.

Cell death by extra-centrosomes de-clustering in mitosis

http://www.biomedcentral.com/content/supplementary/1471-2407-11-412-s1.m4v

A depicted experiment describing ‘mitotic catastrophe’ cell death detected by overnight confocal imaging in multi-centrosomes human mammary cancer cells MDA-MB-231 treated with PARP inhibitor PJ-34. Cells were transfected by vectors encoding for g-tubulin-GFP (for labeling of centrosomes; green) and for histone H2B-RED (for labeling of chromosomes; red).

Publications

Geistrikh I., Visochek L., Klein R., Miller L., Mittelman L., Shainberg A. and **Cohen-Armon M.** 2011. Ca^{2+} induced PARP-1 activation and *ANF* expression are coupled events in cardiomyocytes *Biochem J.* 438: 337–347**.**

Castiel A., Visochek L., Mittelman L., Dantzer F., Izraeli S., and **Cohen-Armon M.** 2011. A phenanthrene derived PARP inhibitor is an extra-centrosomes de-clustering agent exclusively eradicating human cancer cells. *BMC Cancer* 11:412

Inbar D, **Cohen-Armon M**, Neumann D. 2012. Erythropoietin-driven signalling and cell migration mediated by polyADP-ribosylation. *Br J Cancer*. 107:1317-26

Castiel A, Visochek L, Mittelman L, Zilberstein Y, Dantzer F, Izraeli S, **Cohen-Armon M**. 2013. Cell death associated with abnormal mitosis observed by confocal imaging in live cancer cells. *J Vis Exp*. 78:e50568.

Review

Cohen-Armon M. 2012. PARP1 Activation is Required for Long-Term Memory. Chapter in: *Long-Term Memory: Mechanisms, Types and Disorders* (Editors: AK. Alexandrov and LM. Fedoseev, NOVA Publishers, NY). Ch. 4, pp. 103-116.

Grants

2012-2014 ICRF- Human cancer cells exclusively eradicated by extra-centrosomes de-clustering.

May 25, 2014

Prof. Nathan Dascal, Ph.D.

Dept. of Physiology and Pharmacology
Sackler School of Medicine

Tel Aviv University
Email: dascaln@post.tau.ac.il
URL: http://medicine.mytau.org/dascal/

Signal Transduction by Neurotransmitters in Brain and Heart in Health and Disease

Position

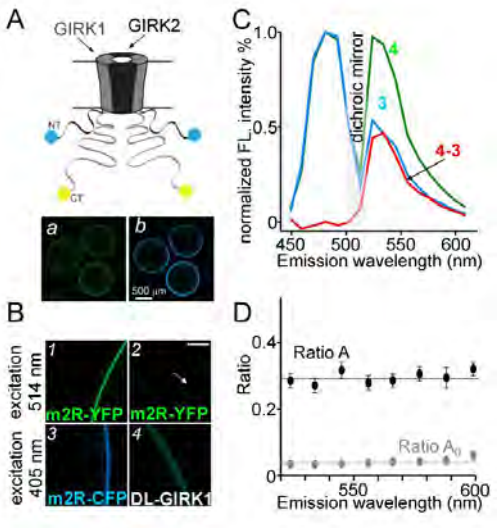
Professor of Physiology, Sackler Faculty of Medicine

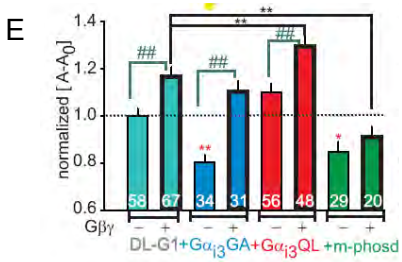
Research

Electrical activity of excitable cells is their most important feature, which allows the performance of fundamental functions of brain, heart and muscle. We are addressing a key issue in modern cardiology and neurobiology: how neurotransmitters regulate cardiac cells and neurons by acting on ion channels – proteins that underlie the electrical activity in these cells; and how errors in these processes cause disease. Main projects in the lab:

Function and regulation of receptors, G proteins, Ca^{2+} and K^+ channels in health and disease; Ion channel-related hereditary cardiac and neurological disorders (channelopathies); Mechanisms of coupling of G protein-coupled receptors with effectors; Molecular mechanisms of bipolar disorder.

Research methods: Electrophysiology, Neurophysiology, Heterologous Expression, Protein Biochemistry, Fluorescence Resonance Energy Transfer (FRET), Molecular biology, Mathematical and Kinetic Modeling and Simulation, Immunocytochemistry





Studying GIRK channels expressed in a heterologous system (*Xenopus* oocytes). Intramolecular fluorescence resonance energy transfer (i-FRET) shows interactions of cytosolic N- and C-termini of the channel. **A**, GIRK channel labeled with two fluorescent proteins. **B**, Imaging the expressed fluorescent proteins with a confocal microscope. **C, D,** Example of use of FRET analysis to study conformational changes in the channel caused by neurotransmitter, G proteins or drugs. **E,** Gα and Gβγ synergistically alter the conformation of GIRK1 subunit.

Publications

Babai N, Kanevsky N, **Dascal N**, Rozanski GJ, Singh DP, Fatma N &Thoreson WB (2010). Anion sensitive regions of L-type $Ca_V1.2$ calcium channels expressed in HEK293 cells. *PLoS One*, 5, e8602.

Berlin S, Keren-Raifman T, Castel R, Rubinstein M, Dessauer CW, Ivanina T & **Dascal N** (2010). $G\alpha_i$ and Gβγ jointly regulate the conformations of a Gβγ effector, the neuronal G-protein activated K^+ channel (GIRK). *J Biol Chem,* 285, 6179-6185.

Edelheit O, Hanukoglu I, Shriki Y, Tfilin M, **Dascal N**, Gillis D & Hanukoglu A (2010). Truncated β epithelial sodium channel (ENaC) subunits responsible for multi-system pseudohypoaldosteronism support partial activity of ENaC. *J Steroid Biochem Mol Biol,* 119, 84-88.

Tselniker I, Tsemakhovich VA, Dessauer CW & **Dascal N**. (2010) Stargazin modulates neuronal voltage-dependent Ca^{2+} channel $Ca_V2.2$ by a Gβγ-dependent mechanism. *J Biol Chem* **285**, 20462-20471.

Laish-Farkash A, Brass D, Marek-Yagel D, Pras E, **Dascal N**, Antzelevitch C, Nof E, Reznik H, Glikson M & Luria D (2010). A novel mutation in the HCN4 gene causes symptomatic sinus bradycardia in Moroccan Jews. *J Cardiovasc Electrophysiol* 21, 1365-1372.

Tselnicker I & **Dascal N**. (2010). Further characterization of regulation of $Ca_V2.2$ by stargazin. *Channels* 4, 351-354.

Oz S, Tsemakhovich V, Christel CJ, Lee A & **Dascal N**. (2011). CaBP1 regulates voltage dependent inactivation and activation of $Ca_V1.2$ (L-type) calcium channels. *J Biol Chem* 286, 13945-13953.

Edelheit O, Hanukoglu I, **Dascal N** & Hanukoglu A. (2011) Identification of the roles of conserved charged residues in the extracellular domain of an epithelial sodium channel (ENaC) subunit by alanine mutagenesis. *Am J Physiol Renal Physiol* 300, F887-897.

Berlin S, Tsemakhovich VA, Castel R, Ivanina T, Dessauer CW, Keren-Raifman T & **Dascal N**. (2011) Two distinct aspects of coupling between $G\alpha_i$ and G protein-activated K^+ channel (GIRK) revealed by fluorescently-labeled $G\alpha_{i3}$ subunits. *J Biol Chem* 287, 19537-19549.

Almagor L, Chomsky-Hecht O, Ben-Mocha A, Hendin-Barak D, **Dascal N** & Hirsch JA. (2012). The role of a voltage-dependent Ca^{2+} channel intracellular linker: a structure-function analysis. *J Neurosci* 32, 7602-7613.

Pankonien I, Otto A, **Dascal N**, Morano I & Haase H. (2012). Ahnak1 interaction is affected by phosphorylation of Ser-296 on $Ca_V\beta2$. *Biochem Biophys Res Commun* 421, 184-189.

Weiss S, Keren-Raifman T, Oz S, Ben Mocha A, Haase H & **Dascal N**. (2012). Modulation of distinct isoforms of L-type calcium channels by G_q-coupled receptors in *Xenopus* oocytes: Antagonistic effects of Gβγ and protein kinase C. *Channels* **6,** 426-437.

Almagor L, Chomsky-Hecht O, Ben Mocha A, Hendin-Barak D, **Dascal N** & Hirsch JA. (2012). $Ca_V1.2$ I-II linker structure and Timothy syndrome. *Channels* **6,** 468-472.

Edvardson S, Oz S, Abulhijaa FA, Taher FB, Shaag A, Zenvirt S, **Dascal N** & Elpeleg O. (2013). Early infantile epileptic encephalopathy associated with a high voltage-gated calcium channelopathy. *J Med Genet* **50**, 118-123

Treiber F, Rosker C, Keren-Raifman T, Steinecker B, Gorischek A, **Dascal N** & Schreibmayer W. (2013) Molecular basis of the facilitation of the heterooligomeric GIRK1/GIRK4 complex by cAMP dependent protein kinase. *Biochim Biophys Acta* 1828, 1214-1221.

Oz S, Benmocha A, Sasson Y, Sachyani D, Almagor L, Lee A, Hirsch JA & **Dascal N**. (2013). Competitive and non-competitive regulation of calcium-dependent inactivation in $Ca_V1.2$ L-type Ca^{2+} channels by calmodulin and Ca^{2+}-binding protein 1. *J Biol Chem*. 288, 12680-12691.

Weisbrod, D., Peretz, A., Ziskind, A., Menaker, N., Oz, S., Barad, L., Eliyahu, S., Itskovitz-Eldor, J., **Dascal, N.**, Khananshvili, D., Binah, O., and Attali, B. (2013) SK4 Ca^{2+} activated K^+ channel is a critical player in cardiac pacemaker derived from human embryonic stem cells. *Proc Natl Acad Sci USA* 110, E1685-1694.

Weiss S, Oz S, Benmocha A, **Dascal N**. (2013) Regulation of cardiac L-type Ca^{2+} channel $Ca_V1.2$ via the β-adrenergic-cAMP-protein kinase A pathway: old dogmas, advances, and new uncertainties. *Circ Res* 2013, 113:617-31.

Farhy Tselnicker I, Tsemakhovich V, Rishal I, Kahanovitch U, Dessauer CW & **Dascal N**. (2014). Dual regulation of G proteins and the G-protein–activated K^+ channels by lithium. *Proc Natl Acad Sci USA* **111,** 5018-5023.

Edelheit O, Ben-Shahar R, **Dascal N**, Hanukoglu A & Hanukoglu I. (2014). Conserved charged residues at the surface and interface of epithelial sodium channel (ENaC) subunits: roles in cell surface expression and Na^+ self-inhibition response. *FEBS J. in press*

Grants

2010-2014: Subunit composition-determined physiology of GIRK channels. US-Israel Binational Science Foundation (BSF). With C.W. Dessauer.

2013-2016: Mechanisms of isoform-specific regulation of L-type Ca^{2+} channels by protein kinases. German-Israel Foundation (GIF), With S. Weiss and E. Klussmann.

May 25, 2014

Prof. Shimon Efrat, Ph.D.

Department of Human Molecular Genetics and Biochemistry
Sackler Faculty of Medicine

Tel Aviv University
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Cell Replacement Therapy for Diabetes

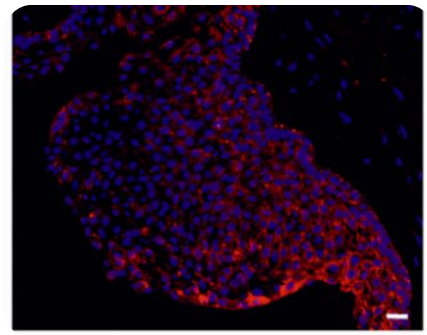
Position

Professor, Sackler Faculty of Medicine
Nancy Gluck Regan Chair in Juvenile Diabetes

Research

Our research focuses on the development of a cell replacement therapy for diabetes, in which the insulin-producing pancreatic beta cells are destroyed or malfunction.

Our approaches for generation of an abundant source of cells for transplantation include expansion and differentiation in tissue culture of beta cells from human organ donors, as well as differentiation of human stem cells into insulin-producing cells.



Pluripotent stem cells derived from human beta cells can be greatly multiplied in tissue culture and then induced to redifferentiate into insulin-producing cells. Red, staining for insulin; blue, cell nuclei.

Publications

Bar-Nur O, Russ HA, **Efrat S**, Benvenisty N (2011) Epigenetic memory and preferential lineage-specific differentiation in induced pluripotent stem cells derived from human pancreatic islet beta cells. *Cell Stem Cell* 9:17-23.

Russ HA, Sintov E, Anker-Kitai L, Friedman O, Lenz A, Toren G, Farhy C, Pasmanik-Chor M, Oron-Karni V, Ravassard P, **Efrat S** (2011) Insulin-producing cells generated from dedifferentiated human pancreatic beta cells expanded in vitro. *PLoS One* 6:e25566.

Bar Y, Russ HA, Anker-Kitai L, Knoller S, **Efrat S** (2012) Redifferentiation of expanded human pancreatic beta-cell-derived cells by inhibition of the NOTCH pathway. *J Biol Chem* 287:17269-17280.

Hansen JB, Tonnesen MF, Madsen AN, Hagedorn PH, Friberg J, Grunnet LG, Heller RS, Nielsen AØ, Størling J, Baeyens L, Anker-Kitai L, Qvortrup K, Bouwens L, **Efrat S**, Aalund M, Andrews NC, Billestrup N, Karlsen AE, Holst B, Pociot F, Mandrup-Poulsen T (2012) Divalent metal transporter 1 regulates iron-mediated ROS and pancreatic beta-cell fate in response to cytokines. Cell Metab 16:449-461.

Reviews

Efrat S (2010) Beta-cell expansion in vitro. In Stem Cell Therapy for Diabetes, Efrat S (ed.), Humana Press, pp. 123-133.

Efrat S (2010) Prospects for cell therapy in diabetes: Introduction to the RDS Special Issue. *Rev Diabet Stud* 7:80-81.

Russ HA, **Efrat S** (2011) In-vivo functional assessment of engineered human insulin-producing cells. In Cell Transplantation, Soto-Gutierrez A, Navarro-Alvarez N, Fox IJ (eds.), Methods in Bioengineering, Yarmush ML, Langer RS (eds.), Artech House, pp. 35-46.

Efrat S (2011) Generation of insulin-producing cells from extra-islet tissues. In Islets: Biology, Immunology, and Clinical Applications, Kandeel FR (ed.), Springer (in press).

Russ HA, **Efrat S** (2011) Development of human insulin-producing cells for cell therapy of diabetes. Ped Endocrinol Rev 9:590-597.

Efrat S, Russ HA (2012) Generation of insulin-producing cells from adult tissues. *Trends Endocrinol Metab* 23:278-285.

Efrat S (2013) Recent progress in generation of human surrogate beta cells. Curr Opin Endocrinol Diab Obes 20:259-264.

Bar Y, Efrat S (2014) The Notch pathway in beta-cell growth and differentiation. In The Pancreatic Beta Cell, Litwack G (ed.), Vitamins and Hormones vol. 95, Academic Press/Elsevier, pp. 391-405.

Grants

2011-2014	Insulin-producing cells from iPS cells derived from human beta cells, Juvenile Diabetes Research Foundation (JDRF)
2011-2014	Beta-cell replacement by human islet beta cells expanded in vitro, Israel Science Foundation (ISF)
2012-2017	Stem cells for biological assays of novel drugs and predictive toxicology, Innovative Medicines Initiative (IMI)
2013-2015	Redifferentiation of expanded human beta-cell-derived cells for cell therapy of diabetes, Israel Ministry of Industry, Trade, and Labor Kamin Program
2013-2017	Generation of human insulin-producing cells by redifferentiation of cells expanded from pancreatic islet beta cells through inhibition of the NOTCH pathway, Israel Science Foundation (ISF)

May 24, 2014

Dr. Neta Erez, Ph.D.

Department of Pathology
Sackler Faculty of Medicine

Tel Aviv University
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Cancer Related Inflammation in Tumor Progression and Metastasis

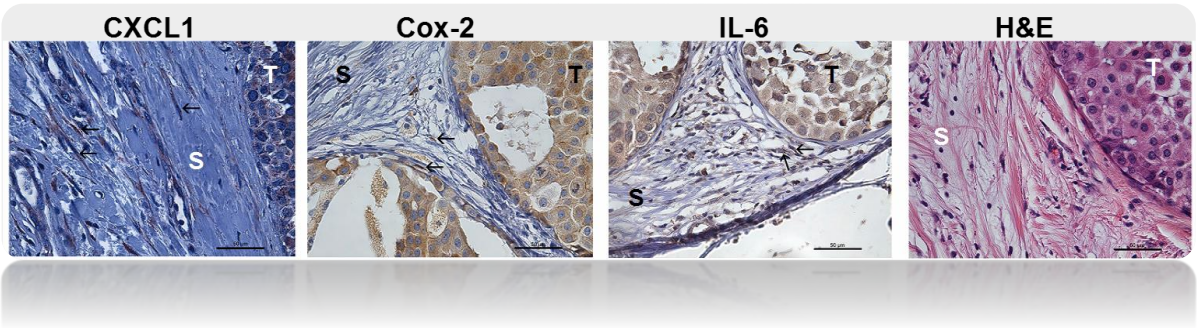
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Tumors are more than just cancer cells- the tumor microenvironment plays a crucial role in all stages of tumorigenesis. One of the hallmarks of all tumors is inflammation; chronic inflammation is highly correlated with many types of human cancer. The main interests of our lab are cancer-related inflammation and the role of the tumor microenvironment, and in particular, Cancer-Associated Fibroblasts (CAFs) in facilitating tumor initiation, progression and metastasis. We study these crucial aspects of cancer using genetically engineered mouse models of human cancer. Our aim is to uncover stromal pathways that contribute to tumorigenesis and metastasis in breast and ovarian cancer, and to identify novel targets for CAF-directed therapies.

Methodologies used include transgenic mouse tumor models, *in vivo* imaging, expression profiling, cell culture models, and immunohistochemistry.



Tumor tissue sections from breast cancer patients were immunostained with antibodies for the pro-inflammatory factors CXCL1, COX-2, IL-6 or with Hematoxylin & Eosin, as indicated. Arrows indicate stained CAFs in the tumor stroma. T=tumor. S=stroma. Scale bar=50uM.

Publications

Erez N., Truitt M., Olson P., and Hanahan D. Cancer Associated Fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-□B-dependent manner. *Cancer Cell* 2010; 17:135-147. *Commentary in: *Cancer Cell* 2010; 17:111-112.

Klein A, Sagi-Assif O, Izraely S, Meshel T, Pasmanik-Chor M, Nahmias C, Couraud PO, **Erez N**, Hoon DS, Witz IP. The metastatic microenvironment: Brain-derived soluble factors alter the malignant phenotype of cutaneous and brain-metastasizing melanoma cells. *Int J Cancer*. 2012; 131:2509-2518.

Sharon, Y., Alon, L., Glanz, S., Servais, S., and **Erez N**. Isolation of normal and cancer-associated fibroblasts from fresh tissues by Fluorescence Activated Cell Sorting (FACS). *J Vis Exp* 2012; 71:e4425.

Erez N., Glanz S., Raz Y., Avivi C., and Barshack I. Cancer associated fibroblasts express pro-inflammatory factors in human breast and ovarian tumors. *Biochem Biophys Res Commun*. 2013 437:397-402.

Raz, Y. and **Erez N.** An inflammatory vicious cycle: fibroblasts and immune cell recruitment in cancer. *Exp Cell Res*. 2013 pii: S0014-4827(13)00130-4.

Reviews

Erez N. and Coussens LM. Leukocytes as paracrine regulators of metastasis and determinants of organ-specific colonization. *Int J Cancer*. 2011;128:2536-44.

Servais C. and **Erez N.** From sentinel cells to inflammatory culprits: cancer-associated fibroblasts in tumor-related inflammation. *J Pathol***.** 2013; 229:198-207.

Erez N. Cancer: Angiogenic Awakening. *Nature*. 2013; 500:37-8.

Grants

2011-2014	The Marie Curie International Reintegration Grant (IRG), EU
2011-2014	Israel Cancer Research Fund (ICRF)
2012-2016	Israel Science Foundation (ISF) Grant: Characterizing Fibroblast-Mediated Inflammation in Breast Cancer Metastasis

May 25, 2014

Prof. Hagit Eldar-Finkelman, Ph.D.

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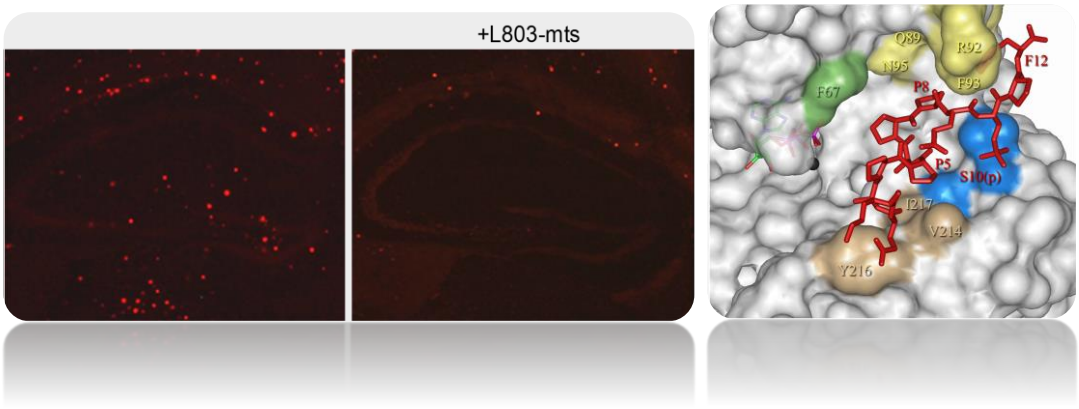
GSK-3 Signaling in Health and Disease

Position

Professor, Sackler Faculty of Medicine
Chair, Sackler Committee for Ph.D. Graduate Studies

Research

Our research is focused on the molecular mechanisms regulating the protein kinase GSK-3 and their implications in human disease. GSK-3 is a central player in diabetes, neurodegenerative and psychiatric disorders, and recently emerged as a promising drug discovery target. We propose that inhibition of GSK-3 should produce therapeutic benefits in treating these disorders. We develop selective substrate competitive GSK-3 inhibitors and evaluate their efficacy and therapeutic effects in relevant in vitro and in vivo systems. So far we could show that our leading compound inhibitor, L803-mts, produces anti-diabetic and anti-depressive effects in animal models. A recent work further indicated that L803-mts lowers beta amyloid burdens and improves cognitive deficits in an Alzheimer's mouse model. Research methods employ cell biology, molecular biology and biochemistry disciplines, combined with bioinformatics, computational biology and drug design.



Treatment with L803-mts reduces beta amyloid burden in brain of an Alzheimer's mouse model (Left). Computational model of L803-mts interaction with the catalytic core of GSK-3 (right).

Publications

Watson, RL Spalding, AC, Zielske, PS, Morgan, M, Kim, AC Guido Bommer, T, **Eldar-Finkelman, H**, Giordano, T, Fearon, ER, Hammer, GD, Lawrence, TS and Ben-Josef, E. 2010, GSK3β and β-catenin modulate radiation cytotoxicity in pancreatic cancer. *Neoplasia*, 12, 357-365.

Leng, S., Zhang, W., Zheng, Y., Liberman, Z., Rhodes, C.J., **Eldar-Finkelman, H**., and Sun, X.J. 2010, GSK-3β mediates high glucose-induced ubiquitination and proteasome degradation of insulin receptor substrate 1. *J Endocrinol* 206, 171-181.

Karyo, R., Eskira, Y., Pinhasov, A., Belmaker, R., Agam, G., and **Eldar-Finkelman, H**. 2010, Identification of eukaryotic elongation factor-2 as a novel cellular target of lithium and GSK-3. *Mol Cell Neurosci*. 45, 449-455.

Shruster, A., **Eldar-Finkelman, H**., Melamed, E., Offen, D. 2011, Wnt signaling pathway overcomes the disruption of neurogenesis induced by oligomeric amyloid ß-peptide. *J Neurochem*. 116: 552-559.

Azoulay-Alfaguter, I. Yaffe, Y., Licht-Murava, A., Urbanska, M., Jaworski, J., Pietrokovski, S., Hirschberg, K. and **Eldar-Finkelman, H.** 2011, Distinct molecular regulation of GSK-3β controlled by it N-terminal region. Functional role in calcium/calpain signaling. *J Biol Chem*. 286:13470-13480

Licht-Murava, A., Plotkin, B., Eisenstein, M., **Eldar-Finkelman, H**. 2011, Elucidating substrate and Inhibitor binding sites on the surface of GSK-3β and the refinement of a competitive inhibitor. J Mol Biol. 408:366-378.

Tsaadon Alon, L., Pietrokovski, S., Barkan, S., Avrahami, L. Kaidanovich-Beilin, O., Woodgett, J. Barnea, A., **Eldar-Finkelman, H**. 2011, Selective loss of GSK-3β in birds reveals distinct roles for GSK-3 Isozymes in tau phosphorylation. FEBS Lett. 585:1158-1162.

Monte, LM, Kramer, T. Boländer, A. Plotkin, B., **Eldar-Finkelman, H**., Fuertes, A., Dominguez, D., Schmidt, B. 2011, Synthesis and biological evaluation of glycogen synthase kinase 3 (GSK-3) inhibitors: an fast and atom efficient access to 1-aryl-3-benzylureas. Bioorg Med Chem Lett. 21:5610-5615.

Monte, LM, Kramer, T., Gu, J., Anumala, R. Marinelli, L., La Pietra, V., Novellino, E., Franco, B., Demedts, D., van Leuven, F., Fuertes, A., Dominguez, JM., Plotkin, B., **Eldar-Finkelman, H**., Schmidt, B. 2012, Identification of glycogen synthase kinase-3 inhibitors with a selective sting for glycogen synthase kinase-3α. J. Med. Chem. 55:4407-4424.

Monte, LM, Kramer, T., Gu, J., Brodecht, M., Fuertes, Dominguez, JM., Plotkin, B., **Eldar-Finkelman, H.,** Schmidt, B. 2013, Structure-based optimization of oxadiazole-based GSK-3 inhibitors. Eur. J. Med. Chem. 61:26-40.

Reviews

Eldar-Finkelman, H., Licht-Murava, A., Pietrokovski, S. Eisenstein, M. Substrate competitive GSK-3 Inhibitors - Strategy and Implications. 2010, Biochim Biophys Acta. 180: 598-603.

Eldar-Finkelman, H., Martinez, A. GSK-3 inhibitors: preclinical and clinical focus on CNS. 2011. Front Mol Neurosci, 4:32.

Grants

2010-2014, Exploring the distinct functions of the mammalian GSK-3 isoforms, Israel Science Foundation (ISF)

May 25, 2014

Dr. Yechiel Elkabetz, Ph.D.

Dept. of Cell and Developmental Biology
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Modeling the Nervous System in Development and Disease Using Pluripotent Stem Cells

Position

Lecturer, Sackler Faculty of Medicine

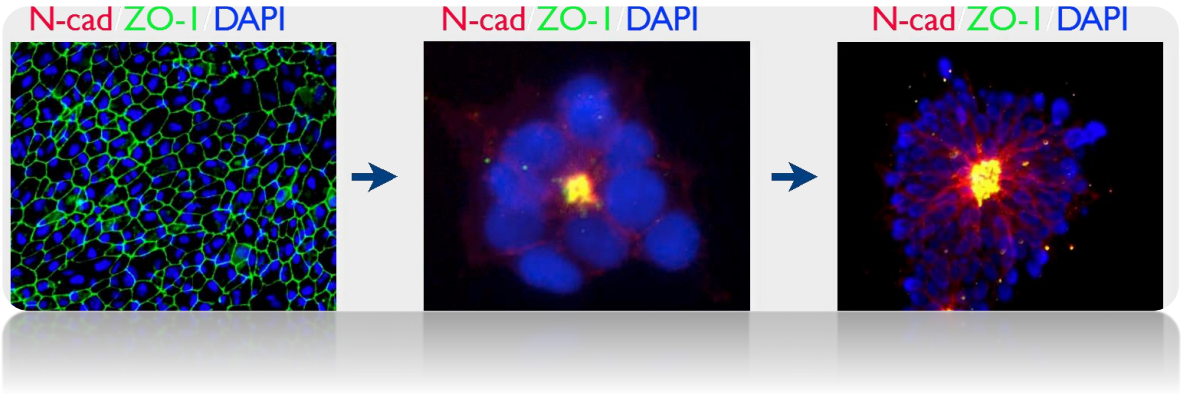
Research

Our lab makes use of *human embryonic stem cells* in order to elucidate developmental programs in the human nervous system, with particular interest in *neural stem cells* (NSCs).

The NSC ontogeny dogma predicts that early developing NSCs are highly potent and can yield all nervous system cell types, but they rapidly lose this potential as development proceeds. Because NSCs behave similarly in culture, they are almost useless for studying differentiation to most neuronal cell types – a major impediment for understanding basic development and application to regenerative medicine.

Our main goal is to learn the biology of early neural stem cells in the lab in order to develop strategies for standardizing their growth in culture without loss of differentiation potential. Such continuously self renewing cells will serve as a *gold standard NSCs* for studying nervous system development and disease, making cells for therapy and discovering novel drugs.

We use a variety of techniques in mouse and human embryonic stem cells and NSCs cells including transgenics (genetic labeling), viral expression of coding genes and microRNAs, classic stem cell assays, FACS-sorting and stem cell differentiation, and two-photon/confocal live cell imaging.



Human embryonic stem cells (Left panel) differentiate into NSCs (Middle and tight panels), which organize in a shape of rosettes. Neural rosettes have strong tight and adherens junctions, and are the earliest and most potent NSCs.

Publications

Lipchina, I., **Elkabetz. Y.**, Hafner, M., Sheridan, R., Mihailovic, A., Tuschl, T., Sander, C., Studer, L., Betel, D. Genome-wide identification of microRNA targets in human ES cells reveals a role for miR-302 in modulating BMP response. *Genes Dev.* 2011; 25:2173-86.

Lafaille FG, Pessach IM, Zhang SY, Ciancanelli MJ, Herman M, Abhyankar A, Ying SW, Keros S, Goldstein PA, Mostoslavsky G, Ordovas-Montanes J, Jouanguy E, Plancoulaine S, Tu E, **Elkabetz Y**, Al-Muhsen S, Tardieu M, Schlaeger TM, Daley GQ, Abel L, Casanova JL, Studer L, Notarangelo LD. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. 2012. *Nature* 2012; 491:769-73.

Grants

2011-2014 Fate Potential and plasticity of human embryonic stem cell derived neural stem cells. Israel Science Foundation (ISF).

2011-2014 Confocal/2-photon microscope system for 3D live cell imaging of neural stem cells. Israel Science Foundation (ISF).

2011-2014 Self-Renewal of embryonic and induced pluripotent stem cell derived neural rosettes. Marie Curie International Reintegration Grants (IRG).

May 25, 2014

Prof. Zvi Fishelson, Ph.D.

Department of Cell and Developmental Biology
Sackler Faculty of Medicine

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URL: http://www2.tau.ac.il/Person/medicine/researcher.asp?id=agcdifeik

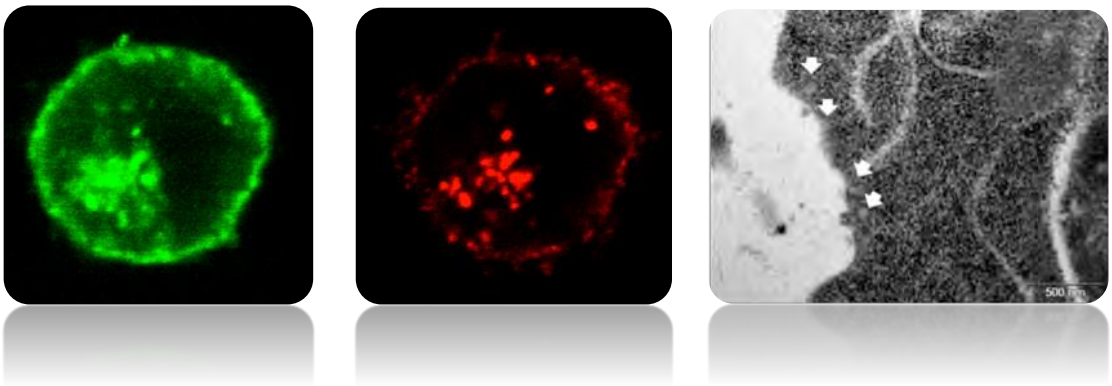
Molecular Analysis of Cancer Immunoresistance

Positions

Professor, Sackler Faculty of Medicine
President, International Complement Society
President, European Complement Network
Advisory Editor, *Molecular Immunology*
Associate Editor, *Frontiers in Molecular Innate Immunity*

Research

The long-term goal of our research is to develop a novel treatment for immune resistant cancers. Our research includes characterization of the mechanism of complement-dependent cytotoxicity and of the basis for elevated resistance of cancer cells to cell death, and design of novel reagents that sensitize cancer cells to cell death. Research methods used include analyses of cell growth and death and mitochondrial activity, western blotting, enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, confocal fluorescence microscopy, Fluorescence-activated Cell Sorting (FACS), peptide analysis by mass spectrometry, electron microscopy, and analysis of cancer growth in animal models.



Caveolin-1 (green) and complement C9 (red) co-localize in early and late endocytic vesicles of K562 cancer cells following complement attack on the cells (2 left panels). Electron microscopy analysis demonstrates elevated formation of caveosomes in K562 cells responding to an ongoing immune attack (right).

Publications

Pilzer D, Saar M, Koya K, **Fishelson Z**. Mortalin inhibitors sensitize K562 leukemia cells to complement-dependent cytotoxicity. Int. J. Cancer. 126: 1428-1435, 2010.

Oren M, Paz G, Douek J, Rosner A, **Fishelson Z**, Goulet TL, Henckel K, Rinkevich B. 'Rejected' vs. 'rejecting' transcriptomes in allogeneic challenged colonial urochordates. Molec. Immunol. 47: 2083-2093, 2010.

Goldberg M, Fremeaux-Bacchi V, Koch P, **Fishelson Z**, Katz Y. A novel mutation in the C3 gene and recurrent invasive pneumococcal infection: A clue for vaccine development. Molec. Immunol. 48: 1926-1931, 2011.

Moskovich O, Herzog L-O, Ehrlich M and **Fishelson Z**. Caveolin-1 and dynamin-2 are essential for removal of the complement C5b-9 complex via endocytosis. J. Biol. Chem. 287: 19904-19915, 2012.

Gancz D, Lusthaus M and **Fishelson Z**. A role for the NF-κb pathway in cell protection from complement-dependent cytotoxicity, J. Immunol. 189: 860-866, 2012.

Rozenberg P, Kocsis J, Saar M, Prohászka Z, Füst G and **Fishelson Z**. Elevated levels of mitochondrial mortalin and cytosolic HSP70 in blood as risk factors in colorectal cancer patients. Int. J. Cancer. 133: 514-519, 2013.

Gurevich M and **Fishelson Z**. Construction and characterization of recombinant human C9 or C7 linked to single Chain Fv directed to CD25. Mol. Immunol. 55: 400-408, 2013.

Saar Ray M., Moskovich O. Iosefson O. and **Fishelson Z.** Mortalin/Grp75 Binds to Complement C9 and Plays a Role in Resistance to Complement-Dependent Cytotoxicity, J. Biol. Chem. June 2014, in press, Epub. April 9, 2014

Reviews

Saar M, Moskovich O and **Fishelson Z**. Mortalin in cell protection from immune attack, in: ”Mortalin Biology: Life, Stress and Death”, Springer, 2012, pp. 129-137.

Moskovich O. and **Fishelson Z.,** Quantification of complement C5b-9 binding to cells by Flow Cytometry, in ‘Methods in Molecular Biology; Complement System: Methods and Protocols’ Gadjeva M. ed., Springer Science+Business Media New York, 2014, pp103-108.

Grants

2011 – 2014, Nanoscale analysis of the molecular interactions that control insertion and elimination of the complement C5b-9 complex, German-Israel Foundation (GIF), Co-PI: Alexander Egner

2011 – 2015, Functional and molecular analysis of cancer cell resistance mechanisms to complement-dependent cytotoxicity, Israel Science Foundation (ISF)

May 25, 2014

Dr. Yankel Gabet, D.M.D., Ph.D.

Department of Anatomy & Anthropology
Sackler Faculty of Medicine

Tel-Aviv University
E-mail: yankel@post.tau.ac.il

Sex & Bone

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Sexual dimorphism skeletal remodeling is well-established, although not completely understood. Recently, we have characterized two pathways with sex-specific influence on the skeleton. (1) Moderate fluctuations in Wnt signaling, a ubiquitous pathway with critical roles in bone formation and resorption, affect preferentially the female skeleton. (2) Deficiency in Krox20 in the monocytic/osteoclastic lineage results in a low bone mass phenotype in females only. The goal of my research group is to investigate the putative role of these pathways, as mediators of the sex-specific skeletal response to sex hormone signaling in osteoblasts (the bone forming cells) and in osteoclasts (the bone resorbing cells.

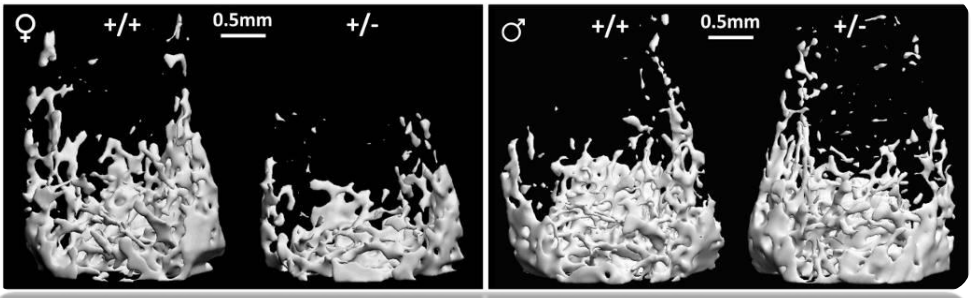


Figure 1: Low bone mass in *Krox20*-haploinsufficient females. µCT images of representative distal femoral trabecular bone of female and male $Krox20^{+/+}$ (*left*) and $Krox20^{+/-}$ (*right*) mice.

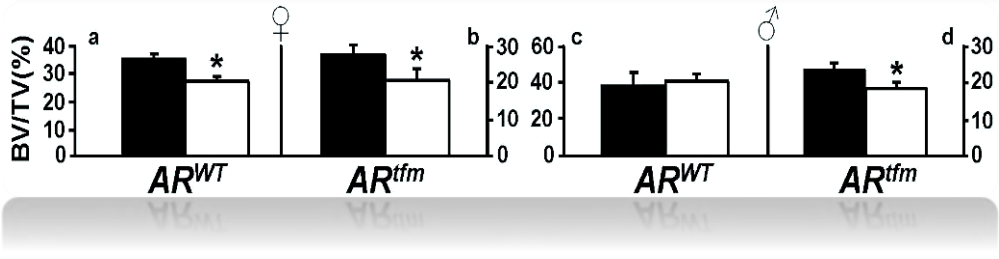


Figure 2. Effect of haploinsufficiency in *Lef1*, a Wnt transcription factor. µCT analysis of the vertebral trabecular bone of female (*left*) and male (*right*) $Lef1^{+/+}$ *(black)* and $Lef1^{+/-}$ *(white)* mice. AR^{tfm} males have no functional AR, while AR^{tfm} females are carriers for the defective *AR* allele. Data represent mean±SEM, * = $p< 0.05$. Note that only males carrying a functional AR are protected against *Lef1* gene dosage

Publications

Frenkel B, Hong A, Baniwal SK, Coetzee GA, Ohlsson C, Khalid O, **Gabet Y.** (2010) Regulation of Adult Bone Turnover by Sex Steroids. J Cell Physiol., 2:305-310.

Baniwal SK, Khalid O, **Gabet Y**, Shah RR, Purcell DJ, Mav D, Kohn-Gabet AE, Shi Y, Coetzee GA, Frenkel B. (2010) Runx2 Transcriptome of Prostate Cancer Cells: Insights into Invasiveness and Bone Metastasis. Mol Cancer, 9:258.

Gabet Y, Leclerc N, Baniwal SK, Shi Y, Kohn-Gabet AE, Cogan J, Dixon A, Chavez M, Guo L, Turman JE-Jr, Frenkel B. (2010) Krox20/EGR2 Deficiency Accelerates Cell Growth and Differentiation in the Monocytic Lineage and Decreases Bone Mass. Blood, 116:3964-71.

Gabet Y, Noh T, Lee C, Frenkel B. (2011) Developmentally-regulated Inhibition of Cell Cycle Progression by Glucocorticoids through Repression of Cyclin A Transcription in Primary Osteoblast Cultures. J Cell Physiol., 226:991-8.

Baniwal SK, Shah PK, Shi S, Haduong JH, DeClerck Y, **Gabet Y**, Frenkel B. (2011) Runx2 Promotes both Osteoblastogenesis and Novel Osteoclastogenic Signals in ST2 Mesenchymal Progenitor Cells. Osteoporos. Int., 23:1399-1413.

Gabet Y, Bab I. (2011) Microarchitectural Changes in the Aging Skeleton. Current Osteoporosis Reports. 9:177-83.

Yen HY, **Gabet Y**, Liu Y, Martin A,Wu N, Pike MC, Frenkel B, Maxson R, Dubeau L. (2012) Potential Consequences of the Brca1 Mutation Carrier State on Estrogen Responsive Organs. Lab Invest. 92:802-11.

Chapter

Smith P, Avishai G, Müller R, and **Gabet Y**. Computerized Reconstruction of Prenatal Growth Trajectories in the Dentition: Implications for the Taxonomic Status of Neanderthals. In S. Condemi and G.-C. Weniger (eds.), Continuity and Discontinuity in the Peopling of Europe: One Hundred Fifty Years of Neanderthal Study, Vertebrate Paleobiology and Paleoanthropology, Springer Science+Business Media B.V. 2011.

Grants

2012-2017 Israel Science Foundation (ISF) Grant

2013 Israel Defense Army Research Grant, “Circulating osteoblast-lineage cells – a novel, simple diagnostic procedure to detect stress fractures”, Co-PI

2013 Turnheim Foundation Research Grant, “Biomechanical evaluation of thermoplastic aligners by way of von Mises strains and stereolithography layers”, Co-PI

May 24, 2014

Dr. Tamar Geiger, Ph.D.

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Sackler Faculty of Medicine

Tel Aviv University
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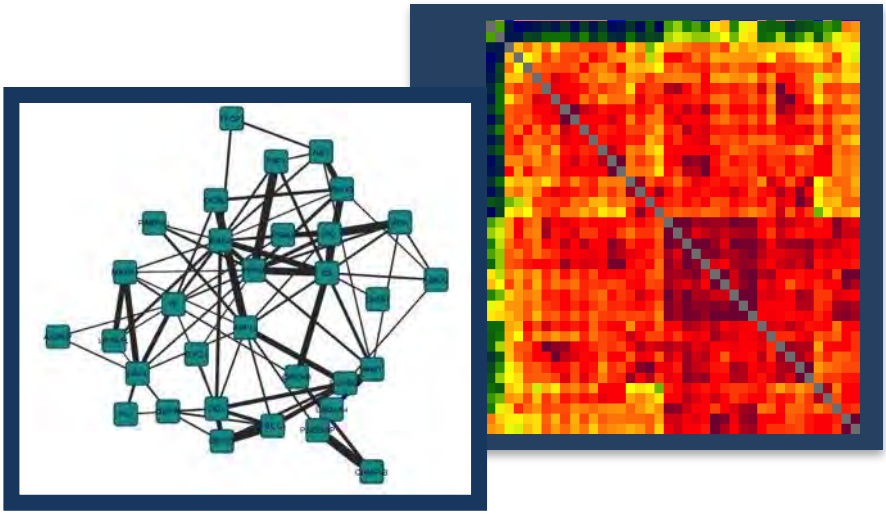
Proteomics of Breast Cancer Progression

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our main interest is to understand the mechanisms of breast cancer progression. We are using state-of-the-art mass spectrometry-based proteomics to obtain a system-wide view of the tumor proteins. Analysis of the changes in protein levels and modifications that occur during tumor development is aimed to discover novel regulators of transformation. Combination of the proteomics technology with biochemical and genetic methods will show the significance of these candidates to cancer development and may suggest novel drug targets and tumor markers. Our laboratory opened at Tel Aviv University in October 2011.



Publications

Rivlin, N., Katz, S., Doody, M., Sheffer, M., Horesh, S., Molchadsky, A., Koifman, G., Shetzer, Y., Goldfinger, N., Rotter, V. and **Geiger, T.** Rescue of ESCs from cellular transformation by proteomic stabilization of mutant p53 and conversion into WT conformation. *Proc Natl Acad Sci USA*. Accepted.

Oren, Y.S., McClure, M.L., Rowe, S.M., Sorscher, E.J., Bester, A.C., Manor, M., Kerem, E., Rivlin, J., Mann, M., **Geiger, T.** and Kerem, B. The Unfolded Protein Response affects readthrough of Premature Termination Codons. *EMBO Molec Med*. Accepted.

Pozniak, Y. and **Geiger, T**. Design and application of super-SILAC for proteome quantification. *Meth Molec Biol.* Accepted.

Aviner, R., **Geiger, T.*** and Elroy-Stein, O. Genome-wide identification and quantification of protein synthesis in cultured cells and whole tissues by puromycin-associated nascent chain proteomics (PUNCH-P). *Nat Protocols* 9, 751-760 (2014). * Single corresponding author.

Aviner, R., **Geiger, T.** and Elroy-Stein, O. PUNCH-P for global translatome profiling; Methodology, insights and comparison to other techniques. *Translation* 1, e27516 (2014).

Waldman, Y.Y., **Geiger, T.** and Ruppin, E. A genome-wide systematic analysis reveals different and predictive proliferation expression signatures of cancerous vs. non-cancerous cells. *PLoS Gen.* 9, e1003806 (2013).

Aviner, R., **Geiger, T*.** and Elroy-Stein, O*. Novel proteomic approach (PUNCH-P) reveals cell cycle-specific fluctuations in mRNA translation. *Genes and Dev* 27:1834-44 (2013). * Equal contribution corresponding authors.

Radovanac, K., Morgner, J., Schulz, J.N., Blumbach, K., Patterson, C., **Geiger, T.,** Mann, M., Krieg, T., Eckes, B., Fässler, R. and Wickström, S.A. Stabilization of integrin-linked kinase by the Hsp90-CHIP axis impacts cellular force generation, migration and the fibrotic response. *EMBO J*. 32(10):1409-24 (2013)

Geiger, T., Velic, A., Macek, B., Lundberg, E., Kampf, C., Nagaraj, N., Uhlen, M., Cox, J. and Mann, M. Initial quantitative proteomic map of 28 mouse tissues using the SILAC mouse. *Mol Cell Proteomics* 12:1709-22 (2013)

Boersema, P.J., **Geiger, T.,** Wisniewski, J.R. and Mann, M. Quantification of the N-glycosylated secretome by super-SILAC during breast cancer progression and in human blood samples. *Mol Cell Proteomics* 12:158-71 (2013)

Jerby, L., Wolf, L., Denkert, C., Stein, G.Y., Hilvo, M., Oresic, M., **Geiger, T.*** and Ruppin E*. Metabolic associations of reduced proliferation and oxidative stress in advanced breast cancer. *Cancer Res.* 72(22):5712-20 (2012). Corresponding authors.

Geiger, T., Madden, S.F., Gallagher, W.M., Cox, J. and Mann M. Proteomic portrait of human breast cancer progression identifies novel prognostic markers. *Cancer Res*. 72:2428-2439 (2012)

Schaab, C., **Geige, T.**, Stoehr, G., Cox, J. and Mann, M. Analysis of high accuracy, quantitative proteomics data in the MaxQB database. *Mol Cell Proteomics*. 11:M111.014068 (2012)

Geiger, T, Wehner, A., Schaab, C., Cox, J. and Mann, M. Comparative proteomic analysis of eleven common cell lines reveals ubiquitous but varying expression of most proteins. *Mol Cell Proteomics*. 11:M111.014050 (2012)

Nagaraj, N., Wisniewski, J.R., Geiger, T., Cox, J., Kircher, M., Kelso, J., Paabo, S. & Mann, M. Deep proteome and transcriptome mapping of a human cancer cell line. Mol Syst Biol. 7:548 (2011).

Meves, A., Geiger, T., Zanivan, S., DiGiovanni, J., Mann, M. & Fässler, R. β1 integrin cytoplasmic tyrosines promote tumorigenesis in a phosphorylation-independent manner. Proc Natl Acad Sci USA 108:15213-15218 (2011)

Thakur, S.*, Geiger, T.*, Chatterjee, B., Bandilla, P., Fröhlich, F., Cox, J. & Mann, M. Deep proteome coverage in single-run liquid chromatography tandem mass spectrometry. Mol Cell Proteomics 10:M110.003699 (2011) * Equal contribution.

Geiger, T., Wisniewski, JR., Cox, J., Zanivan, S., Kruger, M., Ishihama, Y. & Mann, M. Use of stable isotope labeling by amino acids in cell culture (SILAC) as an internal standard in quantitative proteomics. Nat Protocols 6:147-157 (2011).

Lundberg, E., Fagerberg, L., Matic, I., **Geiger, T.**, Cox, J., Klevebring, D., Älgenäs, C., Lundeberg, J., Mann, M & Uhlen, M. Highly ubiquitous expression of the transcriptome and proteome in three functionally different human cell lines. *Mol Syst Biol* 6:450 (2010).

Geiger, T., Cox, J., Ostasiewicz, P., Wisniewski, J.R. & Mann, M. Super-SILAC mix for quantitative proteomics of human tumor tissue. *Nat Methods* 7:383-385 (2010).

Geiger, T., Cox, J. & Mann, M. Proteomics on an Orbitrap benchtop mass spectrometer using all-ion fragmentation. *Mol Cell Proteomics* 9:2252-2261 (2010).

Geiger, T., Cox, J. & Mann, M. Proteomic changes resulting from gene copy number variations in cancer cells. *PLoS Genet* 6:e1001090 (2010).

Reviews

Geiger T*, Zaidel-Bar R*. Opening the floodgates: proteomics and the integrin adhesome. Curr Opin Cell Biol. 24(5):562-8 (2012).* Equal contribution corresponding authors.

Geiger, T. & Geiger, B. Towards elucidation of functional molecular signatures of the adhesive-migratory phenotype of malignant cells. *Semin Cancer Biol* 20, 146-152 (2010).

Grants

2014- 2016	Israel Cancer Research Fund (ICRF): Novel approaches for early-detection biomarkers for ovarian cancer. Co-PI with Keren Levanon and Ariel Hourvitz.
2014- 2016	Melanoma Research Alliance (MRA): Discovery of novel immune checkpoints in melanoma. Co-PI with Gal Markel and Noam Shomron
2012- 2015	Israel Cancer Research Fund (ICRF): Elucidation of regulatory networks in triple-negative breast
2012-2016	Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease
2012-2017	Israel Science Foundation (ISF) Grant: The role of metabolic pathways in the regulation of breast cancer progression.

May 24, 2014

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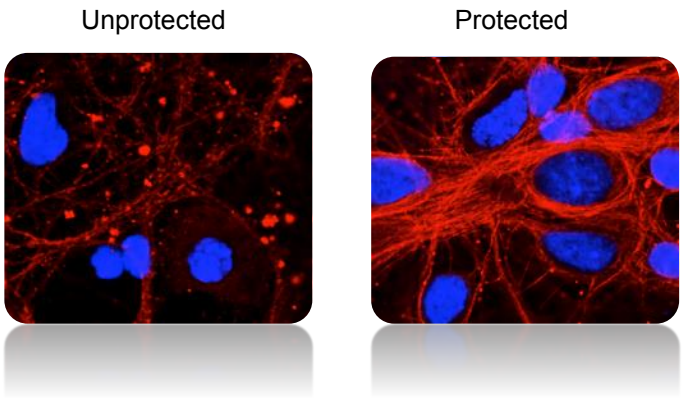
Neuronal Plasticity and Nerve Cell Protection in Disease

Positions

Professor, Sackler Faculty of Medicine
Lily and Avraham Gildor Chair for the Investigation of Growth Factors
Director, Adams Super Center for Brain Studies
Director, Levie-Edershein-Gitter Institute for Functional Brain Imaging
Director, Dr. Diana and Zelman Elton Laboratory for Molecular Neuroendocrinology
Editor-in-Chief, *Journal of Molecular Neuroscience*

Research

Our research is characterized by a multi-level approach to the study of brain function, behavior, memory and drug discovery, from molecules to cures. Targeting Alzheimer's disease and related neurodegeneration and utilizing a multidisciplinary approach, our group investigates different aspects of neuronal plasticity and nerve cell protection, at the molecular, cellular and system level. A major focus in the laboratory is on nerve structure and transport mechanisms. We have discovered novel families of proteins associated with cross talk among nerve cells and their support cells, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotetive proteins (ADNPs). Small ADNF and ADNP derivatives are in clinical development. The lead compound, davunetide is being tested in a Phase II/III clinical trial targeting progressive supranuclear palsy, a fatal neurodegenerative disorder often misdiagnosed as Parkinson disease (www.allontherapeutics.com).



Protecting nerve cell skeleton and transport system

Small ADNF and ADNP derivatives are in (or available for) clinical development (formerly by Allon Therapeutics Inc.). The lead compound, davunetide has shown efficacy in several Phase II clinical trials (i.e. in patients suffering from mild cognitive impairment, preceding Alzheimer's disease and in schizophrenia patients, protecting activities of daily living

Publications

Bassan H, Kidron D, Bassan M, Rotstein M, Kariv N, Giladi E, Davidson A, **Gozes I**, Harel S. The effects of vascular intrauterine growth retardation on cortical astrocytes. *J Matern Fetal Neonatal Med* 23:595-600, 2010.

Fernandez-Montesinos R, Torres M, Baglietto-Vargas D, Gutierrez A, **Gozes I**, Vitorica J, Pozo D. Activity-dependent neuroprotective protein (ADNP) expression in the amyloid precursor protein/presenilin 1 mouse model of Alzheimer's disease. *J Mol Neurosci* 41:114-120, 2010.

Merenlender-Wagner A, Pikman R, Giladi E, Andrieux A, **Gozes I**. NAP (davunetide) enhances cognitive behavior in the STOP heterozygous mouse--a microtubule-deficient model of schizophrenia. *Peptides* 31:1368-1373, 2010. (Gozes I. recipient of Gayle A. Olson and Richard D. Olson prize for most meritorious original research article)

Shiryaev N, Jouroukhin Y, **Gozes I**. 3R tau expression modifies behavior in transgenic mice. *J Neurosci Res* 88:2727-2735, 2010.

Belokopytov M, Shulman S, Dubinsky G, **Gozes I**, Belkin M, Rosner M. Ameliorative effect of NAP on laser-induced retinal damage. *Acta Ophthalmol* 89:e126-131, 2011.

Dresner E, Agam G, **Gozes I**. Activity-dependent neuroprotective protein (ADNP) expression level is correlated with the expression of the sister protein ADNP2: deregulation in schizophrenia. *Eur Neuropsychopharmacol* 21:355-361.

Fleming SM, Mulligan CK, Richter F, Mortazavi F, Lemesre V, Frias C, Zhu C, Stewart A, **Gozes I**, Morimoto B, Chesselet MF. A pilot trial of the microtubule-interacting peptide (NAP) in mice overexpressing alpha-synuclein shows improvement in motor function and reduction of alpha-synuclein inclusions. *Mol Cell Neurosci* 46:597-606, 2011.

Sokolowska P, Passemard S, Mok A, Schwendimann L, **Gozes I**, Gressens P. Neuroprotective effects of NAP against excitotoxic brain damage in the newborn mice: implications for cerebral palsy. *Neuroscience* 173:156-168, 2011.

Idan-Feldman A, Schirer Y, Polyzoidou E, Touloumi O, Lagoudaki R, Grigoriadis NC, **Gozes I**. Davunetide (NAP) as a preventative treatment for central nervous system complications in a diabetes rat model. *Neurobiol Dis.* 44:327-339, 2011 (Cover Picture, December 2011 Issue).

Idan-Feldman, A., Ostritsky, R., and **Gozes, I.** Tau and caspase 3 as targets for neuroprotection. *Int J Alzheimers Dis* 493670, 2012.

Jouroukhin Y, Ostritsky R, **Gozes I**. D-NAP prophylactic treatment in the SOD mutant mouse model of amyotrophic lateral sclerosis: review of discovery and treatment of tauopathy. *J Mol Neurosci* 48:597-602, 2012.

Dresner E, Malishkevich A, Arviv C, Leibman Barak S, Alon S, Ofir R, Gothilf Y, I. **Gozes I**. Novel evolutionary-conserved role for the activity-dependent Neuroprotective Protein (ADNP) family That is important for erythropoiesis. *J Biol Chem* 287:40173-40185, 2012.

Oz S, Ivashko-Pachima Y, **Gozes I**. The ADNP derived peptide NAP modulates the tubulin pool: implication for neurotrophic and neuroprotective activities. *PLoS One* 7: e51458, 2012.

Jouroukhin Y, Ostritsky R, Assaf Y, Pelled G, Giladi E, **Gozes I.** NAP (davunetide) modifies disease progression in a mouse model of severe neurodegeneration: Protection against impairments in axonal transport. *Neurobiol Dis.* 56C:79-94, 2013.

Esteves AR, **Gozes I**, Cardoso SM. The rescue of microtubule-dependent traffic recovers mitochondrial function in Parkinson's disease. *Biochim Biophys Acta*. 1842:7-21, 2014.

Merenlender-Wagner A, Malishkevich A, Shemer Z, Udawela M, Gibbons A, Scarr E, Dean B, Levine J, Agam G, **Gozes I**. Autophagy has a key role in the pathophysiology of schizophrenia. Mol Psychiatry. 2013. doi: 10.1038/mp.2013.174

Gozes I, Schirer Y, Idan-Feldman A, David M, Furman-Assaf S. NAP alpha-aminoisobutyric acid (IsoNAP). J Mol Neurosci. 52:1-9, 2014

Schirer Y, Malishkevich A, Ophir Y, Lewis J, Giladi E, **Gozes I**. Novel marker for the onset of frontotemporal dementia: early increase in activity-dependent neuroprotective protein (ADNP) in the face of Tau mutation. *PLoS One*. 9:1, 2014

Gozes I, Iram T, Maryanovsky E, Arviv C, Rozenberg L, Schirer Y, Giladi E, Furman-Assaf S. Novel tubulin and TAU neuroprotective fragments sharing structural similarities with the drug candidate NAP (Davuentide). J Alzheimers Dis. 2014 [Epub ahead of print].

Boxer A, Lang AF, Grossman M, Knopman DS, Miller BL, Schneider LS, Doody RS, Lees A, Golbe L, Williams DR, Corvol J-C, Ludolph A, Burn D, Lorenzl S, Litvan I, Roberson ED, Koestler M, Jack CR Jr., Van Deerlin, V, Randolph C, Lobach IV, Gozes I, Whitaker S, Hirman J, Stewart AJ, Gold M, Morimoto BH on behalf of the AL-108-231 investigators. Davunetide for Progressive Supranuclear Palsy: a multicenter, randomized, double-blind, placebo controlled trial. (2014) Lancet Neurology, in press.

Reviews

Gozes I. VIP-PACAP 2010: my own perspective on modulation of cognitive and emotional behavior. *J Mol Neurosci* 42:261-263, 2010.

Gozes I. Tau pathology and future therapeutics. *Curr Alzheimer Res* 7:685-696, 2010.

Gozes I. Davunetide (NAP) pharmacology: Neuroprotection and tau. In Emerging Drugs and Targets for Alzheimer's Disease. A. Martinez, editor. Cambridge: Royal Society of Chemistry. 108-128. 2010 (Book Chapter).

Gozes I. NAP (davunetide) provides functional and structural neuroprotection. *Curr Pharm Des* 17:1040-4. 2011.

Gozes I. Microtubules, schizophrenia and cognitive behavior: preclinical development of davunetide (NAP) as a peptide-drug candidate. *Peptides* 32:428-431, 2011.

Gozes I. Microtubules (tau) as an Emerging Therapeutic Target: NAP (Davunetide). *Curr Pharm Des* 17:1040-1044, 2011.

Shiryaev N, Pickman R, Giladi E, **Gozes I**. Protection against Tauopathy by the Drug Candidates NAP (Davunetide) and D-SAL: Biochemical, Cellular and Behavioral Aspects. *Curr Pharm Des.* 17:2603-2612, 2011.

Gold, M., Lorenzl, S., Stewart, A.J., Morimoto, B.H., Williams, D.R., and **Gozes, I.** Critical appraisal of the role of davunetide in the treatment of progressive supranuclear palsy. *Neuropsychiatr Dis Treat* 8:85-93, 2012.

Harmar, A.J., Fahrenkrug, J., **Gozes, I.,** Laburthe, M., May, V., Pisegna, J.R., Vaudry, D., Vaudry, H., Waschek, J.A., and Said, S.I. Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. *Br J Pharmacol* 166:4-17, 2012.

Gozes I. Neuropeptide GPCRs in neuroendocrinology: The case of Activity-Dependent Neuroprotective Protein (ADNP). *Front. Endocrin.* | doi: 10.3389/fendo.2012.00134.

Gozes I, Baas P. Activity-Dependent Neuroprotective Protein (ADNP) and Davunetide (NAP). In: *Handbook of Biologically Active Peptides.* Edited by Abba J. Kastin, Second Edition, Section XVIII, section editor: Illana Gozes (section pp. 1611-1653). Academic Press, pp. 1611-1618, 2013.

Oz S, **Gozes I.** The cytoskeleton as a pharmacological target. In: The Cytoskeleton, imaging, isolation and interaction R. Dermietzel, Editor). Neuromethods 79: 151-169, 2013.

Magen I, **Gozes I**. Microtubule-stabilizing peptides and small molecules protecting axonal transport and brain function: focus on davunetide (NAP). Neuropeptides. 47:489-95, 2013.

Magen I, **Gozes I.** Davunetide: peptide therapeutic in neurological disorders in "Hot Topic" issue: "Peptide Therapeutics In Neurological Disorders". 2014 Feb 17, [Epub ahead of print].

A. Del Carmen Alonso, E. Elakkad, C. Gong, F Liu, T. Tanaka, T. Kudo, Y. Tatebayashi, J. Pei, J. Wang, S. Khatoon, M. Flory, B. Ghetti, **I. Gozes**, M. Novak, M. Novak, N.K. Robakis, M. de Leon, M. Iqbal. Inge Grundke-Iqbal, Ph.D. (1937-2012): The discoverer of the abnormal hyperphosphorylation of Tau in Alzheimer's Disease. *J Mol Neurosci.* 49: 430-435. 2013.

Grants

2007-2014 AMN Foundation

2011-2014 Muscular Dystrophy Association, Inc (together with Maria Pennuto) - consultant

2012-2015 Israeli Ministry of Science and Technology – New Models for ALS (with Rivka Ofir)

May 24, 2014

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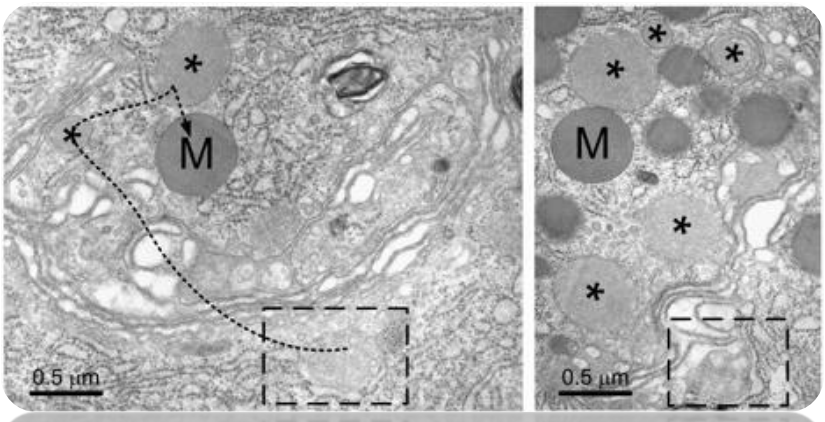
Pathobiology of Secretory Granule Packaging and Growth

Positions

Professor, Sackler Faculty of Medicine
Chair, Department of Pathology, Tel Aviv University
Academic Advisory Committee, ISEF Foundation
Academic Advisory Committee, Gazit-Globe Foundation

Research topics

Unit Granule formation: The classical model of secretory granule formation holds that proteins are transported from the RER to the Golgi zone where they can undergo post-transitional modification. They are then packaged for secretion by concentration within membrane-bound condensing vacuoles. The transportation of secretory proteins occurs in a vectorial way. The newly synthesized proteins in the RER are moved, probably via a vesicular transport, to the proximal side of the Golgi cisternae, the cis Golgi side. While moving through the Golgi cisternae the proteins undergo many modifications; most of the steps of which have not yet been resolved. The processed proteins are packed into vesicles that bud off the Golgi cisternae. The elucidation of this sequence of protein synthesis, packaging and secretion constitutes a major contribution to cell biology. It is well documented that granules in various cellular systems increase in size as time passes. For example, after degranulation is induced in either mast cells or mouse pancreatic acinar cells, granules start to accumulate. If the cell is not re-sensitized, the granule size distribution becomes broader and the mean granule size is increased. We have demonstrated that the unit granule volume is conserved; indicating that the granule size increase is probably due to homotypic fusion. The mechanism of polymerization is theoretically and experimentally investigated by us. It is found that two major mechanisms may lead to polymerization. The first one is defined as unit addition mechanism, while the second one is defined as a random addition process. We have demonstrated that the pancreatic acinar cell and mast cell granule size distribution is better fitted to the unit addition model rather than the random addition model. The Chediak-Higashi syndrome is an example of a random mechanism of granule growth.



Protein movement within pancreatic acinar cells

Publications

Hammel I, Shoichetman T, Amihai D, Galli SJ, Skutelsky E. Localization of anionic constituents in mast cell granules of brachymorphic (bm/bm) mice by using avidin-conjugated colloidal gold. Cell Tissue Res. 2010; 339:561-70.

Nitzany E, **Hammel I,** Meilijson I. Quantal basis of vesicle growth and information content, a unified approach. J Theor Biol. 2010 ;266:202-9.

Hammel I, Lagunoff D, Galli SJ. Regulation of secretory granule size by the precise generation and fusion of unit granules. J Cell Mol Med. 2010; 14:1904-16

Gorzalczany Y, Gilad Y, Amihai D, **Hammel I,** Sagi-Eisenberg R, Merimsky O, Combining an EGFR directed tyrosine kinase inhibitor with autophagy-inducing drugs; A beneficial strategy to combat non-small cell lung cancer. Cancer Letters 2011; 310:207-15.

Hammel I, Wang CC, Hong W, Amihai D. VAMP8/Endobrevin is a critical factor for the homotypic granule growth in pancreatic acinar cells. Cell Tissue Res. 2012; 348:485-490

Hammel I, Meilijson I. Function suggests nano-structure: electrophysiology supports that granule membranes play dice. J R Soc Interface. 2012; 9:2516-26.

Hammel I, Meilijson I. Function suggests nano-structure: towards a unified theory for secretion rate, a statistical mechanics approach. J R Soc Interface. 2013, 10, 20130640.

Kepelová-Dror M, **Hammel I,** Meilijson I. Statistical analysis of the quantal basis of secretory granule formation. Microsc. Res. Tech. 2014;77:1-10.

Azouz NP, Zur N, EferganA, Ohbayashi N, Fukuda M, Amihai D, **Hammel I**, Rothenberg ME, Sagi-Eisenberg R. Rab5 is a novel regulator of mast cell secretory granules: impact on size, cargo and exocytosis. J. Immunol. 2014;192:4043-53.

Chapters

Trachtenberg S, **Hammel I.** Determining the persistence length of biopolymers and rod-like macromolecular assemblies from electron microscope images and deriving some of their mechanical properties. In: Microscopy: Science, Technology, Applications and Education, A. Méndez-Vilas and J. Díaz (Eds.) Microscopy book Series. Number 4, Vol. 3, pp. 1690-1695, 2010.

Hammel I, Meilijson I. Granule size distribution suggests mechanism: the case for granule growth and elimination as a fusion nano-machine. In: NanoCellBiology: Multimodal Imaging in Biology & Medicine, Pan Sanford Publishing Pte. Ltd. Editors: Jena, B.P., Taatjes, D.J. 2013, In press.

Invited editorials

Hammel I, Lagunoff D, Galli SJ. Regulation of secretory granule size by the precise generation and fusion of unit granules. J. Cell. Mol. Med. 2010:14:1904-16

Hammel I, Meilijson I. The stealthy nano-machine behind mast cell granule size distribution. Mol Immunol. 2014. pii: S0161-5890(14)00032-7. doi: 10.1016/ j.molimm.2014.02.005 [Epub ahead of print]

May 24, 2014

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Laboratory for Brain and Emotion Experience
Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center

Brain Mechanisms of Human Emotion Generation & Regulation

Positions

Professor, Tel Aviv University
Director, Functional Brain Center, Cooperation of Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center and Levi-Edersheim-Gitter Institute for Human Neuroimaging, TAU
Steering Committee, I-CORE in Advanced Cognitive Science

Research

Investigating brain mechanisms underlie generation and regulation of the human emotional experience, in healthy and pathological states. The research is based on measuring indices of brain structure and functional dynamics via MRI (functional-MRI, DTI and Volumetric-MRI) and separate or simultaneous recording of electrical signals (scalp-EEG and intracranial-EEG). The characterization of individual brain response is based on correlating neural activity and connectivity with behavioral and physiological measurements of emotionality (e.g. heart rate, hormone secretion, genetic expression, skin conductance, eye movements and verbal output). Induction of emotional states is achieved via film and music media, inter-personal interactions, and interactive social games. Regulation of emotions is modulated via on-line feedback protocols from brain signals in a closed loop set-up (i.e. *NeuroFeedback*). The lab is also involved in studies aim to advance translation while focusing on neural markers of vulnerability and recovery with regard to post traumatic disorders (e.g. anxiety and depression), developmental disorders (e.g. schizophrenia and personality) and neurodegenerative disorders (e.g. parkinson disease). An essential part of this aspect of our work is the development of advanced new tools for acquiring and analyzing whole brain neural measurements; including applying multi-scale mapping for capturing dynamics of brain networks.

A frame from Intra- and inter-Network Cohesion Index (NCI) mapping, obtained from 16 healthy individuals while viewing a sad inducing movie clip (*Stepmom).* The trace on top presents continuous reported sadness intensity indicating that the frame depicts a moment of enhanced sadness (adapted from Raz et al *Neuroimage* 2012).

Publications

Zaretsky M., Mendelsohn A., Mintz M. & **Hendler T**. (2010). In the Eye of the Beholder: Internally Driven Uncertainty of Danger Recruits the Amygdala and Dorsomedial Prefrontal Cortex. *Journal of Cognitive Neuroscience*, 22:2263-75.

Rosenberg K., Nossek E., Liebling R., Fried I., Shapira-Lichter I., **Hendler T**., Ram Z. (2010). Prediction of neurological deficits and recovery after surgery in the supplementary motor area: a prospective study in 26 patients. *Journal of Neurosurgery,* 113:1152-63.

Jacob Y., Rapson A., Kafri M., Baruchi I., **Hendler T**., Ben Jacob E. (2010). Revealing voxel correlation cliques by functional holography analysis of fMRI. *Neuroscience Methods,* 191: 1. 126-137.

Dvash J., Gilam G., Ben-Ze'ev A., **Hendler T.** & Shamay-Tsoory SG. (2010). The envious brain: The neural basis of social comparison. *Human Brain Mapping*, 31:1741-50.

Perry D., **Hendler T**. & Shamay-Tsoory SG. (2011). Projecting memories: the role of the hippocampus in emotional mentalizing. *Neuroimage,* 54:1669-76.

Okon-Singer H., Podlipsky I., Ben Simon E., Zhdanov A., Neufeld M., Siman-Tov T., & **Hendler T**. (2011). Spatio-Temporal Indications of sub-cortical involvement in leftward bias of spatial attention. *Neuroimage*, 54:3010-20.

Weinstein M. Ben-Sira L., Levy Y., Zachor D.A., Ben Itzhak E., Artzi M., Tarrasch R., Eksteine P.M., **Hendler T.** And Ben Bashat D. (2011). Abnormal white matter integrity in young children with autism. *Human Brain Mapping,* 32: 534-543

Böttger J., Margulies DS., Horn H., Thomale UW., Podlipsky I., Shapira-Lichter .I, Chaudhry S., Szkudlarek C., Mueller K., Lohmann G., **Hendler T.**, Bohner G., Fiebach JB., Villringer A., Vajkoczy P & Abbushi A. (2011). A Software tool for interactive exploration of intrinsic functional connectivity opens new perspectives for brain surgery. *Acta Neurochirurgia,* 153: 1561-72.

Nossek E, Korn A, Shahar T, Kanner S, Yaffe H, Marcovici D, Ben-Harosh C, Ben Ami H, Weinstein M, Shapira-Lichter I, Constantini S, **Hendler T** & Ram Z. (2011). Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and three-dimensional ultrasonography-based navigation. *Journal of Neurosurgery*, 114:738-46.

Atzil S., **Hendler T**, Feldman R. (2011). Specifying the neurobiological basis of human attachment: Brain, hormones, and behavior in synchronous and intrusive mothers. *Neuropsychopharmacology*, 36:2603-15.

*S*alomon R.,Bleich-Cohen M., Hahamy-Dubossarsky A., Dinstien I., Weizman R., Poyurovsky M., Kupchik M., Kotler M., **Hendler T.** and Malach R. (2011). Global Functional Connectivity Deficits in SchizophreniaDepend on Behavioral State. *Journal of Neuroscience, 3*1:12972-81.

Bleich-Cohen M., Sharon H., Weizman R., Poyurovsky, M., Faragian S. and **Hendler T.** (2011). Diminished language lateralization in schizophrenia corresponds to impaired inter-hemispheric functional connectivity. *Schizophrenia Research,* 134:131-6.

Raz G., Winetraub Y., Jacob Y, Kinreich S, Maron-Katz A., Shaham G, Podlipsky I, Gilam G, Soreq E, **Hendler T.** (2012). Portraying emotions at their unfolding: a multilayered approach for probing dynamics of neural networks. *Neuroimage,* 60:1448–1461.

Podlipsky I., Ben-Simon E., **Hendler T.** and Intrator N. (2012). Robust Modeling Based on Optimized EEG Bands for Functional Brain State Inference, *Neuroscience Methods,* 203:377-85.

Lerner Y., Singer N., Weintraub Y., Cohen O., Rubin N.,Ungerleider L.G. and Hendler T. (2012) Feeling without Seeing? Engagement of ventral, but not dorsal, amygdala during unaware exposure to emotional faces. *Journal of Cognitive Neuroscience*. 24:531-42.

Perry D., **Hendler T.** and Shamay-Tsoory S.G. (2012) Can we share the joy of others? Empathic neural responses to distress vs. joy. *Social Cognition and Affective NeuroScience,* 7:909-16.

Singer N., Eapen M., Grillon C., Ungerleider L.G, **Hendler T**. (2012) Through the eyes of anxiety: Dissecting threat bias via emotional-binocular rivalry. *Emotion,* 12:960-9.

Gonen T., Admon R., Podlipsky I. and **Hendler T.** (2012) From Animal Model to Human Brain Networking: Dynamic Causal Modeling of Motivational Systems. *Journal of Neuroscience,* 32:7218-24.

Cohen J.E., Shalev H, Admon R, Hefetz S, Gasho C.J, Shachar L.J, Shelef S, **Hendler T** and Friedman A. (2013) Emotional brain rhythms and their impairment in post-traumatic patients. *Human Brain Mapping,* 34:1344-56.

Admon R., Lubin G., Rosenblatt J., Stern O., Kahn I., Assaf M. and **Hendler T**. (2013) Imbalanced neural responsively to threat and reward indicates stress vulnerability in humans. *Cerebral Cortex*, 23:28-35.

Chapters and Reviews

Gruberger M, Ben-Simon E, Levkovitz Y, Zangen A and **Hendler T** (2011) Towards a neuroscience of mind-wandering (review). *Frontiers in Human Neuroscience*. 5:56. doi: 10.3389/fnhum.2011.00056

Jacob Y., Papo D., Papo D., **Hendler T.** and Ben-Jacob E. (2012). Holography and cliques in brain activation patterns. Chapter in *Advances Brain Imaging edt*. (PP 101-126), Tech Publishing.

Raz G., Hagin B. and **Hendler T**. (2013) E-motion pictures of the brain: recursive paths between cinema and neuroscience. A *Shimamura (ed) Psychocinematics*: The Aesthetic Science of Movies. Oxford University Press. DOI: 10.1093/acprof:oso/9780199862139.001.0001

Grants

2011-2014	Euro-Active. *Pre and intraoperative surgical advanced brain mapping capabilities, including multi-scale measurements of brain structure and function (*consortium partner).
2012-2014	Finland-Israel Eureka Program, the Israeli Ministry of Industry, Trade & Labor. *Multi parametric imaging of functional brain networks: integrative unit of MEG, EEG and fMRI* (sub-contractor).

May 24, 2014

Prof. Israel Hershkovitz, Ph.D.

Department of Anatomy and Anthropology
Sackler Faculty of Medicine

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Evolutionary Medicine, Paleopathology and Bio-history

Position

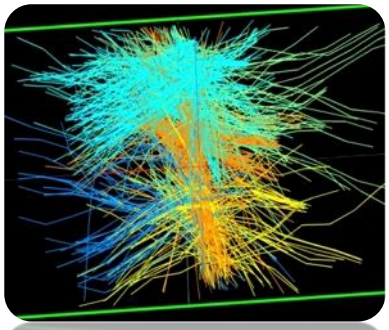
Professor, Sackler Faculty of Medicine
Head, Dan David Laboratory for the Search and Study of Modern Humans
Director, Tassia and Joseph Meychan Chair for the History and Philosophy of Medicine

Research

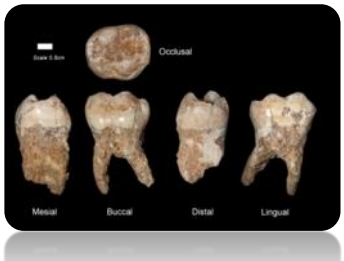
Biohistory: The social and biological impact the transition from foraging and hunting to farming had on human populations. Although a rapid event in human evolution, the 'agriculuture revolution' was the most significant cultural process in human history, something that forever changed the face of humanity (culturally and biologically). Unlike many other paleoanthropological studies, we adopt an 'osteobiographic' approach, i.e., life history as recorded in bones. The study is based on several hundreds of Natufian and Neolithic skeletons (large portion of them were excavated by the team), housed at Tel Aviv University. The study, besides traditional methods, applies new methods and technologies as CT, Micro-CT, SEM, Histochemistry, aDNA, Isotope analyses.

Human evolution: Searching for the origin of anatomically modern humans. The origin of anatomically modern *Homo sapiens* and the fate of the Neanderthals have been fundamental questions in human evolutionary studies for over a century. New fossils excavated at Qesem, Misliya and Manot caves, may shed light on the above questions.

Evolutionary medicine: This section is divided into three topics: 1) Establishing valid methods for identifying diseases in ancient bones, 2) Identifying diseases in the fossil record, 3) Evolutionary perspective of current diseases.



3D reconstruction of the annulus fibrosus, MRI study. Disc herniation project.



Teeth from Qesem cave 300,000 years. Modern human origin project.

Plastered skulls from Yiftahel 9,000. Early farming communities' project. Ancestral cult.

Publications

Masharawi Y, Dar G, Peleg S, Steinberg N, Medlej B, May H, Abbas J, **Hershkovitz I**. A morphological adaptation of the thoracic and lumbar vertebrae to lumbar hyperlordosis in young and adult females. Eur Spine J. 2010, 19: 768-773.

Dar G, Masharawi Y, Peleg S, Steinberg N, May H, Medlej B, Peled N, **Hershkovitz I**. Schmorl's nodes distribution in the human spine and its possible etiology. Eur Spine J. 2010, 19: 670-675.

Hay O, **Hershkovitz I**, Rivlin E. Spine curve modeling for quantitative analysis of spinal curvature.

Conf Proc IEEE Eng Med Biol Soc. 2009;1:6356-9.

Wasser DE, **Hershkovitz I**. The question of ethnic variability and the Darwinian significance of physiological neonatal jaundice in East Asian populations. Med Hypotheses. 75: 187-189.

Galili E, Eshed V, Rosen B, Kislev ME, Simchoni O, **Hershkovitz I**, Gopher A. Evidence for a separate burial ground at the submerged pottery Neolithic site of Neve-Yam, Israel. Paleorient 2010, 35: 31-46.

Abbas J, Hamoud K, Masharawi YM, May H, Medlej B, Peled N**, Hershkovitz I**. Ligamentum flavum thickness in normal and stenotic lumbar spine. Spine 2010, 20:35:1225-1230.

May H, Peled N, Dar G, Abbas J, Medlej B, Masharawi Y, Hershkovitz I. Hyperostosis frontalis interna and androgen suppression. Anat Rec (Hoboken). 2010;293:1333-6.

May H, Peled N, Dar G, Cohen H, Abbas J, Medlej B, **Hershkovitz I**. Hyperostosis frontalis interna: criteria for sexing and aging a skeleton. Int J Legal Med. 2010 Jul 23. [Epub ahead of print]

Abbas J, Hamoud K, May H, Hay O, Medlej B, Masharawi Y, Peled N, **Hershkovitz I**. Degenerative lumbar spinal stenosis and lumbar spine configuration. Eur Spine J. 2010, 19(:1865-1873.

Eshed V, Gopher A, Pinhasi R, **Hershkovitz I**. Paleopathology and the origin of agriculture in the Levant. Am J Phys Anthropol. 2010 Set 143:121-133.

137. N. Steinberg, I. Siev-Ner, S. Peleg, G. Dar, Y. Masharawi, A. Zeev and **I. Hershkovitz**. Injury patterns in young, non-professional dancers. Journal of Sports Sciences 2011, 29:47-54.

May H, Peled N, Dar G, Hay O, Abbas J, Masharawi Y, **Hershkovitz I**. Identifying and classifying hyperostosis frontalis interna via computerized tomography. Anat Rec (Hoboken). 2010; 293:2007-2011.

Dar G, Masharawi Y, Peleg S, Steinberg N, May H, Medlej B, Peled N, **Hershkovitz I**. The epiphyseal ring: a long forgotten anatomical structure with significant physiological function. Spine (Phila Pa 1976). 2011, 36:850-6

Hershkovitz I, Smith P, Sarig R, Quam R, Rodríguez L, García R, Arsuaga JL, Barkai R, Gopher A. Middle pleistocene dental remains from Qesem Cave (Israel). Am J Phys Anthropol. 2010, 144: 575-592.

May H, Peled N, Dar G, Abbas J, **Hershkovitz I**. Hyperostosis frontalis interna: What does it tell us about our health? Am J Hum Biol. 2011, 23:392-7.

Abbas J, Hamoud K, Peleg S, May H, Masharawi Y, Cohen H, Peled N, **Hershkovitz I**. Facet joints arthrosis in normal and stenotic lumbar spines. Spine (Phila Pa 1976). 2011, 36:E1541-6.

Hamoud K, **Hershkovitz I**, Hanani A, Marom L, Abbas J. Internal stabilization of a flexion-distraction injury of the upper cervical spine of a toddler. A new technique and literature review. Spine (Phila Pa 1976)**.** 2011, 37:E400-7.

V. Sloan, Nagar Y, Kuperman T, **Hershkovitz I.** A case of a Dwarfism from the Byzantine city Rehovot-in-the-Negev, Israel**.** Int J Osteoarchaeology 2011, DOI:10.1002/oa.1285.

M. Ben-Dor, Gopher A, **Hershkovitz I**, Barkai R. Man the fat hunter: the demise of Homo erectus and the emergence of a new hominin lineage in the Middle Pleistocene (ca. 400 kyr) Levant. PLoS One. 2011;6:e28689.

N. Steinberg, **Hershkovitz I**, Peleg S, Dar G, Masharawi Y, Siev-Ner I. Paratenonitis of the foot and ankle in young female dancers. Foot Ankle Int. 2011, 32:1115-21.

N. Steinberg, Siev-Ner I, Peleg S, Dar G, Masharawi Y, Zeev A, **Hershkovitz I**. Extrinsic and intrinsic risk factors associated with injuries in young dancers aged 8-16 years. J Sports Sci. 2012, 30:485-95.

N. Steinberg, Siev-Ner I, Peleg S, Dar G, Masharawi Y, Zeev A, **Hershkovitz I**. Joint range of motion and patellofemoral pain in dancers. Int J Sports Med. 2012, 33:561-6.

V. Slon, **Hershkovitz I**, Peled N. Dyke-Davidoff-Masson syndrome in a 6,000-year-old skull. Neuroradiology. 2012, 54:1413-5.

H. May, Mali Y, Dar G, Abbas J, **Hershkovitz I**, Peled N. Intracranial volume, cranial thickness, and hyperostosis frontalis interna in the elderly. Am J Hum Biol 2012, 24:812-819.

H. Cohen, Sarie I, Medlej B, Bocquentin F, Toledano T, **Hershkovitz I.** and Slon, V. Trauma to the skull: A historical perspective from the Southern Levant (4300BCE–1917CE). Int. J. Osteoarchaeol. 2012, DOI: 10.1002/oa.225854

H. Cohen, Slon V, Barash A, May H, Medlej B. and **Hershkovitz I.** Assyrian attitude towards captive enemies: A 2700 years old paleo-forensic study**.** Int. J. Osteoarchaeol. 2012, DOI: 10.1002/oa.2288

R. Sarig, Lianopoulos NV, **Hershkovitz I**, Vardimon AD. The arrangement of the interproximal interfaces in the human permanent dentition. Clin Oral Investig. 2013, 17:731-8

N. Steinberg, **Hershkovitz I**, Peleg S, Dar G, Masharawi Y, Zeev A, Siev-Ner I. Morphological characteristics of the young scoliotic dancer. Phys Ther Sport. 2013;14(4):213-20.

V. Slon, **Hershkovitz I**, May H. The value of cadaver CT scans in gross anatomy laboratory. Anat Sci Educ. 2013 Sep 10. doi: 10.1002/ase.1400

N. Steinberg, Siev-Ner I, Peleg S, Dar G, Masharawi Y, Zeev A, **Hershkovitz I**. Injuries in female dancers aged 8 to 16 years. J Athletic Training, 2013, 48:118-123.

H. Cohen, V. Sloan, H. May, **I. Hershkovitz**, E. Peled, D. Norman. Musculoskeletal wounds characteristic of the second Lebanon war. Forensic Medicine and Anatomy Research. 2013, 1:14-17.

H. May, Cohen H, Medlej B, Kornreich L, Peled N, **Hershkovitz I**. Computed tomography-enhanced anatomy course using enterprise visualization. Anat Sci Educ. 2013 6(5):332-41.

H. Valladas, Mercier N, **Hershkovitz I**, Zaidner Y, Tsatskin A, Yeshurun R, Vialettes L, Joron J-L, Reyss J-L, Weinstein-Evron M. Dating the Lower to Middle Paleolithic transition in the Levant: A view from Misliya Cave, Mount Carmel, Israel J. Hum. Evol. 2013, X: 1-9.

J. Abbas, Hamoud K, May H, Peled N, Sarig R, Stein D, Alperovitch-Najenson D, **Hershkovitz I**. Socioeconomic and physical characteristics of degenerative lumbar spinal stenosis individuals. Spine (Phila Pa 1976). 2013 Feb 1. [Epub ahead of print]

R. Sarig, Slon V, Abbas J, May H, Shpack N, Vardimon AD, **Hershkovitz I**. Malocclusion in early anatomically modern human: a reflection on the etiology of modern dental misalignment. PLoS One. 2013;8(11):e80771

Slon V, Sarig R, **Hershkovitz I**, Khalaily H, Milevski I. The plastered skulls from the Pre-Pottery Neolithic B site of Yiftahel (Israel)--a computed tomography-based analysis. PLoS One. 2014 Feb 19;9(2):e89242

Reviews

V. Slon, **Hershkovitz I**, Peled N. Dyke-Davidoff-Masson syndrome and fibrous dysplasia: response to a “Letter to the Editor”. Neuroradiology. 2012, 54: 1029-1030.

May 24, 2014

Dr. Koret Hirschberg, Ph.D.

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http://www2.tau.ac.il/Person/medicine/researcher.asp?id=agjjgihh
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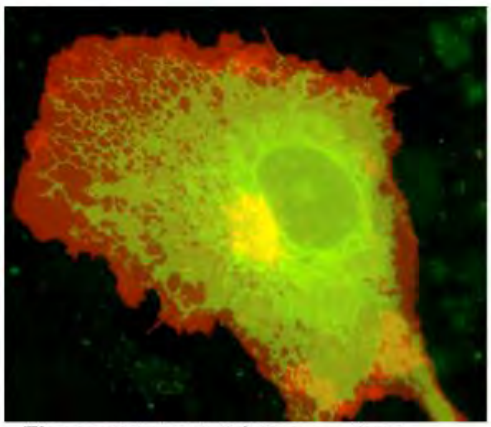
Intracellular Membrane Trafficking

Position
Senior Lecturer, Sackler Faculty of Medicine

Research

Our laboratory focuses on investigating the protein and membrane interactions that delineate membrane transport processes. We are especially interested in the functions of cargo recognition, concentration and targeted delivery to distinct cellular membranes. All transport processes use the membrane as their final substrate for example: fusion, budding, generation of distinct domains and the establishment of curvature. Combined, these functions shape the cellular transport machinery, one of the major systems that maintain homeostasis communication and response to the external environment in health and disease.



The secretory membrane system: PM (red) Golgi apparatus (yellow) and ER (green)

To understand these processes in detail, one must recognize that protein –protein as well as protein lipid interactions are involved. Studying the later, namely protein-lipid interaction is challenging since these interactions are less specific and complex experimental systems are to be used. In other words, to study the association between a protein to its proximal native lipid environment, membranes cannot be disrupted or solubilized.

In our laboratory, we combine traditional biochemical analysis with live cell imaging and quantitative kinetic modeling to gather information on the dynamic features of the cellular secretory transport machinery. Experiments are carried out using expression of fluorescent protein tagged proteins in living intact cells using laser scanning confocal microscopes. We use a range of state-of-the-art experimental setups such as: Time-lapse imaging, three-dimensional reconstruction, multicolor imaging, photobleaching/photoactivation–based manipulations and Bi-Molecular fluorescent complementation (BiFC). Kinetic modeling and simulation software is often used to extract values of kinetic coefficients or to perform model testing from the wealth of information hidden in the images sequences.

Publications

Wagner V, Elke Stadelmeyer E, Riederer M, Regitnig P, Gorischek A, DeVvaney T, Schmidt K, Tritthart HA, **Hirschberg K**, Bauernhofer T, Schreibmayer W. Cloning and characterization of GIRK1 variants resulting from alternative RNA editing of the KCNJ3 gene transcript in a human breast cancer cell line. J Cell Biochem. *J Cell Biochem.*110, 598-608, 2010.

Alfaguter-Azoulay I, Yaffe Y, Licht-Murava A, Urbanska M, Jaworski J, Pietrokovski S, **Hirschberg K,** Eldar-Finkelman H. Distinct molecular regulation of GSK-3alpha isozyme controlled by its N-terminal region. Functional role in calcium/calpain signaling. J Biol Chem. 286, 15, 13470-80. 2011.

Benjamin S, Weidberg H, Rapaport D, Pekar O, Nudelman M, Segal D, **Hirschberg K**, Katzav S, Ehrlich M, Horowitz M. EHD2 mediates trafficking from the plasma membrane by modulating Rac1 activity. Biochemical J. 439:433-42. 2011.

Yaffe Y, Shepshelovitch J, Yeheskel A, Shmerling H, Kwiatek JM, KaGaus K, Pasmanik-Chor M, **Hirschberg K**. The MARVEL transmembrane domain of Occludin mediates oligomerization and targeting to the basolateral surface in epithelia. J. Cell Sci. 125:3545-56. 2012.

Nevo-Yassaf I, Yaffe Y, Asher M, Ravid O, Eizenberg S, Henis YI, Nahmias Y, **Hirschberg K**, Sklan EH**.** A role for TBC1D20 and Rab1 in Hepatitis C virus replication via interaction with LD bound NS5A. J Virol, 86:6491-502. 2012

Grants

2012-2015	German Israel Foundation (GIF)
2012-2016	Israel Science Foundation (ISF) Grant, Surface expression of proteins is regulated by sorting and selection in endoplasmic reticulum exit sites and in the Golgi apparatus

May 24, 2014

Prof. Nurit Hollander, Ph.D.

Department of Clinical Microbiology and Immunology
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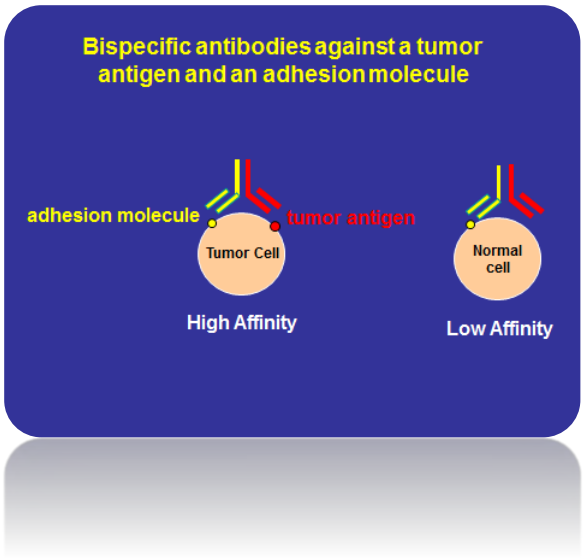
Immunotherapy of Hematologic Malignancies

Positions

Associate Professor, Sackler Faculty of Medicine
Associate Editor, *Frontiers in Immunotherapies and Vaccines*
Editorial Board, *Immunotherapy*

Research

Our research focuses on immunotherapy of hematologic cancers, particularly lymphoma and multiple myeloma. Its goal is to design personalized treatments that combine passive and active immunotherapy. To this end, we generate monoclonal antibodies and vaccines against tumor-specific antigens. We also generate novel bispecific antibodies against tumor antigens and adhesion molecules, antibodies that selectively block tumor metastasis. The effects of combined antibody treatment and vaccination on anti-tumor responsiveness (induction of immune responses and tumor rejection) are analyzed in vivo and in vitro, using methods such as fluorescence imaging of tumor-bearing mice, immunohistochemistry, antibody- and cell-mediated cytotoxicity assays, cell proliferation assays, cell migration assays, enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunospot assay (ELISPOT), and fluorescence-activated cell sorting (FACS).



Schematic presentation of our novel bispecific antibodies

Publications

Haimovich J, Ben Moshe N, Raviv Y, **Hollander N**. All oligosaccharide moieties of the μ chains in the pre-BCR are of the high-mannose type. Mol. Immunol. 48: 351-355, 2010.

Benaroya-Milshtein N, **Hollander N**, Apter A, Yaniv I, Pick CG. Stress conditioning in mice: Alterations in immunity and tumor growth. Stress 14: 301-311, 2011.

Manzur S, Cohen S, Haimovich J, **Hollander N**. Enhanced therapeutic effect of B cell-depleting anti-CD20 antibodies upon combination with in situ dendritic cell vaccination in advanced lymphoma. Clin. Exp. Immunol. 170: 291-299, 2012.

Cohen S, Haimovich J, **Hollander N.** Distinct processing of the pre-B cell receptor and the B cell receptor. Mol. Immunol. 54: 115-121, 2013.

Review

Hollander N. Immunotherapy for B-cell lymphoma: Current status and prospective advances. Front. Immunol. 3:3-17, 2012.

May 25, 2014

Prof. Fuad Iraqi, Ph.D.

Department of Human Microbiology and Immunology
Sackler Faculty of Medicine

Tel Aviv University
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Genetic Bases of Host Response to Infections and Chronic Diseases

Position

Associate Professor, Sackler Faculty of Medicine

Research

The research in my laboratory is focused on understanding the genetic bases of host response to infections and chronic diseases, which are important for human health. My team uses mouse model for speeding up the process of identifying such genes, which may involved of making some people resistant to a diseases while others are not. After finding the genes in mouse, it will be possible to identify the homologous genes in human. The product of our research can be used in developing new prevention and treatment tools for these diseases.

The main ongoing research projects at his lab are:

Identifying and characterizing genes involved in host response to bacterial infection by *Klebsiella Peumonia*.

Identifying and characterizing genes involved in host response to fungal infection by *Aspergillus Fumigatus* (Aspergillosis)

Identifying and characterizing genes involved in host response to bacterial that causes dental infection (periodontitis)

Identifying and characterizing genes involved in development of type-2 diabetes (T2D) in humans as a result of obesity and high fat-diet.

Identifying and characterizing genes involved in host immune response to infectious and chronic diseases.

Identifying and characterizing genes involved in development of colon cancer.

Publications

Behnke, J.M,, Menge, D., Nagda, S., Noyes, H.A., **Iraqi, F.A**., Kemp, S.J., Mugambi, J.M., Baker, L.R., Wakelin, D. and Gibson, J.P. (2010) Quantitative trait loci for resistance to worm infections and associated immunological and pathological traits in mice: Comparison of loci on chromosomes 5, 8 and 11 in F2 and F6/7 intercross lines of mice. Parasitol. 137:311-32.

Nganga, J.K., Soller, M., **Iraqi, F.A**. (2010) Towards high resolution mapping of trypanosomosis resistance loci *Tir*2 and *Tir*3 by using F_{12} advanced intercross lines with major locus *Tir*1 effect depleted. Biomed. Central Gen 11:394.

Schughart, K., Arends, D., Andreux, P., Balling, R., Beyer, A., Bezerianos, A., Brockmann, G.A., Crusio, W.E., Campbell-Tofte, J., Denny, P., Falcon-Perez, J.M., Forejt, J., Franken, P., Hovatta, I., **Iraqi, F.A**., Jansen, R.C., Kaczmarek, L., Kas, M.J., Kashofer, K., Kolisis, F., Kõks, S., Lammert, F., Möller, S., Montagutelli, X., Morahan, G., Mott, R., Pfoertner, S., Prins, P., Przewlocki, R., Ranki, A., Santos, J., Rihet, P., Schalkwyk, L., Smit, A.B., Swert, M., and

Zatloukal, E.Z. (2010) SYSGENET – a meeting report from a new European network for systems genetics. Mamm. Genome 21:331-336.

Goodhead, I., Amwayi, P., Brass, A., Hall, N., Archibald, A., Hughes, M., **Iraqi, F.A**., Kemp, S. and Noyes, H. (2010) A comprehensive genetic analysis of candidate genes regulating response to *Trypanosoma congolense* infection in mice. PLoS Negl Trop Dis. 4: E880.

Kovacs, A., Ben-Jacob, N., Tayem, H., Halperin, E., **Iraqi, F.A**. and Gophna, U. (2011) Genotype is a stronger determinant than sex of the mammalian gut microbiota. Micro Ecol 61:423-8.

Aylor, D.L., Valdar, W., Foulds-Mathes, W., Buus, R.J., Ricardo, A., Verdugo, R.A., Ralph, S., Baric, R.S., Ferris, M.T., Frelinger, F.A., Heise, M., Frieman, M.B., Gralinski, L.E., Bell, T.A., Didion, J.P., Hua, K., Nehrenberg, D.L., Powell, C.L., Steigerwalt, J., Xie, Y., Kelada, S.N.P., Collins, F.S., Yang, I.V., Schwartz, D.A., Branstetter, L.A., Chesler, E.J., Miller, D.R., Spence, J., Liu, E.Y., McMillan, L., Sarkar, A., Wang, J., Wang, W., Zhang, Q., Broman, K.W., Korstanje, R., Durrant, C., Mott, R., **Iraqi, F.A**., Pomp, D., Threadgill, D., Pardo-Manuel de Villena, F. and Churchill, G.A. (2011) Genetic analysis of complex traits in the emerging collaborative cross. Gen Res 21:1213-1222.

Durrant, C., Tayem, H., Yalcin, B., Cleak, J., Goodstadt, L., Pardo-Manuel de Villena, F., Mott, R. and **Iraqi, F.A**. (2011) Mapping QTL associated with host susceptibility to *Aspergillus fumigatus* infection in the Collaborative Cross mouse resource population. Gen Res 21:1239-1248.

Silva, M.V.B., Sonstegard, T., Hanotte, O., Mugambi, J., Garcia, J.F., Nagda, S., Gibson, J., **Iraqi, F.A**., McClintock, S., Kemp, S., Boettcher, P., Malek, M., Van Tassell, C.P. and Baker, L.R. (2012) Identification of quantitative trait loci affecting resistance to gastro-intestinal parasites in a double backcross population of Red Maasai and Dorper sheep. Anim Genet 43:63-71.

Shusterman A, Durrant C, Mott R, Schaefer A, Weiss EI, **Iraqi FA*** and Houri-Haddad Y* (2013) Host susceptibility to periodontitis: Mapping murine genomic regions. Journal of Dental Research 92: 438-443.

Shusterman A, Salaymeh Y, Nashef A, Soller M, Wilensky A, Mott R, Weiss EI, Houri-Haddad Y and. **Iraqi FA** (2013) Genotype is an important determinant factor of host susceptibility to periodontitis in the Collaborative Cross and inbred mouse populations. BMC Genetics 14: 68-79.

Fuad A. Iraqi, Hanifa Athamni, Alexandra Dorman, Yasser Salymah, Ian Tomlinson, Aysar Nashif, Ariel Shusterman, Ervin Weiss, Yael Houri-Haddad, Richard Mott and Morris Soller (2014) The Collaborative Cross mouse reference population is fulfilling its promise as a source of wide genetic variation and high resolution QTL mapping. Mammalian Genome. 25(3): 109-119

Review and editorials

Schughart K, Libert C; SYSGENET consortium, Kas MJ. (2013) Controlling complexity: the clinical relevance of mouse complex genetics. *Eur J Hum Genet.* 21(11):1191-6.

Anna Delprato, Ana M Aransay, Heike Kollmus, Klaus Schughart, Juan M Falcon-Perez (2013) Meeting report of the European mouse complex genetics network SYSGENET. *Mammalian Genome* 24(5-6):190

Maria Hernandez-Valladares, Pascal Rihet and **Fuad A. Iraqi** (2014) Genetic Resistance to Malaria: Two Compatible Approaches in Humans and Mice to Identif:1-16.y Potential Resistant Genes. Physiological Genomics 46

Grants

2012-2015 European Sequence and Genotyping Institutes (ESGI)
Understanding genetic susceptibility to fungal infection using naïve collaborative cross mice (Collaborators: Ron Shamir and Irit Gat-Viks (TAU), Richard Mott (University of Oxford)

2013-2016 EU-FP7-Infrafrontier
European Mouse Mutant and Archiving (EMMA) (co-PI*)
(Collaborators: 23 Members from European countries)

2012-2014 Wellcome Trust
Development of recombinant inbred stock mouse population
The fund is granted to develop the collaborative cross (CC) mouse population and carry research experiments on the population (Collaborator: Richard Mott (UK)

2013-2014 Cancer Biology Research Center (CBRC)
APC gene in intestinal cancer development in Collaborative Cross mice (PI*)

2014-2015 Bela and Zeigmond Altar and Semha Torkeltov Fund for Cancer Research
APC gene in intestinal cancer development in Collaborative Cross mice

June 1, 2014

Prof. Shai Izraeli, M.D

Functional Genomics and Childhood Leukemia Research
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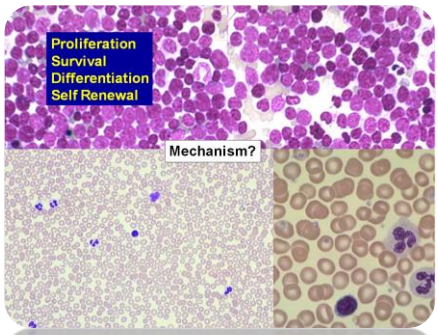
Basic and Translational and Research of Childhood Malignancies and Leukemia

Position
Professor, Sackler Faculty of Medicine
Chair, MD-PhD program

Research

We focus on patient-driven basic research into the pathogenesis of childhood leukemia and cancer. We harness advanced molecular and cellular biology technologies utilizing in-vitro and in-vivo models with the ultimate goal of improving the care of children with cancer.

Our research is divided into two major topics:
1. Basic, translational and clinical research of leukemia.
2. The role of SIL (STIL) protein in mitosis, centrosomal biology and cancer.



Cancer is the deadliest disease of children and leukemia is the most common childhood cancer. We are interested in the fundamental question how normal blood development is diverted into leukemia. What are the genetic and biochemical abnormalities that block cell differentiation, enhance proliferation and survival and confer the unique stem cell properties of self renewal to leukemia stem cells? We focus on chromosome 21 because of the mysterious association of leukemia with Down Syndrome. We utilize advanced genomic technologies, cell based assays of transformation of primary human and mouse stem cells, mouse models including transgenic, transplantation and explants of human leukemia. Our recent discoveries of the major involvement of the TSLP-IL7R-JAK2 pathway in leukemogenesis have lead to clinical trials with novel inhibitors of this pathway for high-risk leukemias in children and adults. The spread of leukemia to the brain is a major clinical problem as preventive therapy to the brain consistingof chemotherapy or irradiation causes long term side effects. We are therefore studying how leukemia cells spread to the central nervous system and developing mouse models to study this challenging problem.

We have discovered that SIL, a gene cloned from childhood leukemia, is required for centrosomal biogenesis and for survival of cancer cells. Targeting SIL by siRNA cause cancer cell death at mitotic entry in-vitro and in-vivo. Current research focuses on the fundamental role

of the SIL protein in centrosome generation in normal and malignant cells and on developing approaches for its targeting for cancer therapy.

Publications

Tal, N., C. Shochat, I. Geron, D. Bercovich, and S. **Izraeli**, Interleukin 7 and thymic stromal lymphopoietin: from immunity to leukemia. *Cell Mol Life Sci*, 2014. 71(3): p. 365-78.

Stary, J., M. Zimmermann, M. Campbell, L. Castillo, E. Dibar, S. Donska, A. Gonzalez, S. **Izraeli**, D. Janic, J. Jazbec, J. Konja, E. Kaiserova, J. Kowalczyk, G. Kovacs, C.K. Li, E. Magyarosy, A. Popa, B. Stark, Y. Jabali, J. Trka, O. Hrusak, H. Riehm, G. Masera, and M. Schrappe, Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *J Clin Oncol*, 2014. 32(3): p. 174-84.

Meissner, B., T. Bartram, C. Eckert, J. Trka, R. Panzer-Grumayer, I. Hermanova, E. Ellinghaus, A. Franke, A. Moricke, A. Schrauder, A. Teigler-Schlegel, P. Dorge, A. von Stackelberg, G. Basso, C.R. Bartram, R. Kirschner-Schwabe, B. Bornhauser, J.P. Bourquin, G. Cazzaniga, J. Hauer, A. Attarbaschi, S. **Izraeli**, M. Zaliova, G. Cario, M. Zimmermann, S. Avigad, M. Sokalska-Duhme, M. Metzler, M. Schrappe, R. Koehler, G. Te Kronnie, and M. Stanulla, Frequent and sex-biased deletion of SLX4IP by illegitimate V(D)J-mediated recombination in childhood acute lymphoblastic leukemia. *Hum Mol Genet*, 2014. 23(3): p. 590-601.

Izraeli, S., A. Vora, C.M. Zwaan, and J. Whitlock, How I treat ALL in Down's syndrome: pathobiology and management. *Blood*, 2014. 123(1): p. 35-40.

Izraeli, S., C. Shochat, N. Tal, and I. Geron, Towards precision medicine in childhood leukemia - Insights from mutationally activated cytokine receptor pathways in acute lymphoblastic leukemia. *Cancer Lett*, 2014.

Buitenkamp, T.D., S. **Izraeli***, M. Zimmermann, E. Forestier, N.A. Heerema, M.M. van den Heuvel-Eibrink, R. Pieters, C.M. Korbijn, L.B. Silverman, K. Schmiegelow, D.C. Liang, K. Horibe, M. Arico, A. Biondi, G. Basso, K.R. Rabin, M. Schrappe, G. Cario, G. Mann, M. Morak, R. Panzer-Grumayer, V. Mondelaers, T. Lammens, H. Cave, B. Stark, I. Ganmore, A.V. Moorman, A. Vora, S.P. Hunger, C.H. Pui, C.G. Mullighan, A. Manabe, G. Escherich, J.R. Kowalczyk, J.A. Whitlock, and C.M. Zwaan*, Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood*, 2014. 123(1): p. 70-7.

Yoshida, K., T. Toki, Y. Okuno, R. Kanezaki, Y. Shiraishi, A. Sato-Otsubo, M. Sanada, M.J. Park, K. Terui, H. Suzuki, A. Kon, Y. Nagata, Y. Sato, R. Wang, N. Shiba, K. Chiba, H. Tanaka, A. Hama, H. Muramatsu, D. Hasegawa, K. Nakamura, H. Kanegane, K. Tsukamoto, S. Adachi, K. Kawakami, K. Kato, R. Nishimura, S. **Izraeli**, Y. Hayashi, S. Miyano, S. Kojima, E. Ito, and S. Ogawa, The landscape of somatic mutations in Down syndrome-related myeloid disorders. *Nat Genet*, 2013. 45(11): p. 1293-9.

Meyer, C., et al. **Izraeli**, L. et al and R. Marschalek, The MLL recombinome of acute leukemias in 2013. *Leukemia*, 2013.

Goldberg, L., M.R. Tijssen, Y. Birger, R.L. Hannah, S.J. Kinston, J. Schutte, D. Beck, K. Knezevic, G. Schiby, J. Jacob-Hirsch, A. Biran, Y. Kloog, G. Marcucci, C.D. Bloomfield, P.D. Aplan, J.E. Pimanda, B. Gottgens, and S. **Izraeli**, Genome-scale expression and transcription factor binding profiles reveal therapeutic targets in transgenic ERG myeloid leukemia. *Blood*, 2013. 122(15): p. 2694-703.

Castiel, A., L. Visochek, L. Mittelman, Y. Zilberstein, F. Dantzer, S. **Izraeli**, and M. Cohen-Armon, Cell death associated with abnormal mitosis observed by confocal imaging in live cancer cells. *J Vis Exp*, 2013(78): p. e50568.

Birger, Y., L. Goldberg, T.M. Chlon, B. Goldenson, I. Muler, G. Schiby, J. Jacob-Hirsch, G. Rechavi, J.D. Crispino, and S. **Izraeli**, Perturbation of fetal hematopoiesis in a mouse model of Down syndrome's transient myeloproliferative disorder. *Blood*, 2013. 122(6): p. 988-98.

Auer, F., F. Ruschendorf, M. Gombert, P. Husemann, S. Ginzel, S. **Izraeli**, M. Harit, M. Weintraub, O.Y. Weinstein, I. Lerer, P. Stepensky, A. Borkhardt, and J. Hauer, Inherited

susceptibility to pre B-ALL caused by germline transmission of PAX5 c.547G>A. *Leukemia*, 2013.

Amartely, H., A. David, M. Lebendiker, H. Benyamini, S. **Izraeli**, and A. Friedler, The STIL protein contains intrinsically disordered regions that mediate its protein-protein interactions. *Chem Commun (Camb)*, 2013.

Birger, Y., L. Goldberg, T.M. Chlon, B. Goldenson, I. Muler, G. Schiby, J. Jacob-Hirsch, G. Rechavi, J.D. Crispino, and S. **Izraeli**, Perturbation of fetal hematopoiesis in a mouse model of Down syndrome's transient myeloproliferative disorder. *Blood*, 2013. 122:988-98.

Elhasid, R., T. Tohami, N. Moustafa-Hawash, J. Ben-Ezra, S. **Izraeli**, and D. Sayar, Spontaneous remission of childhood acute marrow fibrosis and megakaryoblastic leukemia. *J Pediatr Hematol Oncol*, 2012. 34:565-8.

Palmi, C., E. Vendramini, D. Silvestri, G. Longinotti, D. Frison, G. Cario, C. Shochat, M. Stanulla, V. Rossi, A.M. Di Meglio, T. Villa, E. Giarin, G. Fazio, A. Leszl, M. Schrappe, G. Basso, A. Biondi, S. **Izraeli**, V. Conter, M.G. Valsecchi, G. Cazzaniga, and G. Te Kronnie, Poor prognosis for P2RY8-CRLF2 fusion but not for CRLF2 over-expression in children with intermediate risk B-cell precursor acute lymphoblastic leukemia. *Leukemia*, 2012. 26:2245-53.

Shaham, L., V. Binder, N. Gefen, A. Borkhardt, and S. **Izraeli**, MiR-125 in normal and malignant hematopoiesis. *Leukemia*, 2012. 26:2011-8.

Shlush, L.I., N. Chapal-Ilani, R. Adar, N. Pery, Y. Maruvka, A. Spiro, R. Shouval, J.M. Rowe, M. Tzukerman, D. Bercovich, S. **Izraeli**, G. Marcucci, C.D. Bloomfield, T. Zuckerman, K. Skorecki, and E. Shapiro, Cell lineage analysis of acute leukemia relapse uncovers the role of replication-rate heterogeneity and microsatellite instability. *Blood*, 2012. 120:603-12.

Vulprecht, J., A. David, A. Tibelius, A. Castiel, G. Konotop, F. Liu, F. Bestvater, M.S. Raab, H. Zentgraf, S. **Izraeli***, and A. Kramer*, STIL is required for centriole duplication in human cells. *J Cell Sci*, 2012. 125:1353-62. *co-senior authors

Wen, Q., B. Goldenson, S.J. Silver, M. Schenone, V. Dancik, Z. Huang, L.Z. Wang, T.A. Lewis, W.F. An, X. Li, M.A. Bray, C. Thiollier, L. Diebold, L. Gilles, M.S. Vokes, C.B. Moore, M. Bliss-Moreau, L. Verplank, N.J. Tolliday, R. Mishra, S. Vemula, J. Shi, L. Wei, R. Kapur, C.K. Lopez, B. Gerby, P. Ballerini, F. Pflumio, D.G. Gilliland, L. Goldberg, Y. Birger, S. **Izraeli**, A.S. Gamis, F.O. Smith, W.G. Woods, J. Taub, C.A. Scherer, J.E. Bradner, B.C. Goh, T. Mercher, A.E. Carpenter, R.J. Gould, P.A. Clemons, S.A. Carr, D.E. Root, S.L. Schreiber, A.M. Stern, and J.D. Crispino, Identification of regulators of polyploidization presents therapeutic targets for treatment of AMKL. *Cell*, 2012. 150:75-89.

Buitenkamp, T., S. **Izraeli**, M. Zimmermann, E. Forestier, N.A. Heerema, M.M. van den Heuvel, R. Pieters, V. de Haas, L.B. Silverman, K. Schmiegelow, D.C. Liang, K. Horibe, M. Arico, G. Cazzaniga, G. Basso, K.R. Rabin, M. Schrappe, G. Cario, G. Mann, V. Mondelaers, T. Lammens, H. Cave, B. Stark, A.V. Moorman, A.J. Vora, S. Hunger, C.H. Pui, C.G. Mullighan, A. Manabe, G. Escherich, J. Kowalczyk, J.A. Whitlock, and C.M. Zwaan, Acute Lymphoblastic Leukemia in Children with Down Syndrome: A Report From the Ponte Di Legno Study Group. *Blood*, 2011. 118:1527-1528.

Pimanda, J., J. Thoms, Y. Birger, S. Foster, K. Knezevic, Y. Kirschenbaum, V. Chandrakanthan, R. Lock, K. MacKenzie, B. Gottgens, and S. **Izraeli**, ERG promotes t-acute lymphoblastic leukemia and is transcriptionally regulated in leukemic cells by a stem cell enhancer. *Exp Hematol*, 2011. 39:S108-S108.

Stary, J., M. Zimmermann, M. Campbell, L. Castillo, E. Dibar, S. Donska, A. Gonzalez, S. **Izraeli**, D. Janic, J. Jazbec, J. Konja, E. Kaiserova, J. Kowalczyk, G. Kovacs, C.K. Li, E. Magyarosy, A. Popa, B. Stark, Y. Jabali, J. Trka, O. Hrusak, I. Janotova, H. Riehm, G. Masera, and M. Schrappe, Results of the Randomized I-BFM-SG Trial "Acute Lymphoblastic Leukemia Intercontinental-BFM 2002" in 5060 Children Diagnosed in 15 Countries on 3 Continents. *Blood*, 2011. 118:397-398.

Thoms, J.A., Y. Birger, S. Foster, K. Knezevic, Y. Kirschenbaum, V. Chandrakanthan, G. Jonquieres, D. Spensberger, J.W. Wong, S.H. Oram, S.J. Kinston, Y. Groner, R. Lock, K.L. MacKenzie, B. Gottgens, S. **Izraeli**, and J.E. Pimanda, ERG promotes T-acute lymphoblastic leukemia and is transcriptionally regulated in leukemic cells by a stem cell enhancer. *Blood*, 2011. 117:7079-89.

Shochat, C., N. Tal, O.R. Bandapalli, C. Palmi, I. Ganmore, G. Te Kronnie, G. Cario, G. Cazzaniga, A.E. Kulozik, M. Stanulla, M. Schrappe, A. Biondi, G. Basso, D. Bercovich, M.U. Muckenthaler, and S. **Izraeli**, Gain-of-function mutations in interleukin-7 receptor-{alpha} (IL7R) in childhood acute lymphoblastic leukemias. *J Exp Med*, 2011. 208:901-8.

Ozery-Flato, M., C. Linhart, L. Trakhtenbrot, S. **Izraeli**, and R. Shamir, Large-scale analysis of chromosomal aberrations in cancer karyotypes reveals two distinct paths to aneuploidy. *Genome Biol*, 2011. 12:R61.

Castiel, A., L. Visochek, L. Mittelman, F. Dantzer, S. **Izraeli**, and M. Cohen-Armon, A phenanthrene derived PARP inhibitor is an extra-centrosomes de-clustering agent exclusively eradicating human cancer cells. *BMC Cancer*, 2011. 11:412.

Castiel, A., M.M. Danieli, A. David, S. Moshkovitz, P.D. Aplan, I.R. Kirsch, M. Brandeis, A. Kramer, and S. **Izraeli**, The Stil protein regulates centrosome integrity and mitosis through suppression of Chfr. *J Cell Sci*, 2011. 124(Pt 4): 532-9.

Blink, M., T.D. Buitenkamp, M.M. van den Heuvel-Eibrink, A.A. Danen-van Oorschot, V. de Haas, D. Reinhardt, J.H. Klusmann, M. Zimmermann, M. Devidas, A.J. Carroll, G. Basso, A. Pession, H. Hasle, R. Pieters, K.R. Rabin, S. **Izraeli**, and C.M. Zwaan, Frequency and prognostic implications of JAK 1-3 aberrations in Down syndrome acute lymphoblastic and myeloid leukemia. *Leukemia*, 2011. 25:1365-8.

Stepensky, P., R. Brooks, E. Waldman, S. Revel-Vilk, S. **Izraeli**, I. Resnick, and M. Weintraub, A rare case of GATA1 negative chemoresistant acute megakaryocytic leukemia in an 8-month-old infant with trisomy 21. *Pediatr Blood Cancer*, 2010. 54:1048-9.

Stark, B., R. Nirel, G. Avrahami, A. Abramov, D. Attias, A. Ballin, B. Bielorai, Y. Burstein, H. Gavriel, R. Elhasid, J. Kapelushnik, D. Sthoeger, A. Toren, M. Wientraub, I. Yaniv, and S. **Izraeli**, Long-term results of the Israeli National Studies in childhood acute lymphoblastic leukemia: INS 84, 89 and 98. *Leukemia*, 2010. 24:419-24.

Mejstrikova, E., E. Fronkova, T. Kalina, M. Omelka, D. Batinic, K. Dubravcic, K. Pospisilova, M. Vaskova, D. Luria, S.H. Cheng, M. Ng, Y. Leung, J. Kappelmayer, F. Kiss, S. **Izraeli**, B. Stark, M. Schrappe, J. Trka, J. Stary, and O. Hrusak, Detection of residual B precursor lymphoblastic leukemia by uniform gating flow cytometry. *Pediatr Blood Cancer*, 2010. 54:62-70.

Luria, D., E. Rosenthal, D. Steinberg, Y. Kodman, M. Safanaiev, N. Amariglio, S. Avigad, B. Stark, and S. **Izraeli**, Prospective comparison of two flow cytometry methodologies for monitoring minimal residual disease in a multicenter treatment protocol of childhood acute lymphoblastic leukemia. *Cytometry B Clin Cytom*, 2010. 78:365-71.

Izraeli, S., Application of genomics for risk stratification of childhood acute lymphoblastic leukaemia: from bench to bedside? *Br J Haematol*, 2010. 151:119-31.

Hertzberg, L., E. Vendramini, I. Ganmore, G. Cazzaniga, M. Schmitz, J. Chalker, R. Shiloh, I. Iacobucci, C. Shochat, S. Zeligson, G. Cario, M. Stanulla, S. Strehl, L.J. Russell, C.J. Harrison, B. Bornhauser, A. Yoda, G. Rechavi, D. Bercovich, A. Borkhardt, H. Kempski, G. te Kronnie, J.P. Bourquin, E. Domany, and S. **Izraeli**, Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. *Blood*, 2010. 115:1006-17.

Harrison, C.J., O. Haas, J. Harbott, A. Biondi, M. Stanulla, J. Trka, and S. **Izraeli**, Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfurt-Munster study group. *Br J Haematol*, 2010. 151:132-42.

Gefen, N., V. Binder, M. Zaliova, Y. Linka, M. Morrow, A. Novosel, L. Edry, L. Hertzberg, N. Shomron, O. Williams, J. Trka, A. Borkhardt, and S. **Izraeli**, Hsa-mir-125b-2 is highly expressed in childhood ETV6/RUNX1 (TEL/AML1) leukemias and confers survival advantage to growth inhibitory signals independent of p53. *Leukemia*, 2010. 24:89-96.

Cario, G., M. Zimmermann, R. Romey, S. Gesk, I. Vater, J. Harbott, A. Schrauder, A. Moericke, S. **Izraeli**, T. Akasaka, M.J. Dyer, R. Siebert, M. Schrappe, and M. Stanulla, Presence of the P2RY8-CRLF2 rearrangement is associated with a poor prognosis in non-high-risk precursor B-cell acute lymphoblastic leukemia in children treated according to the ALL-BFM 2000 protocol. *Blood*, 2010. 115:5393-7.

Bielorai, B., C. Meyer, L. Trakhtenbrot, H. Golan, E. Rozner, N. Amariglio, S. **Izraeli**, R. Marschalek, and A. Toren, Therapy-related acute myeloid leukemia with t(2;11)(q37;q23) after treatment for osteosarcoma. *Cancer Genet Cytogenet*, 2010. 203:288-91.

Reviews

Tal, N., C. Shochat, I. Geron, D. Bercovich, and S. **Izraeli**, Interleukin 7 and thymic stromal lymphopoietin: from immunity to leukemia. *Cell Mol Life Sci*, 2013 Apr 27. [Epub ahead of print].

Birger, Y. and S. **Izraeli**, DYRK1A in Down syndrome: an oncogene or tumor suppressor? *J Clin Invest*, 2012. 122:807-10.

Izraeli, S., Acute Lymphocytic Leukemia and Down Syndrome. *Blood*, 2011. 118:1810-1810.

Izraeli, S., Similar yet different. *Blood*, 2010. 116:1019-20.

Bourquin, J.P. and S. **Izraeli**, Where can biology of childhood ALL be attacked by new compounds? *Cancer Treat Rev*, 2010. 36:298-306.

Grants

2012-2015 Israel Science Foundation (ISF), The molecular pathogenesis of the acute lymphoblastic leukemia of Down Syndrome

2012-2014 Swiss Bridge Foundation, CRLF2 JAK2 in childhood leukemia

2014-2017 EU ERA-NET TRANSCANCER "TRANSALL" Validation of biomarkers for the diagnosis and risk stratification of childhood ALL

2013-2014 WCRF Foundation, Transcription factors in DS leukemias

May 24, 2014

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Studying Doctor-Patient Relationships, Communication and Medical Professionalism

Positions

Senior Lecturer, Sackler Faculty of Medicine
Adjunct Assistant Research Professor of Medicine, Deparment of Internal Medicine, Indiana University, Indianapolis, USA

Research

Our primary research and teaching interests are focused on:

- Professionalism and humanism in medical schools. Understanding what students experience, how they interpret it and what we should do to help their development as humanistic professionals.
- Developing communication skills for handling and assessing multi-participant conversations (triadic communication) physician-patient-companion. Understanding how we should and could involve family members.
- Teaching medical students and professionals how to break bad news, including assessing how their personal difficulties and biases affect their communication.
- Enhancing medical students self-awareness (e.g., by using reflective diaries and narratives in medical education).
- Defining and applying Shared Decision Making in healthcare.

Publications

Karnieli-Miller, O., Frankel, R.M., & Inui, T.S. (2013). Cloak of compassion or evidence of elitism? an empirical analysis of white coat ceremonies? *Medical Education,* 43, 97-108.

Karnieli-Miller, O., Perlick, D. A., Nelson, A., Mattias, K., Corrigan, P., & Roe, D. (2013). Family members' of persons living with a serious mental illness: Experiences and efforts to cope with stigma. *Journal of Mental Health,* 22, 254-262.

Karnieli-Miller, O. Werner, P. Neufeld Kroszynski, G. Eidelman, S. (2012). Are you talking to me?!? An exploration of the triadic physician-patient-companion encounter in memory-clinics. *Patient Education and Counseling,* 88, 381–390.

Karnieli-Miller*, O. Werner*, P. Aharon-Perets, J. Sinoff, G. Eidelman,, S. (2012). Expectations, experiences and tensions in the memory clinic-- the process of diagnosis disclosure of dementia within a triad. *International Psychogeriatrics,* 24, 1756-1770. *equal contributors

Karnieli-Miller, O. Vu, R.T. Frankel, R.M. Holtman, M. Clyman, S. Hui, S.L, & Inui T.S. (2011). Which Experiences in the Hidden Curriculum Teach Students About Professionalism? *Academic Medicine,* 86, 369-377.

Karnieli-Miller, O., Taylor, A.C. Inui, T.S. Ivy, S.S. Frankel, R.M (2011). Understanding values in a large health care organization through work-life narratives of high performing employees. *Rambam Maimonides Medical Journal*, 2, 1-14.

Goldblatt, H. **Karnieli-Miller, O**. Neumann, M. (2011). Sharing qualitative research findings with participants: Study experiences of methodological and ethical dilemmas. *Patient Education and Counseling,* 82, 389-395

Karnieli-Miller, O. & Salyers, M. (2011). Clinical communications with persons who have severe mental illnesses. In Rudnick, R., & Roe, D. (Eds.) *SMI: Person-centered approaches*. Radcliffe Press, 155-167

Taylor, A. **Karnieli-Miller, O**. Inui, T.S. Ivy, S.S. & Frankel R.M. (2011). Appreciating the power of narratives in healthcare: A tool for understanding organizational complexity and values.In C. N. Candlin and S. Sarangi (Eds.) *Handbook of communication in organizations and professions*. Berlin, Germany: Mouton de Gruyter, pp. 457-479, 2011

Karnieli-Miller, O. Vu, R.T. Holtman, M. Clyman, S. Inui, T.S. (2010). Medical student narratives and professionalism: a window on the 'hidden curriculum'. *Academic Medicine, 85(1*), 124-133.

Werner, P. **Karnieli-Miller, O**. Adler, A. & Eidelman, S. (2010). How neurologists tell their patients with alzheimer disease about their diagnosis another side to tarek et al's study. *Alzheimer Disease & Associated Disorders - An International Journal*, 24(2), 115-117.

Karnieli-Miller, O. Taylor, A. Cottingham, A.H. Inui, T.S. Vu R.T. & Frankel R.M. (2010). Exploring the meaning of respect in medical student education: an analysis of student narratives. *Journal of General Internal Medicine,* 25, 1309-1314.

Moran, G., Oz, G., &_Karnieli-Miller, O. Psychiatrists' Challenges in Considering Disclosure or Schizophrenia Diagnosis in Israel. Qualitative Health Research. (In press).

Reviews

Werner, P., **Karnieli-Miller, O.,** Eidelman, S. (2013). Current knowledge and future directions about the diagnostic disclosure of dementia: A systematic review of the first decade of the 21st century. *Alzheimer's & Dementia, 9*, e74–e88.

Grants

2012-2014 The Magi Foundation, A different beginning: Foundation blocks for combining humor and creativity in constructing doctor-patient relationship (PI)

2014-2015 Israel Cancer Association Using narrative writing on breaking bad news encounters to improve the communication skills of medical professionals in cancer care (PI)

May 24, 2014

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Translational Research on the Development of Cancer Treatment Modalities

Positions

Professor, Sackler Faculty of Medicine
Roberts-Guthman Chair in Immunopharmacology
President, Israeli Society for Cancer Research

Research

Cancer is currently the most devastating chronic disease affecting humankind. Today solid malignant tumors are mainly treated by surgery and/or radiotherapy to eradicate the local primary lesion, and chemotherapy, that is administered mainly to destroy remaining local or distant malignant cells. In spite of the advancement in preventing and treating cancer, morbidity and mortality remain high, especially in cases when tumors are highly metastatic, or cannot be completely removed. The main goal of our research projects is to develop *in situ* tumor ablation treatments of primary tumors and incorporate them with systemic chemotherapy and immuno-stimulatory agents, into combined treatment protocols.

In order to achieve efficient primary tumor ablation we developed two novel and powerful treatment modalities for solid cancer, which can be used instead or in combination with surgery. The first treatment, developed with Prof. Rafi Korenstein (Dept. Physiology and Pharmacology), is base on the use of intratumoral unipolar pulsed electric currents for the ablation (ECTA) of solid primary tumors. ECTA can be enforced by the concomitant use of chemotherapeutic agents in the treatment of tumors. The second cancer treatment, developed with Prof. Itzhak Kelson (School of Physics and Astronomy), is based on insertion into the tumor of radioactive wires which spread in the tumor alpha emitting atoms. This treatment can also be augmented by chemotherapy.

Our teams proved that these treatment modalities effectively destroy primary tumors, and reduce the metastatic load in experimental animal and human cancer models of melanoma, breast, colon, prostate, pancreas, lung, and squamous cell carcinomas. We found that *in situ* ablation of primary antigenic tumors led to the activation of immunological reactions, destroying remaining malignant cells in the primary tumor as well as in distant metastases.

Immunopharmacological methods aimed to stimulate the patient's immune response against the cancer after local tumor ablation can make use of several approaches and we currently study the following: (1) Immunostimulation by adjuvants such as the oligonucleotides, CpG, which enforce weak immune reactions. (2) Inhibition of immunosuppressive mechanisms such as T-regulatory and Myeloid Derived Suppressor cells (MDSC).

Publications

Arazi L, Cooks T, Schmidt M, **Keisari Y**, Kelson I. Treatment of solid tumors by alpha emitters released from ^{224}Ra-loaded sources – internal dosimetry analysis. *Phys Med Biol*, 55:1203-1218, 2010.

Greenberg E, Hershkovitz L, Hajdu S, Nemlich Y, Itzhaki O, Ortenberg R, Gefen N, Edry L, Barschak I, **Keisari Y**, Besser MJ, Schachter J, Shomron N, Markel G. Regulation of cancer aggressive features in melanoma cells by microRNA molecules. *Plos One*, 6:e18936, 2011.

Cafri G, Amram E, Rinot G, Koifman G, Fishman S, **Keisari Y**, Tzehoval E, Eisenbach L, Margalit A, Gross G. Coupling presentation of MHC class I peptides to constitutive activation of antigen-presenting cells through the product of a single gene. *Int Imm*, 23:453-61, 2011.

Lazarov E, Arazi L, Efrati M, Cooks T, Schmidt M, **Keisari Y**, Kelson I. Comparative *in vitro* microdosimetric study of murine and human-derived cancer cells exposed to alpha particles. Radiation Res, 177:280-7, 2011.

Horev-Drori G, Cooks T, Bittan H, Lazarov E, Schmidt M, Arazi L, Efrati M, Kelson I, **Keisari Y**. Local control of malignant pancreatic tumors by a combined treatment with intratumoral ^{224}Radium-loaded wires releasing alpha-emitting atoms and chemotherapy. *Transl Res* 159:32-41, 2012.

Lazarov, E., Arazi, L., Efrati, M., Cooks, T., Schmidt, M., **Keisari, Y**., Kelson, I. Comparative in vitro microdosimetric study of murine and human-derived cancer cells exposed to alpha particles. Radiat Res. 177:280–287, 2012.

Milrot, E., Jackman, A., Flescher, E., Gonen, P., Kelson, I., **Keisari, Y**., Sherman, L. Enhanced killing of cervical cancer cells by combinations of methyl jasmonate with cisplatin, X or alpha radiation. Invest. New Drugs. Epub 6 Sept. 2012.

Cooks, T., Tal, M., Raab, S., Efrati, M., Reitkopf, S., Lazarov, E., Etzyoni, R., Schmidt, M., Arazi, L., Kelson, I., **Keisari, Y**. Intratumoral Ra-224-loaded wires spread alpha emitting atoms inside solid human tumors in athymic mice and can achieve local tumor control. Anticancer Res. 32(12):5315-21, 2012.

Tepper, M., Shoval, A., Hoffer, O., Confino, H., Kelson, I., **Keisari, Y**., Gannot, I. Thermographic investigation of tumor size, and its correlation to tumor relative temperature, in mice with transplantable solid breast carcinoma. J Biomed Optics. 18(11): 111410, 2013.

Keisari, Y., Hochman, I., Confino, H., Korenstein, R., Kelson, I. Activation of local and systemic anti-tumor immune responses by ablation of solid tumors with intra-tumoral electrochemical or alpha radiation treatments. Cancer Immunol. Immunother. 63(1): 1-9, 2014.

Chapters in Books.

Keisari, Y., Korenstein, R. Anti-tumoral effects of pulsed low electric field enhanced chemotherapy: lessons from experimental malignant tumors. In: Electroporation in laboratory and clinical investigations. E. P. Spugnini and A. Baldi, eds. Nova Science Publishers, Inc. Hauppauge, NY., USA, 2012, Ch. 9, pp. 178-204.

Keisari Y., Korenstein R. In-situ ablation of solid tumors by electric forces and its effect on the tumor microenvironment and anti-tumor immunity. In: Tumor Ablation: effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Y. Keisari, Ed. Springer, 2013, Ch. 8, pp. 133-153.

Books

Keisari Y. Tumor Ablation: effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Springer, 2013.

Grants

2011-2014, In situ ablation of primary tumors to induce anti-tumor T-cell reactions and neutralize immunosuppressive tumor microenvironment. German-Israeli Foundation (GIF), Co-PI, Viktor Umansky.

2012-2014, Exploiting in situ tumor destruction techniques for the in vivo modulation of anti-tumor immunity. Cancer Research Institute. Co-investigator. Gosse Adema, UMC St. Radbound, Nijmegen, The Netherlands.

May 24, 2014

Prof. Daniel Khananshvili, Ph.D.

Department of Physiology and Pharmacology
Sackler Faculty of Medicine

Tel Aviv University
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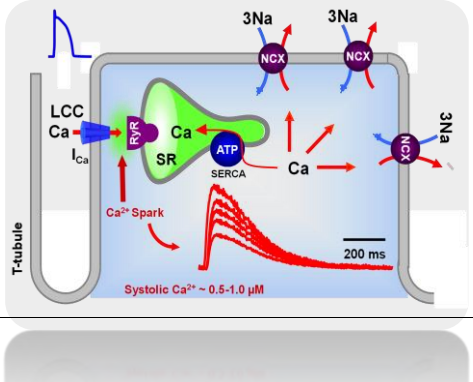
Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

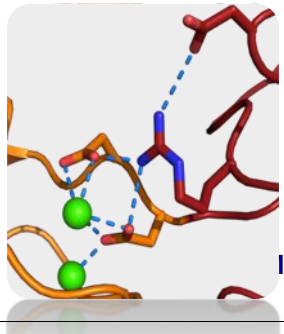
Positions

Associate Professor, Sackler Faculty of Medicine
Chair, Department of Physiology and Pharmacology

Research

Calcium (Ca^{2+}) is a major regulator in the living cell. In many cell-types the Na^{+}/Ca^{2+} exchanger proteins (NCX) represent a major Ca^{2+} extruding system and thus, play a key role in regulating the Ca^{2+}-dependent events in the cell. Three NCX genes form numerous splice variants, which are expressed in a tissue-specific manner to regulate excitation–contraction coupling in heart, long-term potentiation and learning in brain, blood pressure, immune responses, neurotransmitter and hormone secretion, kidney Ca^{2+} reabsorption, mitochondrial bioenergetics, etc. Altered expression and regulation of NCX proteins is a chief contributor to Ca^{2+}-driven tissue-remodeling in heart failure, cerebral ischemia, hypertension, diabetes, renal malfunction, muscle dystrophy, *etc*. For example, in cardiac disease a single isoform/splice variant (NCX1.1) is overexpressed, thereby representing a primary concern for life-threating arrhythmias and contractile malfunction. Selective pharmacological targeting of NCX variants is expected to recover Ca^{2+} homeostasis in predefined cell types and thus, may improve desired activity of altered tissues/organs. Since this breakthrough remains challenging our research efforts are focused on two principle issues: a) To resolve structure-activity relationships underlying the function and regulation of diverse NCX variants; b) To develop new experimental approaches for selective pharmacological targeting of tissue-specific NCX variants with a goal of providing new opportunities for preventing and effective treatment of harmful diseases. In this respect we investigate structure-activity relationships in the wild-type and mutated proteins by exploring a wide spectrum of techniques (stopped-flow and ion-flux assays, FRET, SAXS, ITC, X-ray crystallography, confocal microscopy, patch-clamp, etc). In searching the regulatory mechanisms of CBD1 and CBD2 domains we found that the tissue-specific splice segment, located on CBD2, shapes the regulatory specificity of the primary Ca^{2+} sensor located on CBD1. These findings may allow the identification of drug candidates targeting the disease-related NCX variants.





Publications

Giladi M, Michaely L, Almagor A, Bar-On D, Buki T, Ashery U**, Khananshvili**, Hirsch JA. The C2B domain is the primary Ca^{2+} sensor in DOC2B: A structural and functional analysis. *J Mol Biol,* 2013, 425:4629–4641.

Giladi M, Hiller R, Hirsch JA, **Khananshvili D**. Population shift underlies Ca^{2+}-induced regulatory transitions in the sodium-calcium exchanger (NCX). *J Biol Chem*, 2013, 288:23141-23149.

Giladi, M. and **Khananshvili, D**. Molecular determinants of allosteric regulation in NCX proteins. *Adv Exp Med and Biol*, 2013, 961:35-48**.**

Khananshvili D, Binah O, Attali B. The Ca^{2+}-activated K^+ channel IKCa/SK4: a critical new player in human embryonic cardiac pacemaker. *Proc Natl Acad Sci* USA, 2013, 110:1685-1694.

Nita II, Hershfinkel M, Fishman D, Ozeri E, Rutter GA, Sensi SL, **Khananshvili D**, Lewis EC, Sekler I. The mitochondrial Na^+/Ca^{2+} exchanger upregulates glucose dependent Ca^{2+} signaling linked to insulin secretion. *PloS One* 2012, 7(10):e46649.

Giladi M, Friedberg I, Fang X, Hiller R, Wang YX, **Khananshvili D.** G503 is obligatory for coupling of regulatory domains in NCX proteins. *Biochemistry* 2012, 51:7313-720.

Giladi, M., Bohbot, H., Buki, T., Schulze, D. H., Hiller, R. and **Khananshvili, D**. Dynamic features of allosteric Ca^{2+} sensor in tissue-specific NCX variants. *Cell Calcium*, 51:478-485, 2012.

Giladi M, Sasson Y, Fang X, Hiller R, Buki T, Wang Y-X, Hirsch JA and **Khananshvili D**. A common Ca^{2+}-driven interdomain module governs eukaryotic NCX regulation. *PloS One*, 7:e39985. 2012

Boyman L, Hagen BM, Giladi M, Hiller R, WJ Lederer and **Khananshvili D**. Proton-Sensing Ca^{2+} Binding Domains Regulate the Cardiac Na^+/Ca^{2+} Exchanger. *J Biol Chem,* 286:28811-28820, 2011.

Giladi M, Boyman L, Mikhasenko H, Hiller R and **Khananshvili D**. Essential role of the CBD1-CBD2 linker in slow dissociation of Ca^{2+} from the regulatory two-domain tandem of NCX1. *J Biol Chem* 285:28117–28125, 2010.

Palty R, Silverman WF, Hershfinkel M, Caporale T, Sensi SL, Parnis J, Nolte C, Fishman, D., Shoshan-Barmatz V, Herrmann S, **Khananshvili D** and Sekler I. NCLX is an essential component of mitochondrial Na^+/Ca^{2+} exchange. *Proc Natl Acad Sci USA* 107:436-441, 2010.

Reviews

Khananshvili, D. Sodium-Calcium Exchangers (NCX): Molecular Hallmarks Underlying Tissue-Specific and Systemic Functions, *Pflügers Arch* (in press)

Khananshvili, D. SLC8 gene family of sodium-calcium exchangers (NCX): Structure, function and regulation in health and disease**.** *Mol Asp Med* 34:220-35, 2013.

Giladi, M. and **Khananshvili, D**. (2013) Molecular determinants of allosteric regulation in NCX proteins. *Adv Exp Med Biol* 961:35-48.

Boyman L, GSB Williams, **Khananshvili D**, Sekler I, WJ Lederer. NCLX: The mitochondrial sodium calcium exchanger. *J Mol Cell Cardiology* 2013, 59:205-213.

Grants

Fields Center of Molecular Cardiology 2013-2017

Israel Science Foundation 2010-2014

USA-Israel Binational Science Foundation 2010-2014

May 24, 2014

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Investigating Viral Genetic Diversity

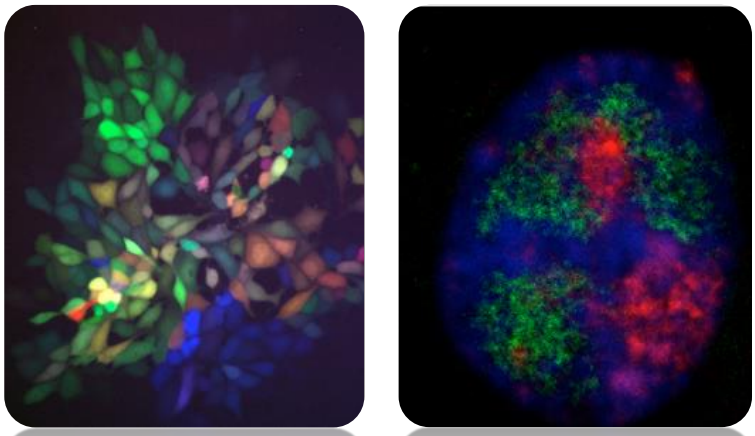
Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our research is focused on understanding how viruses generate and maintain genetic diversity. All virus populations display high genomic diversity, which provides opportunities for survival in the constantly changing environment. In many cases, such diversity results in failure of antiviral treatment (resistance to vaccines and antiviral drugs) and the emergence of zoonotic viral pathogens. DNA viruses and segmented RNA viruses exploit recombination and reassortment as mechanisms for diversity creation. We are interested in the mechanisms allowing DNA viral recombination and finding ways to inhibit these mechanisms.

A B



A. Spread of three alpha herpesviruses (each expressing a different XFP) from a single infected cell suggests that only a limited number of viral genomes are able to be expressed and replicated inside a single cell. B. Replication compartments in a single nucleus infected with two alphaherpesviruses suggest that genomes remain in separate territories in the nucleus.

Publications

Kobiler O., Lipman Y., Therkelsen K., Daubechies I., and Enquist L.W. (2010). Herpesviruses

carrying a Brainbow cassette reveal replication and expression of limited numbers of incoming genomes. *Nat. Commun.* 1:146.

***Kobiler O**., *Card J.P., McCambridge J., Ebdlahad S., Shan Z., Raizada M.K., Sved A.F., and Enquist L.W. (2011). Microdissection of neural networks by conditional reporter expression from a Brainbow Herpesvirus. *Proc Natl Acad Sci U S A.* 108:3377-82.

***Kobiler O**., *Card J.P., Ludmir E.B., Desai V., Sved A.F., Enquist L.W. (2011). A dual infection pseudorabies virus conditional reporter approach to identify projections to collateralized neurons in complex neural circuits. *PLoS One,* 6:e21141.

Kobiler, O., Brodersen, P., Taylor, M.P., Ludmir, E.B. and L.W. Enquist. (2011). Herpesvirus replication compartments originate with single incoming viral genomes. *mBio* 2:e00278-11. doi:10.1128/mBio.00278-11.

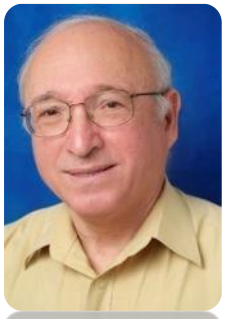
Taylor MP, **Kobiler O**, Enquist LW. (2012) Alphaherpesvirus axon-to-cell spread involves limited virion transmission. *Proc Natl Acad Sci USA*. 109:17046-51.

Kobiler O, Drayman N, Butin-Israeli V, Oppenheim A. (2012) Virus strategies for passing the nuclear envelope barrier. *Nucleus.* 3:526-39.

Reviews

Szpara M.L., **Kobiler O**., and Enquist L.W. (2010). A comon neuronal response to alphaherpesvirus infection. *J Neuroimmune Pharmacol.* 5:418-27.

May 21, 2014



Prof. Rafi Korenstein, Ph.D.

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Interaction of Nanomaterials and Electromagnetic Fields with Cells

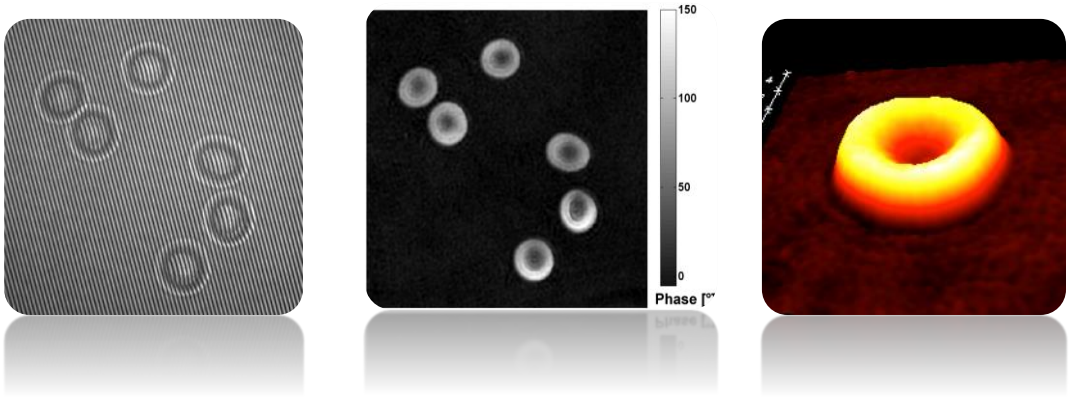
Positions

Professor, Sackler Faculty of Medicine
Chair, Commission K of the Israel National Committee for Radio Science of Israel Academy of Sciences and Humanities on Electromagnetics in Biology and Medicine
Editorial Board, *Bioelectromagnetics*
Director, Marian Gertner Institute for Medical Nanosystems, Tel Aviv University

Research

The research activity addresses the following lines of research:

Adsorption and uptake of nanoparticles by cells in relation to drug delivery and toxicity; Enhancement of uptake by electrical and chemical means. Treatment of cancer by electrochemical based approach; Assessment of genetic and epigenetic risks following in-vitro exposure to electromagnetic fields associated with cell phone communication. Physiological regulation and underlying mechanism of cell membrane-cortical skeleton nanoscale mechanical fluctuations. Research methods used include routine cell biology and biochemical methodologies with emphasis on special cutting edge light microscopies possessing nanometric resolution such as Digital Holographic Microscopy (see below).



Hologram image of red blood cells (left), reconstructed phase image (middle) and 3D reconstruction of a single red blood cell (right)

Publications

Keisari, Y., Hochman, I., Confino, H., Korenstein, R., Kelson, I. (2014) Activation of local and systemic anti-tumor immune responses by ablation of solid tumors with intratumoral

electrochemical or alpha radiation treatments. Cancer Immunology, Immunotherapy 63 (1), pp. 1-9

Madi L., Rosenberg-Haggen, B., Nyska, A., and Korenstein, R. (2013) Enhancing pigmentation via activation of A3 adenosine receptors in B16 melanoma cells and in human skin explants. Experimental Dermatology 22 (1) pp. 74-77.

Hole P., Sillence K., Hannell C., et al., (2013) Interlaboratory comparison of size measurements on nanopartcles using Nanoparticle Tracking Analysis (NTA) J. Nanoparticle Research 15 (12).

Wolf-Goldberg T., Barbul, A., Ben-Dov N**., Korenstein R**. (2013) Low electric fields induce ligand-independent activation of EGF receptor and ERK via electrochemical elevation of H^+ and ROS concentrations. Biochimica et Biophysica Acta -Molecular Cell Research 1833 1396–1408

Ben-Dov N. and **Korenstein R**. (2013) Proton-induced endocytosis is dependent on cell membrane fluidity, lipid-phase order and the membrane resting potential. Biochimica et Biophysica Acta -Biomembranes (11): 2672-2681

Ben-Dov N., and Korenstein R. (2013) Actin-cytoskeleton rearrangement modulates proton-induced uptake. Exp. Cell Res. 319 (7) pp. 946-954.

Horev-Azaria L., Baldi G., Beno D., et al. (2013) Predictive Toxicology of cobalt ferrite nanoparticles: comparative in-vitro study of different cellular models using methods of *knowledge discovery from data.* Particle and Fibre Toxicology 10:32.

Goñi-de-Cerio F., Mariani V., Cohen D., et al., (2013) Biocompatibility study of two di-block co-polymeric NPs for biomedical applications by *in vitro* toxicity testing. Journal of Nanoparticle Research 15:2036

Keisari Y. and Korenstein R. (2013) *In-situ* ablation of solid tumors by electric forces and its effect on the tumor microenvironment and anti-tumor immunity. In: Tumor Ablation: effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Y. Keisari, Ed. Springer, Dordrecht, 2013, Ch. 8, pp. 133-153.

Ben-Dov N, Rozman Grinberg I, Korenstein R (2012) Electroendocytosis Is Driven by the Binding of Electrochemically Produced Protons to the Cell's Surface. PLoS ONE 7(11): e50299

Shock, I., Barbul, A., Girshovitz, P. Nevo, U., Korenstein, R., Shaked N.T. (2012) Optical phase nanoscopy in red blood cells using low-coherence spectroscopy. Journal of Biomedical Optics 17(10), 101509

Shock, I., Barbul, A., Girshovitz, P., Nevo, U., Korenstein, R., Shaked, N.T. (2012) Optical phase measurements in red blood cells using low-coherence spectroscopy. Progress in Biomedical Optics and Imaging - Proceedings of SPIE 8230, art. no. 82300D

Ben-Dov N. and Korenstein R. (2012) Enhancement of cell membrane invaginations, vesiculation and uptake of macromolecules by protonation of the cell surface. PLoS One 7(4) art. no. E35204

Ben-Dov N. and

Ben-Dov N. and **Korenstein R**. (2012) Cell-based detection of electrochemical oxidative stress by a fluorescent tryptophan intermediate. Bioelectrochemistry 84:11-17

Cohen S, Coué G, Beno D, **Korenstein R**, and Engbersen J. F.J. (2011) Bioreducible poly(amidoamine)s as carriers for intracellular protein delivery to intestinal cells. Biomaterials (in-press)

Horev-Azaria L, Kirkpatrick CJ, **Korenstein R** et al., (2011) Predictive toxicology of cobalt nanoparticles and ions: comparative in-vitro study of different cellular models using methods of knowledge discovery from data. Toxicological Sciences 122:489-501

Grants

2011-2015 European Commission - EP7 EC consortium on "*Research Infrastructures for processing, analysis and characterization of engineered nanomaterials*" (acronym – "QNano", 27 partners)

May 21, 2014

Prof. Michael M. Kozlov, Ph.D.

Department of Physiology and Pharmacology
Sackler Faculty of Medicine

Tel-Aviv University
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Theoretical Biophysics of Membranes and Cytoskeleton

Position

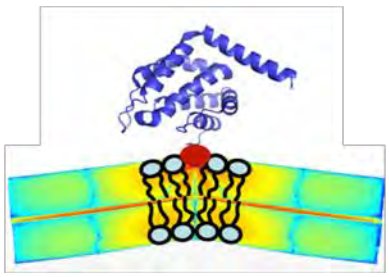
Professor, Sackler Faculty of Medicine

Joseph Klafter Chair in Biophysics

Research

We model the mechanisms of shaping and remodeling of intracellular membranes by specialized proteins that includes generation of large membrane curvatures, membrane fission and fusion. Our goal is to reveal the common mechanistic themes in the function of membrane shaping proteins acting in different intracellular systems. In this way, we hope to be able to understand whether every stage of membrane shaping needs a special protein or the same protein machinery can enable both membrane curvature generation and fission and/or fusion. Specifically, we model the action of BAR domain proteins, Epsins and Dynamins in endocytosis, Reticulons and their partners in shaping the Endoplasmaic Reticulum, and ESCRT-III complexes in fission of cytokinetic tubes.

We model the mechanisms underlying the dynamic organization of the actin cytoskeleton and the system of cell adhesion in polarizing and moving cells. Our major goal is to understand the mechanosensitivity of the cytoskeletal systems and its role in the system temporal rearrangements and steady-state structures.



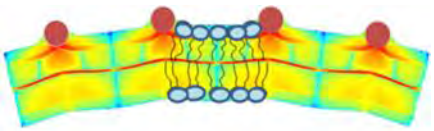
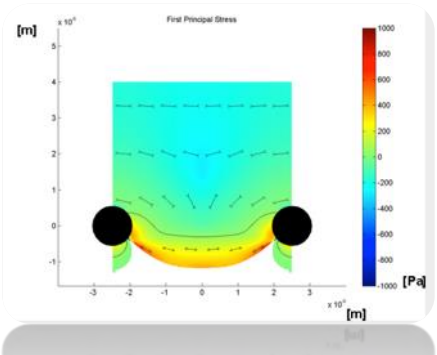


Figure legend: Computational results for membrane curvature generation by amphipathic N-terminal helices of N-BAR domains, ENTH domains and small G-proteins.



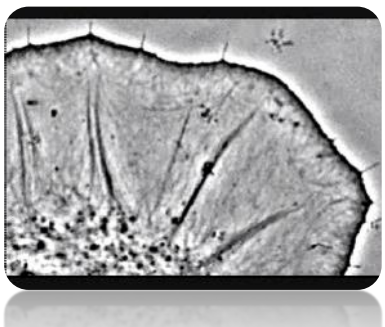


Figure legend: Computational modeling of lamellipodium boundary formation resulting from actin-focal adhesion interaction (left), the phenomenon observed in moving fibroblasts (right, courtesy of A. Verkhovsky).

Publications

Buzon, V., Natrajan, G., Schibli, D., Campelo, F., **Kozlov, M.M**., Weissenhorn, W., Crystal structure of HIV-1 gp41 including both fusion peptide and membrane proximal external regions. PLoS Pathog, 2010. 6: e1000880.

Shibata, Y., Shemesh, T., Prinz, W.A., Palazzo, A.F., **Kozlov, M.M**., Rapoport, T.A., Mechanisms determining the morphology of the peripheral ER. Cell, 2010. 143: 774-88.

Richard P., Leikina E., Langen R., Henne W.M., Popova M., Balla T., McMahon H.T., **Kozlov M.M.**, L.V. Chernomordik. Intracellular curvature generating proteins in cell-to-cell fusion. Biochem J., 2011. 440:185-93.

Bershadsky A.D., **Kozlov M.M.**. Crawling cell locomotion revisited. Proc Natl Acad Sci USA. 2011. 108: 20275-20276.

Boucrot E., Pick A., Camdere G., Liska N., Evergren E., McMahon H.T., **Kozlov M.M.** Hydrophobic insertions promote, while crescent BAR scaffolds limit vesicle membrane fission. Cell. 2012. 149: 124-136.

Elia N., Fabrikant G., **Kozlov M.M.** Lippincott-Schwartz J. Computational model for cytokinetic abscission driven by ESCRT-III polymerization and remodeling. Biophys.J. 2012. 102: 2309-2320

Shemesh T., Bershadsky A.D., **Kozlov M.M.** Physical model for self-organization of actin cytoskeleton and adhesion complexes at the cell front. Biophys J. 2012 ;102:1746-56

Leikina E., Melikov K., Sanyal S., Verma S.K., Eun B., Gebert C., Pfeifer K., Lizunov V.A., **Kozlov M.M.**, Chernomordik L.V. Extracellular annexins and dynamin are important for sequential steps in myoblast fusion. J Cell Biol. 2013. 200:109-23.

Schweitzer Y, **Kozlov M.M.** Cell motion mediated by friction forces: understanding the major principles. Soft Matter. 2013. 9:5186-5195

Terasaki M., Shemesh T., Kasthuri N., Klemm R.W., Schalek R., Hayworth K.J., Hand A.R., Yankova M., Huber G., Lichtman J.W., Rapoport T.A., **Kozlov M.M**. Stacked endoplasmic reticulum sheets are connected by helicoidal membrane motifs. Cell. 2013;154:285-96.

G. Fabrikant, S. Gupta, G.V. Shivashankar, M.M. Kozlov. Model of T-cell nuclear deformation by the cortical actin layer. Biophys J. 105(6):1316-23, 2013

F. Campelo, M.M. Kozlov. Sensing membrane stresses by protein insertions. PLoS Comp. Biol. 10: e1003556, 2014.

Y. Schweitzer, A.D. Lieber, K. Keren, M.M. Kozlov. Theoretical analysis of membrane tension in moving cells. Biophys J.106:84-92, 2014.

Reviews

Graham, T.R. and **Kozlov, M.M.**, Interplay of proteins and lipids in generating membrane curvature. Curr Opin Cell Biol, 2010. 22: 430-6.

Kozlov, M.M., Biophysics: Joint effort bends membrane. Nature, 2010. 463: 439-40.

Kozlov, M.M., H.T. McMahon, and Chernomordik, L.V., Protein-driven membrane stresses in fusion and fission. Trends Biochem Sci, 2010. 35: 699-706.

McMahon, H.T., **M.M. Kozlov**, and Martens, S., Membrane curvature in synaptic vesicle fusion and beyond. Cell, 2010. 140: 601-5.

Chernomordik, L.V. and **Kozlov, M.M.**, eds. Current Topics in Membranes. Vol. 68. 2011, Elsevier.

M.M. Kozlov, F. Campelo, N. Liska, L.V. Chernomordik, S.J. Marrink, H.T. McMahon.

Curr.Opin.Cell Biol. Mechanisms shaping cell membranes. 29:53–60, 2014

F. Campelo, C. Arnarez, S.J. Marrink, M.M. Kozlov. Helfrich model of membrane bending: From Gibbs theory of liquid interfaces to membranes as thick anisotropic elastic layers. Adv Colloid Interface Sci. 2014 Feb 3. pii: S0001-8686(14)00030-X. doi: 10.1016/j.cis.2014.01.018. [Epub ahead of print]

Grants

2011-2015 The Israel Science Foundation (ISF), Membrane Shaping by Proteins

May 24, 2014

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Sackler Faculty of Medicine

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Website: www.tau.ac.il/~limorl

Pancreas Development and Function: the Role of Microenvironmental Cues

Position

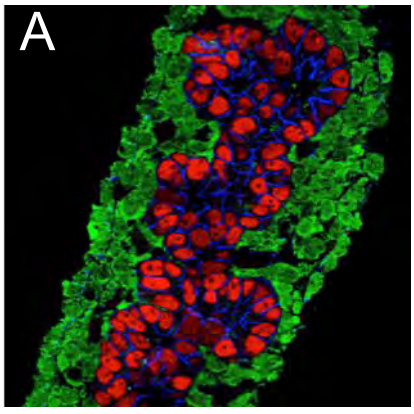
Senior Lecturer, Sackler Faculty of Medicine

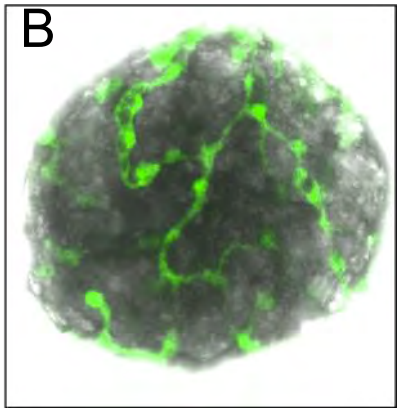
Research

Maintenance of blood glucose levels is dependent upon the tight regulation of insulin secretion from pancreatic beta-cells. Insufficient insulin secretion, whether due to reduced beta-cell numbers, or impaired beta-cell function, leads to diabetes. Our group studies how insulin-producing beta-cells maintain their functionality in health, and how it is lost in diabetes. To this end, we research the cross talk between insulin-producing cells and another pancreatic cell population, the mesenchymal cells. Our results indicate the pivotal role of mesenchymal cells in the regulation of insulin secretion, and blood glucose levels. Using transgenic mouse models, we study how mesenchymal cells and insulin-producing cells communicate with one another, and how this communication is affected during diabetes.

In addition, we study how the pancreas develops during embryogenesis. Our findings, along with previous findings, help to consolidate that pancreas mesenchymal cells are crucial for proper pancreas and beta-cell embryonic development. Using transgenic mouse models, we investigate what signals are produced by mesenchymal cells, and how these signals may guide beta-cell development.

In summary, our goals are to uncover the different aspects of pancreas biology, namely its development in the embryo, and its function in the adult. We aim to answer these scientific questions by focusing on the interplay between mesenchymal and other pancreatic cell types in both healthy and diseased mouse models.





Mesenchymal cells in the embryonic and adult pancreas. A) Mesenchymal cells (green) surround the developing pancreatic bud (red and blue) and support normal organogenesis. B) Mesenchymal cells (green) form a network around the Islet of Langerhans (gray) in the adult pancreas. The islets organize pancreatic endocrine cells, including insulin-producing beta-cells

Publications

Guo T., **Landsman L.,** Li N., Hebrok M. (2013) Factors Expressed by Murine Embryonic Pancreatic Mesenchyme Enhance Generation of Insulin-producing Cells from hESCs. *Diabetes* 62:1581-92.

Landsman L., Parent A. and Hebrok M. (2011) Elevated Hedgehog/Gli signaling causes □-cell dedifferentiation in mice. *Proc Natl Acad Sci USA* 108, 17010-17015.

Landsman L., Nijagal A., Whitchurch T.J., VanderLaan R.L., Zimmer W.E., MacKenzie T.C. and Hebrok M. (2011) Pancreatic mesenchyme regulates epithelial organogenesis throughout development. *PLoS Biology* 9, e1001143.

Grants

2012 - 2016 Marie Curie Career Integration grant (CIG)
Cellular composition of the pancreas: elucidating the role of mesenchymal signaling pathways

2013 - 2018 European Research Council (ERC)
ß-cell Dysfunction in Diabetes: Elucidating the Role of Islet-Associated Mesenchymal Cells

May 21, 2014

Dr. Carmit Levy, Ph.D.

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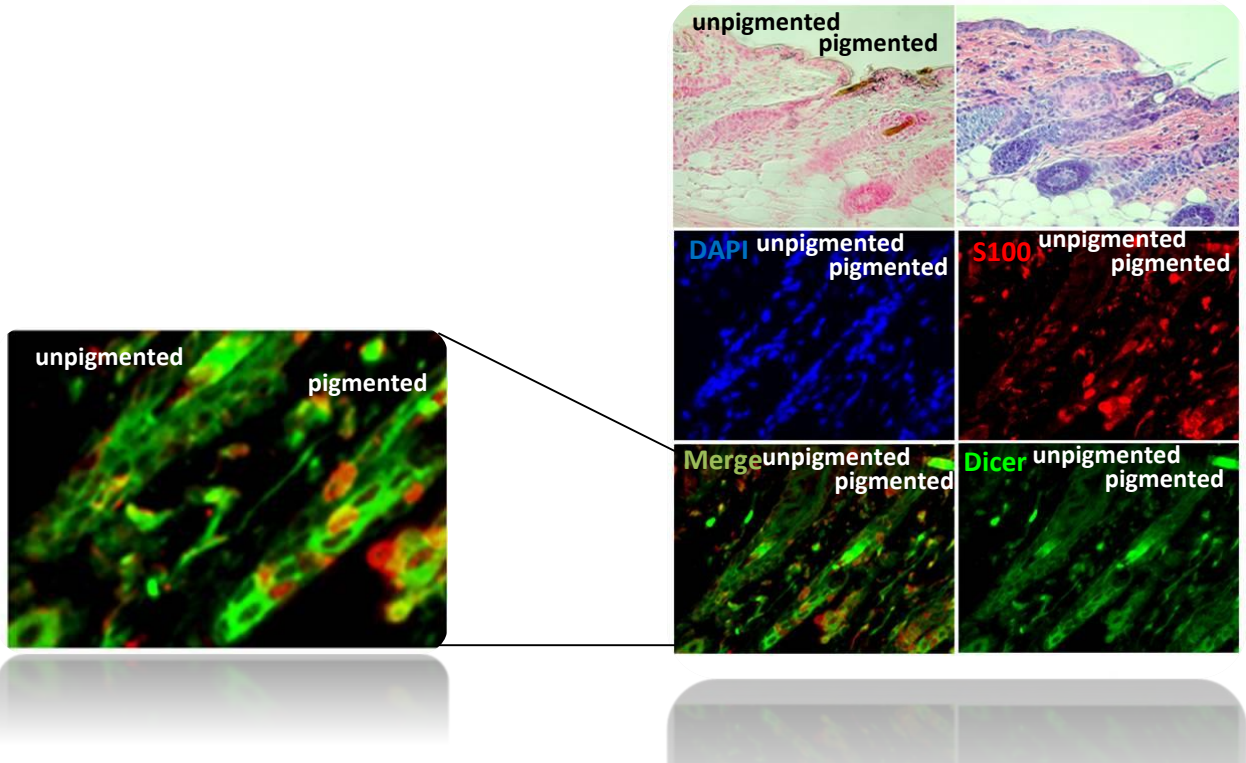
microRNA and DICER in Differentiation and Malignant Transformation of Melanocytes

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Our scientific interests involve the role of microRNAs in development, differentiation and malignant transformation. Focusing our studies on melanocytes will provide the foundation for developing novel approaches in the prevention, diagnosis, and treatment of skin cancer in general and melanoma in particular. In addition, we are intrigued by the possibility of using these systems as a model for exploring basic microRNA biogenesis beyond the cell specific context.



Skin section, subject to H&E (left) and Fontana-Masson staining of melanin (right), shows pigmented and unpigmented regions of (floxed/floxed); Dct(Cre/Cre); Dct-lacZ; K14-scf mouse skin. Immunofluorescent staining of the skin section indicates expression of DICER (green) and S100 (red) (400x magnification). S100-stained epidermal and hair follicle melanocytes appear red; DAPI-stained nuclei appear blue. Merged image shows co-localization of DICER and S100 in the pigmented area of the skin (merge) compared to unpigmented region. Arrows in enlarged merge picture indicate the S100 and DICER co-localization.

Publications

Tabach Y, Golan T, Hernández-Hernández A, Messer AR, Fukuda T, Kouznetsova A, Liu J-G, Lilienthal I, **Levy C*,** Ruvkun G*. Human disease locus discovery and mapping to molecular pathways through phylogenetic profiling. *Mol Syst Biol*, 9:692. 2013

Bell RE, Khaled M, Netanely D, Schubert S, Golan T, Buxbaum A, Janas MM, Postolsky B, Shamir R, **Levy C***. Transcription factor/microRNA axis blocks melanoma adhesion program by miR-211 targeting NUAK1. *J Invest Dermatol,* doi: 10.1038/jid.2013.340. [Epub ahead of print], 2013.

Shaham O, Gueta K, Mor E, Oren-Giladi P, Grinberg D, Xie Q, Cvekl A, Shomron N, Davis N, Keydar- Prizant M, Raviv S, Pasmanik-Chor M, Bell R, **Levy C**, Avellino R, Banfi S, Conte I, Ashery-Padan R. Pax6 regulates gene expression in the vertebrate lens through miR-204. *PLoS Genet,* 9:e1003357. 2013.

Melamed Z, Levy A, Ashwal-Fluss R, Lev-Maor G, Mekahel K, Atias N, Gilad S, Sharan R, **Levy C**, Kadener S*, Ast G*. Alternative splicing regulates biogenesis of miRNAs located across exon-intron junctions. *Mol Cell* 50: 869-881, 2013.

Feige E, Yokoyama S, **Levy C**, Khaled M, Igras V, Richard J. Lin, Lee S, Widlund HR, Scott R. Granter, Andrew L. Kung, Fisher DE. Hypoxia-induced transcriptional repression of the melanoma oncogene MITF by the HIF1-DEC1 axis. *Proc Natl Acad Sci USA* 108:E924-933, 2011.

Janas MM, Khaled M, Schubert S, Bernstein JG, Golan D, Veguilla RA, Fisher DE, Shomron N, **Levy C*,** Novina CD*. Feed-forward microprocessing and splicing activities at a microRNA-containing intron. *PLoS Genet*. 7:e1002330, 2011.

Levy C, Mehdi Khaled, Dimitrios Iliopoulos, Maja Janas, Steffen Schubert, Sophie Pinner, Po-Hao Chen, Shuqiang Li, Anne Fletcher, Satoru Yokoyama, Kenneth L. Scott, Levi A. Garraway, Jun S. Song, Scott R. Granter, Shannon J. Turley, David E. Fisher, and Carl D. Novina, Intronic miR-211 assumes the tumor suppressive function of its host gene in melanoma. *Mol Cell* 40:841-849, 2010. (ranked “must read” on F1000 list; covered in *News and Views* of *Pigm Cell Melan Res*)

Khaled M, **Levy C** and Fisher D.E, Control of melanocyte differentiation by a MITF-PDE4d3 homeostatic circuit. *Genes & Dev* 24:2276-2281, 2010. (covered in *News and Views* of *Pigm Cell Melan Res)*.

Levy C, Khaled M, Robinson K.C, Veguilla R.A, Chen PH, Yokoyama S, Makino E, Jun Lu, Larue L, Beermann F, Chin L, Bosenberg M, Song J.S, and Fisher D.E, Lineage specific transcriptional regulation of DICER by MITF in melanocytes, *Cell* 141:994-1005, 2010. (covered in News and Views of *Pigm Cell Melan Res)*.

Levy C, Golan D, Friedman B and Shomron N. Biased hosting of intronic microRNA genes. *Bioinformatics*. 26:992-995, 2010.

Reviews

Bell RE, **Levy C**. The 3 M’s: Melanoma, MITF and microRNA. *Pigment Cell Melanoma Res* 24:1088-1106, 2011.

Shomron N and **Levy C**. MicroRNA-Biogenesis and Pre-mRNA Splicing Crosstalk. *J Biomed Biotech.* 2009:594678, 2009.

Levy C, and Fisher D.E, Dual role of lineage restricted transcription factors. *Transcription* 2:19-22, 2011.

Grants

2011-2014 Marie Curie CIG Reintegration Grant, EU

2012-2014	BSF grant: Identifying novel miRNA signatures that contribute to melanomagenesis and developing associated targeted delivery systems (with Dr. Michael Goldberg, Harvard)
2012-2014	Israel Cancer Association Award (ICA)
2012-2015	Fritz Thyssen Stiftung
2012-2016	Israeli Center for Research Excellence (I-CORE): Gene Regulation in Complex Human Disease

May 21, 2014

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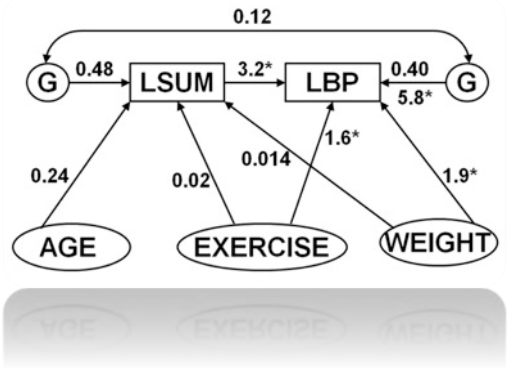
Genetic and Metabolic Research of Age-Dependent Chronic Degenerative Disease

Positions

Professor, Sackler Faculty of Medicine
Chair, Department of Anatomy and Anthropology
Pollak Chair of Biological Anthropology
Honorary Research Fellow, King's College Medical School, London, UK

Research

Our research is focused on age-related chronic degenerative disease, such as osteoporosis, osteoarthritis, including disc degeneration disease and muscle mass loss - sarcopenia. The prevalence of sarcopenia is as high as 30% for those above 60 years old. In the elderly, the loss of muscle mass is correlated with profound physical impairment and disability with severe clinical consequences, including mobility loss, osteoporosis, osteoarthritis, increased fracture risk, dyslipidemia, insulin resistance, and increased mortality. However, it is also often developed at a much younger age. Despite the above clinical significance and despite the fact that a strong familial component in muscular mass variation is well established, there is almost a total lack of molecular genetic studies of this trait. This is in a great contradiction to studies concerning the other two body composition components: bone and fat mass, for each of which many dozens of studies have been published during the past two decades. It is therefore timely and imperative to invest extensive scientific research n the genetic and metabolic mechanisms of early and rapid muscle mass loss. The other important subject of our current research is low back pain, representing most common musculoskeletal disorder in general human population. However, it is still unclear which individuals develop it. We examine the contribution of genetic factors, lumbar disc degeneration and other potential risk factors in a general human population.



Path diagram of the main risk factors for low back pain (LBP) in middle-age women. The figure shows contribution of various factors to LBP, including genetic effects (G) and lumbar disc degeneration (LSUM). The results presented as variance components (portions) and odds ratios (marked by *). According to Livshists et al 2011, Ann Rheumat Dis.

Publications

Cheung C, **Livshits G**, Zhou, Meigs JB, McAteer J, Florez JC, Cupples LA, Demissie S, Kiel DP, Karasik D. Hip geometry variation is associated with bone mineralization pathway gene variants: the Framingham study. JBMR 2010; 25: 1564-1571.

Sergey Ermakov, Mohammad R. Toliat, Zvi Cohen, Ida Malkin, Peter Nürnberg, **Gregory Livshits**. Association study of polymorphisms in the *ALPL and ENPP1* loci, related to bone mineralization and diverse skeletal traits. Bone 2010; 46: 1244-50.

Michael Korostishevsky, Zvi Cohen, Ida Malkin, Olga Yarenchuck, Sergey Ermakov, **Gregory Livshits**. Genetic association between the series of polymorphisms in three mineralization genes and obesity traits in normal human population. Int J Obesity 2010; 34:1308-18.

Sergey Ermakov, Michael Rosenbaum, Ida Malkin, **Gregory Livshits**. Association of ENPP1 gene with cranio-facial morphology. Ann Hum Biol 2010, 37: 754-66.

Yulia Vistoropsky, Sergey Ermakov, Mohammed Toliat, Svetlana Trofimov, Janine Altmüller, Ida Malkin, Peter Nürnberg, **Gregory Livshits**. Genetic determinants of circulating levels of Tumor Necrosis Factor Receptor II and their association with *TNFRII* gene variants. Cytokine 2010; 51: 28-34.

Gregory Livshits, Sergey Ermakov, Maria Popham, Alex J MacGregor, Philip Sambrook, Timothy D Spector, Frances MK.Williams. Evidence that bone mineral density plays role in degenerative disc disease: an MRI-based population study. Ann Rheumat Dis 2010; 69: 2102-6.

Sergey Ermakov, Anna Leonova, Svetlana Trofimova, Ida Malkin, **Gregory Livshits**. Quantitative genetic study of the circulating osteopontin in community selected families. Osteop Intern 2011; 22:2261-71

Anna Leonov, Svetlana Trofimov, Sergey Ermakov**, Gregory Livshits**. Quantitative genetic study of amphiregulin and fractalkine circulating levels - potential markers of arthropathies. Osteoarthr & Carti, 2011; 19:737-742

Gregory Livshits, Maria Popham, Ida Malkin, Philip N. Sambrook, Alex J MacGregor, Timothy Spector, Frances MK Williams. Degenerative disc disease and genetic predisposition are the main risk factors for low back pain in women: The UK Twin Spine Study (TUTSS). Ann Rheumat Dis 2011; 70:1740-1745

Livshits G, Malkin I, Williams FMK, Hart DJ, Hakim A, Spector TD. Longitudinal study of variation in body mass index in middle-aged UK females. Age, 2011; 34:1285-94.

Ermakov S, Trofimov S, Malkin I, **Livshits G.** A significant association exists between receptor tyrosine kinase-like orphan receptor 2 gene variants and the OPG/RANKL ratio in human plasma. Osteoporos Int. 2011; 23:1899-1907

Rony Sapir-Koren and Gregory **Livshits.** Bone mineralization and regulation of phosphate homeostasis. IBMS BoneKEy, 2011; 8:286-300.

Sergey Ermakov, Svetlana Trofimova, Ida Malkin, Gregory **Livshits**. A Significant association exists between receptor tyrosine kinase-like orphan receptor 2 gene variants and the OPG/RANKL ratio in human plasma. Osteoporos Int, 2012; 23:1899-907.

Korostishevsky M, Williams F, Hart D, Blumenfeld O, Spector T, **Livshits G**. Implementation of the simplified stochastic model of aging for longitudinal osteoarthritis data assessment. Ann Hum Biol, 2012; 39:214-22.

Korostishevsky M, Malkin I, Trofimov S, Deng H-W**, Livshits G**. Significant association between body composition phenotypes and the osteocalcin genomic region in normative human population. Bone, 2012; 51:688-94.

Gregory **Livshits**, Ida Malkin, Alireza Moayyeri, Timothy D Spector, Christopher J Hammond. Association of FTO gene variants with body composition in UK twins. Ann Hum Genet 2012; 76:333-41.

Gregory **Livshits**, Ida Malkin, Frances MK Williams, Deborah J Hart, Alan Hakim, Timothy D Spector. Longitudinal study of variation in body mass index in middle-aged UK females. Age, 2012; 34:1285-94.

Orit Blumenfeld, Frances MK Williams, Debora J Hart, Nigel K Arden, Timothy D Spector, Gregory **Livshits**. Lower limbs composition and radiographic knee osteoarthritis (RKOA) in Chingford sample - a longitudinal study. Archives of Gerontology and Geriatrics, 2013; 56:148-54.

Ruth Z. Birk, Sergey Ermakov, Gregory **Livshits**. Common fSNP variants of fourteen Bardet-Biedl syndrome genes and adult body mass. Obesity, 2013, 21:1684-9

Liran Franco, Frances MK Williams, Svetlana Trofimov, Tim D Spector, Gregory **Livshits**. Contribution of putative genetic factors and candidate gene variants to inter-individual variation of circulating fractalkine (CX3CL1) levels in a large UK twins' sample. Human Immunology, 2013; 74:358-63.

Liran Franco, Frances MK Williams, Svetlana Trofimov, Tim D Spector, Gregory **Livshits**. Elevated plasma fractalkine levels are associated with higher levels of IL-6, Apo-B, LDL-C and insulin, but not with body composition. Metabolism, 2013; 62:1081-87.

Orit Blumenfeld, Frances MK Williams, Debora J Hart, Nigel K Arden, Timothy D Spector, Gregory **Livshits**. Association between cartilage and bone biomarkers and incidence of radiographic knee osteoarthritis (RKOA) in UK females: A prospective study. Osteoarthritis and Cartilage, 2013;21:923-9.

Liran Franco, Frances MK. Williams, Svetlana Trofimov, Ida Malkin, Gabriela Surdulescu, Timothy Spector**,** Gregory **Livshits**. Changes in heritability and IGF-1 gene effect on IGF-1 circulating levels variation, AGE, 2014 (in press)

Orit Blumenfeld, Frances MK Williams, Ana Valdes, Debora J Hart, Ida Malkin, Timothy D Spector, Gregory **Livshits**. Association of interleukin-6 gene polymorphisms with hand osteoarthritis and osteoporosis. Cytokine (accepted for publication).

Reviews

Rony Sapir-Koren and Gregory **Livshits**. Are estrogen and estrogen receptors essential to mechanical stimulation of bone formation? Osteoporos Int. 2013; 24:1771–89.

Rony Sapir-Koren and Gregory **Livshits**. Osteocyte Control of Bone Remodeling: Is Sclerostin a Key Molecular Coordinator of the Coupled Bone Resorption-Formation Cycles? Osteopor Int. 2014 (accepted for publication).

Grants

2013-2014 Genetic Epidemiological Approach to Etiology of Low Back Pain and Lumbar Disc Degeneration. Tel Aviv University, Sackler Faculty of Medicine

2013-2017 Genetics, Genomics and Metabolomics of the Low Back Pain and Spinal Disc Degeneration in Complex Arab Pedigrees in Israel. Israel Science Foundation (ISF).

May 21, 2014

Prof. Ilana Lotan, Ph.D.

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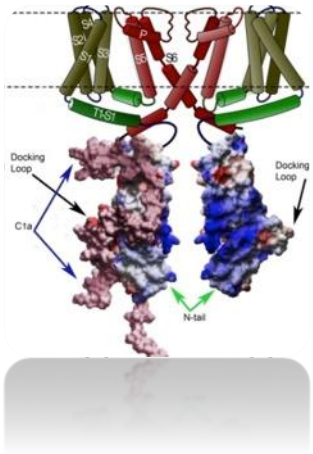
Role of Potassium Channels in Neurotransmitter and Insulin Release in Diabetes

Position

Professor, Sackler Faculty of Medicine

Research

We have a long standing interest in the study the molecular mechanisms of modulation of voltage gated K^+ (Kv) channels by interaction with signaling molecules. We were first to describe modulation of a brain Kv channel by major protein components of the exocytotic machinery. Since then our main focus is the role of Kv channels in transmitter release, finding that it may be far more than just repolarizing the membrane potential: independent of K^+ currents but mediated by protein-protein interactions with the exocytic SNARE proteins. The dual actions of the channel, through its currents and via its interaction with SNAREs, in combination, may reinforce the known activity dependence of dense core vesicle exocytosis.



Kv2.1-C terminal domain, C1a, wraps around the N terminus and is accessible for protein-protein interactions. Using biophysical and FRET analyses, combined with computational biology approach dealing with homology and *ab initio* modeling of protein structures, proteins docking simulations and molecular dynamics.

Kv2.1 (Lvov et al., J. Biol. Chem. (2009)

Main research projects currently in the lab:

1) Study of the novel role of Kv2.1 potassium channel in insulin secretion from pancreatic islet β cells, as a target for novel drug design for the treatment of type-2 diabetes;

2) Study of structure-function and modulations by presynaptic modulators of Kv2.1 and other Kv channels, specifically KCNQ2 and KCNQ3, important in axonal and synaptic excitability.

Research methods:

Biophysical: 1) Two-electrode voltage clamp and patch clamp techniques for the study of whole cell and single channel currents. 2) Membrane capacitance and amperometry measurements for the study of exocytosis.

Biochemical: co-immunoprecipitation, immunohystochemistry, recombinant protein purification, etc, for the study of *in vivo* and *in vitro* protein-protein interactions.

Imaging: 1) Fluorescence Resonance Energy Transfer (FRET) for the study of protein-protein interactions. 2) Total Internal Reflection Fluorescence Microscopy (TIRFM) for the study of neurotransmitter vesicles behavior.

Publications

Feinshreiber, L., Singer-Lahat, D., Friedrich, R., Matti, U, Sheinin, A., Yizhar, O., Nachman, R., Chikvashvili, D., Rettig, J., Ashery, U. and **Lotan, I**. Non-conducting function of the Kv2.1 channel enables it to recruit vesicles for release in neuroendocrine and nerve cells. J Cell Sci. 123:1940-7 (2010)

Etzioni, A., Siloni, S., Chikvashvilli, D., Strulovich, R., Sachyani, D., Regev, N., Greitzer-Antes, D., Hirsch, J.A. and **Lotan, I**. Regulation of neuronal M channel gating in an isoform–specific manner; functional interplay between calmodulin and syntaxin 1A. J Neurosci. 31:14158-71 (2011).

Dai XQ, Manning Fox JE, Chikvashvili D, Casimir M, Plummer G, Hajmrle C, Spigelman AF, Kin T, Singer-Lahat D, Kang Y, Shapiro AM, Gaisano HY, **Lotan I**, Macdonald PE. The voltage-dependent potassium channel subunit Kv2.1 regulates insulin secretion from rodent and human islets independently of its electrical function. Diabetologia. 2012;55(6):1709-20.

Lotan I, Khlebtovsky A, Inbar E, Strenov J, Djaldetti R, Steiner I. Primary brain T-cell lymphoma in an HTLV-1 serologically positive male. J Neurol Sci. 2012;314(1-2):163-5.

Greitzer-Antes D, Barak-Broner N, Berlin S, Oron Y, Chikvashvili D, **Lotan I**. Tracking Ca2+-dependent and Ca2+-independent conformational transitions in syntaxin 1A during exocytosis in neuroendocrine cells. J Cell Sci. 2013;126(Pt 13):2914-23.

Hellmann MA, Mosberg-Galili R, **Lotan I**, Steiner I. Maintenance IVIg therapy in myasthenia gravis does not affect disease activity. J Neurol Sci. 2014;338(1-2):39-42.

Review

Michaelevski, I. and **Lotan, I.** Role of neuronal potassium M-channels in sympathetic regulation of cardiac function. J Physiol. 589:2659-2660 (2011).

May 21, 2014

Dr. Chen Luxenburg, Ph.D.

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The Mechanobiology of Tissue Development Homeostasis and Disease

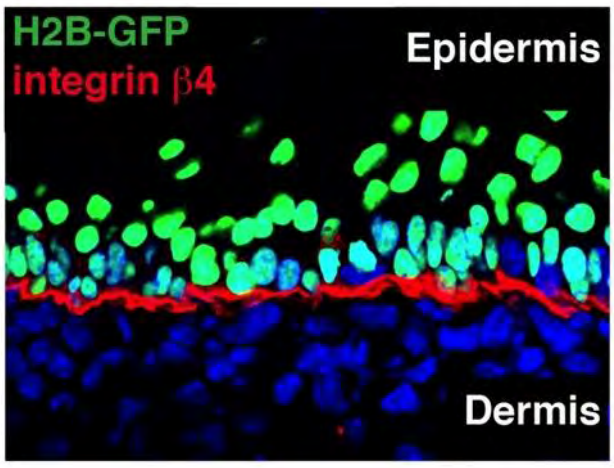
Position

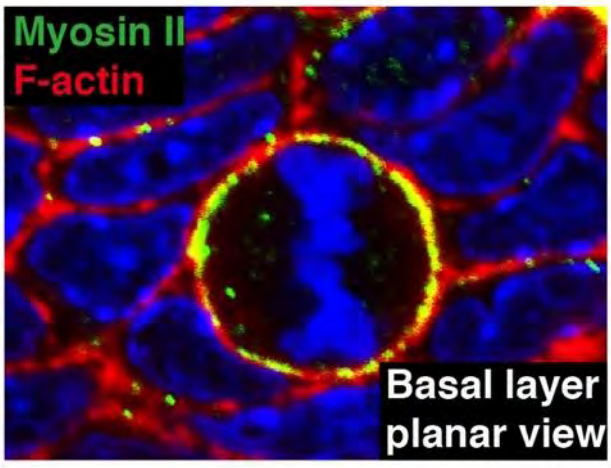
Senior Lecturer, Sackler Faculty of Medicine

Research

Many biological processes such as cell migration and division require mechanical forces. However, similar to chemical cues, mechanical forces also play a key regulatory role that affect many additional key biological processes. Therefore, it is not surprising that changes in the mechanical properties of tissues contribute to the development of common diseases.

Our lab uses the mouse skin epidermis as a model system to study how mechanical and geometrical cues regulate morphogenesis, affect gene expression and contribute to cell fate determination during development, homeostasis and disease. The skin is an ideal model system for these studies for the following reasons: 1) the skin is a mechano-sensitive organ, capable of sensing and responding to mechanical signals. 2) Defects in the mechanical and geometrical properties of epidermal cells are among the hallmarks of common skin diseases including cancer and psoriasis 3) The epidermis can easily and rapidly be manipulated genetically *in vivo*, making it a tractable model system to discover novel genes and study their function.





Left hand side**:** On top of classic mouse genetic tools we use state of the art *in utero* injections of lentivirus (H2B-GFP+ cells in the epidermis) to manipulate gene expression in epidermal stem cells/progenitors early in embryonic development, before cell fate specification.
Right hand side**:** Whole mount image of embryonic epidermis showing an early mitotic cell and its interphase neighbors in planar view. Note the dramatic differences in cell shape. We demonstrated that mitotic rounding is important for cells ability to orient their spindle and undergo asymmetric cell division.

Publications

Luxenburg C, Pasolli HA, Williams SE, and Fuchs E. (2011) Developmental roles for Srf, cortical cytoskeleton and cell shape in epidermal spindle orientation. Nat. Cell Biol. 13:203-14

Luxenburg C, Winograd-Katz S, Addadi L, and Geiger B (2012) Involvement of actin polymerization in podosome dynamics. J. Cell Sci, 125, 1666-1672

May 21, 2014

Dr. Michael Milyavsky, Ph.D.

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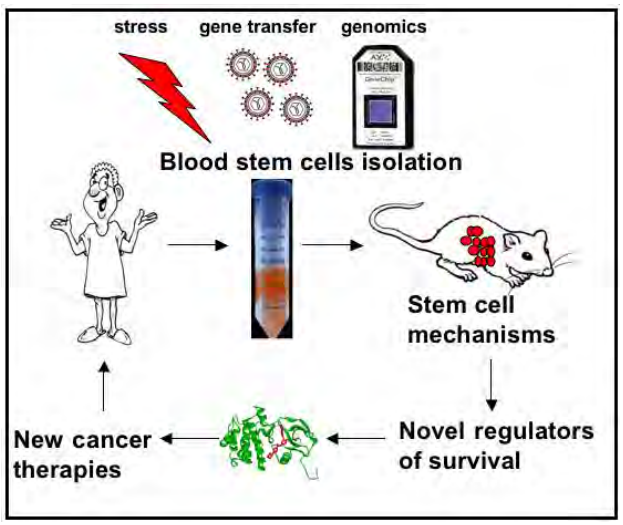
DNA Damage Response in Normal and Leukemia Hematopoietic Stem Cells

Position

Senior Lecturer, Sackler Faculty of Medicine

Research

Accumulation of unrepaired DNA damage in hematopoietic stem cells (HSC) is associated with bone marrow failure and accelerated leukemogenesis. Our laboratory aims to understand how HSC cope with DNA damage to preserve normal blood regeneration and to limit the risk of leukemogenesis. In addition, we strive to discover how leukemia stem cells escape therapy and try to devise strategies to prevent this from happening. To address these questions we study DNA damage signaling and its outcomes in highly purified human normal and leukemia cell subsets. We employ flow cytometry, immunofluorescent and biochemical analyses, lentiviral gene transfer-mediated functional screens, expression/microRNA profiling, clonal *in vitro* assays and, most importantly, *in vivo* repopulation mouse assays of human normal HSC and leukemia-initiating cells.



Publications

Buganim, Y., I. Goldstein, D. Lipson, **M. Milyavsky,** S. Polak-Charcon, C. Mardoukh, H. Solomon, E. Kalo, S. Madar, R. Brosh, M. Perelman, R. Navon, N. Goldfinger, I. Barshack, Z. Yakhini, and V. Rotter. 2010. A novel translocation breakpoint within the BPTF gene is associated with a pre-malignant phenotype. *PLoS ONE*: 5.

Milyavsky, M., Gan, O. I., Trottier, M., Komosa, M., Tabach, O., Notta, F., Lechman, E., Hermans, K. G., Eppert, K., Konovalova, Z., Ornatsky, O., Domany, E., Meyn, M. S., Dick, J. E. 2010. A distinctive DNA damage response in human hematopoietic stem cells reveals an apoptosis independent role for p53 in self-renewal. *Cell Stem Cell*: 7:186-97.

Chan G, Cheung LS, Yang W, **M. Milyavsky**, Sanders AD, Gu S, Hong WX, Liu AX, Wang X, Barbara M, Sharma T, Gavin J, Kutok JL, Iscove NN, Shannon KM, Dick JE, Neel BG, Braun BS. 2011. Essential role for Ptpn11 in survival of hematopoietic stem and progenitor cells. *Blood* 117:4253-61.

Louria-Hayon I., Ruston J.C.F., , Gish G, Jin J, Kofler M. M., Lambert J-P., Adissu H. A., **Milyavsky M**, Herrington R., Minden M. D., Dick J. E., Gingras A-C., Iscove N. N., and T. Pawson. 2013. The Lnk adaptor suppresses radiation resistance and radiation-induced B-cell malignancies by inhibiting IL-11 signaling. PNAS 110(51): 20599-604.

Biechonski, S., and **M. Milyavsky**. 2013. Differences between human and rodent dna-damage response in hematopoietic stem cells: at the crossroads of self-renewal, aging and leukemogenesis. *Translational Cancer Research* **2** (6):372-383.

Review

Biechonski, S, **Milyavsky, M** 2013. DNA-damage response in human hematopoietic stem cells: at the crossroads of self-renewal, aging and leukemogenesis. Translational Cancer Research 2013 (In press)

Grants

2013-2015 FP7-PEOPLE-2012- MARIE CURIE CAREER INTEGRATION GRANTS (CIG)

May 24, 2014

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Regulatory Mechanisms in Mucosal Inflammation

Position

Senior Lecturer, Sackler Faculty of Medicine

Associate Editor, *Journal of Allergy and Clinical Immunology*

Research

The gastrointestinal, respiratory and urogenital tracts are primary entry points of numerous pathogens and antigens. Therefore, complex immunological mechanisms evolved to efficiently and potently respond to such antigens. Notably, exaggerated immune responses such as those observed in asthma and inflammatory bowel disease are often harmful and may lead to substantial morbidity.

Our goal is to identify immunological mechanisms that can be pharmacologically targeted in diseases affecting the lung and gastrointestinal tract. We are specifically interested in defining the roles of immune inhibitory receptors in these mucosal sites. To achieve this goal we use a combination of novel in-vivo (unique gene targeted mice) and in-vitro approaches combining genomics, proteomics, molecular biology and biochemistry.

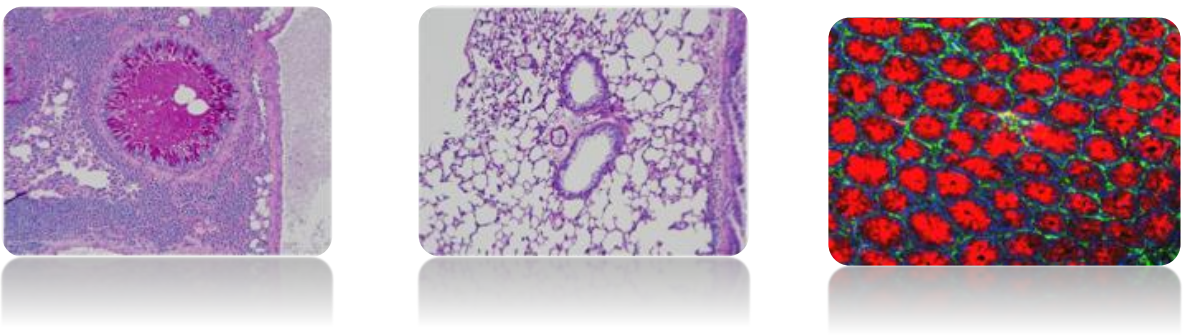

Figure legend: A photomicrograph of a normal lung displaying two large airways and a blood vessel (left). In many inflammatory conditions such as asthma and COPD, the airway is filled with mucus plugs (middle, pink stain). Right - an immunofluorescent stain of resistin-like molecule alpha (red), a proinflammatory, immunoregulatory molecule that is highly upregulated in gastrointestinal epithelial in conditions such as inflammatory bowel disease (IBD).

Publications

Shik D, Moshkovits I, Karo-Atar D, Reichman H, **Munitz A**. IL-33 requires CMRF35-like molecule-1 (CLM-1) expression for induction of myeloid cell activation. *Allergy***.** 2014; *In Press.*

Baruch-Morgenstern NB, Shik D, Moshkovits I, Itan M, Karo-Atar D, Bouffi C, Fulkerson PC, Rashkovan D, Jung S, Rothenberg ME, **Munitz A**. Paired immunoglobulin-like receptor A is an intrinsic, self-limiting suppressor of IL-5-induced eosinophil development. *Nat Immunol*. 2014, 15:36-44.

Moshkovits I, Shik D, Itan M, Karo-Atar D, Bernshtein B, Hershko AY, van Lookeren Campagne M, **Munitz A**. CMRF35-like molecule 1 (CLM-1) regulates eosinophil homeostasis by suppressing cellular chemotaxis. *Mucosal Immunol,* 2013. 7:292-303.

Karo-Atar D, Moshkovits I, Eickelberg O, Königshoff M, **Munitz A.** PIR-B regulates pulmonary fibrosis by suppressing profibrogenic properties of alveoalar macrophages. *Am J Res Cell Mol Biol*; 2013: 48;456-464.

Semis R, Shai N, **Munitz, A**, Zaslavsky Z, Polacheck I, Segal E. Pharmacokinetics, tissue distribution and immunomodulatory effect of intralipid formulation of nystatin in mice. *J of Antimicrob Chem*; 2012;67:1716-21.

Munitz A, Cole ET, Karo-Atar D, Finkelan FD, Rothenberg ME. Resistin-like molecule alpha regulates IL-13-induced chemokine production but not allergen-induced airway responses. *Am J Res Cell Mol Biol*; 2012;46:703-13.

Rothenberg ME. Wen T, Shik D, Cole ET, Mingler M, **Munitz A**. IL-13Rα1 differentialy regulates aeroallergen-induced lung responses. *J Immunol,* 2011; 187:4873-4880.

Waddell A, Ahrens R, Steinbrecher K, Donovan B, Rothenberg ME, **Munitz A**, Hogan SP. Colonic eosinophilic inflammation in experimental colitis is mediated by Ly6C(high) CCR2(+) inflammatory monocyte/macrophage-derived CCL11. *J Immunol.* 2011; 186:5993-6003.

Munitz A, Cole ET, Waddell A, Groschwitz K, Ahrens R, Steinbrecher K, Willson T, Han X, Denson L, Rothenberg ME, Hogan SP. Paired immunoglobulin-like receptor B (PIR-B) negatively regulates macrophage activation in experimental colitis. *Gastroenterology*, 2010; 139:530-541.

Reviews and Chapters

Lacy P, **Munitz A**. Mutations in CCR3 render it “missing in action”. *J Allergy Clin Immunology*. 2010:126:158-159.

Stein M, **Munitz A**. Targeting interleukin 5 in asthma and hypereosinophilic syndromes. *Recent Pat Inflamm Allergy Drug Discov*. 2010:4;201-209.

Shik D, **Munitz A**. Inhibitory receptors in activation and suppression of the immune response. *Clin Exper Allergy*. 2010: 40; 700-709.

Munitz A. Inhibitory receptors on myeloid cells: new targets for therapy? *Pharmacol Ther*. 2010: 125; 128-137.

Munitz A. Eosinophil Receptor-Mediated Inhibition. In *Eosinophils in Health and in Disease.* (Elsevier, ed. Lee JJ and Rosenberg HF), 2013; pp. 179-188.

Grants

2013-2016 Fritz Thyssen Stiftung, The role of IL-13Rα1 in pulmonary fibrosis

2012-2016 US-Israel Binational Scientific Foundation (BSF), The expression and function of paired immunoglobulin-like receptor B in eosinophils

2011-2015 The Israel Science Foundation (ISF), Expression and function of CLM-1 in eosinophils”

2010-2014 Marie Curie FP7 Reintegration Grant, Resistin-like molecules in lung inflammation

2014-2017 Israel Ministry of Health

2014-2015 Israeli Cancer Association

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Sleep and Its Relation to Cognition

Position

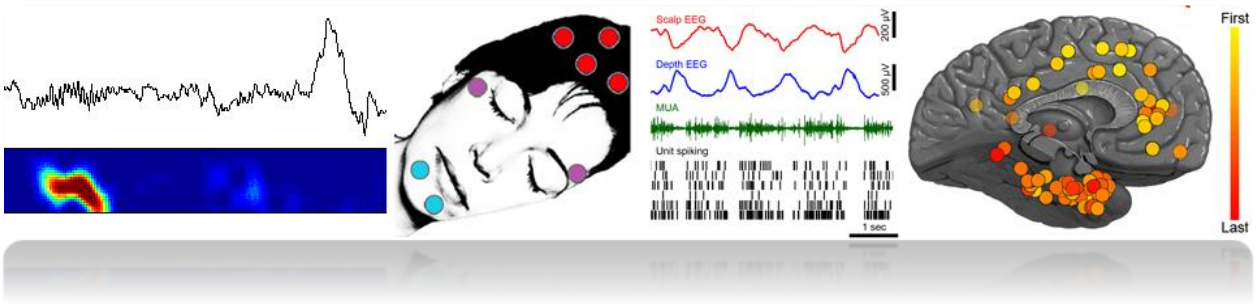
Senior Lecturer, Sackler Faculty of Medicine

Research

Sleep is a universal behavior that is present across the animal kingdom. We spend a third of our lives sleeping, disconnected from the world around us. Our sleep is closely regulated so that when we are sleep deprived, we ultimately compensate with longer, deeper sleep. Sleep helps our cognitive performance, promoting learning and memory consolidation. Lack of sleep immediately affects our cognition, mood, and health. All this suggests that sleep is essential, but what exactly is it about brain activity during sleep that is so crucial for restoring our normal cognition?

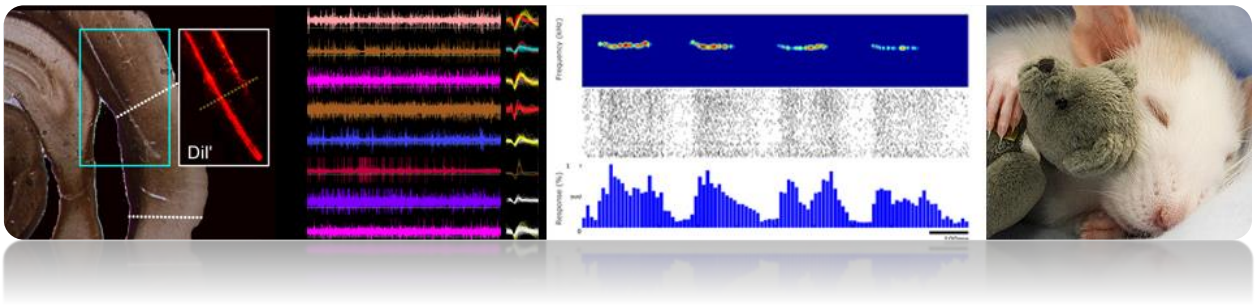
Sleep also involves dramatic changes to our perceptual awareness. Sometimes our consciousness fades altogether while at other times we experience vivid dreams. Although our brain continues to be active, we are mostly disconnected from sensory signals such as sounds, which would otherwise be perceived, trigger plasticity and result in behavior. How does the internal state of brain activity during sleep affect brain responsiveness and perceptual awareness?

Our goal is to understand how sleep relates to cognition and perception. Our research is guided by a belief that such studies require a combination of human and animal models. We therefore use multiple experimental techniques, focusing on the strengths of each setup to investigate the same key questions synergistically. Animal models are used to investigate underlying mechanisms, by performing detailed recordings of electrical activity and by manipulating neuronal activity with optogenetic, electrical and sensory stimulation. Human studies are carried out for careful investigation of cognitive factors and for studying large-scale brain activity (with fMRI, EEG, recordings in neurosurgical patients, and behavioral tests).



Intracranial sleep recordings in neurosurgical patients reveal that slow waves and sleep spindles - the

hallmark EEG oscillations of sleep - occur mostly locally and have a tendency to propagate from medial prefrontal cortex to the medial temporal lobe. Therefore, intracerebral communication during sleep is constrained as sleep oscillations often occur out-of phase in different brain regions.



A comparison of single-unit and LFP responses in rat auditory across wakefulness and sleep states reveals comparable selectivity and response magnitudes of auditory-evoked responses across vigilance states.

Publications

Nir Y, Vyazovskiy VV, Cirelli C, Banks MI, Tononi G. Auditory responses and stimulus-specific adaptation in rat auditory cortex are preserved across NREM and REM sleep. *Cerebral Cortex*. 2013 Dec 8. [Epub ahead of print]

Gilaie-Dotan S, Hahamy-Dubossarsky A, **Nir Y**, Berkovich-Ohana A, Bentin S, Malach R. Resting state functional connectivity reflects abnormal task-activated patterns in a developmental object agnosic. *Neuroimage*. 2013;70:189-98.

Ovadia-Caro S, **Nir Y**, Soddu A, Ramot M, Hesselmann G, Vanhaudenhuyse A, Dinstein I, Tshibanda JF, Boly M, Harel M, Laureys S, Malach R. Reduction in inter-hemispheric connectivity in disorders of consciousness. *PLoS One*. 2012;7:e37238.

Brennan J, **Nir Y**, Hasson U, Malach R, Heeger DJ, Pylkkänen L. Syntactic structure building in the anterior temporal lobe during natural story listening. *Brain and Language*. 2012; 120:163-173.

Soddu A, Vanhaudenhuyse A, Bahri MA, Bruno MA, Boly M, Demertzi A, Tshibanda JF, Phillips C, Stanziano M, Ovadia-Caro S, **Nir Y**, Maquet P, Papa M, Malach R, Laureys S, Noirhomme Q. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Human Brain Mapping*. 2012. 33:778-96.

Andrillon T*, **Nir Y***, Staba RJ, Ferrarelli F, Cirelli C, Tononi G, Fried I. Sleep spindles in humans: insights from intracranial EEG and unit recordings. *Journal of Neuroscience*. 2011;31:17821-34. (* equal contribution)

Vyazovskiy VV, Olcese U, Hanlon EC, **Nir Y**, Cirelli C, Tononi G. Local sleep in awake rats. *Nature*. 2011;472:443-7.

Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, Tononi G. Regional slow waves and spindles in human sleep. *Neuron*. 2011;70:153-69.

Mukamel R, **Nir Y**, Harel M, Arieli A, Malach R, Fried I. Invariance of firing rate and field potential dynamics to stimulus modulation rate in human auditory cortex. *Human Brain Mapping*. 2011; 32:1181-1193.

Reviews

Nir Y, Tononi G. Dreaming and the brain: from phenomenology to neurophysiology. *Trends in Cognitive Sciences*. 2010;14:88-100.

Grants

2014 Margot Shtolz Faculty of Medicine research award
2014 – 2018 EU Marie Curie Career Integration Grant (CIG)
2013 – 2018 I-CORE Cognitive Neuroscience

May 25, 2014

Prof. Nir Osherov, Ph.D.

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Human Mold Infections

Positions

Associate Professor, Sackler Faculty of Medicine
Chair, Department of Human Microbiology and Immunology
Chair, M.Sc. Committee, Sackler School of Medicine
Director, Ella Kodesz Institute of Host Defense against Infectious Diseases

Research

Aspergillus fumigatus is the most common mold pathogen of human beings, causing invasive diseases in immunocompromised (cancer after chemotherapy, bone marrow transplant etc) patients. Poor diagnostic tools and the ineffectiveness of antifungal drugs against established *Aspergillus* infections combine to result in high mortality following *A. fumigatus* infection. Left untreated, mortality rates from invasive pulmonary aspergillosis (IPA) exceed 90% and even following aggressive antifungal treatment fatality rates of 50-70% are common.

The goals of my lab are:

To understand what enables this mold to be such an effective and dangerous pathogen of immunocompromised patients

To develop novel modes of treatment including new antifungal compounds, targeted antibodies and nano medicines.

Publications

Vaknin Y, Shadkchan Y, Levdansky E, Morozov M, Romano J, **Osherov N**. The three Aspergillus fumigatus CFEM-domain GPI-anchored proteins (CfmA-C) affect cell-wall stability but do not play a role in fungal virulence. Fungal Genet Biol. 2014;63:55-64.

Osherov N. Interaction of the pathogenic mold *Aspergillus fumigatus* with lung epithelial cells. Front Microbiol. 2012, 26:346.

Hagag S, Kubitschek-Barreira P, Neves GW, Amar D, Nierman W, Shalit I, Shamir R, Lopes-Bezerra L, **Osherov N**. Transcriptional and proteomic analysis of the *Aspergillus fumigatus ΔprtT* protease-deficient mutant. PLoS One. 2012, 7:e33604.

Arnusch CJ, Albada HB, van Vaardegem M, Liskamp RM, Sahl HG, Shadkchan Y, **Osherov N**, Shai Y. Trivalent ultrashort lipopeptides are potent pH dependent antifungal agents. J Med Chem. 2012, 9:1296-302.

Arnusch CJ, Ulm H, Josten M, Shadkchan Y, **Osherov N**, Sahl HG, Shai Y. Ultrashort peptide bioconjugates are exclusively antifungal agents and synergize with cyclodextrinand amphotericin B. Antimicrob Agents Chemother. 2012, 56:1-9.

Sharon H, Amar D, Levdansky E, Mircus G, Shadkchan Y, Shamir R, **Osherov N**. PrtT-regulated proteins secreted by *Aspergillus fumigatus* activate MAPK signaling in exposed A549 lung cells leading to necrotic cell death. PLoS One. 2011, 6:e17509.

Levdansky E, Kashi O, Sharon H, Shadkchan Y, **Osherov N**. The *Aspergillus fumigatus* cspA gene encoding a repeat-rich cell wall protein is important fornormal conidial cell wall architecture and interaction with host cells. Eukaryot Cell. 2010, 1403-15

Appel E, Vallon-Eberhard A, Rabinkov A, Brenner O, Shin I, Sasson K, Shadkchan Y, **Osherov N**, Jung S, Mirelman D. Therapy of murine pulmonary aspergillosis with antibody-alliinase conjugates and alliin. Antimicrob Agents Chemother. 2010, 54:898-906.

Reviews

Osherov N. The top three areas of basic research on *Aspergillus fumigatus* in 2011. Ann N Y Acad Sci. 2012, 1273:74-7.

Tavanti A, Naglik JR, **Osherov N**. Host-Fungal Interactions: Pathogenicity versus Immunity. Int J Microbiol. 2012, 562480.

Grants

BSF 2012- 2016	Binational Science Foundation
2014-2016	Israel-Italy Cooperation Grant-
2014-2017	Infect-ERA Net Joint European Grant

May 24, 2014

Prof. Udi Qimron, Ph.D.

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Host-Virus Interactions in Bacterial Systems

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our laboratory studies basic aspects of bacteriophage growth with emphasis on phage interactions with their bacterial hosts, and particularly, the recently identified bacterial defense system, the CRISPR. Our ultimate objective is to identify novel phage products and strategies that will assist in overcoming drug resistant pathogens.

We combine genetic and biochemical approaches to identify and characterize interactions of phage proteins with other phage or host proteins. Specifically, we employ the T7 phage and its *Escherichia coli* host as models. We use high throughput screening systems, transposon mutagenesis, tandem affinity purification, mass spectrometry, and classical as well as modern bacterial genetic methods to identify and characterize these viral-host interactions.

Publications

Qimron U, Tabor S, Richardson CC. New details about bacteriophage T7-host interactions. *Microbe,* 5:117-122, 2010.

Edgar R, **Qimron U**. The *Escherichia coli* CRISPR system protects from lysogenization, lysogens, and prophage induction. *J Bacteriol*, 192:6291-6294, 2010.

Yosef I, Goren MG, Kiro R, Edgar R, and **Qimron U**. HtpG is essential for activity of the *Escherichia coli* CRISPR/Cas system. *Proc Natl Acad Sci USA*, 108:20136-41, 2011.

Edgar R, Friedman N, Molshanski-Mor S, and **Qimron U**. Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes. *Appl Environ Microbiol*, 78:744-51, 2012. Highlighted in *Nature Rev Microbiol*, Wall Street Journal, and others.

Goren MG, Yosef I, Edgar R, and Qimron U. The bacterial CRISPR/Cas system as analog of the mammalian adaptive immune system. *RNA Biology*, 9:549-554, 2012.

Yosef I, Goren MG, and Qimron U. Proteins and DNA elements essential for the CRISPR adaptation process in *Escherichia coli*. *Nucl Acid Res*, 40:5569-76, 2012. *Recommended by F1000*

Goren MG, Yosef I, Auster O, and Qimron U. Experimental definition of a clustered regularly interspaced short palindromic duplicon in *Escherichia coli*. *J Mol Biol*, 423:14-16, 2012.

Sberro H*, Leavitt A*, Kiro R*, Koh E, Peleg Y, Qimron U, and Sorek R. Novel families of toxin/immunity modules confer phage resistance in bacteria. *Molec Cell*, 50:136-48, 2013. *contributed equally. *Recommended by F1000*

Kiro R, Goren MG, Yosef I, and Qimron U. CRISPR adaptation in *Escherichia coli* type I-E system. *Biochem Soc Trans*, 41:1412-5, 2013.

Yosef I, Shitrit D, Goren MG, Burstein D, Pupko T, and Qimron U. DNA motifs determining the efficiency of adaptation into the *Escherichia coli* CRISPR array. *Proc Natl Acad Sci USA*, 110:14396-401, 2013. *Recommended by F1000*

Kiro R, Molshanski-Mor S, Yosef I, Milam SL, Erickson HP, and Qimron U. Gene-product 0.4 increases phage competitiveness by inhibiting host cell division. *Proc Natl Acad Sci USA*, 2013. 110:19549-54; Recommended by F1000.

Kiro R, Shitrit D, and **Qimron U.** Efficient engineering of a bacteriophage genome using the type I-E CRISPR-Cas system. *RNA Biol*, 11:42-4, 2014.

Yosef I, Kiro R, Molshanski-Mor S, Edgar E, and **Qimron U.** Different approaches for using bacteriophages against antibiotic-resistant bacteria. *Bacteriophage,* 4:e2849, 2014.

Grants

2010-2014	ERC Marie Curie IRG Grant
2012-2014	KAMIN – Ministry of Industry and Commerce, Grant for Novel Innovations
2014-2017	Israeli Ministry of Health grant
2013-2018	ERC Starting Grant

May 25, 2014

Prof. Drorit Neumann, Ph.D.

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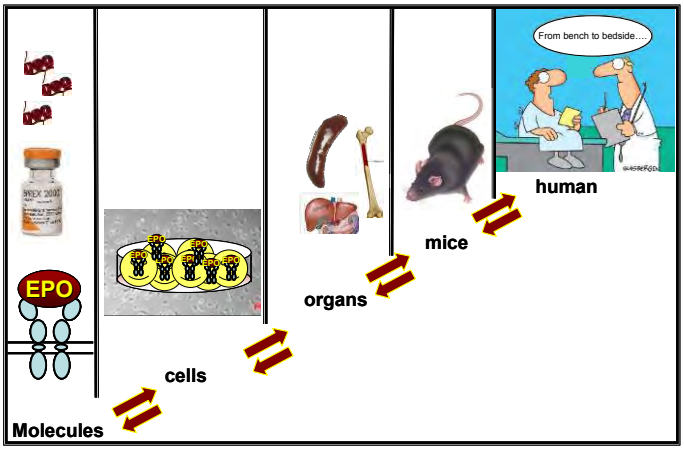
Erythropoietin and Its Receptor in Health and Disease – Basic and Clinical Aspects

Positions

Professor, Sackler Faculty of Medicine
Chair, M.Sc. Studies, Dr. Miriam and Sheldon Adelson Graduate School of Medicine, Sackler Faculty of Medicine

Research

Our research is focused on erythropoietin (EPO), the major hormone that regulates erythropoiesis, operating *via* activation of its cell surface receptor (EPO-R) on erythroid progenitor cells. Our choice to work on this EPO/EPO-R system was initiated to employ it as a model for understanding basic mechanisms of hormone/receptor function and regulation. Through this research we made a novel, original discovery, together with Prof. Mittelman from the Sourasky Medical Center, suggesting that EPO may actually act as a pleiotropic hormone with anti-neoplastic, immunomodulatory activities. Our research is thus focused on both the basic mechanisms of hormone/receptor interaction, as well as the function of this hormone as an immunomodulator. The studies are based on a variety of in-vitro and murine experimental models, and include also an avenue of elucidating the relevance and possible clinical application of the results.



Publications

Katz O., M. Stuible, N. Golishevski, L.Lifshitz, M. L. Tremblay, M. Gassmann, M. Mittelman and **D. Neumann**. Erythropoietin treatment leads to reduced blood glucose levels and body mass: Insights from murine models. J. Endocrinology, 205:87-95 (2010)

Liron T., T. Nahari, M. C. Souroujon and **D. Neumann**. Insertion of an NPVY sequence into the cytosolic domain of erythropoietin receptor selectively affects erythropoietin mediated signaling and function. Biochem. J. 427:305-312 (2010) *Selected by Faculty of 1000: http://www.f1000biology.com/article/id/3771958/evaluation

Bishara A., A. Rudi, M. Aknin, **D. Neumann**, N. Ben-Califa, Y. Kashman. Salarins D–J. Seven new nitrogenous macrolides from the madagascar sponge Fascaplysinopsis sp. Tetrahedron 66, 4339–4345 (2010)

Lifshitz L., G. Tabak, M. Gassmann, M. Mittelman, and **D. Neumann**. Macrophages as novel target cells for erythropoietin. Haematologica 95:1823-1831, (2010)

Ben-Califa N., A. Bishara, Y. Kashman and **D. Neumann**. Salarin C, a member of the salarin superfamily of marine compounds, is a potent inducer of apoptosis. Invest. New Drugs 30:98-104 (2012)

Yosha L., O. Ravid, N. Ben-Califa, and **D. Neumann**. Cytosolic lysine residues enhance anterograde transport and activation of the erythropoietin receptor. Biochem. J. 435:509-518 (2011)

Inbar D., M. Cohen-Armon and **D. Neumann.** Erythropoietin driven signaling and cell migration mediated by polyADP-ribosylation, Brit. J. Cancer 107: 1317-1326 (2012)

Oster H. S., S. Prutchi-Sagiv, O. Halutz, E. Shabtai, M. Hoffman, **D. Neumann**, M. Mittelman. Erythropoietin treatment is associated with an augmented immune response to the influenza vaccine in hematologic patients. Exp. Hematol. 41:167-71 (2013)

Bento C., M Percy, H. Cario*, B. Gardie, T. M. Magalhães, R. van Wijk, S. Perrotta, D. R. Fulvi, H. Almeida, C. Rossi, F. Girodon, M. Åström, **D. Neumann**, S. Schnittger, B. Landin, M. Minkov, M. L. Randi, S. Rives, L. Ribeiro, S. Hermouet, M. F. McMullin*, on behalf of ECE-Consortium§ Genetic basis of Congenital Erythrocytosis: mutation update and online databases. Human Mutation, 35:15–26 (2014)

Reinbothe S., A.M. Larsson, M. Vaapil, C. Wigerup, J. Sun, A. Jögi, **D. Neumann**, L. Rönnstrand, S. Påhlman EPO-independent functional EPO receptor in breast cancer enhances estrogen receptor activity and promotes cell proliferation Biochem. Biophys. Res. Com. 445: 163–169 (2014)

Ohana Haim Y., N. Deshet Unger, M. C. Souroujon, M. Mittelman and **D. Neumann** Resistance of LPS-activated bone marrow derived macrophages to apoptosis mediated by dexamethasone Sci. Rep. 4: 4323 (2014)

Gross M., N. Ben-Califa, M. F. McMullin, M. J. Percy, C. Bento, H. Cario, M. Minkov and **D. Neumann** Polycythemia-inducing mutations in the erythropoietin receptor (EPOR): Mechanism and function as elucidated by epidermal growth factor receptor (EGFR) – EPOR chimeras Br. J. Haematol. (2014) In press

Chapters and Reviews

Mittelman M., H. S. Oster, M. Hoffman and **D. Neumann**. The lower risk MDS Patient a risk of rapid progression Leukemia Research 34:1551-555 (2010)

Oster H. S., **D. Neumann**, M. Hoffman and M. Mittelman. Erythropoietin: the swinging pendulum. Leuk. Res. 36:939-44 (2012)

Ohana Y., Liron T., Prutchi-Sagiv, S., Mittelman M. Souroujon M.C. and **D. Neumann.** Erythropoietin. Second edition, Handbook of Biologically Active Peptides (Abba J. Kastin, ed.), Elsevier, San Diego, pp. 1619-1626 (2013)

Grants

2010 – 2014, Bi-National Science Foundation, together with Constantinos Koumenis U. Penn. Erythropoietin Receptor Metabolism and Function Guided by Hypoxia and by the Unfolded Protein Response

2011 - 2014, **"**Cooperation" – Theme "Health": FP7-HEALTH-2010. Role: coordinator Gaining sage on the Epoetins' saga: assessing long term risks and advancing towards better Epoetin driven treatment modalities – Acronym: EpoCan, Proposal No: 282551

May 24, 2014

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Molecular Mechanisms of Neurodegeneration

Position

Senior Lecturer, Sackler Faculty of Medicine

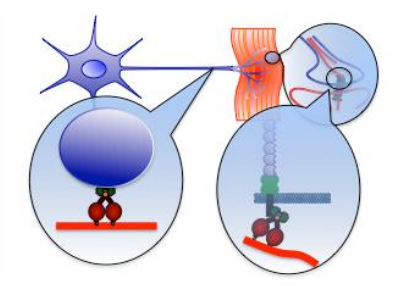
Research

The lab is a new multi-disciplinary molecular and cellular neurobiology lab. The lab uses state-of-the-art single molecule live imaging techniques on neuronal cultures, as well as biochemistry, cell biology and biophysics approaches on mouse model systems to study the role of axonal transport in neurodegenerative diseases, with an initial focus on ALS.

Neuronal survival and proper function depends on cell-cell communication mediated by ligand-receptor mechanisms. During neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), there is considerable synapse/neuromuscular junction (NMJ) disruption and neuronal cell death. It is non-autonomous processes involve interactions between the neurons to its diverse extracellular microenvironments. The molecular basis for this neuronal dysfunction and death is still poorly understood. One possible reason is alterations in the nature, directed movement and spatial localization of vital extra and intracellular signals.

The long-term research goal of the lab is to understand the vital molecular communications mechanisms between the neurons and its environment. More specifically, we seek to understand the role that retrograde signaling plays in (1) neuronal survival and (2) synapse stability.

We believe that our research will generate novel insights into neurodegenerative mechanisms and ultimately, provide a molecular basis for new drugs as well as delivery methods to treat a range of neurodegenerative diseases.



The dual role of dynein in spatiotemporal signaling. Dynein serve as a motor protein conducting long distance signaling process (left callout) or may play a role in receptors clustering and lateral movement in and out of membrane microdomain (right callout) for example in the neuromuscular junction. Alterations in its function leads to neurodegeneration.

In-vitro microfluidic platform with motor neuron cell bodies on one side and muscle cells on the other, creating a powerful system to study neurodegeneration mechanisms.

Publications

Lilo E, Wald S, Solmesky L, Ben Yaakov K, Gershoni- Emek N, Gotkine M, Karosis D, Bulvik S, **Perlson E** and Weil M. (2013). Characterization of human sporadic ALS biomarkers in the familial transgenic mSOD1G93A mouse model. *Hum Mol Genet*. 22:4750-5.

Yashunsky V, Kharilker **L,** Zahavi E**,** Mercone S, Golosovskii M, **Perlson E**, Davidov D, Aroeti B (2013) Real-time sensing of enteropathogenic *E. coli*-induced effects on epithelial host cell height, cell-substrate interactions, and endocytic processes by infrared surface plasmon spectroscopy. *PLoS One*. 8:e78431

Perlson E, Hendricks AG, Wilson MH, Lazarus JE, Ben-Yaacov K, Zhang X, Xiang X, Holzbaur EL. (2013). Dynein interacts with NCAM180 to tether and stabilize synaptic microtubules. *J Biol Chem*. 27;288:27812-24

Castle M, **Perlson E**, Holzbaur EL, Wolf JH, (2013) Long-distance axonal transport of AAV9 is driven by dynein and kinesin-2 and is trafficked in a highly motile Rab7-positive compartment. *Mol Therapy*. 22:554-66.

Hendricks AG, Lazarus JE, **Perlson** E, Gardner MK, Odde DJ, Goldman YE, Holzbaur EL (2012) Dynein tethers and stabilizes dynamic microtubule plus ends. *Curr Biol*. 22:632-637.

Hendricks, A.*/**Perlson, E**.*, Ross, J., Schroeder, H., Tokito, M., Holzbaur, E. (2010) Motor coordination via tug-of war mechanism drives bidirectional vesicle transport. *Curr Biol*. 20: 697-702. **Equally contributing authors*

Reviews and chapters

Perlson, E., Maday, S., Fu, M., Moughamian, A., Holzbaur, E. (2010) Retrograde axonal transport: pathways to cell death? *Trends in Neuroscience*. 33: 335-44.

Gershoni-Emek, N., Zahavi EE., Gluska S., Slobodskoy Y and **Perlson E.** (2014) The Molecular Communication Mechanism of Neuron Survival and Synapse Maintenance. In press.

Grants

2010-2014 Retrograde signaling, Marie Curie International Reintegration Grants (IRG)

2011-2015 ISF (Israel Science Foundation), The dual role of dynein in GDNF signaling

2011-2014 Molecular Mechanisms of Neurodegeneration in ALS, Legacy Heritage Biomedical Science Partnership

2011-2014, Molecular Mechanisms of Rabies Virus Transport, GIF, (German-Israeli Foundation).

2012-2014 Young BSF grant, Novel Screen for Axonal Transcriptomes and non-coding RNAomes along the process of Motor Neuron Death, Axon Degeneration and Neuromuscular Junction Disruption Occurring in Amyotrophic Lateral Sclerosis, with Dr. Dianna Willis, Burke Medical Research Institute, Weill Medical College, Cornell University

2012-2015 Small molecule screen for neuromuscular junction maintenance, Rosetrees Trust

2012-2017 Molecular Communication Mechanism of Motor Neuron Survival and Synapse Maintenance, European Research Council (ERC) Starting Grant

May 24, 2014

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Brain Injuries: Cognitive, Behavioral and Cellular Outcome

Position

Professor, Sackler Faculty of Medicine

Research

My group has a long history in mTBI research, not only in characterizing behavioral and biochemical sequelae of blunt head trauma, but also in developing preclinical models of mTBI of translational relevance to support the development of new treatment strategies and drugs. In order to look for answers regarding the blast induced traumatic brain injury, we have developed a blast injury model for mice that resembles, as much as possible, the conditions on the battlefield or at a terror-attack site. As such, the outcomes of the “real-life-like” exposure to the blast in our model may vary from severe to mild brain injury under controlled conditions for each mouse.

Publications

Rubovitch V, Edut S, Sarfstein R, Werner H, **Pick, C.G**. The intricate involvement of the insulin-like growth factor receptor signaling in mild traumatic brain injury in mice. *Neurobiology of Disease* 38:299-303 (2010).

Baratz, R., Rubovitch, V., Frenk, H. and **Pick, C.G**. The Influence of Alcohol on behavioral recovery following mTBI in mice. *J Neurotrauma* 27:555-63 (2010).

Defrin R, Gruener, H, Schreiber, S and **Pick C.G**, Quantitative somatosensory testing of subjects with chronic post traumatic headache: implications on its mechanism. *Eur J Pain* 14:924-31 (2010).

Katzav, A., Faust-Socher, A., Kvapil, F., Michaelson. D.M., Blank, M., **Pick C.G**., Shoenfeld, Y., Korczyn, A., Chapman, J. Antiphospholipid syndrome induction exacerbates a transgenic alzheimer disease model on a female background. *Neurobiol Ageing* 32: 272- 279 (2011).

Zohar O., Lavy R., Zi X., Nelson T.J., Hongpaisan J., **Pick C.G**., Alkon D.L. PKC activator therapeutic for mild traumatic brain injury in mice. *Neurobiol of Dis* 41: 329-337 (2011).

Shen, H, Harvey, B.K, Chiang, Y-H, **Pick C.G**, Wang, Y. Methamphetamine potentiates behavioral and electrochemical responses after mild traumatic brain injury in mice. *Brain Res* 1368: 248- 253 (2011). *Equal contribution

Benaroya-Milshtein, N., Hollander, N., Apter, A., Yaniv, I., **Pick, C.G**. Stress conditioning in mice: alterations in behavior, immunity and tumor growth. Stress 14:301-311(2011).

Edut S., Rubovitch, V., Schreiber, S., **Pick C.G**. The intriguing effects of ecstasy (MDMA) on cognitive function in mice subjected to a minimal traumatic brain injury (mTBI). *Psychopharmacology* 214: 877-889 (2011).

Rubovitch, V., Werner H, and **Pick C.G**. The neuroprotective effect of IGF-1 administration after a mild traumatic brain injury in mice is mediated by the adaptive arm of ER stress. *Neurochemistry International* 58: 443-446 (2011).

Zohar, O., Rubovitch, V., Milman, A., Schreiber, S., **Pick C.G**. Behavioral Consequences of Minimal Traumatic Brain Injury in Mice. *Acta Neurobiologiae Experimentalis* 71:36-45 (2011).

Rubovitch, V. Ten-Bosch, M., Zohar, O., Harrison, C., Tempel-Brami, C., Stein, E., Hoffer, B.J., Balaban, C.D., Schreiber, S., Chiu, W.T. and **Pick C.G**. A Mouse Model of Blast-Induced mild Traumatic Brain Injury. *Exp Neurology*, 232:280-89 (2011).

Baratz, R., Tweedie, D., Rubovitch, V., Greig N.H**., Pick, C.G**. Tumor necrosis factor-α synthesis inhibitor, 3,6'-dithiothalidomide, reverses behavioral impairments induced by minimal traumatic brain injury in mice. *J Neurochem*. 118(6):1032-42. (2011)

Domachevsky, L., **Pick C.G**. Arieli, Y., Krinsky, N., Abramovich, A. and Eynan, M. Do hyperbaric oxygen-induced seizures cause brain damage? Epilepsy Res. 100:37-41 (2012).

Saykally, J.N., Rachmany, L., Hatic, H., Shaer, A., Rubovitch, V., **Pick, C.G.** and Citron, B.A. The Nrf2 activator, tert-butylhydroquinone (tbhq), improves cognitive performance in mice after mild traumatic brain injury. Neuroscience, 223: 305-314 (2012).

Rachmany, L., Tweedie D., Li, Y., Rubovitch, V., Holloway, H.W., Miller, J., Hoffer, B.J., Greig, N.H. and **Pick, C.G.** Exendin-4 Induced Glucagon-like Peptide-1 Receptor Activation Reverses Behavioral Impairments of Mild Traumatic Brain Injury in Mice. Aging 35:1621-36 (2013).

Tweedie, D,. Rachmany, L., Rubovitch, V., Lehrmann, E., Zhang, Y., Backer, K.G., Parez, E., Miller, J., Hoffer, B.J., Greig, N.H. and **Pick, C.G.** Exendin-4, a glucagon-like peptide-1 receptor agonist prevents mTBI-induced changes in hippocampus gene expression and memory deficits in mice. Exp. Neurology, 239:170-82 (2013).

Menachem, A., Chapman, J., Deri, Y., **Pick, G.C.** and Katzav, A. Immunoglobulin mediated neuro-cognitive impairment: review and preliminary experimental findings. Clinical Reviews in Allergy & Immunology 45:62-68 (2013).

Woods, A.S., Colsch, B., Jackson, S.N., Post, J., Baldwin, C., Roux, A., Hoffer, B.J., Cox, B., Hoffer M., Rubovitch,V. **Pick, C.G.** J.A., Schultz. and Balaban, C. Gangliosides and ceramides changes in a mouse model of a blast induced traumatic brain injury. ACS Chemical Neuroscience 17:594-600 (2013).

Domachevsky, L., **Pick, C. G.,** Peled, N., Gomori, J.M., Abramovich, A. and Tempel-Brami, C. MRI Findings after Hyperbaric Induced Seizures. Epilepsy Research 105: 62-68 (2013).

Tweedie, D., Rachmany, L., Rubovitch, V., Lehrmann, E., Zhang, Y., Becker, K.G., Perez, E., Hoffer, B.J., **Pick, C.G.** and Greig, N.H. Physical- versus Blast-Traumatic Brain Injury: commonalities in cognitive dysfunction and hippocampal gene transcriptome in mice. Neurobiology of Disease 54:1-11 (2013).

Katzav, A., Ginsburg, D., Evert, T., Blank, M., **Pick, C.G.,** Shoenfeld, Y. and Chapman, J. Coagulopathy Triggered Autoimmunity: Experimental Antiphospholipid Syndrome in Factor V Leiden Mice. BMC Medical **11**:92 doi:10.1186/1741-7015-11-92 (2013).

Domachevsky, L., Rachmany, L., Barak, Y.,Rubovitch, V., Abramovich, A. and **Pick, CG.** Do hyperbaric oxygen-induced seizures cause a transient decrement in cognitive function. Neuroscience. 247: 328-334 (2013).

Rachmany, L., Tweedie, D., Rubovitch, V., Yu, Q., Wang, J.Y., Pick**, C.G.***, Greg, N.H*. Cognitive impairments accompanying rodent mild traumatic brain injury involve p53-dependent neuronal cell death and are ameliorated by the tetrahydrobenzothiazole PFT-a. PLoS One

28;8(11) (2013).

Schreiber, S., Hostovsky, A., Volis, I., Rubovitch, V. **Pick, CG**. The impact of antidepressant drugs on the antinociceptive properties of methadone in mice. J. Molecular Neuroscience 52: 598-604 (2014).

Benaroya-Milshtein, N., Apter, A., Yaniv, I., Oded, Y., Stern, B., Bengal, Y., Kodman, Y., Shemer, E., **Pick, G.C.,** Buchwald I. and Valevski A. Neuroimmunological function in parents of children suffering from cancer. Journal of Neural Transmission 121: 299-306 (2014).

Itsekson, Z., Shavit-Stein, E., Weissberg, I., Katzav,A., Rubovich, V., Friedman, A., **Pick C.G.** and J. Chapman. Increased Levels of Thrombin and its Receptor PAR-1 in Minimal Traumatic Brain Injury in Mice. J. Molecular Neuroscience 53: 87-95 (2014).

Greg, N.H, Tweedie, D. Rachmany, L., Yu, Q., Rubovitch, V, Schreiber,S., Chiang, Y-H. Hoffer, B.J., Lahiri, D., Kumar Sambamurti, K., Becker,R.E., **Pick, C.G.** Incretin mimetics as pharmacological tools to elucidate and as a new drug strategy to treat traumatic brain injury. Alzheimer's & Dementia 10: S62-S75 (2014).

Eakin, K., Baratz-Goldstein, R., **Pick, C.G.,** Zindel, O., Hoffer, B.J., Balaban, C., Hoffer, M.E. Lockwood, M. Miller, and Hoffer, B.J. J. Efficacy of N-Acetyl Cysteine in Traumatic Brain Injury. PLoS One 16;9(4) (2014).

May 24, 2014

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Assembly of the Superoxide-Generating NADPH Oxidase Complex in Health and Disease

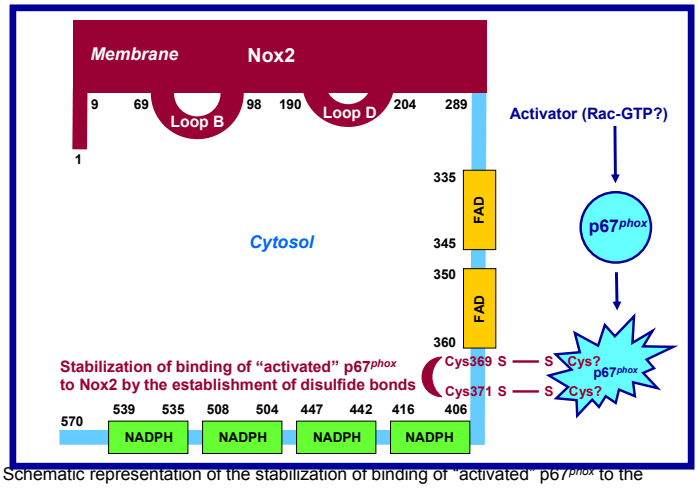
Position

Professor Emeritus, Sackler Faculty of Medicine

Research

We are studying the production of reactive oxygen species (ROS) by phagocytes. ROS are generated by an enzyme complex, known as the NADPH oxidase. Our group is responsible for many of the seminal advances in the biochemistry and molecular biology of the NADPH oxidase complex, including: the standard micro-assay for the measurement of ROS; the development of the first cell-free system of ROS production; the discovery of the cytosolic oxidase components; the discovery of the role of the small GTPase Rac in oxidase activation; the introduction of "peptide walking" to identify sites of protein-protein interaction, and the construction of chimeric cytosolic oxidase activators. The laboratory is fully equipped for the performance of advanced biochemical and molecular biology techniques.

The most recent interest of our group is focused on the mapping of the hotspots of interaction between the catalytic oxidase component Nox2 and the cytosolic activator $p67^{phox}$. We found that the dehydrogenase region of Nox2 (residues 288-570) contains a Cys-Gly-Cys (CGC) triad (residues 369-371), which serves as a binding site for $p67^{phox}$. This finding is based on a novel methodology, designed by us, in which we measure the binding of recombinant $p67^{phox}$ to an array of synthetic overlapping peptides covering the sequence of the dehydrigenase region of Nox2. Two Nox2 peptides which share the CGC triad, at their C- and N-termini, respectively, were found to bind $p67^{phox}$. “Mutating” either C369 or C371 to R resulted in loss of $p67^{phox}$ binding. Chemical reduction of CGC-containing peptides also led to loss of binding. Linking the two cysteines by a disulfide bond resulted in a marked increase in binding. We concluded that binding of $p67^{phox}$ to the catalytic component of the NADPH oxidase complex is redox regulated and involves the establishment of disulfide bonds between $p67^{phox}$ and Nox2. The CGC triad might have a double role by acting both as a protein disulfide isomerase (PDI) and by providing the cysteines for the establishment of disulfide bonds with $p67^{phox}$. This novel hypothesis rests on the evidence that the CGC motif mimics functionally and structurally the CGPC catalytic site of members of the PDI family. These findings have a key *in vivo* equivalent because a C369R mutation in human Nox2 causes Chronic Granulomatous Disease (CGD), an inborn defect resulting in the inability of phagocytes to produce ROS, leading to the failure to resist infections by bacteria and fungi.



Schematic representation of the stabilization of binding of "activated" p67^{phox} to the dehydrogenase region of Nox2, involving the establishment of disulfide bonds between cysteines 369 and 371 in Nox2 and yet unidentified cysteines in p67^{phox}

Schematic representation of the stabilization of binding of "activated" p67^{phox} to the dehydrogenase region of Nox2, involving the establishment of disulfide bonds between cysteines 369 and 371 in Nox2 and yet unidentified cysteines in p67.

Pick, E. When charge is in charge - "Millikan" for leukocyte biologists. *J. Leukoc. Biol.* 87, 537-540, 2010

Mizrahi, A., Berdichevsky, Y., Casey, P. J., and **Pick, E.** A prenylated p47^{phox}-p67^{phox}-Rac1 chimera is a quintessential NADPH oxidase activator. Membrane association and functional capacity. *J. Biol. Chem.* 285, 25485-25499, 2010

Hayee, B., Antonopoulos, A., Murphy, E. J., Rahman, F. Z., Sewell, G., Smith, B. N., McCartney, S., Furman, M., Hall, G., Bloom, S. L., Haslam, S. M., Morris, H. R., Boztug, K., Klein, C., Winchester, B., **Pick, E.**, Linch, D. C., Gale, R. E., Smith, A. M., Dell, A., and Segal, A. W. *G6PC3* mutations are associated with a major defect of glycosylation: A novel mechanism for neutrophil dysfunction. *Glycobiology* 21, 914-924, 2011**Pick, E.**, and Dahan, I. Strategies for identifying synthetic peptides to act as inhibitors of NADPH oxidases, or "All that you did and did not want to know about Nox inhibitory peptides". *Cell. Mol. Life Sc*i., 69:2283-305, 2011

Bosco, E., Marchioni, F., Kumar, S., Biesiada, J., Kordos, M., Szczur, K., Meller, J., Seibel, W., Mizrahi, A., **Pick, E.**, Filippi, M-D., and Zheng, Y. Rational design of small molecule inhibitors targeting the Rac GTPase - p67^{phox} signaling axis in inflammation. *Chem. Biol.,* 19:228-242, 2012

Dahan, I., Molshanski-Mor, S., and **Pick, E.** Inhibition of NADPH oxidase activation by peptides mapping within the dehydrogenase region of Nox2-A "peptide walking" study. *J. Leukoc. Biol.*, 91:501-515, 2012

Dahan, I., and **Pick, E**. Strategies for identifying synthetic peptides to act as inhibitors of NADPH oxidases, or "All that you did and did not want to know about Nox inhibitory peptides". *Cell. Mol. Life Sci*. 69, 2283-2305, 2012

Chapters and reviews

Pick, E., Cell-Free NADPH Oxidase Activation Assays - *"In Vitro Veritas",* In *Neutrophil Methods and Protocols*, 2nd Edition (Quinn, M. T., and DeLeo, F. R., eds), Methods Mol Biol. 2014;1124:339-403

Pick, E., Role of the Rho GTPase Rac in the activation of the phagocyte NADPH oxidase: Outsourcing a key task.. *Small GTPases*, 5(1), 2014

Grants

2009-2014 The pivotal encounter in NADPH oxidase activation – The molecular mechanisms of Nox2 – p67^{phox} interaction, Israel Science Foundation

2013-2017 Assembly of the phagocyte NADPH oxidase complex, Israel Science Foundation

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Investigating Normal and Deficient Visual Functions

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our research focuses on function, development and plasticity of perceptual interactions in normal and abnormal visual cortex. In our research, we have revealed a unique pattern of neural interactions, both excitatory and inhibitory, underlying global behavior involved in contour integration and texture segmentation. Specifically, a network of long-range intra-cortical connections supporting integration of collinear elements of the visual input is characterized beyond its spatial properties, especially emphasizing the temporal dynamics. Using of training protocols based on spatial and temporal masking paradigms is another area of interest. Studies on the effects of perceptual learning on visual function are conducted, including cases of abnormal visual development, considered as untreatable, such as amblyopia.

The laboratory combines techniques such as psychophysics, visual evoked potentials (VEP), event-related potentials (ERP) and eye movement recording. Computational modeling of neural networks of long-range interactions provides theoretical framework for our empirical findings.

Ongoing studies:

Clinical: Amblyopia, Major depression, ADHD, Pharmacological effects on vision, Vision in eye diseases

Development: Visual acuity, Contrast sensitivity, Lateral interactions, Visual crowding, Contour integration, Visual grouping

Learning: Learning to see faster, Improvement of normal vision, Improvement of impaired vision, Adaptation vs. learning, Visual rehabilitation, Refraction plasticity, Visual Performance

Visual performance: Night vision, Driving, Color blindness, Aging, Binocular vision, Visual masking, Peripheral vision, Tracking eye movements, Video game playing, Decision making, Visual stress, Fatigue.

Publications

Hirshler- Kotner, Y., **Polat, U**, Biegon, A., (2010) Intracranial electrode implantation produces regional neuroinflammation and memory deficits in rats. *Experimental Neurology* 222, 42-50.

Katz., G., Levkovitch-Verbin H., Triester G., Belkin M., Ilany J., **Polat U**. (2010) Mesopic Foveal Contrast Sensitivity is Impaired in Diabetic Patients Without Retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 248, 1699-1703

Lahav K., Levkovitch-Verbin H., Belkin M., Glovinsky Y., **Polat U**. (2011) Reduced foveal photopic and scotopic contrast sensitivity in glaucoma. *Arch Ophthalmol*. 129, 16-22.

Yehezkel O., Sterkin A., Sagi D., **Polat U**., (2010) Learning to adapt: Dynamics of readaptation to geometrical distortions. *Vision Res,* 50, 1550-1558.

Li R., **Polat U**., Scalzo F., Bavelier D. (2010) Reducing backward masking through action game training. *Journal of Vision* 10.

Cohen, Y., Belkin, M., Yehezkel, O., **Polat, U**. (2011) Dependency between Light Intensity and Refractive Development under Light-Dark Cycles. *Exp. Eye Res.* 92, 40-6.

Amiaz, R., Zomet, A., **Polat, U**. (2011) Excitatory Repetitive Transcranial Magnetic Stimulation over the Dorsolateral Prefrontal Cortex does not Affect Perceptual Filling-in in Healthy Volunteers. *Vision Res,* 51, 2071-2076.

Sterkin, A., Yehezkel, O., **Polat, U**., Learning to be fast: gain accuracy with speed (2011) *Vision Res,* 50,1550-1558

Lev, M., **Polat, U**. Collinear facilitation and suppression at the periphery (2011) *Vision Res,* 51:2488-2588.

Polat, U., Schor, C.,Tong, JL., Zomet, A., Lev, M., Yehezkel, O., Sterkin, A., Levi, D. (2012) Training the brain to overcome the effect of aging on the human eye. *Scientific Reports*, 2.

Cohen, Y., Peleg, E., Belkin, M., **Polat, U**., Solomon, A., (2012) Ambient Illuminance, retinal dopamine release and refractive development in chicks. *Exp. Eye Res.* 103:33-40.

Grants

2010-2014 ISF From local to global: a spatio-temporal theory for visual integration

May 24, 2014

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Molecular Mechanisms of Drugs for Neuropsychiatric Disorders

Positions

Professor, Sackler Faculty of Medicine
Dr. Miriam and Sheldon G. Adelson Chair in Biology of Addictive Diseases
Head, Varda and Shalom Yoram Institute for Human Genome Research

Research

Main projects in the lab include:

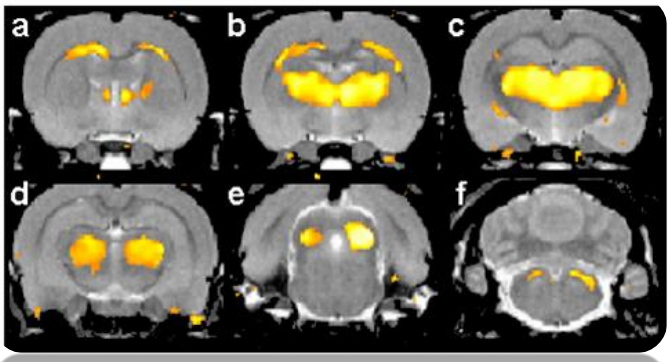
1. Presynaptic monoamine transportes and the vesicular monoamine transporter as targets for neuropsychiatric drugs.

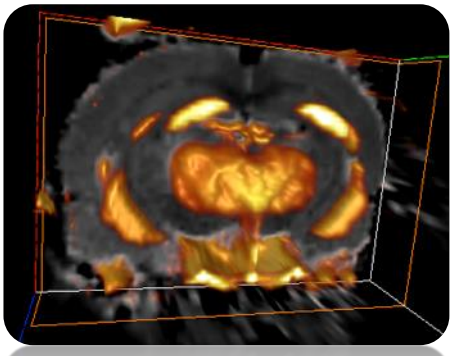
2. Anxiolytic effects of new herbal treatment: mice models of anxiety and biochemical studies.

3. Quaternary serotonin-reuptake inhibitors as novel anti-platelet drugs.

4. Methylphenidate (Ritalin): abuse potential and long-term effects.

5. Neuronal rescue by Rasagiline (MAO-B inhibitor) in thiamine deficiency.

A 

B 

(A) Six representative coronal slices of T_2-weighted MR images from untreated thiamine-deficient rats on day 14. The yellow areas represent abnormalities characterized by a significant increase in signal intensity that occurred on day 14 as compared to day 0 (ANOVA, $p<0.01$). (a,b) thalamus and corpus callosum; (c,d) thalamus; (e) inferior colliculi; (f) superior cerebellar peduncle. (B) A Three-dimensional Maximum intensity projection (MIP) image of the T_2 maps, demonstrating the damaged thiamine-deficient areas on day 14.

Publications

Dror, V., Eliash, S., **Rehavi, M**., Assaf, Y., Biton I.E., Fattal-Valevsky, A. (2010). Neurodegeneration in thiamine deficient rats- A longitudal MRI study. Brain Res. 1308, 176-184.

Morag, A., Kirchheiner, J., **Rehavi, M**., and Gurwitz, D. (2010). Human lymphoblastoid cell line panels: novel tools for assessing shared drug pathways. Pharmacogenomics 11, 327-340.

Simchon, Y., Weizman, A., and **Rehavi, M**. (2010). The effect of methylphenidate administration on presynaptic dopaminergic parameters in a rat model for ADHD. Eur. Neuropsychopharmacol. 20, 714-720.

Valevsky, A., Pickholtz, E., Roz, N., Weizman, A., and Rehavi, M. (2010). Lack of modulatory effect of short-term repeated electroconvulsive therapy on platelet vesicular monoamine transporter 2 (VMAT2) in depressed patients. J.Neural. Transm. 117, 881-885.

Bismuth-Evenzal, Y., Roz, N., Gurwitz, D., and **Rehavi, M**. (2010). N-methyl- Citalopram: A quaternary selective serotonin uptake inhibitor. Biochem. Pharmacol. 80, 1546-1552.

Morag A, Pasmanik-Chor M, Oron-Karni V, **Rehavi M**, Stingl JC, Gurwitz D. (2011). Genome-wide expression profiling of human lymphoblastoid cell lines identifies CHL1 as a putative SSRI antidepressant response biomarker. Pharmacogenomics. 12:171-84.

Zalsman G, **Rehavi M**, Roz N, Laor N, Weizman A, Toren P. (2011). Altered affinity of the platelet vesicular monoamine transporter 2 to dihydrotetrabenazine in children with major depression. J Neural Transm. 118:1383-7.

Bismuth-Evenzal Y, Gonopolsky Y, Gurwitz D, Iancu I, Weizman A, **Rehavi M**. (2012). Decreased serotonin content and reduced agonist-induced aggregation in platelets of patients chronically medicated with SSRI drugs. J Affect Disord. 2012;136(1-2):99-103

Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, Shomron N, **Rehavi M**, Stingl JC, Gurwitz D. Genome-wide miRNA expression profiling of human lymphoblastoid cell lines identifies tentative SSRI antidepressant response biomarkers. Pharmacogenomics. 2012;13:1129-39.

Doron R, Lotan D, Rak-Rabl A, Raskin-Ramot A, Lavi K, **Rehavi M**. Anxiolytic effects of a novel herbal treatment in mice models of anxiety. Life Sci. 2012 ;90(25-26):995-1000

Oved K, Morag A, Pasmanik-Chor M, **Rehavi M**, Shomron N*, Gurwitz D*. Genome-wide expression profiling of human lymphoblastoid cell lines implicates integrin beta-3 in the mode of action of antidepressants. Transl Psychiatry. 2013; 3:e313.

Doron R, Lotan D, Einat N, Yaffe R, Winer A, Marom I, Meron G, Kately N, **Rehavi M** (2014) A novel herbal treatment reduces depressive-like behaviors and increases BDNF levels in the brain of stressed mice. Life Sci. 94(2):151-7

Dror V, **Rehavi M**, Biton IE, Eliash S. (2014) Rasagiline prevents neurodegeneration in thiamine deficient rats-A longitudinal MRI study. Brain Res. 1557:43-54

Kornilov P, Peretz A, Lee Y, Son K, Lee JH, Refaeli B, Roz N, **Rehavi M**, Choi S, Attali B. (2014) Promiscuous gating modifiers target the voltage sensor of Kv7.2, TRPV1, and Hv1 cation channels. FASEB J (in press)

Doron R, Lotan D, Versano Z, Benatav L, Franko M, Armoza S, Kately N, **Rehavi M** (2014) Escitalopram or novel herbal mixture treatments during or following exposure to stress reduce anxiety-like behavior through corticosterone and BDNF modifications. PLoS One 9(4):e91455

Grants

2011-2015 Novel herbal treatment for anxiety disorder, Israel Science Foundation

May 25, 2014

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The Wnt Signaling Pathway and Colorectal Cancer

Position

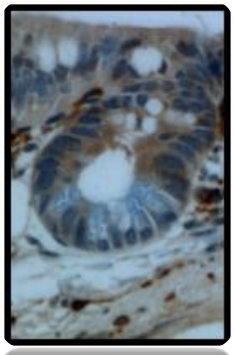
Senior Lecturer, Sackler Faculty of Medicine

Research

The Wnt signaling pathway is involved in virtually every aspect of human development, as well as in adult homeostasis. Hyperactivation of this pathway has been linked to a wide range of cancers and especially colorectal cancer. Our aim is to understand the molecular events underlying Wnt signal transduction, as well as develop novel therapeutic strategies to fight colorectal cancer.

Current projects in the lab include:

1. Identifying and characterizing new Wnt signaling components.
2. Developing new anti-colorectal cancer treatment strategies.



Carboxypeptidase E (CPE), a novel Wnt inhibitor, is excluded from the colonic crypt bottom.

Publications

Zilberberg, A., Lahav, L., and **Rosin-Arbesfeld, R**. Aminoglycoside antibiotics treatment restores the function of the APC tumour suppressor in colorectal cancer cells. Gut. 4, 496-507, 2010.

Chay-Koren, A., Caspi, M., and **Rosin-Arbesfeld, R**. The EDD E3 ubiquitin ligase ubiquitinates and up-regulates beta-catenin. Mol Biol Cell. 22, 399-411. 2011.

Raviv, Z., Zilberberg, A., Cohen, S., Reischer-Pelech, D., Horrix, C., Berger, M.R., **Rosin-Arbesfeld, R**. and Flescher, E. Methyl jasmonate downregulates surviving expression and sensitizes colon carcinoma cells towards TRAIL-induced cytotoxicity. Br J Pharmacol. 10, 1476-5381, 2011.

Shalev M, Kandasamy J, Skalka N, Belakhov V, **Rosin-Arbesfeld R**, Baasov T. Development of generic immunoassay for the detection of a series of aminoglycosides with 6'-OH group for the treatment of genetic diseases in biological samples. J Pharm Biomed Anal. 75:33-40, 2013

Skalka N, Caspi M, Caspi E, Loh YP, **Rosin-Arbesfeld R**. Carboxypeptidase E: a negative regulator of the canonical Wnt signaling pathway. Oncogene. 32:2836-47, 2013

Dovrat S, Caspi M, Zilberberg A, Lahav L, Firsow A, Gur H, **Rosin-Arbesfeld R**. 14-3-3 and β-catenin are secreted on extracellular vesicles to activate the oncogenic Wnt pathway. Mol Oncol. pii: S1574-7891(14)00059-3, 2014.

Naumov I, Zilberberg A, Shapira1 S, Avivi1 D, Kazanov1 D, **Rosin-Arbesfeld R**, Arber N, Kraus S. CD24 knockout prevents colorectal cancer in chemically induced colon carcinogenesis and in APC_{Min} /CD24 double knockout transgenic mice. Int J Cancer. 2014 Feb 5. doi: 10.1002/ijc.28762.

Grants

2011 – 2015 The US-Israel Binational Scientific Foundation (BSF)

May 24, 2014

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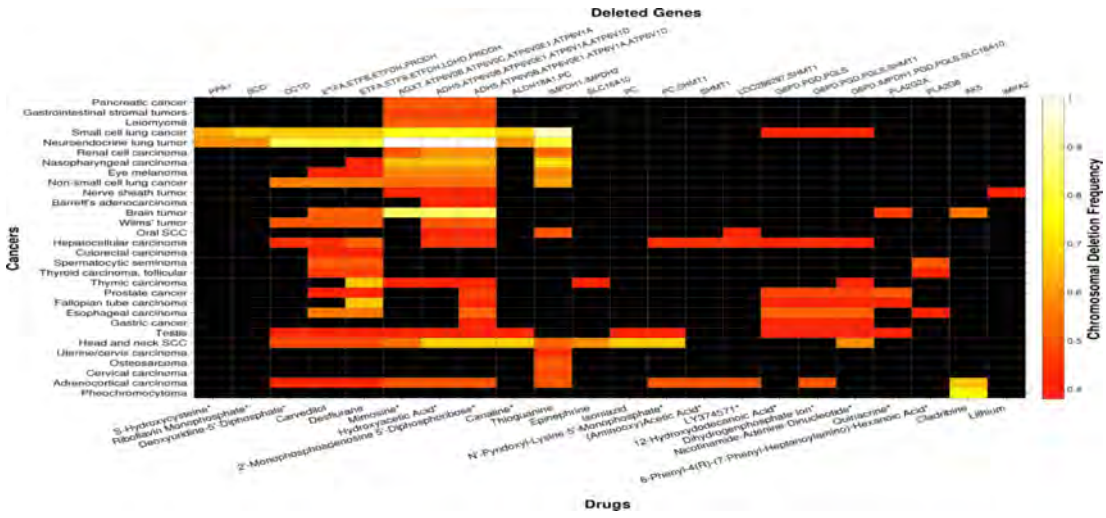
Computational Analysis of Metabolic Alterations in Cancer and Aging

Positions

Professor, Sackler Faculty of Medicine
Co-chair, TAU Bioinformatics Training Program
Joint appointment, Blavatnik School of Computer Science

Research

Our research focuses on computational biology with an emphasis on metabolic modeling. Our lab is currently working on the development and study of large-scale models of metabolism in a variety of human tissues, in both healthy and disease states. Our efforts are focused on two main subjecst: (1) We have generated the first model of cancer metabolism. This development has paved the way for the first large-scale computational search for new and selective metabolic drug targets in cancer (Nature/MSB 2011) – some which are already under various stages of further experimental testing and validation (Nature 2011). (2) We have recently developed a new approach for inferring drug target for extending life span in humans (anti-aging), which are currently under experimental investigation. Taken together, these studies and others ongoing in the lab offer new ways for harnessing computers to advance our understanding of metabolically-related human disorders, and further our ability to diagnose and treat them in a rationale-designed manner.



Metabolic drug targets (x-axis) that are predicted to selectively kill cancer cells of different types (y-axis).

Publications

Goldstein I, Yizhak K, Madar S, Goldfinger N, **Ruppin E**, Rotter V. p53 promotes the expression of gluconeogenesis-related genes and enhances hepatic glucose production. Cancer Metab.1(1):9, 2013.

Wagner A, Zarecki R, Reshef L, Gochev C, Sorek R, Gophna U, **Ruppin E**. Computational evaluation of cellular metabolic costs successfully predicts genes whose expression is deleterious. Proc Natl Acad Sci USA. 110(47):19166-71, 2013

Y. Waldman, T. Geiger, **E. Ruppin**. A genome-wide systematic analysis reveals different and predictive proliferation expression signatures of cancerous vs. non-cancerous cells. PLoS Genetics, 9:e1003806, 2013

K. Yizhak, O. Gabay, H. Cohen, **E. Ruppin**. Model-based identification of drug targets that revert disrupted metabolism and its application to aging. Nature Comm, **4**:2632, 2013.

G. Romano, Y. Harari, T. Yehuda, A. Podhorzer, L. Rubinstein, R. Shamir, A. Gottlieb, Y. Silberberg, D. Pe'er, **E. Ruppin**, R. Sharan, M. Kupiec. Environmental stresses disrupt telomere length homoestasis. PLoS Genetics, 9(9):e1003721, 2013

A. Gottlieb, G.Y. Stein, **E. Ruppin**, R.B. Altman, R. Sharan. A method for inferring medical diagnoses from patients similarities. BMC Medicine, 2013, 11:194.

T. Tuller, S. Atar, **E. Ruppin**, M. Gurevich, A. Achiron. Common and specific signatures of gene expression and protein-protein interactions in autoimmune diseases. Genes and Immunity, 14, 67-82 (2013).

I. Goldstein, K. Yizhak, S. Madar, N. Goldfinger, **E. Ruppin**, V. Rotter. p53 promotes the expression of gluconeogenesis-related genes and enhances hepatic glucose production. Cancer & Metabolism 2013, 1:9 (2013)

L. Jerby, L. Wolf, C. Denkert, G.Y. Stein, M. Hilvo, M. Oresic, T. Geiger, and **E. Ruppin**. Metabolic Associations of Reduced Proliferation and Oxidative Stress in Advanced Breast Cancer. Cancer Research, 72, 5712-5720 (2012)

L Jerby, and **E. Ruppin**. Predicting Drug Targets and Biomarkers of Cancer via Genome-Scale Metabolic Modeling. Clinical Cancer Research, 18, 5572-5584 (2012)

S. Stempler, **E. Ruppin**. Analyzing Gene Expression from Whole Tissue vs. Different Cell Types Reveals the Central Role of Neurons in Predicting Severity of Alzheimer's Disease. PLoS One, 7: e45879 (2012)

G.Y. Stein, N. Yosef, H. Reichman, J. Horev, A. Laser-Azogui, A. Berens, J. Resau, **E. Ruppin**, R. Sharan, and I. Tsarfaty. Met Kinetic Signature Derived from the Response to HGF/SF in a Cellular Model Predicts Breast Cancer Patient Survival. PLoS One, 7: e45969 (2012)

L. Lobel, S. Nadejda, I. Borovok, **E. Ruppin**, and A. Hershkovitz. Integrative Genomic Analysis Identifies Isoleucine and CodY as Regulators of Listeria monocytogenes Virulence. *PLoS Genet*, 8: e1002887 (2012)

O. Magger, Y.Y. Waldman, **E. Ruppin**, and R. Sharan. Enhancing the Prioritization of Disease-Causing Genes through Tissue Specific Protein Interaction Networks. PLoS Comp Biol 8:e1002690 (2012)

S. Stempler, Y.Y Waldman, L. Wolf, and **E. Ruppin**. Hippocampus neuronal metabolic gene expression outperforms whole tissue data in accurately predicting Alzheimer's disease progression. Neurobiol Aging, 33, 2230.e13 (2012)

A. Gottlieb, G.Y. Stein, Y. Oron, **E. Ruppin**, and R. Sharan. INDI: a computational framework for inferring drug interactions and their associated recommendations. Mol Syst Biol, 8, 592 (2012)

L. Vardi, **E. Ruppin**, and R. Sharan: A Linearized Constraint-Based Approach for Modeling Signaling Networks. J Comp Biol 19: 232-40 (2012).

Y. Silberberg, A. Gottlieb, M. Kupiec **E. Ruppin**, and R. Sharan: Large-Scale Elucidation of Drug Response Pathways in Humans. J Comp Biol 19: 163-74 (2012).

T. Ben-Shitrit , N. Yosef, K. Shemesh, R. Sharan, **E. Ruppin** and M. Kupiec: Systematic Identification of Gene Annotation Errors in the widely used Yeast Mutation Collections. Nature Methods 9: 373-U82 (2012).

S. Mintz-Oron, S. Meir, S. Malitsky, **E. Ruppin**, A. Aharoni and T. Shlomi: Reconstruction of Arabidopsis Metabolic Network Models Accounting for Subcellular Compartmentalization and Tissue-Specificity. Proc Natl Acad Sci USA 109: 339-44 (2012)

Selection for translation efficiency on synonymous polymorphisms in recent human evolution. (Y. Waldman, T. Tuller*, A. Keinan*, **E. Ruppin***), Genome Biology & Evolution, doi: 10.1093/gbe/evr076, 2011

Haem oxygenase is synthetically lethal with the mitochondrial tumour suppressor fumarate hydratase. (C. Frezza, L. Zheng, O. Folger, K. Rajagopalan, E.D. MacKenzie, L. Jerby, M. Micaroni, B. Chaneton, J. Adam, A. Hedley, G. Kalna, I.P.M. Tomlinson, P.J. Pollard, D.G. Watson, R.J. Deberardinis, T. Shlomi*, **E. Ruppin***, E. Gottlieb), Nature, 477:225-228, 2011.

Global map of physical interactions among differentially expressed genes in multiple sclerosis relapses and remissions. (T. Tuller, S. Atar, **E. Ruppin**, M. Gurevich, A. Achiron) Human Molecular Genetics, 20:3606-3619, 2011.

Genome-scale analysis of translation elongation with a ribosomal flow model. (S. Reuveni,i I. Meilijson, M. Kupiec, **E. Ruppin**, T. Tuller), PLoS Computational Biology, 7: e10021272011, 2011.

Predicting selective drug targets in cancer through metabolic networks. (O. Folger, L. Jerby, C. Frezza, E. Gottlieb, E. Ruppin*, T. Shlomi*), Molecular Systems Biology (MSB), 2011.

PREDICT: A method for inferring novel drug indications with application to personalized medicine, (A. Gottlieb, G.Y. Stein, **E. Ruppin**, R. Sharan), Molecular Systems Biology (MSB), 7, 490, 2011.

Metabolic modeling of endosymbiont genome reduction on a temporal scale.(K. Yizhak, T. Tuller, B. Papp, E. Ruppin), Molecular Systems Biology (MSB), 7, article number 479, 2011.

Gene expression in the rodent brain is associated with its regional connectivity. (L. Wolf, C. Goldberg, N. Manor, R. Sharan, **E. Ruppin**), PLoS Computational Biology, 7, e1002040, 2011.

Genome-scale metabolic modeling elucidates the role of proliferative adaptation in causing the Warburg effect. (T. Shlomi, T. Benyamini, E. Gottlieb, R. Sharan, **E. Ruppin**), PLoS Computational Biology, 7, e1002018, 2011

Associations between translation efficiency and horizontal gene transfer within microbial communities. (T. Tuller, Y. Girshovich, Y. Sella, A. Kreimer, S. Freilich, M. Kupiec, U. Gophna, **E. Ruppin**), Nucleic Acids Research, 39: 4743-475, 2011.

iMAT: an integrative metabolic analysis tool. (H. Tzur, **E. Ruppin***, T. Shlomi*), Bioinformatics, doi: 10.1093/bioinformatics.btq602.

Combining drug and gene similarity metrics for drug-target elucidation. (L. Perlman, A. Gottlieb, N. Atias, **E. Ruppin**, R. Sharan), Journal of Computational Biology, DOI: 10.1089/cmb.2010.0213.

A novel HMM-based method for detecting enriched transcription factor binding sites reveals RUNX3 as a potential target in pancreatic cancer biology. (L. Levkovitz, N. Yosef, M.C. Gershgoren, **E. Ruppin**, R. Sharan, Y. Oron), PLoS One, DOI: 10.1371/journal.pone.0014423.

Transcriptional regulation by CHIP/LDB complexes. (R. Bronstein, L. Levkovitz, N. Yosef, M. Yanku, **E. Ruppin**, R. Sharan, H. Westphal, B. Oliver, D. Segal), PLoS Genetics, 6, e10001063, 2010.

Computational reconstruction of tissue-specific metabolic models: Application to human liver metabolism. (L. Jerby, T. Shlomi*, **E. Ruppin***), Molecular Systems Biology (MSB), 6, 401, 2010

MuD: an interactive web-server for the prediction of non-neutral using protein structural data. (G. Wainreb, Y. Bromberg, H. Ashkenazy, A. Starovolsky-Shitrit, T. Haliloglu, **E. Ruppin**, K. Avraham, B. Rost, N. Ben-Tal), Nucleic Acids Research, 38:W523-8, 2010.

Reconstructing ancestral genomic sequences by co-evolution: formal definitions, computational issues and biological examples. (T. Tuller, H. Birin, M. Kupiec, **E. Ruppin**), Journal of Computational Biology (JCB), 17(9), 1327-1344, 2010.

Cooperation and cheating in exoenzyme production by microorganisms -- theoretical analysis in view of biotechnological applications. (S. Schuster, J.U Kreft, N. Brenner, F. Wessely, G. Theiben, **E. Ruppin, A**. Schroeter), Biotechnology Journal, 5, 2010.

Flux balance analysis accounting for metabolite dilution. (T. Benyamini, Ori Folger, **E. Ruppin**, T. Shlomi), Genome Biology, 11:R43, 2010.

Integrating quantitative proteomics and metabolomics with a genome-scale metabolic network model. (K. Yizhak, T. Benyamini, W. Liebermeister, **E. Ruppin**, T. Shlomi), Bioinformatics, 26, ISMB 2010.

The large scale organization of the bacterial network of ecological co-occurence interactions. (S. Freilich, A. Kreimer, I. Meilijson, U. Gophna, R. Sharan, **E. Ruppin**), Nucleic Acids Research (NAR), 2010, doi:10.1093/nar/gkq118.

Translation efficiency in humans: tissue specificity, global optimization and the differences between developmental stages. (Y. Waldman, T. Tuller, T. Shlomi, R. Sharan, **E. Ruppin**), Nucleic Acids Research, 38, 2010.

A systems level strategy for analyzing the cell death network: Implication in exploring the apoptosis/autophagy connection. (E. Zalckvar, N. Yosef, S. Reef, Y. Ber, A. Rubinstein, R. Sharan, **E. Ruppin**, A. Kimchi), Cell Death and Differentiation, 2010.

Translation efficiency is determined by both codon bias and folding energy. (T. Tuller, Y. Waldman, M. Kupiec, **E. Ruppin**), Proceedings of the National Academy of Sciences, 2010.

Decoupling environmental-dependent and independent genetic robustness across bacterial species. (S. Freilich*, A. Kreimer*, E. Borenstein, U. Gophna, R. Sharan, **E. Ruppin**; PLoS Computational Biology, 6, e1000690, 2010.

Associating genes and protein complexes with disease via network propagation. (O. Vanunu, O. Magger, **E. Ruppin**, T. Shlomi, R. Sharan), PLoS Computational Biology, 6: e1000641, 2010.

Network-free prediction of knockout effects in yeast. (T. Peleg, N. Yosef, E. Ruppin, R. Sharan), PLoS Computational Biology, 6: e1000635, 2010.

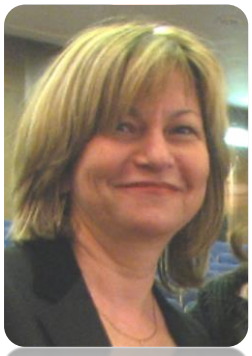
Review

M. Oberhardt*, K. Yizhak*, E. Ruppin. Metabolically re-modeling the drug pipeline. Curr. Opin. in Pharmacology, http://dx.doi.org/10.1016/j.coph.2013.05.006, 2013

Grants

2011-2014	Ministry of Science and Technology (MOST) grant for studying plant metabolism
2011-2015	US-Israeli Binational Science Foundation (BSF) for studying human host-pathogen metabolic interactions in the gut

May 24, 2014



Prof. Ronit Sagi-Eisenberg, Ph.D.

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Molecular Basis of Allergic Diseases: Genomic and Functional Analyses

Positions

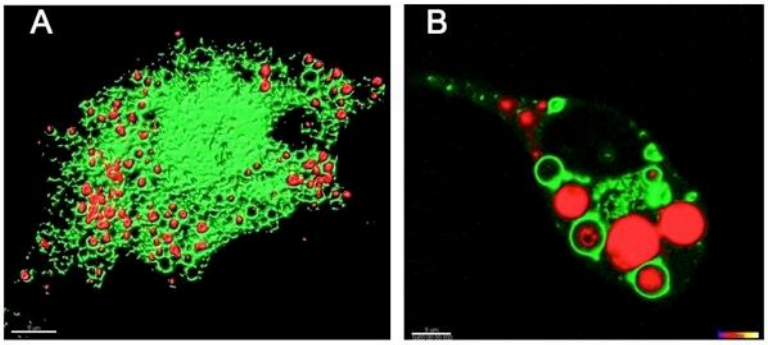
Professor, Sackler Faculty of Medicine
Chair, Scholarship Committee, Graduate School of Medicine

Research

Our primary interest is the molecular basis of allergic and allergy related diseases, including skin allergy and asthma. Specifically, we explore the mechanisms underlying release of allergic (i.e. histamine) and inflammatory (i.e. cytokines) mediators from activated mast cells. Our research focuses on deciphering the signaling networks that link mast cell activation with mediator release and characterization of genes that could serve as cellular targets for the future development of anti allergic and asthma drugs. To this end, we combine functional genomics and phenotype driven screens of mast cells, activated by multiple stimuli, in order to recapitulate human pathophysiologic conditions. Research methods used include confocal microscopy in live and fixed cells; gene cloning; quantitative RT-PCR, pull down-assay; mass spectrometry, and bioinformatics.

Current projects in the lab include:

1) Exploring the genetic connections between the size of the mast cell secretory granules and mastocytosis.
2) Mast cells and cancer- the good, the bad and the ugly.
3) Decoding the Rab networks that control mast cell function.



Cell imaging of mast cells (RBL-2H3 mast cell line), which were co-transfected with NPY-mRFP (red), as reporter for the secretory granules, and GFP-tagged wild type (A) or active mutant (B) of the small GTPase Rab5A (green) reveals a dramatic effect of this Rab active mutant on the secretory granules size.

Publications

Azouz, N.P., Zur, N., Efergan, Ohbayashi, N., Fukuda, M., Amihai, D., Hammel, I., Rothenberg, ME and **Sagi-Eisenberg, R.** Rab5 is a novel regulator of mast cell secretory granules: impact on size, cargo and exocytosis. J. Immunol. 192(9):4043-53 (2014)

Bar-Gill-Benado, A., Efergan, A., Seger, R., Fukuda, M., and **Sagi-Eisenberg R.** The extra-cellular signal regulated kinases ERK1 and ERK2 segregate displaying distinct spatiotemporal characteristics in activated mast cells. Biochim Biophys Acta. 1833, 2070-2082, (2013).

Bernstein-Molho R., Kollender, Y., Issakov, J., Bickels, J., Dadia S., Flusser, G., Meller, I., **Sagi-Eisenberg. R**. and Merimsky O. Clinical activity of mTOR inhibition in combination with cyclophosphamide in the treatment of recurrent unresectable chondrosarcomas. Cancer Chemother Pharmacol. 70, 855-860, (2012).

Azouz NP, Matsui, T., Fukuda, M. and **Sagi-Eisenberg, R.** Decoding the regulation of mast cell exocytosis by networks of Rab GTPases. J Immunol. 189, 2169-2180. (2012).

Gorzalczany Y, Gilad Y, Amihai D, Hammel I, **Sagi-Eisenberg R**, and Merimsky O. Combining an EGFR directed tyrosine kinase inhibitor with autophagy-inducing drugs: a beneficial strategy to combat non-small cell lung cancer. Cancer Lett. 310:207-215. (2011).

Baram D, Dekel O, Mekori YA, and **Sagi-Eisenberg R**. Activation of mast cells by trimeric G protein Gi3; coupling to the A3 adenosine receptor directly and upon T cell contact. J Immunol. 184:3677-3688. (2010).

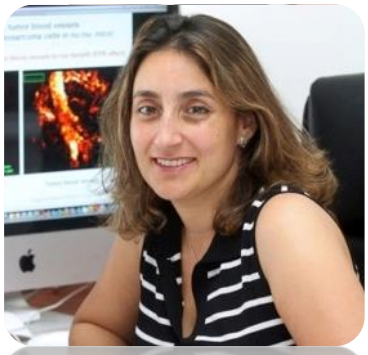
Review

Rudich N, Ravid K, and **Sagi-Eisenberg R**. Mast cell adenosine receptors function: a focus on the A3 adenosine receptor and inflammation. Front Immunol. 3:134. (2012).

Grants

2012-2015 The Israel Science Foundation**,** Dissecting the molecular mechanisms underlying mast cell exocytosis; new insights provided by the small GTPase Rab5

May 24, 2014



Prof. Ronit Satchi-Fainaro, Ph.D.

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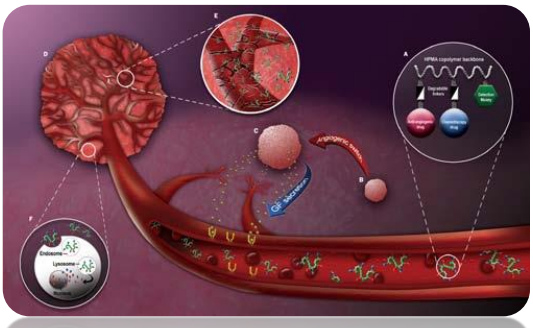
Angiogenic Switch Using Rationally-Designed Theranostic Nanomedicines

Positions

Associate Professor, Sackler Faculty of Medicine
President, Israeli Chapter of the Controlled Release Society (ICRS)
Chair, Tel Aviv University Institutional Animal Care and Use Committee (IAUCUC)
Faculty Coordinator, Postgraduate Program in Nanotechnology
Editorial board member, *Advanced Drug Delivery Reviews*
Co-Editor-in-Chief, *Clinical Cancer Drugs*

Research

Our research interests include investigations relating to tumor biology, tumor dormancy, mechanism of action of angiogenesis inhibitors, self-assembly of polymeric architectures and novel approaches to target cancer. Throughout, we have maintained an interest in understanding the biological rationale for the design of polymer therapeutics suitable for transfer into clinical testing. Our primary interests are the molecular basis of tumor angiogenesis and the rational design of polymer therapeutics. Our research includes identification and characterization of genes and microRNAs associated with the switch from a dormant avascular tumor phenotype to a fast-growing angiogenic tumor in human cancers and their corresponding mouse models. We focus on the design and characterization of novel drug delivery platforms, including dendrimers and hyperbranched polymer–based nanoparticles, and the design of highly-selective targeting molecules integrating biology, chemistry, protein engineering, computational approaches, material sciences and nanotechnology to selectively guide drugs into pathological sites. Our vision is that novel approaches to target anticancer, anti-angiogenic drugs, miRNA and siRNAs to endothelial and tumor cells to potentially treat angiogenesis-dependent diseases could transform cancer into a chronically-manageable disease. Research methods used include sequencing, gene cloning, quantitative RT-PCR, immunofluorescence, cell culture, scanning electron microscopy, mass spectrometry, NMR, HPLC, in situ hybridization, bioinformatics, polymer chemistry, molecular imaging, angiogenesis assays, animal models of cancer (human xenografts in mice, syngeneic and transgenic mice models), pharmacokinetics and pharmacodynamics.



The angiogenic switch and the use of nanomedicines such as Polymer Therapeutics to treat angiogenic tumors. The enhanced permeability and retention (EPR) effect allows nanoconjugates to extravasate through the tumor leaky vessels, accumulate in the tumor bed selectively and internalize into the tumor epithelial and tumor endothelial cells via endocytosis.

Publications

Weinstain R*, Segal E*, **Satchi-Fainaro R** and Shabat D, Real-time monitoring of drug release, *Chemical Communications (Camb)* 46, 553-555 (2010).

Ofek P, Fischer W, Calderón M, Haag R and **Satchi-Fainaro R**, In vivo delivery of small interfering RNA to tumors and their vasculature by novel dendritic nanocarriers, *FASEB Journal*, 24, 3122-3134 (2010).

Polyak D, Ryppa C, Ofek P, Licha K, Many A, Kratz F and **Satchi-Fainaro R**, Development of PEGylated doxorubicin-E-[c(RGDfK)$_2$] conjugate for integrin-targeted cancer therapy, *Polymers for Advanced Technology*, 22, 103–113 (2011).

Marom H, Miller K, Bechor-Bar Y, Tsarfaty G, **Satchi-Fainaro R*** and Gozin M*, Toward development of targeted nonsteroidal antiandrogen-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-gadolinium complex for prostate cancer diagnostics., *Journal of Medicinal Chemistry*, 53, 6316-6325 (2010). *Corresponding authors.

Ofek P, Miller K, Eldar-Boock A, Polyak D, Segal E and **Satchi-Fainaro R**, Rational design of multifunctional polymer therapeutics for cancer theranostics, Special Theme issue: Polymer Therapeutics as novel nanomedicines, *Israel Journal of Chemistry*, 50, 185-203 (2010).

Eldar-Boock A, Miller K, Sanchis J, Lupu R, Vicent MJ and **Satchi-Fainaro R**, Integrin-assisted drug delivery of nano-scaled polymer therapeutics bearing paclitaxel, *Biomaterials,* 32, 3862-3874 (2011).

Miller K, Eldar-Boock A, Polyak D, Segal E, Benayoun L, Shaked Y and **Satchi-Fainaro R**, Antiangiogenic Antitumor Activity of HPMA Copolymer-Paclitaxel-Alendronate Conjugate on Breast Cancer Bone Metastasis Mouse Model, *Molecular Pharmaceutics*, 8,1052-1062 (2011).

Clementi C, Miller K, Mero A, **Satchi-Fainaro R** and Pasut G, Dendritic Poly(ethylene glycol) Bearing Paclitaxel and Alendronate for Targeting Bone Neoplasms, *Molecular Pharmaceutics*, 8:1063-1072 (2011).

Segal E, Pan H, Benayoun L, Kopečková P, Shaked Y, Kopeček J and **Satchi-Fainaro R**, Enhanced anti-tumor activity and safety profile of targeted nano-scaled HPMA copolymer-alendronate-TNP-470 conjugate in the treatment of bone malignances, *Biomaterials,* 32:4450-4463 (2011).

Scomparin A, Salmaso S, Bersani S, **Satchi-Fainaro R**, Caliceti P, Novel folated and non-folated pullulan bioconjugates for anticancer drug delivery, *European Journal of Pharmaceutical Sciences*, 42, 547-558 (2011).

Karton-Lifshin N, Segal E, Omer L, Portnoy M, **Satchi-Fainaro R***, Shabat D*, A Unique Paradigm for a Turn-ON Near-Infrared Cyanine-Based Probe: Non-Invasive Intravital Optical Imaging of Hydrogen Peroxide, *Journal of the American Chemical Society (JACS)*, 133, 10960-10965 (2011). *Corresponding authors.

Fante C, Eldar-Boock A, **Satchi-Fainaro R**, Osborn H, Greco F, Synthesis and biological evaluation of a polyglutamic acid-dopamine conjugate: a new anti-angiogenic agent, *Journal of Medicinal Chemistry*, 54, 5255-5259 (2011).

Satchi-Fainaro R*, Ferber S*, Segal E, Ma L, Dixit N, Ijaz A, Hlatky L, Abdollahi A, Almog A, Prospective identification of glioblastoma cells generating dormant tumors, *PLoS One,* 7: e44395. (2012).

Herzog IM, Green KD, Berkov-Zrihen Y, Feldman M, Vidavski RR, Eldar-Boock A, **Satchi-Fainaro R**, Eldar A, Garneau-Tsodikova S and Fridman M, 6"-Thioether tobramycin analogues: Towards selective targeting of bacterial membranes, *Angewandte Chemie*, **51**, 5652-5656 (2012)**.**

Benayoun L, Gingis-Velitski S, Voloshin T, Segal E, Segev R, Munster M, Bril R, **Satchi-Fainaro R**, Scherer SJ, Shaked Y, Tumor-initiating cells of various tumor types exhibit differential angiogenic properties and react differently to antiangiogenic drugs, *Stem Cells* -Cancer Stem Cells, 30, 1831-41 (2012).

Benayoun L, Schaffer M, Brill R, Gingis-Velitski S, Segal E, Nevelsky A, **Satchi-Fainaro R**, Shaked Y, Porfimer-sodium (Photofrin-II) in combination with ionizing radiation inhibits tumor initiating cell proliferation and improves glioblastoma treatment efficacy, *Cancer Biology & Therapy*, 31;14(1) (2012). (Cover feature).

Miller K, Clementi C, Polyak D, Eldar-Boock A, Benayoun L, Barshack I, Shaked Y, Pasut G and **Satchi-Fainaro R**, Anti-angiogenic activity of polyethyleneglycol-based paclitaxel and alendronate for the treatment of breast cancer bone metastases, *Biomaterials*, 34(15): 3795–3806 (2013).

Chuderland D, Ben-Ami I, Kaplan-Kraicer R, Grossman H, Komsky A, **Satchi-Fainaro R**, Eldar-Boock A, Ron-El R, Shalgi R, Hormonal regulation of pigment epithelium derived factor (PEDF) in granulosa cells, *Molecular Human Reproduction*, 19(2), 72-81 (2013).

Ferber S, Tiram G and **Satchi-Fainaro R**, Evaluation of microvessels density, morphology and functionality in matrigel plugs by non-invasive intravital microscopy, *The Journal of Visualized Experiments (JoVE)*, in press (2014).

Redy O, Kisin-Finfer E, Shiran Ferber, **Satchi-Fainaro R*,** and Shabat D*, Synthesis and use of qcy7-derived modular probes for detection and imaging of biologically relevant analytes, *Nature Protocols*, 9(1):27-36 (2014). *Corresponding authors

Kisin-Finfer E, Ferber S, Blau R, **Satchi-Fainaro R**, Shabat D, Synthesis and evaluation of new NIR-fluorescent probes for cathepsin B: ICT versus FRET as a turn-ON mode-of-action, *Bioorganic and Medicinal Chemistry Letters*, 24(11):2453-8 (2014).

Ferber S, Baabur-Cohen H, Blau R, Epshtein Y and **Satchi-Fainaro R**, Nanomedicines for personalized theranostics of angiogenesis-dependent diseases, *Cancer Letters*, in press (2014).

Eldar-Boock A, Ryppa C, Sanchis J, Baabur-Cohen H, Many A, Vicent MJ, Kratz F, **Satchi-Fainaro R,** Integrin-targeted nano-sized polymeric systems for paclitaxel: A comparative study, *Polymers for Advanced Technologies, in press* (2014).

Markovsky E, Baabur-Cohen H, **Satchi-Fainaro R,** Anticancer polymeric nanomedicine bearing synergistic drug combination is superior to a mixture of individually-conjugated drugs**,** *Journal of Controlled Release*, in press (2014).

Reviews

Ofek P, Miller K, Eldar-Boock A, Polyak D, Segal E and **Satchi-Fainaro R,** Rational design of multifunctional polymer therapeutics for cancer theranostics, Special Theme issue: Polymer Therapeutics as novel nanomedicines, *Israel Journal of Chemistry*, 50, 185-203 (2010).

David A and **Satchi-Fainaro R,** Special Theme issue: Polymer Therapeutics as novel nanomedicines, Editorial- Polymer Therapeutics- from bench to bedside, *Israel Journal of Chemistry*, 50, 145-146 (2010).

Markovsky E, Baabur-Cohen H, Eldar-Boock A, Omer L, Tiram G, Ferber S, Ofek P, Polyak D, Scomparin A and **Satchi-Fainaro R**, Administration, distribution, metabolism and elimination of polymer therapeutics, Theme issue: Drug Delivery Research in Europe, *Journal of Controlled Release,* 161, 446–460 (2012).

Eldar-Boock A*, Polyak D*, Scomparin A, **Satchi-Fainaro R**, Nano-sized polymers and liposomes designed to deliver combination therapy for cancer, *Current Opinion in Biotechnology*, 24: 682–689 (2013).

Ofek P, Tiram G, **Satchi-Fainaro R**, RNAi Anti-angiogenic Nanomedicines, *Advanced Drug Delivery Reviews*, in press (2014).

Polyak D*, Eldar-Boock A*, Baabur-Cohen H and **Satchi-Fainaro R**, Polymer conjugates for focal and targeted delivery of drugs, *Polymers for Advanced Technologies*, 24, 777–790 (2013).

Tiram G, Scomparin A, Ofek P and **Satchi-Fainaro R,** Interfering cancer with polymeric siRNA nanocarriers, *Journal of Biomedical Nanotechnology*, 10, 50-66 (2014).

Ben-Shushan D*, Markovsky E*, Gibori H*, Tiram G, Scomparin A, **Satchi-Fainaro R**, Overcoming obstacles in microRNA delivery towards improved cancer therapy, *Drug Delivery and Translational Research*, 4(1), 38-49 (2014).

Chapters

Eldar-Boock A, Polyak D and **Satchi-Fainaro R,** Ligand-assisted vascular targeting of polymer therapeutics, In Drug Delivery in Oncology - From Basic Research to Cancer Therapy, Eds. Kratz F and Senter P, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2, p. 591-625 (2011).

Baabur-Cohen H, Omer L, and **Satchi-Fainaro R,** Recent progress in polymer therapeutics as nanomedicines, In Handbook of Harnessing biomaterials in Nanomedicine: Preparation, toxicity and applications, Ed. Peer D, Pan Stanford Publishing Pte. Ltd., Hackensack, NJ, USA, Chapter 4, p. 77-122 (2011).

Gabizon A, Shmeeda H, Baabur H and **Satchi-Fainaro R,** Targeting the folate receptor with liposomes and polymer therapeutics, In Targeted Drug Strategies for Cancer and Inflammation, Eds. Leamon C and Jackman A, Springer-Verlag, Heidelberg, Germany, p. 217-247 (2011).

Grants

2010-2014 Israel Science Foundation (ISF) grant (1309/10): “Anti-angiogenic polymer therapeutics to target bone neoplasms”.

2011-2014 Swiss Bridge Award: "Deciphering the molecular mechanism of tumor dormancy using bone-targeted polymer therapeutics".

2011-2014 The Association for International Cancer Research (AICR): "In vivo targeting of Akt1siRNA to tumors and their stroma".

2011-2014 German-Israel Foundation (GIF): siRNA delivery to brain tumors" (German collaborator: Rainer Haag, Frei University Berlin)

2102-2104 Sheba Medical Center - Tel Aviv University Grant: "Targeting NCAM-expressing cancer stem cells with nano-scaled polyglutamic acid-doxorubicin-peptide conjugate".)Co-PI: Benjamin Dekel, Sheba Medical Center)

2102-2106 MAGNET Rimonim Consortium, Office of the Chief Scientist of the Ministry of Industry, Trade & Labor: "siRNA delivery to ovarian cancer”.

2102-2107 Israel National Nanotechnology Initiative (INNI), Focal Technology Area in nanotechnology, "Theranostic Nanomedicines for Personalized Medicine”

May 24, 2014

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Novel Antioxidant and Stem Cells for Treatment of Degenerative Diseases

Positions

Professor, Sackler Faculty of Medicine
Director, Goldschleger Eye Research Institute
Chair, Maratier Institute for the Study of Blindness & Visual Disorders

Research

We are studying the potential of S-allylmercapto-N-acetylcysteine (ASSNAC) a newly developed derivative of allicin (the active component in garlic) to serve as a treatment for diabetes and degenerative diseases of the eye. The research involves cell biology tools and animal models.

The following specific subjects are studied:

- Demonstrating the capacity of ASSNAC to activate the transcription factor Nrf2 resulting in up-regulation of the antioxidant cellular mechanisms that increases the protective capacity of cells against reactive oxygen species.
- Testing the potential of ASSNAC to attenuate the clinical manifestations of diabetes such as nephropathy, retinopathy and osteoporosis.
- Testing the potential of ASSNAC to attenuate ocular degenerative diseases such as cataract and light-induced retinal damage.

Publications

R. Ankri, H. Friedman, **N. Savion**, S. Kotev-Emeth, H. Breitbart, R. Lubart. Visible light induces nitric oxide (NO) formation in sperm and endothelial cells. Lasers in Surg. and Med., 42: 348–352, 2010.

R. Beigel, H. Hod, P. Fefer, E. Asher, I. Novikov, B. Shenkman, **N. Savion**, D. Varon and S. Matetzky. Relation of aspirin failure to clinical outcome and to platelet response to aspirin in patients with acute myocardial infarction. Am. J. Cardiol. 107: 339–342, 2011.

S. Matetzky, P. Fefer, B. Shenkman, M. Shechter, I. Novikov, **N. Savion**, D. Varon, H. Hod. Statins have an early antiplatelet effect in patients with acute myocardial infarction. Platelets 22: 103-110, 2011.

N. Izigov, N. Farzam, **N. Savion**. S-allylmercapto-N-acetylcysteine up-regulates cellular glutathione and protects vascular endothelial cells from oxidative stress. Free Radic. Biol. Med. 50: 1131–1139, 2011.

M. Shechter, A. Shechter, H. Hod, P. Fefer, B. Shenkman, N. Koren-Morag, M.S. Feinberg, D. Harats, B.A. Sela, **N. Savion**, D. Varon, S. Matetzky. Brachial artery endothelial function predicts platelet function in control subjects and in patients with acute myocardial infarction. Platelets, 23:202-210, 2012.

S. Mendelboum Raviv, K. Szekeres-Csiki, A. Jenei, J. Nagy, B. Shenkman, **N. Savion**, J. Harsfalvi. Coating conditions matter to collagen matrix formation regarding von Willebrand factor and platelet binding. Thromb. Res. 129: e29–e35, 2012.

G. Spectre, L. Zhu, M. Ersoy, P. Hjemdahl, **N. Savion**, D. Varon, N. Li. Platelets selectively enhance lymphocyte adhesion on subendothelial matrix under arterial flow conditions. Thromb. Haemost. 108: 328-337, 2012.

J. Schneiderman, K. Schaefer, F.D. Kolodgie, **N. Savion**, S. Kotev-Emeth, R. Dardik, A.J. Simon, M. Halak, C. Pariente, I. Engelberg, S. Konstantinides, R. Virmani. Leptin locally synthesized in carotid atherosclerotic plaques may be associated with lesion instability and cerebral emboli. J. Am. Heart Assoc. 2012; 1: e001727.

M. Tao, P. Yu, B.T. Nguyen, B. Mizrahi, **N. Savion**, G. Sukhova, F.D. Kolodgie, R. Virmani, C.K. Ozaki, J. Schneiderman. Locally applied leptin induces regional aortic wall degeneration in apoe deficient mice preceding aneurysm formation. Arterioscler. Thromb. Vasc. Biol. 33:311-20, 2013.

I. Ben Aharon, H. Bar Joseph, M. Tzabari, B. Shenkman, N. Farzam, M. Levi, R. Shalgi, S.M. Stemmer, **N. Savion**. Doxorubicin-induced vascular toxicity - Targeting potential pathways may reduce procoagulant activity. PLoS ONE, 8: e75157, 2013.

E. Asher, P. Fefer, M. Shechter, R. Beigel, D. Varon, B. Shenkman, **N. Savion**, H. Hod, S. Matetzky. Increased Mean Platelet Volume is Associated with Non-responsiveness to Clopidogrel. Thromb. Haemost. Apr 3;112(1), 2014 [Epub ahead of print]. (doi: 10.1160/TH13-10-0845)

P. Fefer, R. Beigel, N. Rozenberg, M. Shechter, S. Gannot, D. Varon, **N. Savion**, S. Matetzky. Evaluation of Platelet Response to Different Clopidogrel Dosing Regimens in Patients with Acute Coronary Syndrome in Clinical Practice. Platelets, Mar 11, 2014 [Epub ahead of print].

Grants

2013 – 2014 Baharv Fund for Glaucoma Research, Sackler Faculty of Medicine.

May 24, 2014

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Reproduction in Animal Models and in Humans

Positions

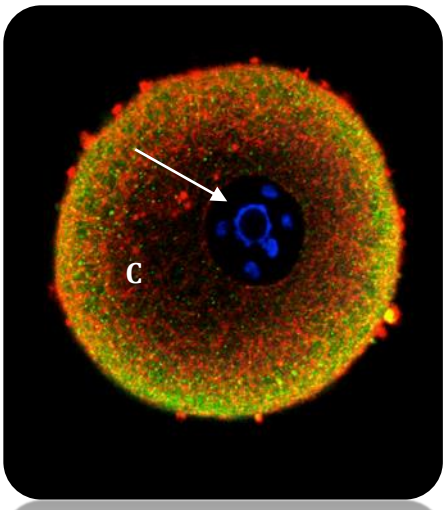
Professor, Sackler Faculty of Medicine
Gabriel Pinkas Chair for the Prevention and Diagnosis of Congenital Anomalies
Chair, Faculty Search Committee
Executive Committee, Open University, Member

Research

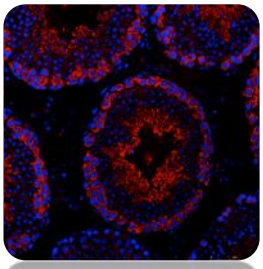
Our research focuses on Reproductive Physiology in animal models and in humans. The current research directions investigated in the laboratory are:

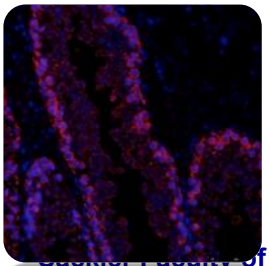
- The role of Fyn kinase, member of the Src family kinases, during meiosis and early events of oocyte activation, as well as in cancer cells (Figure-left panel).
- Fertility preservation - the signaling pathway leading to apoptosis in aging oocytes and in oocytes exposed to chemotherapeutic treatments and potential protectants (Figure -right panel).
- Regulation of angiogenesis in reproductive organs by Pigment epithelium derived factor (PEDF) and treatment of reproductive angiogenic-related pathologies.
- The role of Interleukin-1alpha in reproductive aging and in chemotherapy-induced exhaustion of ovarian follicular pool.

Various research methods are routinely used in the laboratory, ranging from *in vivo* animal studies and cells cultures to an array of protein methodologies such as western blotting, immunohistochemistry, molecular biology techniques as well as cellular and molecular imaging.



Left panel- Human oocyte stained for DNA (blue); cytoskeleton (tubulin; red); protein (Fyn kinase; green). Arrow - Germinal vesicle (genetic material); C- Cytoplasm. Confocal microscopy. Right panels -Section of sperm producing tubules in mouse testis before (left) and after treatment with chemotherapy (right). The drug led to loss of sperm (S) production. DNA (blue); protein (DAZL; red). Immunofluorescent microscopy.





Publications

Levi M and **Shalgi R.** The role of fyn kinase in the release from metaphase in mammalian oocytes. Mol. Cell. Endocr. 314: 228-233, 2010.

Ben-Aharon, I., Bar-Joseph, H., Tzarfaty, G., Kuchinsky, L., Rizel, M., Stemmer, S.M. and **Shalgi, R.** Doxorubicin-induced ovarian toxicity. Reprod. Biol. Endocr. 8: 20-26. 2010.

Levi M, Maro B and **Shalgi R.** The involvement of Fyn kinase in resumption of the first meiotic division in mouse oocytes. Cell cycle. 9: 1577-1589, 2010.

Bar-Joseph, H., Ben-Aharon, I., Rizel, S., Stemmer, S.M., Tzabari, M. and **Shalgi, R.** Doxorubicin-induced apoptosis in germinal vesicle (GV) oocytes. Reprod. Toxicol. 30:566-72, 2010**.**

Levi, M., Maro, B. and **Shalgi R.** Fyn kinase is involved in cleavage furrow ingression during meiosis and mitosis. Reproduction. 140: 827-834, 2010.

Haberman, Y., Tsaadon, L., Eliyahu, E., and **Shalgi, R.** Receptor for activated C kinase (RACK) facilitates protein kinase C (PKC) mediated cortical granules exocytosis (CGE). Theriogenology, 75: 80-9, 2011.

Levi, M., Maro, B. and **Shalgi R.** The conformation and activation of Fyn kinase in the oocyte determine its localization to the spindle poles and cleavage furrow. Reprod. Fertil. Dev. 23: 846-857, 2011.

Bar-Joseph, H., Ben-Aharon, I., Stemmer, S.M., Tzabari, M. and **Shalgi, R.** Novel *in vivo* imaging of acute chemotherapy-induced vascular toxicity. PLos One, 9: e23492, 2011.

Levi, M., Kraicer-Kaplan, R. and **Shalgi, R.** Regulation of division in mammalian oocytes: Implications for polar body formation. Mol. Hum. Reprod. 17:324-338, 2011.

Eliyahu, E., Shtraizent, N., **Shalgi, R**. and Schuchman, E. H. cation of cystatin SA as a novel inhibitor of acid ceramidase. J. Biol. Chem. 286:35624-33, 2011.

Eliyahu, E., Shtraizent, N., **Shalgi, R.** and Schuchman, E. H. Construction of conditional acid ceramidase knockout mice and in vivo effects on oocyte development and fertility Cell Physiol. Biochem. 30:735-748, 2012.

Chuderland, D., Dvashi, Z., Kaplan-Kraicer, R., Ben-Meir, D., **Shalgi, R.** and Lavi S. De novo synthesis of PPM1a is engaged in oocyte maturation. Cell Mol. Biol. Lett. 17:433-45. 2012.

Levi, M., Ninio-Mani, L. and **Shalgi R.** SRC protein kinases in mouse and rat oocytes and embryos. Results Probl. Cell Differ. 55:93-106, 2012.

Chuderland*, D., Ben-Ami* I., Ronel, R., Kraicer-Kaplan, R., Grossman, H., Satchi- Fainaro, R., Eldar-Boock, A. and, **Shalgi, R**. Hormonal regulation of pigment epithelium derived factor (PEDF) in granulosa cells. Mol Hum Reprod. 19:72-81 2013

Chuderland*, D., Ben-Ami* R., Kraicer-Kaplan, R., Grossman, H., Ronel, R. and **Shalgi, R.** The role of pigment epithelium-derived factor in the pathophysiology and treatment of ovarian hyperstimulation syndrome in mice. J Clin. Endocr. Metab. 98:E258-66, 2013.

Chuderland, D.*, Hasky, N.*, Ben-Ami, I., Kaplan-Kraicer, R., Grossman, H. and **Shalgi R.** A physiological approach for treating endometriosis by recombinant pigment epithelial derived factor (PEDF). Hum. Reprod. 28:1626-34, 2013.

Ninio-Many, L., Grossman, H., Chuderland D., Shomron, N. and **Shalgi, R.** microRNA-125a-3p reduces proliferation and migration of HEK 293T cells by targeting Fyn. J Cell Sci, 126:2867-2876, 2013.

Levi M, Ghetler Y, Shulman A and **Shalgi, R**. Morphologic and molecular markers indicate maturation-competence of human oocytes. Hum Reprod. 28:2482-9. 2013.

Ben Aharon, I., Bar Joseph, H., Tzabari, M., Shekman, B., Farzam, N., Levi, M., **Shalgi, R.,** Stemmer, SM. and Savion, N. Doxorubicin-induced vascular toxicity – Targeting potential pathways may reduce procoagulant activity. PLos One, 8 (9) e75157, 2013.

Chuderland D., Ben-Ami, I., Fridler, S., Hasky, N., Ninio-Many, L., Goldberg, K., Bar-Josef, H., Grossman, H., and **Shalgi, R.** Hormonal regulation of Pigment epithelium-derived factor (PEDF) expression in the endometrium. Mol. Cell Endocr. 390, 85-92, 2014.

Ninio-Many, L., Grossman, H., Levi, M., Zilber, S., Tsarfaty, I., Shomron, N., Tuvar, A., Chuderland D., Stemmer, S.M., Ben-Aharon, I.* and **Shalgi R.*** MicroRNA miR-125a-3p modulates molecular pathway of motility and migration in prostate cancer cells. Oncoscience. In Press 2014.

Reviews

Levi, M., Kraicer-Kaplan, R. and **Shalgi, R.** Regulation of division in mammalian oocytes: Implications for polar body formation. Review. Mol. Hum. Reprod. 324-338, 2011.

Levi, M., Ninio-Mani, L. and **Shalgi R.** Src protein Kinases in oocytes and embryos. Chapter 4 submitted to the book: "Mouse Development: From Oocyte to Stem Cells", Results and Problems in Cell Differentiation (RPCD) Series, Springer Publishing. 55:93-106. 2012.

Ben-Aharon, I. and **Shalgi, R.** What lies beyond chemotherapy induced ovarian toxicity. Reproduction, 144:153-163, 2012.

Grants

2010-2014 Binational Science Foundation (BSF) - Does acid Ceramidase regulate the fate of female germ cells and somatic cells?

2013-2014 Bayer Healthcare Pharmaceuticals - A physiological approach for treating endometriosis by recombinant pigment epithelium-derived factor (PEDF)

May 24, 2014

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The NMDA Preconditioning-Induced Neuroprotective Mechanism

Position

Professor, Sackler Faculty of Medicine

Research

The main subject of interest currently in my laboratory is the subject of neuroprotection, finding the means to protect the brain against all kinds of injurious events such as stroke, ischemia and neurodegenerative diseases. Our laboratory is focusing on deciphering the mechanism of activation of endogenous protective mechanisms. Of special interest is the mechanism of the phenomenon termed “preconditioning”. By this mechanism, exposure of the brain to low, sub-lethal dose of injurious conditions or substances preconditions the brain to resist a subsequent lethal exposure to damaging conditions. The preconditioned brain activates signal transduction pathways leading to enhanced synthesis of protective proteins. Understanding the preconditioning mechanism will enhance the development of drugs that will activate when necessary neuroprotection against stroke and other similar devastating injurious conditions. Presently our research is focused on the phenomenon of NMDA preconditioning. NMDA activates specifically one type of the ionotropic glutamate receptors (NMDA receptors). In presence of excessive glutamate concentration, these receptors mediate much of the neuronal damage, due to excitotoxicity, but at moderately elevated, yet sublethal glutamate concentration, glutamate stimulates the NMDA receptors inducing the activation of the protective NMDA preconditioning mechanism. NMDA preconditioning is one of the most important neuroprotective preconditioning mechanisms. This protective mechanism is involved in many of the various other preconditioning mechanisms, such as the ischemic preconditioning. We are now in the midst of deciphering the involvement of several signal transducing proteins in the protective mechanism.

Publications

Sragovich S, Bromberg Y, Sperling O, **Zoref-Shani E**. Molecular alterations associated with the NMDA preconditioning-induced neuroprotective mechanism against glutamate cytotoxicity. J Mol Neurosci. 2012; 47:519-32.

Navon, H., Bromberg, Y., Sperling, O., **Shani, E**., Neuroprotection by NMDA preconditioning against glutamate cytotoxicity is mediated through activation of ERK 1/2, inactivation of JNK and by prevention of glutamate-induced CREB inactivation. J Mol Neurosci, 2012; 46:100-8.

May 24, 2014

Prof. Levana Sherman, Ph.D.

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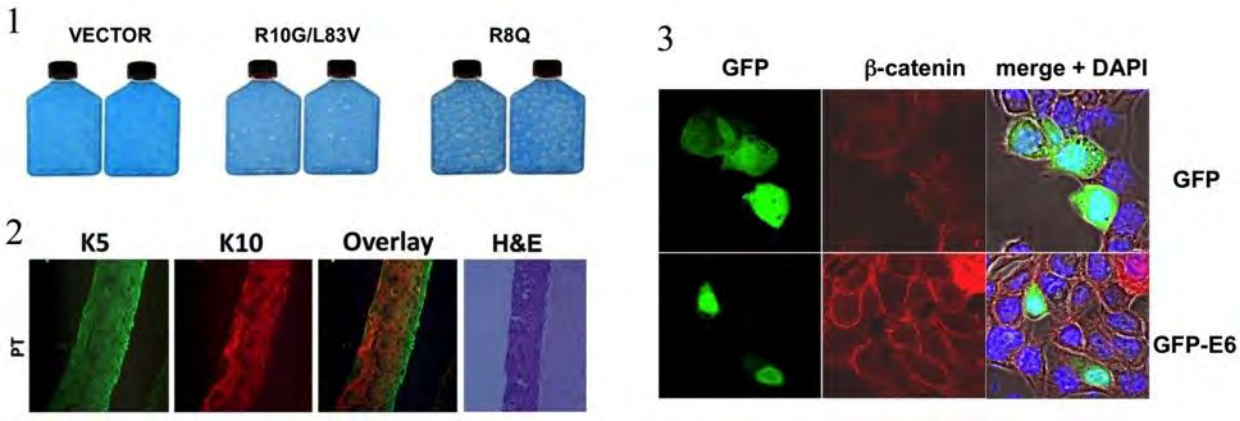
Transforming Functions of Human Papillomaviruses

Position

Professor, Sackler Faculty of Medicine

Research

Research in my laboratory focuses on the study of human papillomaviruses (HPVs) and their role in the development of anogenital and skin cancer. Employing various biochemical and molecular biology tools, epithelial cell culture models and immunofluorescence techniques, our studies aim at elucidating the molecular mechanism(s) by which HPVs contribute to epithelial cell transformation. The major topics under investigation are: 1. Inhibition of human keratinocyte terminal differentiation by the E6 oncoprotein. 2. Role of HPV polymorphism in cervical carcinogenesis. 3. Augmentation of the Wnt/β- catenin signaling pathway by the E6 oncoprotein. 4. Transforming activities of the E6 and E7 genes of cutaneous human papillomavirus. 5. Novel anticancer agents for cervical cancer and modulation of their activity by the HPV oncoproteins



1. HPV16 E6 variants differ in their ability to induce differentiation resistant colonies in human keratinocytes.
2. HPV 16 E6 dysregulates keratinocyte differentiation induced in organotypic cultures. Immunofluorescence for basal cell keratinocyte marker, K5, suprabasal cell markrer, K10, the overlay of both and H+E staining.
3. HPV16 E6 does not alter cellular localization of β-catenin.

Publications

Lichtig Kinsbruner, H., Avital Gilboa, D., Jackman, A., Levav-Choen, Y., Haupht, Y., **Sherman, L.** (2010) HPV16 E6 augments Wnt signaling in an E6AP dependent manner. *Virology*, 396:47-58, 2010.

Richard, C., Lanne, C, Naryzhny, S.N, **Sherman, L**., Lee H., Lambert, P.F., Zehbe I. (2010) The immortalizing and transforming ability of two common human papillomavirus 16 E6 variants with different prevalence in cervical cancer. *Oncogene*, 29:3435-3445, 2010.

Zebbe I., Lichtig H., Westermark A., Lambert P.F., Tommasino, M., **Sherman, L.** (2011) Rare human papillomavirus 16 E6 variants reveal significant oncogenic potential. *Mol. Cancer* 10:77

Milrot E, Jackman A, Kniazhanski T, Gonen E, Flescher E, **Sherman L.** (2012) Methyl jasmonate reduces the survival of cervical cancer cells and downregulates HPV E6 and E7, and survivin. *Cancer Lett*. 319:31-38.

Milrot E., Jackman A, Flescher E, Gonen E, Kelson I, Keisari Y, **Sherman L** (2013) Enhanced killing of cervical cancer by combinations of methyl jasmonate with cisplatin, X or alpha radiation. *Invest. New Drugs* 31: 333-44.

Grants

2010-2014 Augmentation of the Wnt/β-catenin signaling by the E6 oncoprotein: Role of the ubiquitin ligase E6AP and biological significance, Israel Science Foundation

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The ATM-Mediated DNA Damage Response

Positions

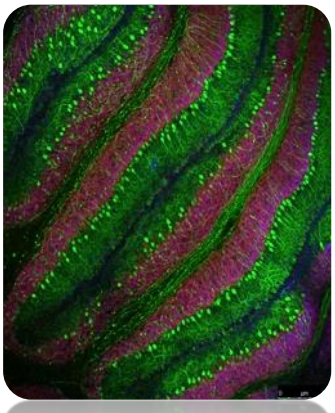
Professor, Sackler Faculty of Medicine
David and Inez Myers Chair in Cancer Genetics

Research

Our laboratory investigates the cellular DNA damage response. This research stems from our interest in the human genetic disorder ataxia-telangiectasia (A-T), in which a central axis of the DNA damage response is missing.

Genetic defects in the DNA damage response lead to genomic instability syndromes, which usually include tissue degeneration, cancer predisposition, and sensitivity to specific DNA damaging agents. A prototype genomic instability syndrome is A-T. The disease is characterized by neuronal degeneration, immunodeficiency, chromosomal instability, sensitivity to ionizing radiation, and cancer predisposition. Our lab has been investigating A-T since its establishment in 1985. In 1995, after 8 years of intensive work, we identified the gene that is defective (mutated) in A-T patients and called it *ATM* (A-T, Mutated). We went on to study the activity of its product, the ATM protein, which turned out to be an enzyme with an activity alled "protein kinase".

Our current research is aimed at a broader understanding of the ATM-mediated DNA damage response. Particular attention is paid to the molecular and physiological basis of A-T, which may eventually lead to new treatment modalities for the disease. We investigate this system with cell biology methods, gene targeting in mice, and systems biology strategies including high-throughput screens, advanced proteomics and bioinformatics. A study is underway aimed at understanding the DNA damage response in the part of the brain called the cerebellum, which is badly damaged in A-T patients. Another project is searching for a drug treatment for A-T patients based on our recent understanding of the disease.



Microscopic image of a slice of mouse cerebellum in culture. The cells stained green are called Purkinje cells. These cells are the first to be damaged and lost in A-T patients. Such cultures are used to study the DNA damage response in this complex organ.

Publications

Ulitzky, I., Maron-Katz, A., Shavit, S., Sagir, D., Linhart, C., Elkon, R., Tanay, A., Sharan, R., **Shiloh, Y**., and Shamir, R. (2010) Expander: from expression microarrays to networks and functions. Nature Protocols 5:303-322.

Barash, H., Gross, E., Edrei, Y., Ella, E., Cohen, I., Corchia, N., Ben-Moshe, T., Pappo, O., Pikarsky, E., Goldenberg, D., **Shiloh, Y**., Galun, E., and Abramovitch, R. (2010) Accelerated carcinogenesis following liver regeneration is associated with chronic inflammation-induced double-strand DNA breaks. Proc. Natl. Acad. Sci. USA 107:2207-2217.

Salton, M., Lerenthal, Y., Wang, S.-Y., Chen, D.J., and **Shiloh, Y**. (2010) Involvement of Matrin 3 and SFPQ/NONO in the DNA damage response. Cell Cycle 9:1568-1576.

Bensimon, A., Schmidt, A., Ziv, Y., Elkon, R., Wang, S.-Y., Chen, D., Aebersold, R., and **Shiloh, Y**. (2010) ATM-dependent and independent dynamics of the nuclear phosphoproteome following DNA damage. Science Signaling 3:rs3.

Paz, A., Brownstein, Z., Ber, Y., Bialik, S., David, E., Sagir, D., Ulitsky, I., Elkon, R., Kimchi, A., Avraham, K., **Shiloh, Y.**, and Shamir, R. (2011) SPIKE: A database of highly curated human signaling pathways. Nucleic Acids Res. 39:D793-799.

Kepkay, R., Attwood, K.M., Ziv, Y., **Shiloh, Y**., and Dellaire, G. (2011) KAP1 depletion increases PML nuclear body number in concert with ultrastructural changes in chromatin. Cell Cycle 10:308-322.

Galron, N., Gruber, R., Lifshitz, V., Lu, H., Kirshner, M., Ziv, N., Wang, Z.-Q., **Shiloh, Y**., Barzilai, A., and Frenkel, D. (2011) Astrocyte dysfunction associated with cerebellar attrition in a Nijmegen breakage syndrome animal model. J. Mol. Neurosci. 5:202-11.

Dar, I., Yosha, G., Elfassy, R., Galron, R., Wang, Z.-Q., **Shiloh, Y**., and Barzilai, A. (2011) Investigation of the functional link between ATM and NBS1 in the DNA damage response in the mouse cerebellum. J. Biol. Chem. 286:15361-15376.

Moyal, L., Gana-Weisz, M., Lerenthal, Y., Mass, G., So, S., Wang, S.-Y., Eppink, B., Chung, Y.-M., Shalev, G., Shema, E., Shkedy, D., Smorodinsky, N.I., van-Vliet, N., Kuster, B., Mann, M., Ciechanover, A., Dahm-Daphi, J., Kanaar, R., Hu, M.C-T., Chen, D.J., Oren, M., and **Shiloh, Y.** (2011) Requirement of ATM-dependent monoubiquitylation of histone H2B for timely repair of DNA double strand break. Mol. Cell, 41:529-542. Featured article.

Segal-Raz, H., Mass, G., Ziv-Lehrman, S., Wang, S.-Y., Strom, C., Helleday, T., Chen, D.J., and **Shiloh, Y**. (2011) ATM-mediated phosphorylation of polynucleotide kinase is required for effective DNA double-strand break repair. EMBO Reports, 12:713-719.

Raz-Prag, D., Galron, R., Segev-Amzaleg, N., Barzilai, A**., Shiloh, Y**., and Frenkel, D. (2011) A role for vascular deficiency in retinal pathology in a mouse model of ataxia-telangiectasia. Am. J. Pathol.

Rashi-Elkeles, S., Elkon, R., Shavit, S., Lerenthal, Y., Linhart, C., Kupershtein, A., Amariglio, N., Rechavi, G., Shamir, R., and **Shiloh, Y**. (2011) Transcriptional modulation induced by ionizing radiation: p53 remains a central player. Mol. Oncol., 5:336-348

Salton-Morgenstern, M., Elkon, R., Borodina, T., Davydov, A., Yaspo, M.-L., Halperin, E., and **Shiloh, Y**. (2011) Matrin 3 binds and stabilizes mRNA. PLoS ONE 6:e23882.

Levy-Barda, A., Lerenthal, Y., Davis, A.J., Chung, Y.M., Essers, J., Shao, Z., van Vliet, N., Chen, D.J., Hu, M.C-T., Kanaar, R., Ziv, Y., and **Shiloh, Y**. (2011) Involvement of the nuclear proteasome activator PA28γ in the cellular response to DNA double-strand breaks. Cell Cycle, 10:4300-4310.

Shiloh, Y., Shema, E., Moyal, L., and Oren, M., (2011) RNF20-RNF40: a ubiquitin-driven link between gene expression and the DNA damage response. FEBS Letters, 585:2795-2802.

Kirshner, M., Galron, R., Frenkel, D., Mandelbaum, G., **Shiloh, Y.,** Wang, Z.-Q., and Barzilai, A.

(2012) Malfunctioning DNA damage response (DDR) leads to the degeneration of nigro-straiatal pathway in mouse brain. J. Mol. Neurosci. 46:554-68.

Tzur-Gilat, A., Ziv, Y., Dusart, I., Mittelman, L., Barzilai, A., and **Shiloh, Y.** (2013) Studying the cerebellar DNA damage response in the tissue culture dish. Mech. Ageing Dev. 134(10):496-505.

Rasmussen LJ, **Shiloh Y**, Bergersen LH, Sander M, Bohr VA, Tønjum T. (2013) DNA damage response, bioenergetics, and neurological disease: the challenge of maintaining brain health in an aging human population. Mech Ageing Dev. 134(10):427-33

Rashi-Elkeles S, Warnatz HJ, Elkon R, Kupershtein A, Chobod Y, Paz A, Amstislavskiy V, Sultan M, Safer H, Nietfeld W, Lehrach H, Shamir R, Yaspo ML, **Shiloh Y**. (2014)

Parallel profiling of the transcriptome, cistrome, and epigenome in the cellular response to ionizing radiation..Sci Signal. 2014 May 13;7(325):rs3.

Reviews

Jochemsen, A.A., and **Shiloh, Y**. (2010) USP10: Friend or foe? Cell, 140:308-310.

Sander, M., Begley, T.J., Desaintes, C., Gavin, A.-C., Pelroy, R., Pothof, J., **Shiloh, Y**., van Gent, D., van Houten, B., Yaffe, M., and Mullenders, L. (2010) 3rd US-EU Workshop on Systems Level Understanding of DNA Damage Responses. Mutat. Res .692:53-60.

Bensimon, A., Aebersold, R., and **Shiloh, Y**. (2011) Beyond ATM: the proteinkinase landscape of the DNA damage response. FEBS Letters 585:1625-1639.

Shiloh, Y., Shema, E., Moyal, L., and Oren, M., (2011) RNF20-RNF40: a ubiquitin-driven link between gene expression and the DNA damage response. FEBS Letters, 585:2795-2802.

Shiloh, Y., and Ziv, Y. The ATM protein: the importance of being active (Commentary) J. Cell Biol. 198:273-275.

Shiloh, Y., and Ziv, Y. (2013) The ATM protein: regulating the DNA damage response, and more. Nature Rev. Mol. Cell Biol. 14:197-210.

Book Chapter

Shiloh, Y. (2010) The ATM-mediated DNA damage response. In: Molecular Oncology (Gelmann, I., Sawyers, G.L. and Rauscher, F., eds.) Cambridge University Press, pp. 297-309.

Grants

2011-2015 Israel Science Foundation: The ATM and WRN Proteins at the Crossroads of Genomic Stability, Cancer and Aging

2011-2015 German-Israel Foundation for Scientific Research and Development: UBE4B: A New Player in the Interface between the Ubiquitin Arena and the DNA Damage response

May 24, 2014

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Gene Regulation by Small RNAs

Positions

Senior Lecturer, Sackler Faculty of Medicine
Director, Functional Genomics Laboratory
Academic Director, BioAbroad
Editor-in-Chief, *Genetics Research*

Research

Our laboratory focuses on the analysis of regulation of gene expression aimed at understanding human disease. Combining high-throughput methods and bioinformatics, one aspect of our team's research explores microRNA regulation in order to reach a global, systems perspective of the mechanistic roles microRNAs play during disease development. Among our projects:

- Identification of a microRNA molecule that controls several oncogenes. Their discovery is paving the way for a potentially revolutionary drug for cancer treatment.
- Revealing the influence of microRNAs on pharmacogenomics and personalized medicine, thus leading to tailored drugs for cancer treatment.
- Exposing pathogens in human tissues based on deep sequencing of small RNA molecules followed by subtraction and assembly of the various genomes.

Publications

Mor E, He L, Torchinsky A, **Shomron N**. MicroRNA-34a is dispensable for p53 function as teratogenesis inducer. Arch Toxicol. 2014 Mar 13.

Nachmani D, Zimmermann A, Oiknine Djian E, Weisblum Y, Livneh Y, Khanh Le VT, Galun E, Horejsi V, Isakov O, **Shomron N,** Wolf DG, Hengel H, Mandelboim O. MicroRNA Editing Facilitates Immune Elimination of HCMV Infected Cells. PLoS Pathog. 2014, 10:e1003963.

Agranat-Tamir L, **Shomron N,** Sperling J, Sperling R. Interplay between pre-mRNA splicing and microRNA biogenesis within the supraspliceosome. Nucleic Acids Res. 2014 Jan 24.

Lustig Y, Barhod E, Ashwal-Fluss R, Gordin R, **Shomron N**, Baruch-Umansky K, Hemi R, Karasik A, Kanety H. RNA-Binding Protein PTB and MicroRNA-221 Coregulate AdipoR1 Translation and Adiponectin Signaling. Diabetes. 2014; 63:433-45.

Feinberg-Gorenshtein G, Guedj A, Shichrur K, Jeison M, Luria D, Kodman Y, Ash S, Feinmesser M, Edry L, **Shomron N**, Weizman A, Yaniv I, Avigad S. MiR-192 directly binds and regulates Dicer1 expression in neuroblastoma. PLoS One. 2013, 8:e78713.

Oved K, Morag A, Pasmanik-Chor M, Rehavi M, **Shomron N***, Gurwitz D*. Genome-wide expression profiling of human lymphoblastoid cell lines implicates integrin beta-3 in the mode of action of antidepressants. Transl Psychiatry. 2013; 3:e313. * Equal corresponding

Eytan O, Morice-Picard F, Sarig O, Ezzedine K, Isakov O, Li Q, Ishida-Yamamoto A, **Shomron N,** Goldsmith T, Fuchs-Telem D, Adir N, Uitto J, Orlow SJ, Taieb A, Sprecher E. Cole Disease Results from Mutations in ENPP1. Am J Hum Genet. 2013; 93:752-7.

Isakov O, Rinella ES, Olchovsky D, Shimon I, Ostrer H, **Shomron N**, Friedman E. Missense mutation in the MEN1 gene discovered through whole exome sequencing co-segregates with familial hyperparathyroidism. Genet Res (Camb). 2013; 95:114-20.

Barak B, Shvarts-Serebro I, Modai S, Gilam A, Okun E, Michaelson DM, Mattson MP, **Shomron N**, Ashery U. Opposing actions of environmental enrichment and Alzheimer's disease on the expression of hippocampal microRNAs in mouse models. Transl Psychiatry. 2013; 3:e304.

Samuelov L, Sarig O, Harmon RM, Rapaport D, Ishida-Yamamoto A, Isakov O, Koetsier JL, Gat A, Goldberg I, Bergman R, Spiegel R, Eytan O, Geller S, Peleg S, **Shomron N,** Goh CS, Wilson NJ, Smith FJ, Pohler E, Simpson MA, McLean WH, Irvine AD, Horowitz M, McGrath JA, Green KJ, Sprecher E. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. Nat Genet. 2013; 45, 1244–1248.

Ninio-Many L, Grossman H, **Shomron N**, Chuderland D, Shalgi R. microRNA-125a-3p reduces cell proliferation and migration by targeting Fyn. J Cell Sci. 2013; 126(Pt 13): 2867-76.

Gilam A, Edry L, Mamluk-Morag E, Bar-Ilan D, Avivi C, Golan D, Laitman Y, Barshack I, Friedman E, **Shomron N**. Involvement of IGF-1R regulation by miR-515-5p modifies breast cancer risk among BRCA1 carriers. Breast Cancer Res Treat. 2013; 138:753-60.

Mor E, Kano S, Colantuoni C, Sawa A, Navon R, **Shomron N**. MicroRNA-382 expression is elevated in the olfactory neuroepithelium of schizophrenia patients. Neurobiol Dis. 2013; 55:1-10.

Shaham O, Gueta K, Mor E, Oren-Giladi P, Grinberg D, Xie Q, Cvekl A, **Shomron N**, Davis N, Keydar-Prizant M, Raviv S, Pasmanik-Chor M, Bell RE, Levy C, Avellino R, Banfi S, Conte I, Ashery-Padan R. Pax6 regulates gene expression in the vertebrate lens through miR-204. PLoS Genet. 2013; 9:3.

Rukov JL, Wilentzik R, Jaffe I, Vinther J, **Shomron N**. Pharmaco-miR: linking microRNAs and drug effects. Brief Bioinform. 2013; Advance Access 10.1093/bib/bbs082.

Vincent M, Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, **Shomron N**, Gurwitz D. Genome-wide transcriptomic variations of human lymphoblastoid cell lines: insights from pairwise gene-expression correlations. Pharmacogenomics. 2012; 13:1893-904.

Oved K, Morag A, Pasmanik-Chor M, Oron-Karni V, **Shomron N,** Rehavi M, Stingl JC, Gurwitz D. Genome-wide miRNA expression profiling of human lymphoblastoid cell lines identifies tentative SSRI antidepressant response biomarkers. Pharmacogenomics. 2012;13:1129-39.

Buda I, Bachar G, Gilam A, Modai S, Strenov Y, Pasmanik-Chor M, Feinmesser R, Shomron N. Differential expression of microRNAs between aggressive and non-aggressive papillary thyroid carcinoma. Head Neck Oncol. 2012 Sep 9.Carmel I, **Shomron N**, Heifetz Y. Does base-pairing strength play a role in microRNA repression? RNA 2012; 18:1947-56.

Ben-Zvi S, Givati A, **Shomron N**. GenomeGems: evaluation of genetic variability from deep sequencing data. BMC Res Notes. 2012; 5:338.

Meshesha MK, Veksler-Lublinsky I, Isakov O, Reichenstein I, **Shomron N**, Kedem K, Ziv-Ukelson M, Bentwich Z, Avni YS. The microRNA Transcriptome of Human Cytomegalovirus (HCMV). Open Virol J. 2012; 6:38-48.

Neuman JA, Isakov O, **Shomron N**. Analysis of insertion-deletion from deep-sequencing data: software evaluation for optimal detection. Brief Bioinform. 2013; 14:46-55.

Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, Nousbeck J, Richard K, Winnepenninckx V, Vernooij M, **Shomron N**, Uitto J, Fleckman P, Richard G, Sprecher E. Familial Pityriasis Rubra Pilaris is caused by mutations in CARD14. Am J Hum Genet. 2012; 91:163-170.

Grinberg M, Gilad S, Meiri E, Levy A, Isakov O, Ronen R, **Shomron N**, Bentwich Z, Shemer-Avni

Y. Vaccinia virus infection suppresses the cell microRNA machinery. Arch Virol. 2012; 157:1719-1727.

Rokah OH, Granot G, Ovcharenko A, Modai S, Pasmanik-Chor M, Toren A, Shomron N, Shpilberg O. Downregulation of miR-31, miR-155, and miR-564 in chronic myeloid leukemia cells. PLoS One. 2012; 7:e35501.

Alon S, Mor E, Vigneault F, Church GM, Locatelli F, Galeano F, Gallo A, **Shomron N**, Eisenberg E. Systematic identification of edited microRNAs in the human brain. Genome Res. 2012;22:1533-1540.

Isakov O, Ronen R, Kovarsky J, Gabay A, Gan I, Modai S, **Shomron N**. Novel insight into the non-coding repertoire through deep sequencing analysis. Nucleic Acids Res. 2012;40:e86.

Pando R, Even-Zohar N, Shtaif B, Edry L, **Shomron N**, Phillip M, Gat-Yablonski G. MicroRNAs in the growth plate are responsive to nutritional cues: association between miR-140 and SIRT1. J Nutr Biochem. 2012, 23:1474-81.

Shichor I, **Shomron N**, Lawlor MW, Bae SA, Zoldan J, Langer R, Kohane DS. Toxicogenomic analysis of a sustained release local anesthetic delivery system. Biomaterials. 2012; 33:3586-93.

Kiezun A, Artzi S, Modai S, Volk N, Isakov O, **Shomron N**. miRviewer: a multispecies microRNA homologous viewer. BMC Res Notes. 2012; 5:92.

Sarfstein R, Pasmanik-Chor M, Yeheskel A, Edry L, **Shomron N**, Warman N, Wertheimer E, Maor S, Shochat L, Werner H. Insulin-like growth factor-I receptor (IGF-IR) translocates to nucleus and autoregulates IGF-IR gene expression in breast cancer cells. J Biol Chem. 2012; 287:2766-76.

Janas MM, Khaled M, Schubert S, Bernstein JG, Golan D, Veguilla RA, Fisher DE, **Shomron N,** Levy C, Novina CD. Feed-forward microprocessing and splicing activities at a microRNA-containing intron. PLoS Genet. 2011; 7:e1002330.

Brownstein Z*, Friedman LM*, Shahin H, Oron-Karni V, Kol N, Abu Rayyan A, Parzefall T, Lev D, Shalev S, Frydman M, Davidov B, Shohat M, Rahile M, Lieberman S, Levy-Lahad E, Lee M, **Shomron N**, King M-C, Walsh T, Kanaan M, Avraham KB. Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families. Genome Biol. 2011; 12: R89.

Isakov O, Modai S, **Shomron N**. Pathogen detection using short-RNA deep sequencing subtraction and assembly. Bioinformatics. 2011; 27:2027-30.

Volk N, **Shomron N**. Versatility of MicroRNA Biogenesis. PLoS One. 2011;6:e19391.

Greenberg E, Hershkovitz L, Itzhaki O, Hajdu S, Nemlich Y, Ortenberg R, Gefen N, Edry L, Modai S, Keisari Y, Besser MJ, Schachter J, **Shomron N**, Markel G. Regulation of cancer aggressive features in melanoma cells by microRNAs. PLoS One. 2011; 6:e18936.

Rukov JL, Vinther J, **Shomron N**. Pharmacogenomics genes show varying perceptibility to microRNA regulation. Pharmacogenet Genomics. 2011; 21:251-62

Mor E, Cabilly Y, Goldshmit Y, Zalts H, Modai S, Edry L, Elroy-Stein O, **Shomron N**. Species-specific microRNA roles elucidated following astrocyte activation. Nucleic Acids Res. 2011; 39:3710-23.

Ronen R, Gan I, Modai S, Sukacheov A, Dror G, Halperin E, **Shomron N**. miRNAkey: a software for microRNA deep sequencing analysis. Bioinformatics. 2010; 26:2615-6.

Shomron N, Hamasaki-Katagiri N, Hunt R, Hershko K, Pommier E, Geetha S, Blaisdell A, Dobkin A, Marple A, Roma I, Newell J, Allen C, Friedman S, Kimchi-Sarfaty C. A splice variant of ADAMTS13 is expressed in human hepatic stellate cells and cancerous tissues. Thromb Haemost. 2010;10:531-5. Erratum in: Thromb Haemost. 2010; 104:861

Golan D, Levy C, Friedman B, **Shomron N.** Biased hosting of intronic microRNA genes. Bioinformatics. 2010; 26:992-5.

Gueta K, Molotski N, Gerchikov N, Mor E, Savion S, Fein A, Toder V, Shomron N, Torchinsky A. Teratogen-induced alterations in microRNA-34, microRNA-125b and microRNA-155 expression: correlation with embryonic p53 genotype and limb phenotype. BMC Dev Biol. 2010; 10:20.

Gefen N, Binder V, Zaliova M, Linka Y, Morrow M, Novosel A, Edry L, Hertzberg L, **Shomron N**, Williams O, Trka J, Borkhardt A, Izraeli S. Hsa-mir-125b-2 is highly expressed in childhood ETV6/RUNX1 (TEL/AML1) leukemias and confers survival advantage to growth inhibitory signals independent of p53. Leukemia. 2010; 24:89-96

Reviews

Shomron N. Genetics research: jumping into the deep end of the pool. Genet Res (Camb). 2013; 95:1-3.

Mor E, **Shomron N**. Species-specific microRNA regulation influences phenotypic variability: Perspectives on species-specific microRNA regulation. Bioessays. 2013 doi: 10.1002/bies.201200157. [Epub ahead of print].

Shomron N. A personal perspective on personalized medicine. Genet Res (Camb). 2013; 95:51.

Isakov O, Perrone M, **Shomron N**. Exome sequencing analysis: a guide to disease variant detection. Methods Mol Biol. 2013; 1038:137-58.

Kol N, **Shomron N**. Assembly algorithms for deep sequencing data: basics and pitfalls. Methods Mol Biol. 2013; 1038:81-91.

Rukov JL, **Shomron N**. MicroRNA pharmacogenomics: Post-transcriptional regulation of drug response. Trends Mol Med. 2011; 17:412-423.

Shomron N. MicroRNAs and developmental robustness: a new layer is revealed. PLoS Biol. 2010; 8:e1000397.

Shomron N. MicroRNAs and pharmacogenomics. Pharmacogenomics. 2010; 11:629-32.

Grants

2011-2014	Wolfson Family Charitable Fund, Functional Genomics Center for Complex Diseases, Lead PI (representing 20 co-PIs)
2011-2015	I-CORE Program of the Planning and Budgeting Committee, The Israel Science Foundation (grant number 41/11)
2012-2104	Claire and Amedee Maratier Institute for the Study of Blindness and Visual Disorders
2013-2016	Israel Cancer Research Fund (ICRF), Research Career Development Award (RCDA)
2014-2015	Earlier.org—Friends for an Earlier Breast Cancer Test
2014-2015	Israeli Ministry of Defence, office of Assistant Minister of Defence for Chemical, Biological, Radiological and Nuclear (CBRN) Defence
2014	Saban Family Foundation—Melanoma Research Alliance
2014-2016	Foundation Fighting Blindness

May 24, 2014

Prof. Ella Sklan, Ph.D.

Department of Clinical Microbiology and Immunology
Sackler Faculty of Medicine

Tel Aviv University
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Viral Host Interactions of Positive Strand RNA Viruses

Position

Associate Professor, Sackler Faculty of Medicine

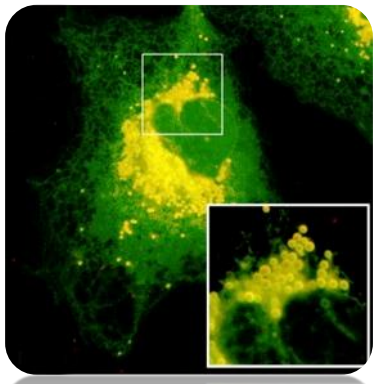
Research

Our long-term goal is identification and characterization of the interactions of viruses with their host cells. Our current model systems include Hepatitis C virus (HCV) and Dengue virus. Current projects in the lab include:

1. Development of systems for the identification and characterization of new interactions between viral and host cell proteins.

2. Using live cell imaging techniques to study HCV assembly.

3. Characterization of the membrane association mechanisms of Dengue virus non-structural proteins.



A live hepatoma cell (Huh7) expressing the viral non-structural protein 5A that localizes to the endoplasmic reticulum and lipid droplets.

Publications

Parameswaran P, **Sklan E**, Wilkins C, Burgon T, Samuel M, Lu R, Ansel KM, Heissmeyer V, Einav S, Jackson W, Doukas T, Paranjape S, Polacek C, Barreto dos Santos F, Jalili R, Babrzadeh F, Gharizadeh B, Grimm D, Kay M, Koike S, Sarnow P, Ronaghi M, Ding S, Harris E, Chow M, Diamond MS, Kirkegaard K, Glenn JS, Fire AZ. Six RNA viruses and forty one hosts: viral small RNAs and modulation of small RNA repertoires in vertebrate and invertebrate systems. (2010) PLOS Pathog, 6:e1000764.

Matto M*, **Sklan EH*,** David, N, Melamed-Book N, Casanova, JE, Glenn JS, Aroeti B. A Role for ADP-ribosylation factor 1 in the regulation of hepatitis C virus replication. (2011) J Virol, 85:946-56. *Equal contribution.

Lee C, Ma H, Hang JQ, Leveque V, **Sklan EH**, Elazar M, Klumpp K, Glenn JS. The hepatitis C virus NS5A inhibitor (BMS-790052) alters the subcellular localization of the NS5A non-structural viral protein. (2011). Virology, 414:10-8.

Nachmias D, **Sklan EH**, Ehrlich M, Bacharach E. Human immunodeficiency virus type 1 envelope proteins traffic toward virion assembly sites via a TBC1D20/Rab1-regulated pathway. (2012) Retrovirology. 9:7.

Nevo-Yassaf I, Yaffe Y, Asher M, Ravid O, Eizenberg S, Henis YI, Nahmias Y, Hirschberg K, **Sklan EH**. Role for TBC1D20 and Rab1 in hepatitis C virus replication via interaction with lipid droplet-bound nonstructural protein 5A. (2012) J Virol. 86:6491-502.

Shlomai A, Rechtman MM, Burdelova EO, Zilberberg A, Hoffman S, Solar I, Fishman S, Halpern Z, **Sklan EH**. The metabolic regulator PGC-1α links hepatitis C virus infection to hepatic insulin resistance. (2012) J Hepatol. 57:867-73.

Stern O, Hung YF, Valdau O, Yaffe Y, Harris E, Hoffmann S, Willbold D, **Sklan EH**. An N-terminal amphipathic helix in dengue virus nonstructural protein 4A mediates oligomerization and is essential for replication. (2013) J Virol. 87:4080-5.

Hanin G, Shenhar-Tsarfaty S, Yayon N, Hoe YY, Bennett ER, **Sklan EH**, Rao DC, Rankinen T, Bouchard C, Geifman-Shochat S, Shifman S, Greenberg DS, Soreq H. (2014) Competing targets of microRNA-608 affect anxiety and hypertension. Hum Mol Genet. 2014 Apr 25. [Epub ahead of print]

Grants

2012-2016 Israel Science Foundation (ISF) Grant

May 24, 2014

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Sackler Faculty of Medicine

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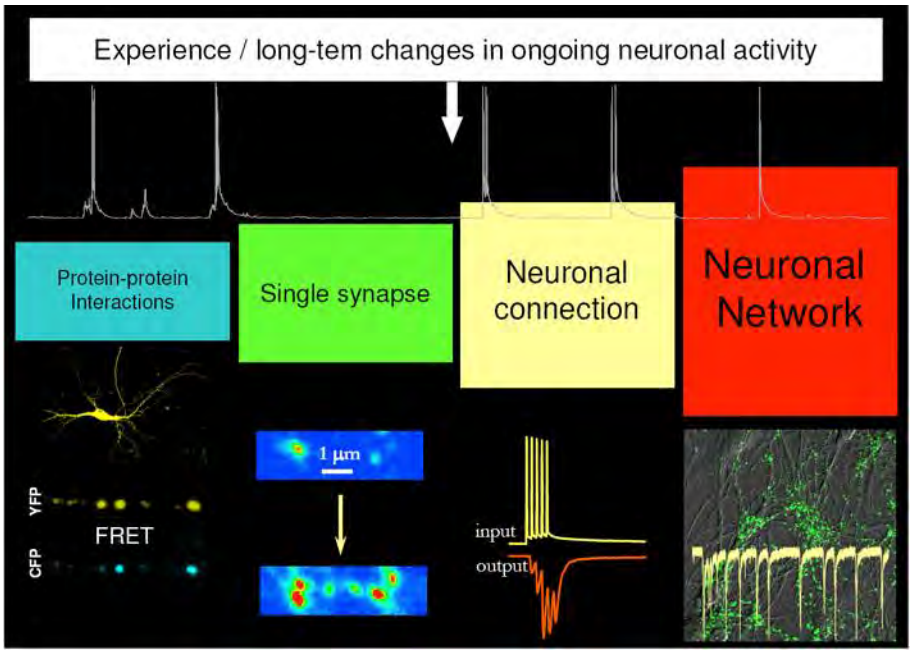
Regulation of Hippocampal Plasticity: Single Synapses to Alzheimer's Disease

Positions

Senior Lecturer, Sackler Faculty of Medicine
Committee Member, IBRO
Scientific Advisory Council Member, American Federation for Aging Research (AFAR)
Organizing Committee Member, Israel Society for Physiology and Pharmacology
Committee Member, Sagol School of Neuroscience, TAU
Committee Member, Center for Nanoscience and Nanotechnology, TAU

Research

The research in the laboratory is focused on understanding the basic mechanisms underlying synaptic function and primary mechanisms initiating synaptic dysfunction at very early stages of Alzheimer's Disease. To achieve this goal, we developed an integrated system that enables simultaneous real-time visualization of structural reorganization in spatially-restricted signaling complexes and functional modifications of single synapses in brain circuits. Utilizing FRET spectroscopy, high-resolution optical imaging, electrophysiology, molecular biology, and biochemistry we explore experience-dependent mechanisms regulating the number and plasticity of hippocampal synapses under physiological and pathological conditions.



Publications

Fogel H, Frere S, Segev O, Bharill S, Shapira I, Gazit N, O'Malley T, Slomowitz E, Berdichevsky Y, Walsh Dominic M, Isacoff Ehud Y, Hirsch Joel A, **Slutsky I** (2014) APP homodimers transduce an amyloid-β-mediated increase in release probability at excitatory synapses. *Cell Reports*, http://dx.doi.org/10.1016/j.celrep.2014.04.024.

Becker W, Shcheslavkiy V, Frere S, **Slutsky I.** (2014) Spatially resolved recording of transient fluorescence-lifetime effects by line-scanning TCSPC. *Microsc Res Tech*. 77:216-24

Dolev I*, Fogel H*, Milshtein H, Berdichevsky Y, Lipstein N, Brose N, Gazit N, **Slutsky I** (2013) Spike bursts increase amyloid-beta 40/42 ratio by inducing a presenilin-1 conformational change. *Nature Neurosci*. 16: 587-595.

Laviv T, Vertkin I, Berdichevsky Y, Fogel H, Riven I, Bettler B, Slesinger PA, **Slutsky I**. (2011) Compartmentalization of the GABAB receptor signaling complex is required for presynaptic inhibition at hippocampal synapses. *J Neurosci*. 31:12523-12532.

Laviv, T., Riven, I., Dolev, I., Vertkin, I., Balana, B., Slesinger, P. A., and **Slutsky, I**. (2010). Basal GABA Regulates GABA(B)R Conformation and Release Probability at Single Hippocampal Synapses. *Neuron 67*, 253-267.

Slutsky, I., Abumaria, N., Wu, L. J., Huang, C., Zhang, L., Li, B., Zhao, X., Govindarajan, A., Zhao, M. G., Zhuo, M., Tonegawa, S., Liu, G. (2010). Enhancement of Learning and Memory by Elevating Brain Magnesium. *Neuron 65*, 165-177.

Grants

2011 – 2016, Evolution of Alzheimer's Disease: From Dynamics of Single Synapses to Memory Loss, European Research Council Starting Grant.

2011 – 2014, Targeting Amyloid-beta: From Molecular Composition to Synaptic Function, Israel Science Foundation and Legacy Heritage Fund.

2010 – 2014, Interactions Between Presynaptic GABA(B) and Muscarinic Receptors: From Multicomplex formation to Regulation of Synaptic Filter, Binational Science Foundation (BSF).

May 24, 2014

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Basic and Applicative Research of Eye Physiology, Diseases and Function

Positions

Associate Professor, Sackler Faculty of Medicine
Editorial Board, *Translational Vision Science & Technology (TVST*)
International Committee Member, ARVO

Research

The eye presents many challenges for research regarding unsolved conditions such as retinal and optic nerve assaults, damage to eye by surrounding conditions of work and every day activity. The following specific subjects are studied:

- Optic nerve research: creating models of trauma and disease to investigate the mechanisms of degeneration and regeneration
- Investigate ways to treat corneal injury and diseases
- Ultraviolet light damage to the eye
- Research on the neovascular process in the eye and search ways to prevent it
- Occupational and environmental factors affecting eye and vision

Publications

Rosenzweig S, Raz-Prag D, Nitzan A, Galron R, Paz M, Jeserich G, Neufeld G, Barzilai A **Solomon AS**. Graefes Arch Clin Exp Ophthalmol 2010;248:1423-35.

Cohen Y, Belkin M, Yehezkel O, Solomon AS, Polat U. Dependency between light intensity and refractive development under light-dark cycles. Exp Eye Res 2011;92:40-6.

Skaat A, **Solomon AS**, Moroz I, Hai OV, Rechtman E, Vishnevskaia Dai V, Rotenstreich Increased electroretinogram a-wave amplitude after intravitreal bevacizumab injection for neovascular age-related macular degeneration. Acta Ophthalmol 2011;89:269-73.

Raz-Prag D, Galron R, Segev-Amzaleg N, **Solomon AS**, Shilo Y, Barzilai A, Frenkel D. A role for vascular deficiency in retinal pathology in a mouse model of ataxia-telangiectasia. Am J Pathol 2011;179:1533-41.

Azizi E, Pavlotsky F, Kudish A, Flint P, **Solomon AS**, Lerman Y, Oberman B, Sadetzki S. Serum levels of 25-Hydroxy-Vitamin D3 among sun-protected outdoor workers in Israel. Photochem Photobiol 2012:1751-57.

Cohen, Y., Peleg, E., Belkin, M., Polat, U., **Solomon, A.,** (2012) Ambient Illuminance, retinal dopamine release and refractive development in chicks. *Exp. Eye Res.* 103:33-40.

Grants

2012- 2013 Baharav Research Grant
2012- 2014 WP7 EC VISION

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Met Proto-Oncogene and its Ligand, HGF/SF and Breast Cancer

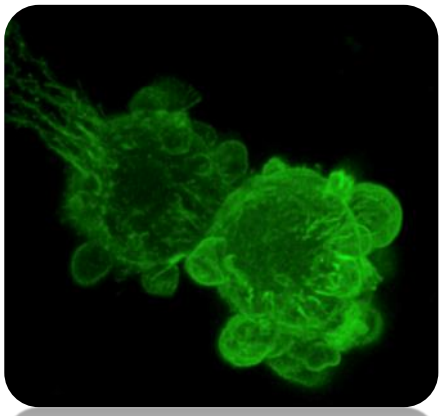
Position

Associate Professor, Sackler Faculty of Medicine
Director, Sackler Cellular and Molecular Imaging Center (SCMIC)

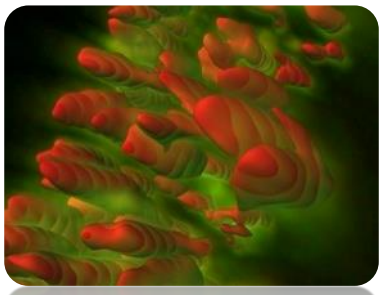
Research

Breast cancer is the most common malignant disease in western women. In the majority of cases the cause of death in cancer patients is not the primary tumors, but complications derived from metastases at distant sites. The *met* proto-oncogene product (Met - a receptor tyrosine kinase) and its ligand, hepatocyte growth factor/scatter factor (HGF/SF), mediate cell motility and proliferation *in* vitro and tumorigenicity, angiogenesis and metastasis *in vivo*. Mimp/Mtch2, a mitochondrial carrier homologue cloned in our lab, is induced by Met-HGF/SF signaling and is involved in metabolic and bioenergetic processes. We have previously shown that activation of Met by HGF/SF induces an increase in tumor blood volume in a dose-dependent manner. Mimp/Mtch2 reduces cells proliferation *in vitro* and tumor growth *in vivo*. Several anti-Met targeted therapies are in development and some have entered phase III clinical trials.

Met localization in blebbing cells



Mimp localization in mitochondrial cells (Red inner mitochondria marker, Green Mimp-GFP)



The goal of our studies is to further understand the role of Met-Mimp/Mtch2 in cancer progression and metastasis, and to develop modalities for personalizing targeted Met therapy. Fluorescent tagged–Met proteins were used to study Met mitogenic effect on cells. Met induced cell motility is mediated by the formation of membrane structures such as ruffles, pseudopodia and blebs. Over expression of GFP-Met WT results in its constitutive activation, cell rounding and detachment, and dynamic non-apoptotic membrane blebbing. Bleb retraction results in numerous membrane microspikes where CFP-Met WT, YFP-actin and membrane markers accumulate. Expression of Dominant-Negative (DN) YFP-Met alone did not induce any membrane blebbing, and co-

expression of CFP-Met WT and YFP-Met DN significantly reduces membrane blebbing. Using confocal based molecular imaging we also show that Mimp/Mtch2 reduces the levels of reactive oxygen species ROS and prevents the HGF/SF induced increase in ROS. Mimp/Mtch2 also reduces the polarization of the mitochondrial membrane potential.

To study Met activation by HGF/SF *in vivo*, we used a xenograft mouse model in which DA3 cells expressing the fluorescent protein mCherry (DA3-mCherry) are injected orthotropicly into mice mammary glands. Contrast media ultrasound-based Met functional molecular imaging (FMI) demonstrated that HGF/SF-induced increased hemodynamics is dependent on Met concentration and can be dramatically reduce upon inhibition of the receptor and it's signaling pathway; Whole animal spectral imaging enabled detection of sub-millimeter metastases demonstrating fast developing micrometastatic spread of the tumor; Macro to Micro and two photon confocal imaging demonstrated HGF/SF-induced changes in blood flow at single vessel resolution, localization of metalloprotease and catapsine activity at the tumor edge and increase in single cell motility.

Met molecular imaging demonstrated that Met signaling modulation plays a major role in breast cancer tumor growth and development. These emerging MI modalities may help tailor Met-targeted therapy.

Publications

Zaritsky A, Natan S, Horev J, Hecht I, Wolf L, Ben-Jacob E and **Tsarfaty I.** Multi-cellular differential interference contrast based segmentation algorithm as a tool for understanding and quantifying cell motility dynamics. *PloS One*. 2011. 6: e27593.

Stein GY, Yosef N, Reichman H, Horev J, Laser-Azogui A, Berens A, Resau J, Ruppin E, Sharan R, **Tsarfaty I**. Met kinetic signature derived from the response to HGF/SF in a cellular model predicts breast cancer patient survival. *PLoS One*. 2012. 7:e45969.

Zaritsky A, Natan S, Ben-Jacob E, **Tsarfaty I**. Emergence of HGF/SF-induced coordinated cellular motility. *PLoS One*. 2012. 7:e44671.

Laser-Azogui, A., Diamant-Levi, T., Israeli, S., Roytman, Y. & **Tsarfaty**, I. Met-induced membrane blebbing leads to amoeboid cell motility and invasion. Oncogene (2013).

Shaul, P. Frenkel, M. Goldstein. Mittelman, L.; Grunwald, A.; Ebenstein, Y. **Tsarfaty, I**. Fridman, M. The structure of anthracycline derivatives determines their subcellular localization and cytotoxic activity. *ACS Medicinal Chemistry Letters*, 4, 323-328 (2013).

Rivlin, M. Horev, J. **Tsarfaty, I.** Navon G. Molecular imaging of tumors and metastases using chemical exchange saturation transfer (CEST) MRI. Sci Rep. 25;3:3045 (2013)

Zaritsky, A., Manor, N., Wolf, L., Ben-Jacob, E. & **Tsarfaty, I**. Benchmark for multi-cellular segmentation of bright field microscopy images. BMC Bioinformatics, *BMC Bioinformatics* , **14**:319 (2013).

Natan, S*. Tsarfaty, G*. Horev, J. Haklai, R. Kloog, Y. **Tsarfaty, I.** Interplay between HGF/SF–Met-Ras signaling, tumor metabolism and blood flow as a potential target for breast cancer therapy. Oncoscience, 1: 30 (2014).

Ninio-Many, L. Grossman, H. Levi, M. Zilber S., **Tsarfaty I.** Shomron, N. Tuvar, A. Chuderland, M Stemmer, D. S. Ben-Aharon, I. Shalgi, R. MicroRNA miR-125a-3p modulates molecular pathway of motility and migration in prostate cancer cells. Oncoscience, 1: 250 (2014)

Review

Tsarfaty I, Ben-Jacob E. Secrets of tubule engineering by epithelial cells. *Proc Natl Acad Sci USA*. 2012. 109:6790-1.

Grants (last 3 years)

2010 – 2014 BSF, The Interplay between Tumor Cell Glucose Metabolism and Met Tyrosine Kinase Growth Factor Receptor Signaling as a Target for Anti Tumor Therapy

2010 – 2015 Sackler Foundation, Establishment of the Tel Aviv University Sackler Cellular and Molecular Imaging Center (SCMIC)

May 24, 2014

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Molecular Biology of the Insulin-Like Growth Factor System

Positions

Professor, Sackler Faculty of Medicine
Lady Davis Chair in Biochemistry
Chair, Department of Human Molecular Genetics and Biochemistry
Vice Director, MD Graduate Program, Sackler School of Medicine

Research

The insulin-like growth factors (IGF1, IGF2) are a family of hormones with important roles in growth and development. The biological actions of the IGFs are mediated by the IGF1 receptor (IGF1R), a cell-surface receptor related to the insulin receptor. The IGF1R signaling pathway has an important role in the biochemical chain of events linking obesity, diabetes, and cancer. Our work is aimed at understanding the molecular and cellular events responsible for IGF1R expression in cancer. These studies are expected to generate information that might translate into more efficient IGF1R targeting approaches. Furthermore, a better understanding of the molecular biology of the IGF system will have important ramifications in areas such as obesity, metabolic syndrome, diabetes, and cancer research. Specific topics include:

- Interplay between the IGF signaling pathways and cancer genes (p53, BRCA).
- IGF1R targeting as a therapeutic approach in cancer.
- Epigenetic mechanisms in cancer development.
- Biological activities of insulin analogues.
- Metabolism and cancer.

Publications

Schayek, H., Bentov, I., Rotem, I., Pasmanik-Chor, M., Ginsberg, D., Plymate, S.R. and **Werner, H.** (2010) Transcription factor E2F1 is a potent transactivator of the insulin-like growth factor-I receptor gene. *Growth Hormone & IGF Res.* 20:68-72.

Rubovitch, V., Edut, S., Sarfstein, R., **Werner, H.** and Pick C.G. (2010) The intricate involvement of the insulin-like growth factor receptor signaling in mild traumatic brain injury in mice. *Neurobiol. Dis.* 38:299-303.

Sarfstein, R., Belfiore, A. and **Werner, H.** (2010) Identification of IGF-I receptor gene promoter-binding proteins in estrogen receptor (ER)-positive and ER-depleted breast cancer cells. *Cancers (Basel)* 2:233-261.

Aiello, A., Pandini, G., Sarfstein, R., **Werner, H.**, Manfioletti, G., Vigneri, R. and Belfiore, A. (2010) HMGA1 protein is a positive regulator of the insulin-like growth factor-I receptor gene. *Eur. J. Cancer* 46:1919-1926.

Schayek, H., Bentov, I., Sun, S., Plymate, S.R. and **Werner, H**. (2010) Progression to metastatic stage in a cellular model of prostate cancer is associated with methylation of the androgen receptor gene and transcriptional suppression of the insulin-like growth factor-I receptor gene. *Exp. Cell Res.* 316:1479-1488.

Schayek, H., Seti, H., Greenberg, N., Sun, S., **Werner, H**. and Plymate, S.R. (2010) Differential regulation of insulin-like growth factor-I receptor gene expression by wild-type and mutant androgen receptor in prostate cancer cells. *Mol. Cell. Endocrinol.* 323:239-245.

Bruchim, I., Amichay, K., Kidron, D., Attias, Z. Biron-Shental, T., Drucker, L., Friedman, E., **Werner, H.** and Fishman, A. (2010) BRCA-1/2 germline mutations in Jewish patients with uterine serous carcinoma. *Int. J. Gynecol. Cancer* 20:1148-1153.

Werner, H. and Bruchim, I. (2010) Basic and clinical significance of IGF-I-induced signatures in cancer. *BMC Medicine* Jan 5; 8:2.

Yehezkel, E., Weinstein, D., Simon, M., Sarfstein, R., Laron, Z. and **Werner, H.** (2010) Long-acting insulin analogues elicit atypical signalling events mediated by the insulin receptor and insulin-like growth factor-I receptor. *Diabetologia* 53:2667-2675.

Attias-Geva, Z., Bentov, I., Fishman, A., **Werner, H.** and Bruchim, I. (2011) Insulin-like growth factor-I receptor inhibition by specific tyrosine kinase inhibitor NVP-AEW541 in endometrioid and serous papillary endometrial cancer cell lines. *Gynecol. Oncol.* 121:383-389.

Attias-Geva, Z., Bentov, I., Ludwig, D.L., Fishman, A., Bruchim, I. and **Werner, H.** (2011) Insulin-like growth factor-I receptor targeting with monoclonal antibody cixutumumab (IMC-A12) inhibits IGF-1 action in endometrial cancer cells. *Eur. J. Cancer* 47:1717-1726.

Rubovitch, V., Shachar, A., **Werner, H.** and Pick, C. (2011) Does IGF-1 administration after a mild traumatic brain injury in mice activate the adaptive arm of ER stress? *Neurochem. Int*. 58:443-446.

Werner, H. and Chantelau, E. (2011) Differences in bioactivity between human insulin and insulin analogues approved for therapeutic use – compilation of reports from the past 20 years. *Diabetol. Metab. Syndr* 29, 3:13.

Sarfstein, R., Bruchim, I., Fishman, A. and **Werner, H.** (2011) The mechanism of action of the histone deacetylase inhibitor vorinostat involves interactions with the insulin-like growth factor signaling pathway. *PLoS One*, 6:e24468.

Attias-Geva, Z., Bentov, I., Kidron, D., Amichay, K., Sarfstein, R., Fishman, A., Bruchim, I. and **Werner, H.** (2011) p53 regulates IGF-I receptor gene expression in uterine serous carcinoma and predicts responsiveness to an IGF-IR-directed targeted therapy. *Eur. J. Cancer*, 4:1570-1580.

Sarfstein, R., Pasmanik-Chor, M., Yeheskel, A., Edry, L., Shomron, N., Warman, N., Wertheimer, E., Maor, S., Shochat, L. and **Werner, H.** (2012) Insulin-like growth factor-I receptor (IGF-IR) translocates to nucleus and autoregulates *IGF-IR* gene expression in breast cancer cells. *J. Biol. Chem*. 287:2766-2776.

Amichay, K., Kidron, D., Attias-Geva, Z., Schayek, H., Sarfstein, R., Fishman, A., **Werner, H.** and Bruchim, I. (2012) BRCA1 is expressed in uterine serous carcinoma (USC) and controls insulin-like growth factor-I receptor (IGF-IR) gene expression in USC cell lines. *Int. J. Gynecol. Cancer* 22:748-754.

Schayek, H., Bentov, I., Jacob-Hirsch, J., Yeung, C., Khanna, C., Helman, L.J., Plymate, S.R. and **Werner, H.** (2012) Global methylation analysis identifies PITX2 as an upstream regulator of the androgen receptor and IGF-I receptor genes in prostate cancer. *Hormone Metab. Res*. 44:511-519.

Sarfstein, R., Friedman, Y., Attias-Geva, Z., Fishman, A., Bruchim, I. and **Werner, H.** (2013)

Metformin down-regulates the insulin/IGF-I signaling pathway and inhibits different uterine serous carcinoma cells proliferation and migration in p53-dependent or -independent manners. *PLoS One* 8:e61537.

Bitelman, C., Sarfstein, R., Sarig, M., Attias-Geva, Z., Fishman, A., **Werner, H.** and Bruchim, I. (2013) IGF1R-directed targeted therapy enhances the cytotoxic effect of chemotherapy in endometrial cancer. *Cancer Lett.* 335:153-159.

Hermani, A., Shukla, A., Medunjanin, S., **Werner, H.** and Mayer, D. (2013) Insulin-like growth factor binding protein-4 and -5 modulate ligand-dependent estrogen receptor-a activation in breast cancer cells in an IGF-independent manner. *Cell. Signal.* 25:1395-1402.

Weinstein, D., Sarfstein, R., Laron, Z. and **Werner, H.** (2014) Insulin receptor compensates for IGF1R inhibition and directly induces mitogenic activity in prostate cancer cells. *Endocrine Connect.* 3:24-35.

Canetti, L., **Werner, H.** and Leikin-Frenkel, A. (2014) Linoleic and alpha-linolenic acids ameliorate streptozotocin-induced diabetes in mice. *Arch. Physiol. Biochem.* 120:34-39.

Rubinfeld, H., Kammer, A., Cohen, O., Gorshtein, A., Cohen, Z.R., Hadani, M., **Werner, H.** and Shimon, I. (2014) IGF1 induces cell proliferation in human pituitary tumors – Functional blockade of IGF1 receptor as a novel therapeutic approach in non-functioning tumors. Mol. Cell. Endocrinol**.** 390:93-101.

Reviews

Werner, H., Weinstein, D., Yehezkel, E. and Laron, Z. (2011) Controversies in the use of insulin analogues. *Expert Opinion Biol. Ther.* 11:199-209.

Werner, H. (2011) Tumor suppressors govern insulin-like growth factor signaling pathways: implications in metabolism and cancer. *Oncogene* 31:2703-2714.

Werner, H. and Bruchim, I. (2012) Convergence of the IGF-1 and BRCA1 signaling pathways in familial cancer. Lancet Oncology, 13:E537-544.

Werner, H., Attias-Geva, Z., Bentov, I., Sarfstein, R., Schayek, H., Weinstein, D. and Bruchim, I. (2012) Cancer genes, tumor suppressors, and regulation of IGF-1R gene expression in cancer. In: Insulin-like growth factors and cancer: from basic biology to therapeutics, ed. by LeRoith, D., Springer Science, New York, pp.159-177.

Bentov, I. and **Werner, H.** (2013) Insulin-like growth factor-1. In: Handbook of Biologically Active Peptides, Second edition, ed. by Kastin, A., Elsevier Press, San Diego. pp. 1627-1632.

Werner, H. and Sarfstein, R. (2013) Insulin receptor family. In: The Receptor Tyrosine Kinase Handbook, ed. by Wheeler, D.L. and Yarden, Y., Springer Science, New York, in press.

Werner, H. (2012) Tumor suppressors govern insulin-like growth factor signaling pathways: implications in metabolism and cancer. *Oncogene* 31:2703-2714.

Bruchim, I. and **Werner, H.** (2013) Targeting IGF-I signaling pathwys in gynecologic malignancies. *Expert Opinion Ther. Targets*. 17:307-320.

Sarfstein, R. and **Werner, H.** (2013) Nuclear insulin and insulin-like growth factor receptors: a novel paradigm in signal transduction. *Endocrinology* 154:1672-1679.

LeRoith, D. and **Werner, H.** (2013) Insulin and IGF1 receptors in the brain. *Eur. Neuropsychopharmacol*. in press.

Bruchim, I., Sarfstein, R. and **Werner, H.** (2014) The IGF hormonal network in endometrial cancer: functions, regulation, and targeting approaches. **Front. Endocrinol.** 5:76.

Werner, H. and Sarfstein, R. (2014) Transcriptional and epigenetic control of IGF1 receptor gene expression: implications in metabolism and cancer. *Growth Hormone & IGF Res.,* in press.

Grants

2010-2014 "Identification of signaling pathways associated with protection of congenital IGF-I deficient patients from cancer". US-Israel Binational Science Foundation.

2012-2014 "Insulin/IGF-1R transcription factors: new players in regulation of cancer cell metabolism". European Foundation for the Study of Diabetes, Düsseldorf, Germany.

2013-2014 "Genome-wide identification of cancer-protecting pathways in Laron syndrome: data mining a rare disease translates into new discoveries in oncology". Cancer Biology Research Center, Tel Aviv University

2013-2014 "Identification of signaling and metabolic pathways elicited by insulin analogues in gynecologic and colon cancers". Insulin Dependent Diabetes Trust, U.K.

2014-2015 "Identification of a metabolic gene associated with protection of Laron syndrome patients from malignant transformation". Carl and Leonora Fingerhut Fund for Cancer Research, Sackler School of Medicine, Tel Aviv University

May 24, 2014

Steyer School of Health Professions

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Paralinguistic Communication, Phonetics and Psychoacoustics

Positions

Senior Lecturer, Sackler Faculty of Medicine

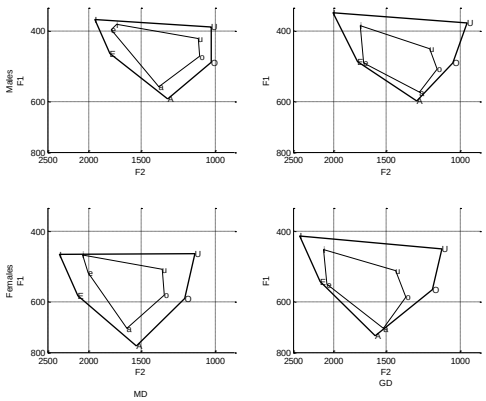
Research

Our interests lie on the frontier between signal processing and human communication in both speech and music. One general field we have been involved in in recent years is the paralinguistic aspect of verbal communication. In this research my colleagues and we have been been exploring two main directions:

1. Emotion: Production and perception of emotions in speech, mostly in Hebrew, along with several excursions into cross lingual studies – Hebrew/German and Hebrew/Arabic. I've been looking at emotions as expressed in many different settings: films, event recollection, interviews, psychotherapy, and acted with conflicting textual and prosodic content.
2. Pragmatics: Production and perception of word stress (i.e. "I love my cat" vs. "I love my cat"), in Hebrew and Arabic, and lately also the manifestations of lexical stress in Hebrew.

We have also been interested in signal processing aspects of music and musical acoustics for a very long time. Recent works we have participated in have been related to vibrato in the singing voice: quantifying it and relating it to factors such as singer proficiency, vocal warmup and singing style. Situated in the heart of the Middle East, we have become interested in acoustic phonetics of Hebrew and Spoken Arabic. Along with our colleagues, we have studied Hebrew vowels in everyday, connected speech, and in several dialects of Spoken Arabic, which have been studied very little. For example, vowel spaces of a Galilean dialect and the Kfar Kassem dialect are presented in the figure below.

Finally, the perceptual aspects of the subjects above have led us to examine their interaction with psychoacoustic thresholds. Starting with frequency perception thresholds, and now branching into intensity and spectral thresholds, our collaborators and we have been looking at their correlation to perception of of emotion and music.



Vowel spaces of Spoken Arabic in a Galilean Dialect (GD) and a "Muthallath Dialect" (MD) for men and women. External polygons are long vowels, internal polygons are short vowels. Note that short vowels are more centralized, and exhibit larger differences between dialects.

Publications

G. Caridakis, K. Karpouzis, M. Wallace, L. Kessous, **N. Amir**, “Multimodal user’s affective state analysis in naturalistic interaction“, Journal on Multimodal user Interfaces, Vol. 3(1-2), 49-66 (2010)

A. Batliner, S. Steidl, B. Schuller, D. Seppi, T. Vogt, J. Wagner, L. Devillers, L. Vidrascu, V. Aharonson, L. Kessous, **N. Amir**, “Whodunnit - Searching for the Most Important Feature Types Signalling Emotion-Related User States in Speech”, Computer Speech and Language, VOl. 25(1), 4-28 (2011)

Amir, O., Engel, M., Shabtai, E., **Amir N.** Identification of children’s gender and age by listeners. Journal of Voice, 26(3), 314-321 (2012)

M. Inspector, D. Manor, N. Amir, T. Kushnir, A. Karni. A word by any other intonation: FMRI evidence for implicit memory traces for pitch contours of spoken words in adult brains. PLoS ONE, 8(12) (2013)

E. Globerson, N. Amir, O. Golan, L. Kishon, M. Lavidor. Psychoacoustic abilities as predictors of vocal emotion recognition. Attention Perception and Psychophysics, 75, 1799 -1810 (2013)

May 25, 2014

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Voice, Speaking Rate, Stuttering and Fluency Disorders

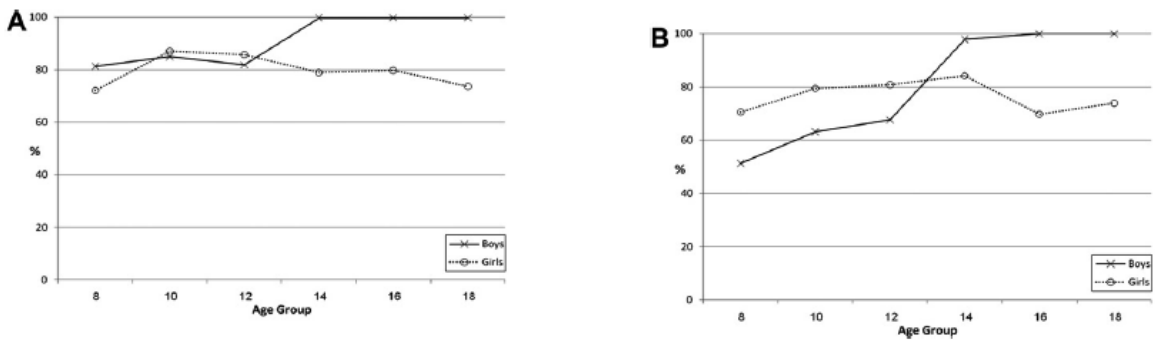
Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Our research, as well as our clinical interest, focuses on two major fields: *Stuttering* and *Voice*. In the area of stuttering and other fluency disorders, we are interested in identifying and measuring various fluency charcteristics, providing normative data on speaking rate in Hebrew and exploring therapeutic approaches for stuttering, cluttering and other related fluency disorders. To this end, we are conducting studies on the perception of stuttering, and on the acoustic properties of speaking rate, normal disfluency and stuttering. In addition, we are currently collaborating with researchers in other research centers in a study that utilizes advanced methods for brain imaging related to stuttering and and language.

In the area of voice, we are highly interested in characterizing vocal properties related to different physical, physiological and emotional conditions, and on the professional voice. This line of research involves exploring and identifying acoustic, aerodynamic, percpetual and acoustic measures that differentiate, for example, between people with and without laryngeal pathologies, people who experience various emotional or social conditions, and women at different hormonal conditions and phases (e.g., using birth-control pills, pregnancy, menstrual cycle, etc.).



Correct gender identification rates for boys and girls in the six age groups for (A) sentences and (B) vowels.

Publications

Amir, O., Stern, D. & Cohen, N. (2010). Self reports on voice disorders among yeshiva students and university students. *The Israeli Journal of Language, Speech and Hearing Disorders, 29,* 11-21 (Hebrew).

Diamond, G.M., Rochman, D. & **Amir, O.** (2010). Arousing primary vulnerable emotions in the context of unresolved anger: "Speaking about" versus "speaking to". *Journal of Counseling Psychology, 57,* 402-410.

Ezrati, R., & **Amir, O**. (2011). Stuttering in early childhood. *Israeli Journal of Pediatrics, 75, 37-38* (Hebrew).

Amir, O., & Grinfeld, D. (2011). Articulation rate in childhood and adolescence: Hebrew speakers. *Lanaguage and Speech, 54,* 225-240.

Fischer, J., Semple, S., Fickenscher, G., Jürgens, R., Kruse, E., Heistermann. M. & **Amir, O.** (2011). Do women's voices provide cues of the likelihood of ovulation? The importance of sampling regime. *PLoS One, 6, (9),* e24490.

Amir, O., Engel, M., Shabtai, E., & Amir, N. (2012). Identification of children's gender and age by listeners. *Journal of Voice, 26, 313-321*

Amir, O., Primov-Fever, A., Kushnir, T., Kandelshine-Waldman, O. & Wolf M. (in press). Evaluating voice charcteristics of first-year acting-students in Israel: Factor analysis. *Journal of Voice.* 27, (1), 68-77.

Amir, O. & Levine-Yundof, R. (2013). Listeners' attitude toward people with dysphonia. Journal of Voice. 27, (4), 524.e1-524.e10.

Galili, L., **Amir, O**. & Gilboa-Schechtman, E. (2013). Acoustic Properties of Dominance and Request Utterances in Social Anxiety. Journal of Social & Clinical Psychology, 32, (6), 651-673.

Rochman, D. & **Amir O.** (2013). Examining in-session expressions of emotions with speech/vocal acoustic measures: An introductory guide. Psychotherapy Research, 23, (4), 381-393.

Finkelstein, M. & **Amir, O**. (2013). Speaking rate among professional newscasters: Hebrew speakers. Studies in Media and Communication, 1, 131-139.

Amir, O., Lebi-Jacob, N. & Harari, O. (2014) The effect of In-Vitro Fertilization treatment on women's voice. Journal of Voice .pii: S0892-1997(13)00248-8

Gilboa-Schechtman, E., Galili, L., Sahar, Y. & **Amir, O**. (2014). Being "in" or "out" of the game: Subjective and acoustic reactions to exclusion and popularity in social anxiety. Frountiers in Human Neuroscience. 8:147, 1-13.

Chapters

Ezrati, R., & **Amir, O.** (2011). Stuttering in early childhood. In: *Babies' and Toddlers' Health – Usful Information for the Maternal and Child Health Team.* Urkin, J., Amitiai, Y., & Honovich, M. (eds.). Tel-Aviv, Israel: Dionon Ltd. Ch. 37, pp. 213-215 (Hebrew).

Amir, O. (2013). Current issues in voice assessment and intervention in Israel. In: *International Perspective on Voice Disorders*. Yiu, E. M-L. Bristol, UK: Multilingual Matters. Ch. 6. pp. 62-67.

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Learning and Plasticity and Early Detection of Hearing Loss - Clinical Implications

Positions

Lecturer, Sackler Faculty of Medicine

Research

Our research focuses on two main fields:

(a) Learning and plasticity in the auditory system:
Our research goal focuses on investigating perceptual learning and plasticity in the auditory system throughout the life span. Our interest in this area is motivated by the constant need in clinical practice to seek for better understanding of the learning characteristics and limitations of brain plasticity in the auditory modality which will in turn contribute to the better development of habilitation strategies in a variety of populations with hearing difficulties. We conduct behavioral studies in adults and children (i.e. single and multi-session training) using both non-verbal and verbal stimuli in order to explore the different characteristics of skill learning in the auditory system such as the time course of learning, the role of sleep for the establishment of delayed gains in performance, the generalization of the learning gains to untrained conditions etc. In order to provide evidence for functional plasticity in the neural encoding of sounds in the auditory system following training, we are currently also utilizing electrophysiological measures. Specifically, we record auditory brainstem responses to speech stimuli which provide us with a unique opportunity to follow changes in the neural signatures of the acoustic properties of the input signal (e.g., pitch tracking, harmonics, onset timing etc) that occur before and following training. We plan to explore the learning characteristics and limitations of brain plasticity in the auditory modality in different populations (e.g. middle-aged, elderly adults, hearing impaired, auditory processing disorders etc.) using both behavioral and electrophysiological measures.

(b) Early detection of hearing loss in neonates and its clinical limplications:
Our interest in this field is motivated by the growing evidence that early identification of hearing loss and intervention prior to six months of age can diminish the negative impact of hearing loss on speech and language acquisition. One line of research we conduct focuses on the prevalence and characteristics of hearing loss among different populations of infants such as infants with very low birth weight infants and congenital cytomegalovirus infection. Universal newborn hearing screening allows us not only identify special populations at risk for hearing loss but also, for the first time, to follow the developmental milestones of these children at a very young age and assess the communicative skills of infants with different types of hearing loss (e.g., unilateral hearing loss, mild hearing loss). These early communicative skills are known to be necessary to language and speech development. Thus, another line of research focuses on the effects of different degrees of hearing loss (e.g., unilateral hearing loss) on early auditory and pre-lexical productions. Learning the consequences of early detection and as a result early intervention

provides insights to the ability to reverse the negative influence of auditory deprivation due to brain plasticity in young children.

Publications

Y. Zaltz, **D. Ari-Even Roth**, L. Kishon-Rabin. Does feedback matter in an auditory frequency discrimination learning task? Journal of Basic and Clinical Physiology & Pharmacology, 21(3), 241-254, 2010.

Y. Zaltz, **D. Ari-Even Roth**, L. Kishon-Rabin. How specific is the learning in an auditory frequency discrimination task? Journal of Basic and Clinical Physiology & Pharmacology, 22(3), 69-73, 2011.

D. Ari-Even Roth, C. Muchnik, E. Shabtai, M. Hildesheimer, Y. Henkin. Evidence for atypical auditory brainstem responses in young children with suspected autism spectrum disorders. Developmental Medicine and Child Neurology, 54(1), 23-29, 2012.

G. Barkai, A. Barzilai, E. Mendelson, M. Tepperberg-Oikawa, **D. Ari-Even Roth**, J. Kuint. Newborn screening for congenital cytomegalovirus using real-time polymerase chain reaction in umbilical cord blood. Israel Medical Association Journal, 15(6), 279-283, 2013.

L. Kishon-Rabin, M. Avivi-Reich, **D. Ari-Even Roth**. Improved gap detection thresholds following auditory training: Evidence of auditory plasticity in older adults. The American Journal of Audiology, 22(2), 343-346, 2013.

C. Muchnik, **D. Ari-Even Roth**, M. Hildesheimer, M. Arie, Y. Bar-Haim, Y. Henkin. Abnormalities in auditory efferent activities in children with selective mutism. Audiology and Neurotology, 18(6), 353-361, 2013.

Y. Henkin, R. Taitelbaum-Swead, **D. Ari-Even Roth**, L. Kishon-Rabin, Y. Shapira, L. Migirov, M. Hildesheimer, R. Kaplan-Neeman. Evidence for a right cochlear implant advantage in simultaneous bilateral cochlear implantation. Laryngoscope, doi:10.1002/lary.24635, 2014.

G. Barkai*, **D. Ari-Even Roth***, A. Barzilai, M. Hildesheimer, M. Tepperberg-Oikawa, E. Mendelson, J. Kuint. Universal neonatal cytomegalovirus screening using saliva - report of clinical experience. Journal of Clinical Virology, 2014 in press. *equal contribution

June 1, 2014

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Investigating Sensory Modulation Disorder (SMD) Over Life Span

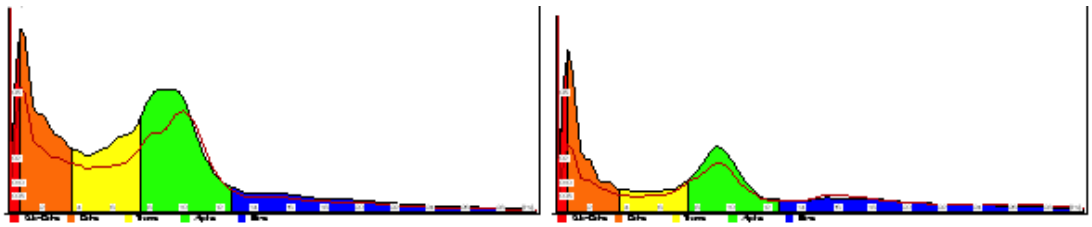
Positions

Lecturer, Sackler Faculty of Medicine

Research

SMD is a health condition in which abnormal responses to naturally occurring stimuli is demonstrated in a manner that interferes with daily life, affecting 13% of otherwise healthy individuals. Our research is aiming to better understand and expand the therapeutic modalities by identifying biomarkers that would specify this health condition, applying psychophysical and neurophysiological methodologies (see below) to characterize children and adults with SMD, suggesting a unique perspective associating SMD with pain.

Moreover in trying to understand the potential role of SMD in neurodevelopmental trajectory, we study this disorder in other health conditions such as chronic pain, mental health, substance abuse, and neurodevelopmental disorders.



EEG of resting state (5 min) in controls and SMD adults recorded from frontal and central cortical sites demonstrated lower power cortical oscllations at δ (orange), β (yellow) and a (green)

Another area of research is embedded in occupational science: Leisure activities are usually perceived as promoting health and well-being. In recent years we're witness to such activities that are harmful, specifically substance abuse activities. This research is exploring substance abuse activities in Israeli adolescents applying an occupational perspective.

Publications

Manuscripts

Bar-Shalita, T., Vatine, J.J., Yanitsky, D., Parush, S., Weissman-Fogel, I. (2014) Atypical central pain processing in sensory modulation disorder: absence of temporal summation and higher after-sensation. Exp Brain Res 232, 587-595.

Bar-Shalita, T., Parush,S. Pain and sensory modulation disorder (abstracts from the Gerry Schwartz and Heather Reisman 3rd International Conference). Int J Child Health Hum Dev 2013;6:385

Bar-Shalita, T., Boni, O., Gevir, D., & Doryon, Y. (2013). The Israeli Occupational Therapy Code of Ethics. The Israeli Occupational Therapy National higher professional committee, Israel's Occupational Therapy Association.

Bar-Shalita, T., Vatine, J.J., Parush, S., Deutsch, L., Seltzer, Z. Psychophysical correlates in adults with sensory modulation disorder. Disabil Rehabil. 2012, 34:943-50.

Bar-Shalita, T., Vatine, J.J., & Parush, S. Hebrew translation to the Faces Pain Scale-Revised (FPS-R) in languages other than English. In: Pediatric Sourcebook, 7th ed. 2010, www.painsourcebook.ca

Bar-Shalita, T., Yochman, A., Shapiro-Rihtman, T., Vatine, J.J., Parush, S. The Participation in Childhood Occupations Questionnaire (PICO-Q): A Pilot Study. Physical & Occupational Therapy In Pediatrics. 2009, 29: 295- 310.

Bar-Shalita, T., Vatine, J.J., Seltzer, Z., Parush, S. Psychophysical correlates in children with sensory modulation disorder (SMD). Physiol Behav. 2009, 98:631-639.

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May 24, 2014

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Nursing Genetics and Information Technologies

Positions

Associate Professor, Sackler Faculty of Medicine
Chair, Department of Nursing, Stanley Steyer School of Health Professions

Research

Our research focuses on two main fields: 1. Genetics 2. Nursing and Information Technologies

In genetics our interest is in factors influencing individual decision-making on taking genetic tests. The decision whether or not to take a test may be influenced by factors relating to the illness tested for such as its severity or how far it can be controlled, or by personality factors such as risk-perception and optimism, or by the identity of the agent recommending the test (doctor or nurse) and their perceived epistemic authority. In a series of studies we are currently conducting we are trying to find linkages between these factors and the decision whether or not to take genetic tests.

Another issue being studied is the question "to whom does genetic information belong?" Genetic information is of importance to the tested individual's family as well as to them self. However, not all test subjects share the findings with their relatives. In a large-scale study, conducted together with Dr. Roy Gilbar of the Leicester University and funded by the Israel Cancer Association we examined the attitudes, opinions and behavioral intentions of genetic counselees regarding the disclosure of their genetic information to their families. We are planning a qualitative study to examine views of genetic counselors on this topic.

Information Technologies: Due to the rise of internet technology, medical information is no longer the exclusive property of medical service givers – it is now accessible to everybody— and this new situation has an effect on patient-caregiver relations. Among the research studies we are carrying out, we have investigated the attitudes of nurses towards patients who come forward with information found on the web, what affects those attitudes, and the reactions of nursing teachers to students who bring such information to class. Up to now, most research into this issue has concentrated on the professional caregiver's point of view. We wish to turn the spotlight onto the patient's point of view, and on how they feel after bringing Internet information to an appointment with their doctor or nurse.

Publications

***Barnoy, S.**,* Levy, O. and Bar-Tal Y. (2010). Nurse or Physician: whose recommendation influences more the decision to take genetic tests? *Journal of Advanced Nursing,* 66, 806-813.

Elkind, S, Rottem, S., Rechnitzer, H., Vaisid, T., **Barnoy, S.** & Kosower, N.S. (2010). Calpastatin is elevated in *Mycoplasma hyorhinis*-infected SH-SY5Y neuroblastoma cells. *FEMS Microbiology letters,* 304, 62-68,

Kushnir, T., Bachner, Y. and **Barnoy, S**. (2010). Exploration of the link between speaking English as a foreign language and Internet use among nurses in Israel. *Online Journal of Nursing Informatics,* 14*(3).*

Elkind, E., Vaisid, T., Kornspan, J. D., **Barnoy, S**., Rottem, S. & Kosower, N. S. (2011). Neuroprotective effects of Mycoplasma hyorhinis against amyloid-□-peptide toxicity in SH-SY5Y human neuroblastoma cells are mediated by calpastatin upregulation in the mycoplasma-infected cells. *Neurochemistry International*, 58, 497-503.

Barnoy, S., Levy, O. & Bar-Tal, Y. (2011). What makes patients perceive their health care worker as an epistemic authority? *Nursing Inquiry, 19, 128-133.*

Barnoy, S., Pruss*, D.,* Ehrenfeld, M. and Kushnir. T. *(*2011). Epistemic authority and nurses' reactions to medical information retrieved from internet sites of different sites of different credibility. *Nursing and Health Sciences*, 13, 366-370*.*

Itzhaki, M., Bar-Tal, Y. & **Barnoy, S**. (2013). Staff and lay people's reactions to family presence during resuscitation: The effect of blood, resuscitation outcome and gender - a quasi-experimental study. *Journal of Advanced Nursing*, In press.

Itzhaki, M., Bluvstein, I., Raz, S. and **Barnoy, S**. (2013). Factors affecting the actions and emotional reactions of nursing teachers following encounters with students who present them with Internet Information. *Nursing Education Today*, 33, 8842–846.

Elkind, E Vaisid, T., Kornspan, J. D., **Barnoy, S**., Rottem, S. & Kosower, N.S. (2012)**.** Calpastatin upregulation in *Mycoplasma hyorhinis*-infected cells is promoted by the mycoplasma lipoproteins via the NF-kB pathway. *Cellular Microbiology,* 14:840-851.

Gilbar, R. & **Barnoy, S.** Disclosure of genetic information to relatives in Israel: between privacy and solidarity. (2012). *New Genetics and Society*, 31:391-407.

Skirton, H., **Barnoy, S**. Erdem, Y., Ingvoldstad, C., Pestoff, R., Teksen, F. & Williams, J. (2012). Suggested components of the curriculum for nurses and midwives to enable them to develop essential knowledge and skills in genetics. *Journal of Genetic Counseling*, 3:323-9.

Prows, C. A., Hopkin, R. J., **Barnoy, S.** & Van Riper, M. (2013). An update of childhood genetic disorders. *Journal of Nursing Scholarship,* 45, 34-42. *(Nursing, IF 1.61, 13/116; cited by 0)*.

Tabak, N., Itzhaki, M., Sharon, D. and **Barnoy, S**. (2013). Intentions of nurses and nursing students to tell the whole truth to patient and family members. *Journal of Clinical Nursing*, 22, 1434-1441. DOI: 10.1111/j.1365-2702.2012.04316.x

(Nursing, IF 1.32, 25/116; cited by 0).

Menshadi, N., Bar-Tal, Y. and **Barnoy, S.** (2013). The relationship between learned resourcefulness and cancer related fatigue in patients suffering from Non-Hodgkin's Lymphoma. *Oncology Nursing Forum*, 40, 133-138. *(Nursing, IF 2.39, 2/116; cited by 0)*

Kagan, I. and **Barnoy, S.** (2013). Organizational culture safety and medical error reporting by Israeli nurses. *Journal of Nursing Scholarship,*45, 273-280. *(Nursing, IF 1.61, 13/116; cited by 1).*

May 24, 2014

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Co-Morbidity of Sensory-Motor and Cognitive Dysfunction and Psychosocial Problems

Positions

Senior Lecturer, Sackler Faculty of Medicine
Chair, Department of Occupational Therapy
Member, Israeli National Board for Certification of Occupational Therapy – Ministry of Health
Member, National Advisory Committee on Services for Child Development – Ministry of Health

Research

Our research is focused on the association between sensory- motor function and psychological aspects (anxiety, sense of coherence, hope, loneliness, etc.) of typically developed children and children with developmental problems such as Developmental coordination disorder (DCD), Attention Deficit Hyperactive Disorder (ADHD), and Sensory Processing Disorder (SPD). In the studies I conduct I try to learn and understand more about the mechanism behind the co-morbidity of sensory-motor dysfunctions and psychosocial problems. Further more, there are some studies where we assess the efficacy of sensory-motor intervention and its influence on the psychological behavior of the treated children.

Another related topic that is in the focus of my research is children's participation. According to the International Classification of Functioning, Disability and Health (ICF, 2001), Participation is relatively a new concept that reflects a new approach to functioning and serves as an outcome measure. Therefore we developed a questionnaire to assess pre-school children's participation. We are now developing additional questionnaires to assess infants, preschoolers and school age participation. We are running a few studies to assess differences in participation patterns of children with various developmental problems. Moreover I have started to investigate the influence of Occupational Therapy (OT) intervention and sensory-motor approaches on children's satisfaction and participation.

Publications

O. Bart, L. Rosenberg, N.Z. Ratzon, T. Jarus. Development and initial validation of the Performance Skills Questionnaire (PSQ). *Research in Developmental Disabilities,* 31, 46-56, 2010

N.Z. Ratzon, K. Zabaneh-Tannas, L. Ben-Hemo, **O. Bart.** The Efficiency of the Home Parental Program in Visual-Motor Home Activity Among First Grade Children Treated in Occupational Therapy. *Child Care Health and Development,* 36**,** 249-254, 2010.

T. Jarus, D. Anaby, **O. Bart,** B. Engel-Yeger, M. Law. Childhood participation in after-school activities– What is to be expected? *British Journal of Occupational Therapy*, 73, 344-350, 2010.

O. Bart, T. Podoly, Y. Bar Haim. A preliminary Study on the Effect of Methylphenidate on Motor Performance in Children with Comorbid DCD and ADHD.*Research in Developmental Disabilities,* 31, 1443-1447, 2010

L. Rosenberg, N. Z. Ratzon, T. Jarus, **O. Bart**. Development and initial validation of the Environmental Restriction Questionnaire, ERQ. *Research in Developmental Disabilities,* 31, 1323-1331, 2010.

L. Rosenberg, T. Jarus, **O. Bart**. Development and initial validation of the Child Participation Questionnaire. *Disability and Rehabilitation,* 32, 1633-1644, 2010

O. Bart, M. Avrech Bar, V. Hamudot, L. Rosenberg, T. Jarus. Development and validation of the Documentation of Occupational Therapy Session during Intervention (D.O.T.S.I.). *Research in Developmental Disabilities,* 32, 719-726, 2011

L. Rosenberg, T. Jarus, **O. Bart**, N. Z. Ratzon. Canpersonal and environmental factors explain dimensions of participation of children without developmental disabilities? *Child: Care, Health & Development*, 37, 266-275, 2011

O. Bart, T. Jarus, Y. Erez, L. Rosenberg. How do young children with DCD participate and enjoy dailyactivities? *Research in Developmental Disabilities,* 32, 1317-1322, 2011

T.Jarus, **O. Bart,** G. Rabinovich, A. Sadeh, L. Bloch, T. Dolfin, I. Litmanovitz. Effects of prone and supine positions on sleep state and stress responses in preterm infants. *Infant Behavior and Development,* 34, 257–263, 2011

O. Bart, T. Agam, P. L. Weiss, R. Kizony. Using video capture virtual reality for children with acquired brain injury. *Disability and Rehabilitation*. 33, 1579-86, 2011.

T. Jarus, Y. Lourie-Gelberg, B. Engel-Yeger, **O. Bart.** Participation patterns of school-aged children with and without DCD. *Research in Developmental Disabilities.* 32, 1323-1331, 2011.

O. Bart, S. Shayevits, L. V. Gabis, I. Morag. Prediction of Participation and Sensory Modulation of Late Preterm Infants at 12 months: A Prospective Study. *Research in Developmental Disabilities, 32,* 2732-8, 2011.

B. Soref, N.Z. Ratzon, L. Rosenberg, Y. Leitner, T. Jarus, **O. Bart.** Personal and Environmental Pathways to Young Children's Participation. *Child: Care, Health & Development*, 38, 561–571, 2012.

L. Rosenberg, N. Z. Ratzon, T. Jarus, **O. Bart.** Perceived environmental restrictions for the participation of children with mild developmental disabilities. *Child: Care, Health & Development*, 38, 836-43, 2012

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Investigating Pain Perception and Mechanisms of Chronic Pain

Position

Associate Professor, Sackler Faculty of Medicine

Research

We study the perception of pain among healthy subjects as well as among individuals with mental disorders and cognitive impairments. We are interested in the manner with which the brain processes various temporal and spatial aspects of painful evens and in inter-personal differences in pain perception.

We are also interested in the underlying mechanisms of chronic pain that develops after traumatic events. These include physical injuries such as spinal cord injury, brain injury and brain stroke as well as psychological traumas such as shell shock, captivity and torture. We are particularly interested in the effects of stress on the function of the pain system in these conditions and in healthy subjects.

We use state of the art devices such as computerized thermal stimulators, mechanical and electrical stimulators and a recording system for event related brain potentials. We perform experiments in the pain laboratory at TAU and in hospitals.

Publications

Defrin R, Ginzburg K, Mikulincer M, Solomon Z. The long-term impact of tissue injury on pain processing and modulation: a study on ex-prisoners of war who underwent torture. Eur J Pain. 2014;18(4):548-58.

Geva N, **Defrin** R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. Pain. 2013;154(11):2317-23.

Ginzburg K, Tsur N, Barak-Nahum A, **Defrin** R. Body awareness: differentiating between sensitivity to and monitoring of bodily signals. J Behav Med. 2014;37(3):564-75.

Zeilig G, Rivel M, Weingarden H, Gaidoukov E, **Defrin** R. Evidence of a neuropathic origin in hemiplegic shoulder pain. Pain. 2013;154(6):959-60.

Defrin R, Lurie R. Indications for peripheral and central sensitization in patients with chronic scalp pain (trichodynia). Clin J Pain. 2013;29(5):417-24.

Zeilig G, Rivel M, Weingarden H, Gaidoukov E, **Defrin** R. Hemiplegic shoulder pain: evidence of a neuropathic origin. Pain. 2013;154(2):263-71.

Ratmansky M, **Defrin** R, Soroker N. A randomized controlled study of segmental neuromyotherapy for post-stroke hemiplegic shoulder pain. J Rehabil Med. 2012;44(10):830-6.

Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, **Defrin** R, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede RD, Waxman SG, Widerström-Noga E, Yezierski RP,

Dijkers M. International spinal cord injury pain classification: part I. Background and description. Spinal Cord. 2012;50(6):413-7.

Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, **Defrin R**, Ivan E, Lundeberg T, Norrbrink C, Richards JS, Siddall P, Stripling T, Treede RD, Waxman SG, Widerström-Noga E, Yezierski RP, Dijkers M. International Spinal Cord Injury Pain (ISCIP) Classification: Part 2. Initial validation using vignettes. Spinal Cord. 2012;50:404-12.

G. Zeilig, S. Enosh, D. Rubin-Asher, B. Lehr, **R. Defrin**. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. Brain 2012;135:418-30.

Weisman-Fogel, N. Zwi, **R. Defrin**. The resolution of the pain system as evaluated with psychophysical testing reveals a proximal to distal gradient of improvement. Exp Brain Res. 2012;216:181-90.

R. Defrin, A. Sheraizin, L. Malichi, O. Shachen. Spatial summation and spatial discrimination of cold-pain: effect of spatial configuration and skin type. Pain. 2011;152:2739-45.

R. Defrin, I. Eli, D. Pud. The interaction among sex, ethnicity and gender role expectations of pain. Gender Medicine 2011;8(3):172-83.

R. Defrin, I. Tsedek, I. Lugasi, I. Moriles, G. Urca. The interactions between spatial summation and DNIC: effect of the distance between two painful stimuli and attentional factors on pain perception. Pain 2010;151:489-95.

E. Peles, S. Schreiber, T.Hetzroni, M. Adelson, **R. Defrin**. The Differential Effect of Methadone Dose and of Chronic Pain on Pain Perception of Former Heroin Addicts Receiving Methadone Maintenance Treatment. Journal of Pain 2011;12:41-50.

R. Defrin, H. Gruener, S. Schreiber, CG. Pick. Quantitative somatosensory testing of subjects with chronic post-traumatic headache: Implications on its mechanisms. European Journal of Pain 2010;14:924-931.

M. Ziv, R. Tomer, **R. Defrin**, T Hendler. Individual sensitivity to pain expectancy is related to differential activation of the hippocampus and amygdala. Human Brain Mapping 2010;31:326-38.

Chapter

R. Defrin, Chronic central pain after spinal cord injury. In: Principles of Rehabilitation Medicine, A Ohry Editor, Tel-Aviv: probook, 2011; 99-113.

Grants

2012-2014, IRP- International Foundation for research in Paraplegia

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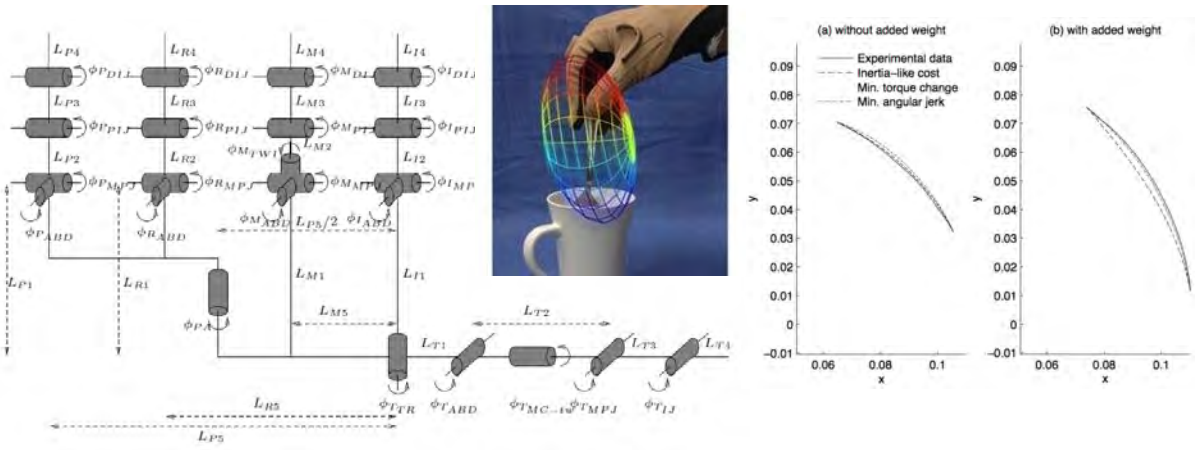
Models and Rehabilitation of Grasping

Positions

Senior Lecturer, Sackler Faculty of Medicine
Associate Investigator, ARC Centre of Excellence in Cognition and its Disorders, Australia

Research

We study human movement in typical and clinical populations, with a focus on grasping and finger movements. Our approach is to construct mathematical models that describe movement and force generation by the hand, taking into account the biomechanics of the hand and the neural processes leading up to making movements. This approach gives us insights into the strategies behind the complex movements and force coordination required to successfully perform grasping and manipulation, as well as a greater understanding of the causes of differences in performance in individuals with motor disorders. A goal of this research is to improve rehabilitation of hand function through improving our knowledge of these strategies.



Left: We use a model of the hand with the finger joints modelled as revolute joints, with twenty degrees of freedom. **Middle:** Based on models such as these, we can determine the properties of grasps subjects select, for example, when stirring with a spoon, to determine what are the important factors used when generating these grasps. The ellipsoid shows that the subject selected the grasp to maximize the angular velocity about the up-down axis (i.e., to stir the coffee!). Figure from the cover of Cortex, 2007. **Right:** Comparing different models of finger movement to experimental data allowed us to adjudicate between different theoretical models of movement generation (from Friedman and Flash, Exp. Brain Res, 2009).

Publications

Friedman, J., Brown, S. and Finkbeiner, M. (2014) Linking cognitive and reaching trajectories via intermittent movement control. Journal of Mathematical Psychology, 57(3-4):140-151.

Park, J., Pažin, N. **Friedman, J.**, Zatsiorsky, V.M. and Latash, M.L. (2014) Mechanical properties of the human hand digits: Age-related differences. Clinical Biomechanics, 29(2): 129-137.

Awasthi, B., Sowman, P., **Friedman, J.** and Williams, M.A. (2013) Distinct spatial scale sensitivities for early categorisation of Faces and Places: Neuromagnetic and Behavioural Findings. Frontiers in Neuroscience, 7:91.

Friedman, J., & Korman, M. (2012). Kinematic Strategies Underlying Improvement in the Acquisition of a Sequential Finger Task with Self-Generated vs. Cued Repetition Training. PLoS One, 7, e52063.

Awasthi, B., **Friedman, J.**, & Williams, M. A. (2012). Reach Trajectories Reveal Delayed Processing of Low Spatial Frequency Faces in Developmental Prosopagnosia. Cognitive Neuroscience, 3, 120–130.

Awasthi, B., **Friedman, J.**, & Williams, M. (2011). Faster, stronger, lateralized: Low spatial frequency information supports face processing. Neuropsychologia, 49, 3583–3590.

Awasthi, B., **Friedman, J.**, & Williams, M. A. (2011). Processing of low spatial frequency faces at periphery in choice reaching tasks. Neuropsychologia, 49, 2136–2141.

Finkbeiner, M., & **Friedman, J.** (2011). The flexibility of nonconsciously deployed cognitive processes: Evidence from masked congruence priming. PLoS ONE, 6, e17095.

Friedman, J., Latash, M. L., & Zatsiorsky, V. M. (2011). Directional variability of the isometric force vector produced by the hand in multi-joint planar tasks. Journal of Motor Behavior, 43, 451–463.

Nahab, F., Kundu, P., Gallea, C., Kakareka, J., Pursley, R., Pohida, T., Miletta, N., **Friedman, J.**, Hallett, M. (2011). The neural processes underlying self-agency. Cerebral Cortex, 21, 48–55.

Zopf, R., Truong, S., Finkbeiner, M., **Friedman, J.**, & Williams, M. A. (2011). Viewing and feeling touch modulates hand position for reaching. Neuropsychologia, 49, 1287–1293.

Kapur, S., **Friedman, J.**, Zatsiorsky, V. M., & Latash, M. L. (2010). Finger interaction in a three-dimensional pressing task. Experimental Brain Research, 203, 101–118.

Latash, M. L., **Friedman, J.**, Kim, S.W., Feldman, A.G., Zatsiorsky, V.M. (2010). Prehension Synergies and Control with Referent Hand Configurations. Experimental Brain Research, 202, 213–229.

May 24, 2014

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Auditory Processing in the Normal and Impaired Auditory System

Positions

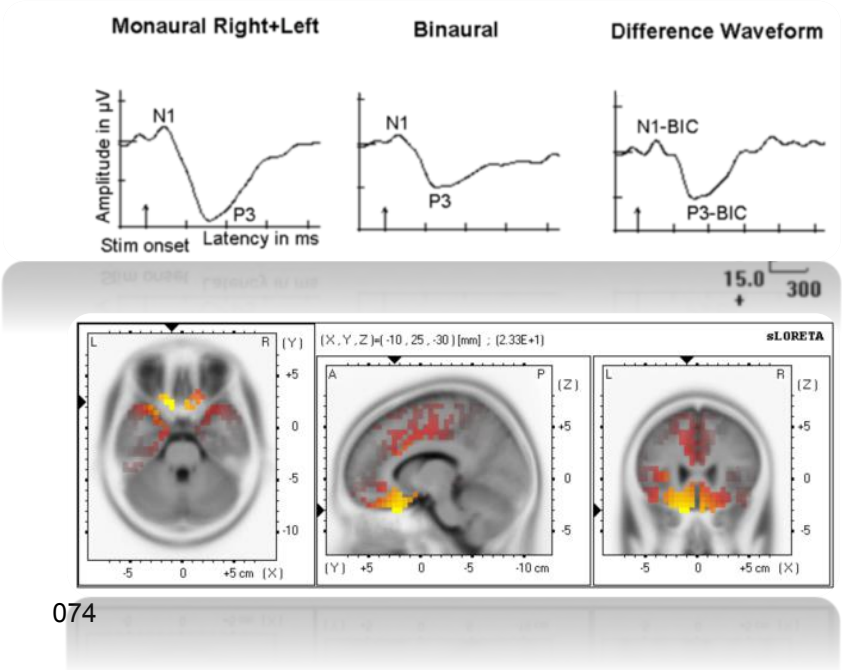
Senior Lecturer, Department of Communication Disorders, Sackler Faculty of Medicine
Head, Hearing, Speech, and Language Center, Sheba Medical Center, Tel Hashomer

Research

Research focuses on neurophysiologic and behavioral manifestations of auditory processing, as well as the relation between the two, in the normal and impaired auditory system. By means of event-related potentials (ERPs), voltage changes recorded from the scalp that trace events in time known to reflect discrete stages of neural processing, and a functional imaging technique (sLORETA), we study the time-course and cortical activation patterns during auditory (speech) processing. Of special interest are patients that have experienced bilateral and/or unilateral auditory deprivation and are habilitated by cochlear implants (CI) and/or hearing aids (HA). Currently under study are neurophysiologic processes that underlie: (1) Binaural processing in children that were sequentially or simultaneously implanted, in those using CI and HAs (bimodal hearing), and in those with HAs; and (2) Auditory-cognitive processing in elderly patients with CI.

Additional lines of research incorporate neurophysiologic and behavioral measures for studying: (1) The effect of auditory processing disorders (APD) on perceptual and post-perceptual stages of linguistic processing; and (2) The involvement of the peripheral and central auditory system in selective mutism and autism.

Understanding normal and impaired auditory processing contributes to the formation of rehabilitative technologies and approaches for auditory disorders.



Grand average waveforms of normal hearing children elicited during a speech discrimination task presented monaurally and binaurally. Shown are the sum of monaural right and left waveforms, the binaural response, and the difference waveform (Binaural interaction component=Sum of right+left –binarual response). Also shown are sLORETA images indicating the major site of activation during P3-BIC in the inferior and medial frontal gyri, (BA 11, 25) and orbital gyrus (BA 47) bilaterally.

Publications

D. Reznik, **Y. Henkin,** N. Schadel, R. Mukamel. Lateralized enhancement of auditory cortex activity and increased sensitivity to self-generated sounds. Nature Communications, in press**.**

Y. Henkin, Y. Bar-Haim. Perturbed auditory efferent activity in selective mutism. Frontiers in System Neuroscience, in press

Y. Henkin, R. Taitelbaum-Swead, D. Ari-Even Roth, L. Kishon-Rabin, Y. Shapira, L. Migirov, M. Hildesheimer, R. Kaplan-Neeman. Evidence for a right cochlear implant advantage in simultaneous bilateral cochlear implantation. The Laryngoscope DOI: 10.1002/lary.24635, 2014

C. Muchnik, D. Ari-Even Roth, M. Hildesheimer, Y. Bar-Haim, **Y. Henkin.** Abnormalities in Auditory Efferent Activities in Children with Selective Mutism. Audiology & Neurootology 18:353-361, 2013

Y. Henkin. Auditory event-related potentials: a potential objective tool for evaluating auditory-cognitive processing in older adults with cochlear implants. Journal of Hearing Science, 4(2)1-3, 2012

R. Kaplan-Neeman, C. Muchnik, M. Hildesheimer, **Y. Henkin**. Hearing aid satisfaction and use in the advanced digital era. The Laryngoscope, 122(9):2029-36, 2012

D. Ari-Even Roth, , C. Muchnik, E. Sabtai, M. Hildesheimer, **Y. Henkin.** Evidence for atypical auditory brainstem responses in young children with suspected autism spectrum disorders. Developmental Medicine and Child Neurology**,** 54:23-9, 2012

Y. Henkin, L. Givon, Y.Yaar-Soffer, M. Hildesheimer. Cortical binaural interaction during speech processing in children with bilateral cochlear implants. **C**ochlear Implants International, 12:61-5, 2011

Y. Henkin, M. Feinholz, M. Arie, Y. Bar-Haim. P50 suppression in children with selective mutism. Journal of Abnormal Child Psychology, 38:43-8, 2010

Y. Henkin, Y. Yaar-Soffer, S. Gilat, C. Muchnik. Auditory conflict processing: behavioral and electrophysiological manifestations of the Stroop effect. Journal of the American Academy of Audiology, 21:474-86, 2010.

Grants

2012- 2014 - Auditory-cognitive processing in older adult cochlear implant recipients: electrophysiological and behavioural manifestations. MED-EL Research Grant, Innsbruck, Austria

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Hearing Science and Clinical Audiology

Position
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Research

- Normal and abnormal auditory function
- Brain plasticity in cochlear Implants, Auditory Processing Disorders (APD)
- Clinical Audiology

Our research has been conducted in two areas:

A. Study of inner ear function in guinea pigs under three conditions: hypoxia, acoustic over-stimulation and differentiation. The study of these subjects has required the development of three special experimental techniques:

- A method of chronic implantation of an electrode into the facial nerve canal to enable longitudinal follow-up of hearing function in the awake state.
- A rheological model, which was developed for research on cochlear hypoxia in guinea pigs.
- A surgical method to completely eliminate the auditory efferent innervation to the cochlea while ensuring the animal's full recovery from this procedure. Thus it is possible to study the hearing function over time without the influence of the efferent system with the guinea pigs in an awake state.

B. Research on auditory plasticity in human subjects

The cochlear implant is a rehabilitative alternative in which an electrode inserted into the inner ear, directly stimulates the auditory nerve. Research is conducted in the area of programming the implant and speech perception using the implant. The research deals with the plasticity of the auditory system in acquisition of hearing and language skills and contributes basic theoretical and clinical knowledge about the importance of the auditory feedback to normal speech and hearing development and function.

Hearing in neonates and Auditory Processing Disorders: The Transient Evoked Oto-Acoustic Emission (TEOAE) is applied in hearing screening in neonates. Research was conducted to examine the reliability and validity of the test. We also investigated the development and activity of the efferent inhibitory system in newborns and premature babies using the suppression of the TEOAE test. We suggested the use of the test as a clinical tool for evaluation of auditory brain-stem function in neonates. We postulate that central auditory processing disorders (CAPD) manifested later in life can already be detected at this early stage of life using this method. We plan to continue to investigate the development of the efferent system and its importance for

hearing throughout the life span, from childhood to old age, under difficult listening conditions and in subjects with communication disorders.

Publications

Kaplan-Neeman, R., **Hildesheimer, M**., Muchnik, C., Kronenberg, J. & Migirov, L. (2010). Cochlear implant recipients hearing sensation as manifested by their maps during pregnancy and postpartum. *Otology & Neurotology*, 31, 923-925.

Henkin, Y., GIVON, L., Yaar-Soffer, Y. & **Hildesheimer, M**. (2011). Cortical binaural interaction during speech processing in children with bilateral cochlear implant. *Cochlear Implant International,* 12 (sup 1), 61-65.

Potter-Katz, H., Feldman, I. & **Hildesheimer, M**. (2011). Binaural masking level difference in skilled reading children and children With dyslexia. *Journal of Basic and Clinical Physiology & Pharmacology,* 22 (3),59-63.

Kaplan-Neeman, R., Muchnik, C. & **Hildesheimer, M**. (2012). Hearing aid satisfaction and use in the advanced digital era. *The Laryngoscop*e, 122 (9), 2029-2036.

Ari-Even Roth, D., Muchnik, C., Shabtai, E., **Hildesheimer, M**. & Henkin, Y. (2012). Evidence for atypical auditory brainstem response in young children with suspected autism spectrum disorders. *Developmental Medicine & Child Neurology*, 54, 23-29.

Van Den Abbeele, T., **Hildesheimer, M**., Kronenberg, J. & Arnold, A. (2012). Multicentre investigation on electrically evoked compound action potential and stapedius Reflex. *Cochlear Implants International*, 13 (1), 26-34.

Muchnik, C., Ari-Even Roth, D., **Hildesheimer, M**., Arie, M., Bar-Haim, Y. & Henkin, Y. (2013). Abnormalities in auditory efferent activities in children with selective mutism*. Audiology & Neurology*. 18:353–361

Henkin Y, Swead RT, Roth DA, Kishon-Rabin L, Shapira Y, Migirov L, **Hildesheimer M**, Kaplan-Neeman R. Evidence for a right cochlear implant advantage in simultaneous bilateral cochlear implantation. Laryngoscope. 2014 Feb 4. doi: 10.1002/lary.24635

May 24, 2014

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Knowledge and Perceptions of Patients and Caregivers on Health and Illness Situations

Position

Lecturer, Sackler Faculty of Medicine

Research

Qualitative and quantitative research methods are used to study nurses' and patients' attempts to structure their emotions through the process of emotional management. We focus on self-care research: understanding the interventions, correlates and outcomes of nurses' self care by International research on caritas as healing. Our research involves studying cultural competence, which enables nurses to care for and to communicate with patients from different cultural and ethnic backgrounds. Furthermore, the focus is on acculturation and job satisfaction among immigrant nurses from different countries. The theory of family-centered care is studied: the preferences of lay people regarding family involvement in medical decisions. Moreover, we research the attitudes of lay people and staff members to family presence during resuscitations and invasive procedures. Understanding these aspects is essential for creating caring environments for nurses, patients and families within today's complex health care organizations.

Publications

Koren A, Mintz A & **Itzhaki M**. Is this a mistake? Perception of nursing students' errors by clinical perceptors. *Body of Knowledge – The Israel Journal for Nursing Research* 2014, 11, 2-04. (Hebrew)

Melnikov S*, **Itzhaki M*,** Kagan I. Israeli nurses' intention to report for work in an emergency or disaster. *Journal of Nursing Scholarship* 2013, DOI:10.1111/jnu12056

(*Equally contributing authors)

Itzhaki M & Koton S. Knowledge, perceptions and thoughts of stroke among Arab-Muslim Israelis. *European Journal of Cardiovascular Nursing* 2013, DOI:10.1177/1474515113479721

Coffey A, McCarthy G, Weathers E, Friedman M, Gallo K, Ehrenfeld M, **Itzhaki M,** Chan S, Li W, Poletti P, Zanotti R, Molloy D, McGlade C & Fitzpatrick J. Nurses' preferred end-of-life treatment choices in five countries. *International Nursing Review* 2013, 33, 842–846.

Itzhaki M, Ea E, Ehrenfeld M, Fitzpatrick J. Job satisfaction among immigrant nurses in Israel and in the United States. *International Nursing Review.* 2013, 60, 122-128.

Tabak N*/**Itzhaki M*** Sharon D, Barnoy S. Intentions of nurses and nursing students to tell the whole truth to patients and family members. *Journal of Clinical Nursing*. 2013, 22:1434-41 (*Equally contributing authors)

Itzhaki M, Bluvstein I, Raz S, Barnoy S. Factors affecting the actions and emotional reactions of nursing teachers following encounters with students who present them with internet information. *Nurse Education Today* 2013, DOI: 10.1016/j.nedt.2012.02.002

Itzhaki M, Bar-Tal Y, Barnoy S. Reactions of staff members and lay people to family presence during resuscitation: the effect of visible bleeding, resuscitation outcome and gender. *Journal of Advanced Nursing* 2012*,* 68:1967-77.

Shalish Y, Gelbert O, **Itzhaki M**, Rubinstein D, Raanan O, Siebzehner MI. Happiness among elderly people*. Body of Knowledge – The Israel Journal for Nursing Research* 2012, 9, 55-60. (Hebrew).

Itzhaki M, Koton S. Primary prevention of stroke: Knowledge and attitudes among healthy adult population*. JINA- Journal of the Israeli Neurological Association,* 2011, 6, 26-27. (Hebrew)

Harpaz I, Mozes V, Mintz L, Zilberman N, **Itzhaki M.** Self fulfillment as a motive to change. From Hi Tech to nursing*. Nurse in Israel,* 2011, 186, 40-44. (Hebrew).

Ea E**, Itzhaki M**, Ehrenfeld M, Fitzpatrick J. Acculturation among immigrant nurses in Israel and the US. *International Nursing Review,* 2010, *57*, 443-448.

Rubinstein D, Raanan O, **Itzhaki M**, Gelbert O, Shalish Y, Shatzman C, Siebzehner MI. Successful aging in an assisted living facilty. *Body of Knowledge – The Israel Journal for Nursing Research,* 2010, 7, 26-35. (Hebrew).

Chapter

Nelson J, **Itzhaki M,** Ehrenfeld M, Tinker A, Hozak S, Johnson S. Nurses' caring for self: A four – country descriptive study (England, Israel, New Zealand and the USA). In J. Nelson & J. Watson (Eds.), *Measuring caring. International research on caritas as healing* (pp. 357-370). 2011, New York, NY: Springer Publishing Company

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Quality of Care and Patient Safety

Positions

Lecturer, Sackler Faculty of Medicine
Head, Nursing Continuous Education Unit

Research

Peri-operative Factors and Their Impact on Post-operative Recovery

Our research area is developing in two tracks: a) discovering the factors that affect quality and safety behavior of healthcare workers (HCWs) and b) examination of psycho-social and bio-physiological factors before and after surgery and their impact on short-/long-term recovery and rehabilitation. The first research track focuses on both the "human element" variables and the systemic approach to the quality improvement, clinical risk management and patient safety issues such as medical error-reporting, safety culture, disclosure errors to patients, patient empowerment and more. The studies highlight the barriers that have to be addressed when planning and implementing changes to improve quality and patient safety in healthcare. The second track addresses the influence of variables such as personal self-efficacy, situational anxiety, health literacy, subjective readiness to surgery, gender, ethnicity etc., on post-operative recovery. These studies aim to identify variables that could have a positive or negative effect on readiness to leave hospital after surgery, to comply with the recommendations on discharge from hospital, to adhere rehabilitation programs and more.

Publications

Toren, O., Kerzman, H., **Kagan, I**. (2011). The difference between professional image and job satisfaction of nurses who studied in a post-basic education program and nurses with generic education: a questionnaire survey. *Journal of Professional Nursing, 27,* 28-34

Hendel, T. & **Kagan, I**. (2011). Professional image and intention to emigrate among Israeli nurses and nursing students. *Nurse Education Today, 31,* 259-262.

Baum, A., Pinchuk., M., **Kagan, I**. (2012). Job satisfaction and intention to leave the workplace among psychiatric nurses working in mental health hospital", *The Nurse in Israel, 190*, 42-46 [in Hebrew]

Melnikov, S., Kigli-Shemesh, R., Shor, R., Gon-Osishkin, M. **Kagan, I** (2012). Closing an Open Psychiatric Ward: Organizational Change and Its Effect on Staff Uncertainty, Self-Efficacy, and Professional Functioning. *Perspectives in Psychiatric Care,* E-published, doi: 10.1111/ppc.12001

Hendel, T. & **Kagan, I.** (2012). Organizational values and commitment: Do nurses' ethno-cultural differences matter? *Journal of Nursing Management,* E-pub ahead of print, doi: 10.1111/jonm.12010

Kagan, I. and Barnoy, S. (2013). Organizational Safety Culture and error-reporting by Israeli nurses. *Journal of Nursing scholarship,* E-pub ahead of print, doi: 10.1111/jnu.12026

Melnikov, S., Itzhaki, M., **Kagan, I** (2013). Intention to report to work in emergency and disasters among Israeli nurses. Journal of Nursing Scholarship, 1-9. doi: 10.1111/jnu.12056. Chosen as 'March 2014 Editor's Choice Article' of JNS.

Kagan, I., Cohen, R., Fish, M., Peri, H. (2014). Developing and implementing a computerized nursing quality control system in general medical center. Journal of Nursing Care Quality (JNCQ), 29 (1), 83-90

Frishman, S., Theilla, M., Singer, P., Avraham, Z., Libman, C., **Kagan, I**. (2014). JCI Accreditation and Its multiprofessional Impact on nutrition care at Rabin Medical Center, Israel. Invited (peer-reviewed) paper, published on official site of Joint Commission International (JCI): http://www.jointcommissioninternational.org/new-study-jci-accreditation-and-nutrition-care-at-rabin-medical-center/ and also in JCInsight, official newsletter of JCI, http://www.jointcommissioninternational.org/assets/3/7/jcinsightapril2014.pdf

Grants

2013-2015	PI, study "Patient's and health caregivers' perception on quality, safety culture and patient involvement in medical care in general hospitals in Israel"	Research Board, The Israel National Institute for Health Policy and Health Services Research (NIHP), Israel

May 24, 2015

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'Bottom-Up' and 'Top-Down' Processes in Human Auditory Perception and Recognition

Position

Associate Professor, Sackler Faculty of Medicine
Committee Member, Israel Auditory Society of Research
Chairperson, Committee of Head of Communication Disorders Depts in Israel (CHE)

Research

Our research focuses on understanding the influence and relative contribution of sensory information ("bottom-up" processes) compared to cognitive capabilities and listening experience ("top-down" processes) on the perception of speech and language development. We test our hypotheses in a range of special populations including hearing-impaired infants, children and adults with cochlear implants and/or hearing aids, children on the autistic spectrum, bilingual and trilingual children and adults and middle-aged and elderly adults. We always compare performance with the typically developing population. We develop tests that are aimed to assess different levels of sensory, linguistic and cognitive processing. These include psychoacoustic tests of frequency, temporal and intensity resolution that involve non-speech auditory stimuli, linguistic tests that involve phonetic, word, and sentence material in optimal and degraded or difficult listening conditions (e.g. background noise, time-compressed speech, multi-talker, multi-accented) and cognitive tasks, such as, selective auditory attention using auditory adaptation of the 'stroop' task for attending relevant and irrelevant information (e.g. lexical-emotional stroop). In order to understand the influence of repeated exposure to auditory stimuli on performance, we train our subjects in single- or in multiple sessions thus providing us with insights to the auditory memory systems. We use different training tasks that involve the implicit and explicit memory systems that are assumed to be analogoues to language learing in infants and in older children. We utilze primarily behavioral measures that are occasionally supplemented with electriphysiological measures. Our studies are conducted in an infant speech perception/language lab which is unique of its kind in the country and is equipped to test different infant populations with behavioral techniques, and in an acoustically treated state-of-the art psychoacoustic lab. Understanding the factors that influence speech perception throughout the life span have important implications in the design of aural rehabilitation for the hearing impaired and intervention protocols in populations with developmental delays.

Publications

Kishon-Rabin L, Harel T, Hildesheimer M, Segal O. Listening preference for the native language compared to an unfamiliar language in hearing and hearing-impaired infants following cochlear implantation. *The Journal of Otology and Neurotology,* 31, 1275-1280, 2010.

Zaltz Y, Ari-Even Roth D, **Kishon-Rabin L**. Does feedback matter in an auditory frequency discrimination learning task? *Journal of Basic Clinical Physiology and Pharmacology*. 241-254, 2010.

Segal O, **Kishon-Rabin L**. Listening preference to child-directed speech versus on-speech stimuli in hearing and hearing-impaired infants following cochlear implantation. *Ear & Hearing*, *32,* 358-372, 2011.

Zaltz Y, Ari-Even Roth D, **Kishon-Rabin L.** How specific is the learning in an auditory frequency discrimination task? *Journal of Basic Clinical Physiology and Pharmacology*, 22(3), 69–73, 2011.

Chordekar S, Kriksunov L, **Kishon-Rabin L**, Adelman C, Sohmer H. Mutual cancellation between tones presented by air conduction, by bone conduction and by non-osseous (soft tissue) bone conduction. *Hearing Research*, 283, 180-184, 2012.

Segal O, **Kishon-Rabin L.** Evidence for language-specific influence on the preference of stress patterns in infants learning an iambic language (Hebrew). *Journal of Speech & Hearing Research*, 55, 1329-1341, 2012.

Globerson E, Amir N, Golan O, **Kishon-Rabin L**, Lavidor M. Psychoacoustic abilities as predictors of vocal emotion recognition. *Attention, Perception & Psychophysics*. 75(8):1799-810, 2013.

Kishon-Rabin L, Avivi-Reich M, Ari-Even Roth D. Improved gap detection thresholds following auditory training: Evidence of auditory plasticity in older adults. *The American Journal of Audiology*. 22(2):343-6, 2013.

Henkin Y, Taitelbaum-Swead R, Hildesheimer M, Ari-Even Roth D, **Kishon-Rabin L,** Kaplan-Neeman R. Evidence for a right cochlear implant advantage in simultaneous bilateral cochlear implantation. *Laryngoscope*. doi:10.1002/lary.24635. 2014.

Ben-Itzhak D, Greenstein T, **Kishon-Rabin L**. Parent report of the development of auditory skills in infants and toddlers who use hearing aids. *Ear & Hearing*. 2014. In press.

Segal O, Kaplan D, Patael S, **Kishon-Rabin L**. Judging emotions in lexical-prosodic congruent and incongruent speech stimuli in adolescents on the ASD. *Folia Phonitrica*. Accepted for publication.

Chapters in Books

Kishon-Rabin L, Taitelbaum R, Segal O. Prelexical infant scale evaluation (PRISE): from vocalization to audition in hearing and hearing-impaired infants. In L. Eisenberg (ed): *Clinical Management of Children with Cochlear Implants*. San Diego, Plural Publishing, Inc; 2009: 325-368**.**

Perez R, **Kishon-Rabin L**. Cochlear Implantation-Pediatric. In S. E. Kountakis (ed.): *Encyclopedia of Otolaryngology, Head and Neck Surgery*. Springer-Verlag Berlin Heidelberg, 2013.

June 1, 2014

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Epidemiology of Cardiovascular Diseases

Position

Senior Lecturer, Sackler Faculty of Medicine
Chair, Post Basic B.A. Program for Registered Nurses

Research

Our research focuses on the epidemiology of cardiovascular diseases with especial interest in epidemiology of stroke. During the last years, our studies have covered diverse subjects including trends in stroke morbidity and mortality among different population groups, strategies for primary and secondary prevention of stroke, determinants of stroke outcomes and novel risk factors acting long-term and as immediate triggering factors. Taking advantage of our knowledge and skills in the environmemtal and occupational health area, we also study the health effects of pollution mainly among survivors of cardiovascular diseases.

Since the establishment of the ongoing triennial National Acute Stroke Israeli (NASIS) registry in 2004, as a member of the registry's steering committee, I carry out nationwide studies in collaboration with specialists in neurology and stroke research. Theses studies are aimed at characterizing management and outcomes of acute stroke patients and are an important means for providing both clinicians and health policy makers with data required for optimizing prevention strategies and care of stroke patients in Israel.

Publications

Koton S, Tanne D, Green MS, Bornstein NM. Mortality and predictors of death one month and three years after first-ever ischemic stroke: data from the first National Acute Stroke Israeli Survey (NASIS 2004). *Neuroepidemiology* 2010;34:90-6**.**

Schwammenthal Y, Bornstein MN, Schwammenthal E, Schwartz R, Goldbourt U, Tsabari R, **Koton S**, Grossman E, Tanne D. Relation of effective anticoagulation in patients with atrial fibrillation to stroke severity and survival (from the National Acute Stroke Israeli Survey [NASIS]**).** *Am J Cardiol.* 2010;105:411-6.

Koton S, Bornstein NM, Tsabari R, Tanne D; on behalf of the NASIS Investigators. Derivation and validation of the Prolonged Length of Stay (PLOS) score in acute stroke patients**.** *Neurology* 2010;1511-*6.*

Gerber Y, Myers V, Broday DM**, Koton S,** Steinberg DM, Drory Y. Cumulative exposure to air pollution and long term outcomes after first acute myocardial infarction: A population based cohort study. Objectives and methodology. *BMC Public Health* 2010,10:369.

Koton S, Luengo-Fernandez R, Metha Z, Rothwell PM. Independent validation of the Prolonged Length of Stay (PLOS) score. *Neuroepidemiology* 2010;35:263-6**.**

Gerber Y, **Koton S**, Goldbourt U, Myers V, Benyamini Y, Tanne D, Drory Y; for the Israel Study Group on First Acute Myocardial Infarction. Poor neighbourhood socioeconomic status predicts long-term risk of ischemic stroke after myocardial infarction. *Epidemiology* 2010;22:162-9.

Koton S. Risk factors for ischemic stroke and intracerebral hemorrhage: Updated review based on the INTERSTROKE study. *JINA* 2010;4:24-5. (Invited review in Hebrew)

Schwammenthal Y, Bornstein NM, Goldbourt U, **Koton S**, Schwartz R, Koren-Morag N, Grossman E, Tanne D. Anticoagulation remains underused in prevention of stroke associated with atrial fibrillation: Insights from two consecutive national surveys. *Int J Cardiol.* 2011;152:356-61.

Itzhaki M, **Koton S.** Primary prevention of stroke: knowledge and attitudes among healthy adult population. *JINA* 2011;6:26-7. (Review in Hebrew)

Koton S, Gerber Y, Goldbourt U, Drory Y; for the Israel Study Group on First Acute Myocardial Infarction. Socioeconomic risk factor aggregation and long-term stroke incidence in patients after a first acute myocardial infarction. *Int J Cardiol.* 2012;157:324-9.

Koton S,Tashlykov V,Molshatzki N, Merzeliak O, Schwammenthal Y,Toashi M, Orion D, Tsabari R, Tanne D. Cerebral artery calcification in patients with acute cerebrovascular diseases: Determinants and long-term clinical outcome. *Eur J Neurol*. 2012;19:739-45.

Tanne D, **Koton S**, Molshazki N, Goldbourt U, Shohat T, Tsabari R, Grossman E, Bornstein NM, on behalf of the NASIS Investigators. Trends in Management and Outcome of Hospitalized Patients with Acute Stroke and TIA: The National Acute Stroke Israeli (NASIS) Registry. *Stroke* 2012;43:2136-41.

Gur AY, Tanne D, Bornstein NM, Milo R, Auriel E, Shopin L, **Koton S**. Stroke in the very elderly: Characteristics and predictors of outcome in patients aged ≥ 85 years with a first-ever ischemic stroke. *Neuroepidemiology* 2012;39:57-62.

Koton S, Tanne D, Bornstein NM, on behalf of the NASIS Investigators. Ischemic stroke on-awakening: Patients' characteristics, outcomes and potential for reperfusion therapy. *Neuroepidemiology* 2012;39:149-53.

Dombe S, Barzilai B, **Koton S**, Tabak N. Variables influencing the attitudes of nurses toward euthanasia of severely damaged newborns and premature babies. *Refuah Ve-mishpat* 2012; 45:77-89 (in Hebrew).

Koton S, Molshatzki N, Bornstein NM, Tanne D. Low cholesterol, statins and outcomes in patients with first-ever acute ischemic stroke**.** *Cerebrovasc Dis.* 2012; 34:213-20.

Paul NL, **Koton S**, Simoni M, Geraghty OC, Luengo-Fernandez R, Rothwell PM. Feasibility, safety and cost of outpatient management of acute minor ischaemic stroke: a population-based study. J Neurol Neurosurg Psychiatry. 2013; 84:356-61.

Koton S, Molshatzki N, Yuval, Myers V, Broday DM, Drory Y, Steinberg DM, Gerber Y. Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes. Prev Med. 2013: 57(4):339-44

Tanne D, **Koton S**, Bornstein NM. National stroke registries: what can we learn from them? *Neurology.* 2013; 81:1257-1259.

Koton S, Tsabari R, Molshazki N, Kushnir M, Shaien R, Eilam A, Tanne D; NASIS Investigators. Burden and outcome of prevalent ischemic brain disease in a national acute stroke registry. *Stroke*. 2013; 44(12):3293-3297.

Koton S, Telman G, Kimiagar I, Tanne D; NASIS Investigators. Gender differences in characteristics, management and outcome at discharge and three months after stroke in a national acute stroke registry. *Int J Cardiol.* 2013; 168:4081-4084.

Itzhaki M, **Koton S**. Knowledge, perceptions and thoughts of stroke among Arab- Muslim Israelis. Eur J Cardiovasc Nurs. 2014: 3(1):78-85

Cobb LK, McAdams-Demarco MA, Huxley RR, Woodward M, **Koton S**, Coresh J, Anderson CA. The association of spousal smoking status with the ability to quit smoking: the Atherosclerosis Risk in Communities study. *Am J Epidemiol.* 2014; 179:1182-1187.

Gerber Y, Myers V, Broday DM, Steinberg DM, Yuval, **Koton S**, Drory Y. Frailty status modifies the association between air pollution and post-myocardial infarction mortality: a 20-year follow-up study. *J Am Coll Cardiol.* 2014; 63:1698-1699.

May 25, 2014

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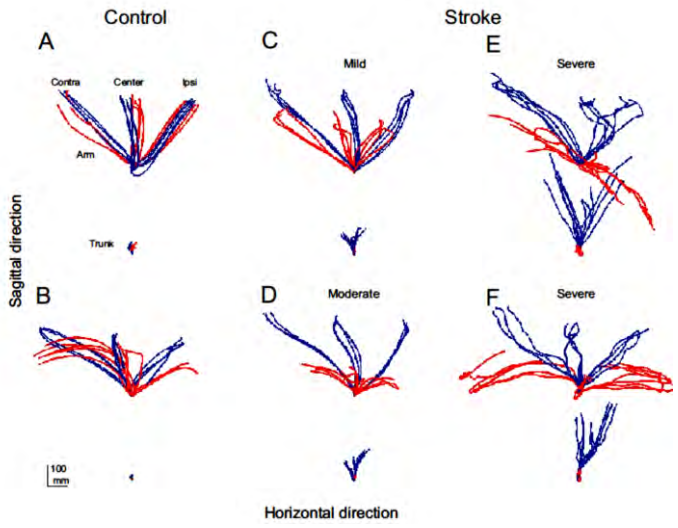
Computational Motor Control and Clinical Applications to Upper-Limb Rehabilitation

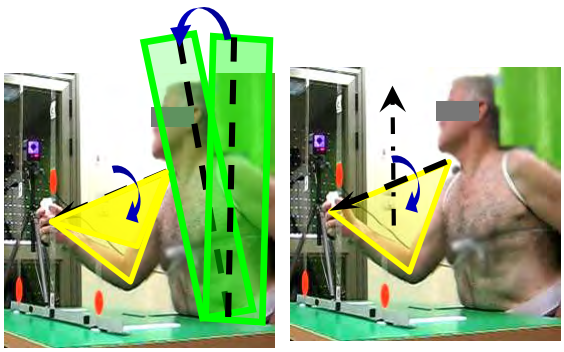
Position

Senior Lecturer, Sackler Faculty of Medicine
Chair, Department of Physical Therapy
Associate Editor, Rehabilitation, Journal of Electromyography & Kinesiology

Research

Behavioral and computational motor control is our field of research. This is a main venue for understanding the motor system and its organization, in healthy and clinical populations. In the last years, we have dedicated major efforts in investigating methods and technologies (virtual reality, robot-based rehabilitation, neuro-stimulation) that can potentially enhance motor recovery and functional performance in clinical populations with a focus on upper-limb motion in stroke survivors. Mathematical model-based, as well as empirical neuromotor approaches, are used in our research for studying and understanding laws of motor control and sensorimotor integration.





Top: Schematic view of arm and trunk rotation used in modeling arm-trunk coordination based on a geometric algebra approach**. Right**: Arm endpoint and trunk paths (horizontal plane view; i.e., from the above) during reaching movements to contra-, center and ipsilateral visual targets for two healthy controls (A, B) and four stroke patients with mild (C), moderate (D) and severe (E-F) hemiparesis. Center-out paths to targets in the physical environment are depicted in blue traces and 2D virtual environment in red traces.

Publications

Arzi H, Krasovsky T, Pritsch (Perry) M, **Liebermann, D.G.** Movement Control in Patients with Shoulder Instability Before and After Open Surgery. Journal of Shoulder and Elbow Surgery 2013, pii: S1058-2746(13)00505-3. doi: 10.1016/j.jse.2013.09.021. [Epub ahead of print].

Frenkel-Toledo S., Bentin S., Perry A., **Liebermann, D.G.**, Soroker N. Mirror-neuron system recruitment by action observation: Effects of focal brain damage on mu suppression. NeuroImage 2013, 87C, 127-137. doi: 10.1016/j.neuroimage.2013.10.019. [Epub 2013 Oct 18].

Berman S., **Liebermann D.G.**, McIntyre J., Constrained Motion Control on a Hemispherical Surface - Optimal Path Planning. J. of Neurophysiology 2014;111(5):954-68. doi: 10.1152/jn.00132.2013. [Epub 2013 Nov 20].

Frenkel-Toledo S., Bentin S., Perry A., **Liebermann D.G.**, Soroker N. Dynamics of the EEG Power in the Frequency and Spatial Domains During Observation and Execution of Manual Movements. Brain Research 2013, 1509, 43-57. doi: 10.1016/j.brainres.2013.03.004. [Epub 2013 Mar 13]

Merdler T., **Liebermann D.G.**, Levin M.F., Berman S. Arm-plane representation of shoulder compensation during pointing movements in patients with stroke. J. Electromyography & Kinesiology, 2013, 23:938-47.

Liebermann D.G., Berman S., Weiss P.L., Levin F.M., Kinematic validity of reaching movements in a 2D virtual environment in adults with and without stroke. IEEE Transactions on Neural Systems and Rehabilitation Engineering, 2012, 20, 778-787.

Levin M.F., Snir O., **Liebermann D.G.**, Weingarden H., Weiss P.L., Virtual reality versus conventional treatment of reaching ability in chronic stroke: clinical feasibility study. Neurology & Therapy 2012, 1:1-15.

Biess A., Flash T., **Liebermann D.G.**, Riemannian geometric approach to human arm dynamics, movement optimization, and invariance, Physical Review E, 2011, 83, 031927.

Liebermann D.G., McIntyre J., Levin, M.F.; Weiss, P.L., Berman, S. Arm path fragmentation and spatiotemporal features of hand reaching in healthy subjects and stroke patients. IEEE Engineering in Medicine and Biological Sciences 2010, IEEE Xplore, 5242-5245.

Krasovsky T., Berman S., **Liebermann D.G.**, Kinematic features of continuous hand reaching movements under simple and complex rhythmical constraints. J. Electromyography & Kinesiology 2010, 20, 636-641

Röijezon U., Djupsjöbacka M., Björklund M., Häger-Ross Ch., Grip H., **Liebermann D.G.** Kinematics of fast cervical rotations in persons with chronic neck pain: a cross-sectional and reliability study. BMC Musculoskeletal Disorders 2010, 11:222.

Meltzer I., Krasovsky T., Oddsson L., **Liebermann D.G.** Age-related differences in lower limb force-time relation during the push-off in rapid voluntary stepping. Clinical Biomechanics, 2010, 25: 989-94.

Meltzer I., **Liebermann D.G.**, Krasovsky T., Oddsson L. Cognitive Load Affects Lower Limb Force-Time Relations During Voluntary Rapid Stepping in Healthy Old and Young Adults. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2010, 65A, 400-406.

Chapters

Levin, M.F., Deutsch J., Kafri M., **Liebermann D.G.** Validity of virtual reality environments for motor rehabilitation. In: Virtual Reality for Physical and Motor Rehabilitation, *Virtual Reality Technologies for Health and Clinical Applications,* P.L. (Tamar) Weiss, E.A. Keshner, M.F. Levin (Eds.), Springer Science+Business Media, New York 2014 (in press), doi: 10.1007/978-1-4939-0968-1_6.

Liebermann, D.G. and Franks I.M. "Video-based technologies, substitution of reality and performance feedback"; In M. Hughes and I.M. Franks (Eds.), *The Essentials of Performance Analysis,* Routledge: London, 2014 (in press).

May 24, 2014

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Spinal Form and Function

Position

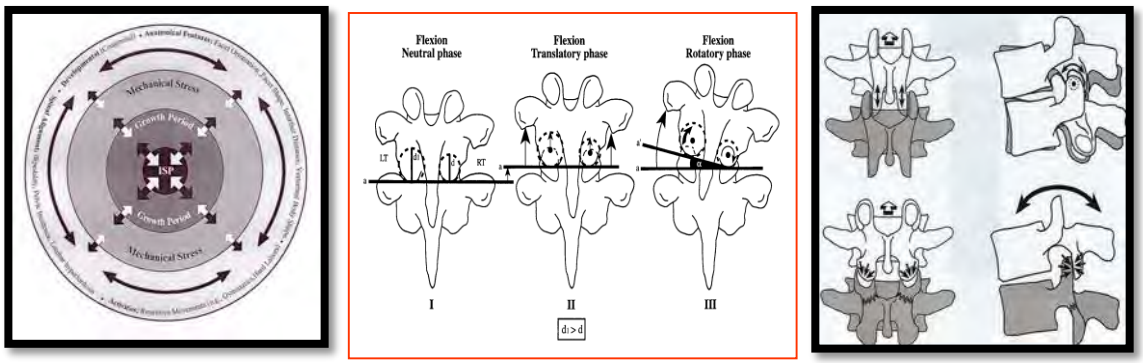
Senior Lecturer, Sackler Faculty of Medicine
Member, Associate Board, Spine Journal

Research

Clinical, diagnostic, therapeutic, epidemiological, kinematical, and anthropometric investigations of the normal and pathological human spine.

During the last decade, we have focused our research on studying the form and function of the human spine in normal and pathological conditions (Figure 1). We proposed some unique models for the pathogenesis and biomechanics of several spinal pathologies. Specifically, the following research projects were investigated and categorized as clinical (diagnostic, therapeutic and clinical reasoning), kinematical and morphological:

- ***Clinical/kinematic:*** a. Directional and positional preference of group exercising in individuals with chronic low back pain and osteoporosis; b. Clinical reasoning and decision making; c. Kinematical evaluation of lumbar rotations in erected and fully flexed standing and sitting positions in patients with chronic low back pain.
- ***Morphological/Anatomical:*** a. A morphometric analysis of the normal and pathological human spine; b. Spinal shape variation and postural changes during growth.
- ***Epidemiological:*** An epidemiological study on spinal osteoporosis in females and sport related back injuries in children.



A *B* *C*

Figure 1. The suggested pathogenesis (A) and kinematics (B-C) in isthmic spondylolysis (ISP).

Publications

Dar G., **Masharawi Y.**, Peleg S., Steinberg N., May H., Medlej B., Hershkovitz I. Schmorl's nodes distribution in the human spine and its possible etiology. European Spine Journal 19:670-675, 2010.

Masharawi Y., Dar G., Peleg S., Steinberg N., Medlej B., May H., Hershkovitz I. A morphological adaptation of the thoracic and lumbar vertebrae to lumbar hyperlordosis in young and adult females. European Spine Journal 19:768-773, 2010.

Abbas J., Hamoud K., **Masharawi Y.**, May H., Medlej B., Ori H., Peled N., Hershkovitz I. Ligamentum flavum thickness in normal and stenotic lumbar spines. Spine 20:1225-30, 2010.

Abbas J., Hamoud K., May H., Hay O., Medlej B., **Masharawi Y.** Peled N., Hershkovitz I. Degenerative lumbar spinal stenosis and lumbar spine configuration. European Spine Journal 19:1865-73, 2010.

Steinberg N., Siev-Ner I., Peleg S., Dar G., **Masharawi Y.**, Hershkovitz I. Injury pattern in young non-professional dancers. Journal of Sports Sciences 29:47-54, 2011.

Dar G., **Masharawi Y.**, Peleg S., Steinberg S., May H., Medlej B., Hershkovitz I. The epiphyseal ring: a long forgotten anatomical structure with significant physiological function. Spine 36:850-6, 2011.

Abbas J., Hamoud K., Peleg S., May H.**, Masharawi Y.**, Cohen H., Peled N**.,** Hershkovitz I**.** Facet joint orthrosis in normal and stenotic lumbar spines. Spine 36:E1541-6, 2011.

Masharawi Y., Salame K. Shape variation of the neural arch in the thoracic and lumbar spine: characterization of its asymmetry and relationship with the vertebral body. Clinical Anatomy 24:858-67, 2011.

Moller A., **Masharawi Y**. The effect of first ballet classes in the community on thoracic kyphosis, lumbar lordosis, hip external rotation and joint laxity in young girls. Physical Therapy in Sport 12:188-93, 2011.

Beladev N., **Masharawi Y**. The effect of group-exercising on females with non-specific chronic low back pain in a sitting position. A pilot study. Journal of Back and Musculoskeletal Rehabilitation 24:181-8, 2011.

Masharawi Y. Lumbar Shape characterization of the neural arch and vertebral body in spondylolysis: A comparative skeletal study. Clinical Anatomy 25:224-230, 2012.

Mannion A., O'Riordan D, Dvorak J, **Masharawi Y.** The relationship between psychological factors and performance on the Biering-Sorensen back muscle endurance test. Spine Journal 11:849-57, 2011.

Masharawi Y., Kjaer P., Manniche C., Bendix T. Lumbar sagittal shape variation vis-à-vis sex during growth: a 3-year follow-up magnetic resonance imaging study in children from the general population. Spine 37:501-7, 2012.

Masharawi Y. Lumbar Shape characterization of the neural arch and vertebral body in spondylolysis: A comparative skeletal study. Clin Anat, 25(2):224-230, 2012.

Steinberg N., Siev-ner I., Peleg S., Dar G., **Masharawi Y.,** Zeev A., Hershkovitz I. Extrinsic and Intrinsic risk factors associated with injuries in young dancers aged 8-16 years. J sports Sc., 30(5):485-495, 2012.

Steinberg N., Siev-Ner I., Peleg S., Dar G, **Masharawi Y.**, Zeev A., Hershkovitz I. Joint Range of Motion and Patellofemoral Pain in Dancers. Int J Sports Med, 33(7):561-566, 2012.

Steinberg N., Hershkovitz I., Peleg S., Dar G., **Masharawi Y**., Zeev A., Siev-Ner I. Morphological characteristics of the young scoliotic dancer. Phys Ther Sport. 14(4):213-220, 2013.

Masharawi Y., Nadaf N. The effect of non-weight bearing group-exercising on females with non-specific chronic low back pain: A randomized single blind controlled pilot study. J. of Back Musculo. Reh. 26(4):353-359, 2013.

Steinberg N., Siev-Ner I, Peleg S., Dar G., **Masharawi Y**., Zeev A., Hershkovitz I. Injuries in Female Dancers Aged 8 to 16 Years. J of Athl Train. 48 (1):118-123, 2013.

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Hearing Science and Clinical Audiology

Position

Associate Professor, Sackler Faculty of Medicine and School of Education

Research

- Speech perception and production by the hearing impaired
- The implications of hearing loss on communication, cognitive and socio-emotional functionning in school, in the family and in general
- Educational Audiology
- Auditory rehabilitation of people with hearing loss

Our research focus is on evaluating the hearing and communication profile of individuals with a hearing loss and understanding the relationship between these functions and their functional management in various life environments. This research analysis expands the knowledge and understanding of theoretical models that examine the functioning of the individual with a hearing loss and constitutes a scientific basis for the development of intervention programs suited to the hearing and communication profile.

Our research activities focus on two main areas:

1. Research in the field of speech perception and communication through spoken language of individuals with a hearing loss.

We focus on the perception of suprasegmental and paralinguistic features of the spoken message. These provide information on the communication intentions of the speaker (e.g. asking a question in comparison to stating a fact) as well as the speaker's emotional state.

2. Research of the ramifications of a hearing loss and communication difficulties on the individual's ability to function in various life environments: educational system, home and work environment, as well as the ramifications of the hearing loss and the communication difficulties on the people in the individual's environment.

Our research focuses on the relationship between hearing loss and communication function through the use of spoken language in general and the speech intelligibility in particular.

With the current trend to integrate children with a hearing loss into regular educational frameworks either individually or in a group, we also investigate the effect of hearing loss on the pupil's ability to function within these frameworks. This research is carried out in different sectors of the population (Jewish (secular & orthodox) and Arab), and on a range of age groups.

Within the framework of the research examining the implications of hearing loss on the different aspects of a child's life, we investigate not only the individual's functioning but also those aspects that relate to the people in their environment such as their parents, siblings and teachers.

Publications

Most, T. & Kozlovski, L. (2010). Academic and social functioning of adolescents with hearing loss who are included individually in regular classrooms. *DASH-Dibur, Safa & Shmia, 29*, 103-122 (Hebrew)

Appel-Korman, S. & **Most, T.** (2010). Parental stress and social and personal adaptation of hearing siblings of hearing impaired children in comparison to parents and siblings of hearing children. *DASH-Dibur, Safa & Shmia, 29*, 23-41 (Hebrew)

Most, T. & Tsach, N. (2010). School functioning of children with unilateral hearing loss in comparison to the functioning of children with normal hearing. *JADARA, 43(2*), 101-120

Yehudai, N., Masoud, S., **Most, T**., & Luntz, M. (2010). Depth of stapes prosthesis in the vestibule: baseline values and correlation with stapedectomy outcome. Acta Oto-Laryngologica, 130(8), 904-908.

Luntz, M. Yehudai, N., Zach, N., **Most, T**., & Shpak, T. (2010). Sequential bilateral implantation in children. *HAREFUA, 149(6*), 157-161.(Hebrew)

Most, T., Shrem, H. Duvdevani, I. (2010). Cochlear implantation in late-implanted adults with prelingual deafness. *American Journal of Otolaryngology, 31 (6)*, 418-423

Most, T. August-Shina, E. Melejson, S. (2010). Pragmatic abilities of children with hearing loss using cochlear implants or hearing aids compared to hearing children. *Jurnal of Deaf Studies and Deaf Education, 15*, 422-437

Most, T. Harel, T. Shpak, T. & Luntz, M. (2011). Perception of suprasegmental speech features via bimodal stimulation: Cochlear implant on one ear and hearing aid on the other. *Journal of Speech, Language, and Hearing Research, 54*, 668–678

Yehudai, N., Tzach, N. Shpak, T., **Most, T**., & Luntz, M. (2011). Demographic factors influencing educational placement of the hearing-impaired child with a cochlear implant. *Otology & Neurotology, 32*, 943-947

Most, T. Gaon-Sivan, G., Shpak, T., & Luntz, M. (2012). Contribution of a contralateral hearing aid to perception of consonant voicing, intonation, and emotional state in adult cochlear implantees. *JDSDE, 17 (2)*, 244-258. doi:10.1093

Most, T., Ingber, S. Ariam-Heled, E. (2012). Social competence, sense of loneliness and speech intelligibility of young children with hearing loss in individual inclusion and group inclusion. *JDSDE, 17 (2)*, 259-271. doi: 10.1093

Most, T. Adi-Bensaid, L. Sharkiya, S., Shpak, T., Luntz, M. (2012). Everyday hearing performance in unilateral versus bilateral hearing aid users. *American Journal of Otolaryngology, 33*, 205-211

Most, T., Bachar, D., & Dromi, E. (2012). Auditory, visual and auditory-visual identification of emotions by nursery school Children. *Journal of Speech-Language Pathology and Applied Behavior Analysis, 5*, 25-34

Adi-Bensaid, L. & **Most, T.** (2012). The effect of speaker's gender and number of syllables on the perception of words by young children: a developmental study. *Journal of Speech-Language Pathology and Applied Behavior Analysis, 5*, 17-24

Most, T & Michaelis, H. (2012). Auditory, visual, and auditory-visual perception of emotions by young children with hearing loss versus children with normal hearing. *Journal of Speech, Language, and Hearing Research, 55*, 1148–1162

Ingber, S., **Most, T**. (2012) Fathers' involvement in preschool programs for children with and without hearing loss. *American Annals of the Deaf*, 157, 276-88.

Adi-Bensaid, L., Michael, R., Most, T., Cinamon, R.G. (2012) Parental and spousal self-efficacy of young adults who are deaf or hard of hearing: relationship to speech intelligibility. *The Volta Review*, 112, 113-130.

Yehudai, N., Shpak, T., **Most, T.,** Luntz, M. (2012) Natural history of of contralateral residual hearing in unilateral cochlear implant users long-term findings. *Acta Oto-Laryngologica*, 132, 1073-1076.

Michael, R. Cinamon R.G. & **Most, T**. (2013) The contribution of perceived parental support to the career self-efficacy of deaf, hard of hearing, and hearing adolescents. *JDSDE,* 18, 329-343.

Ziv, M., **Most, T**. & Cohen, S. (2013) Understanding of emotions and false beliefs among children with normal hearing versus children with hearing loss. *JDSDE* 18, 161-174.

Yehudai, N., Shpak, T., **Most, T**., Luntz, M (2013) Functional status of hearing aids in bilateral-bimodal users. *Otology & Neurotology*, 34, 675-681.

Luntz M., Yehudai N., Haifler, M., Sigal, G. & **Most T**. (2013) Clinical significance of sensorineural hearing loss in chronic otitis media. *Acta Oto-laryngologica*, 133, 1173-1180

Shpak, T., **Most, T.,** Luntz, M. (2014) Fundamental frequency information for speech recognition via bimodal stimulation: cochlear implant on one ear and hearing aid on the other. *Ear and Hearing*, 35, 97-109.

Chapter

Most, T. & Ringvald, D. (Eds.) (2014). Theoretical and applied aspects in rehabilitation and education of deaf and hard of hearing individuals. MOFET Publishing House. Tel Aviv (In Hebrew).

May 29, 2014

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Hearing Science and Clinical Audiology

Position

Professor, Sackler Faculty of Medicine
Audiologist, Speech and Hearing Center, Sheba Medical Center

Research

One of our main research areas is related to the effect of noise on speech perception, in young, middle aged and elderly populations. A major complaint of hearing impaired and normal hearing adults is the difficulty to understand speech in the presence of noise. Our attempt to address this challenging problem encompasses several aspects:

a. Improving the signal to noise ratio in sensory aids (hearing aids and cochlear implants). Recently we demonstrated a significant beneficial effect of a single channel Cochlear-based Noise Reduction Algorithm (CNRA) in hearing aids users and cochlear implants recipients. Further investigation is required for improving CNRA performance at lower SNRs and in different noise spectra.

b. Investigating the influence of aging on the recognition of speech in background noise: Aging is known to induce physio-pathological changes in the entire auditory pathways. While there is a comprehensive documentation of this difficulty amongst elderly people aged 65 years and above, limited information is available on middle-aged listeners.

Another topic in our research is the estimation of the potential risk for hearing loss as a result of listening to music with Personal Listening Devices (PLDs). We are studying the function of the efferent auditory system in normal and pathological populations such as children and adults with Auditory Processing Disorders and Childhood Selective Mutism.

Cochlear Implants are another area of research interest. In particular we are studying the characteristic features of the electrical nerve response in cochlear implant recipients.

Publications

R. Kaplan-Neeman, M. Hildesheimer**, C. Muchnik**, J. Kronenberg, L. Migirov Cochlear Implant Recipients' Hearing Sensation as Manifested by Their Maps During Pregnancy and Postpartum. Otol Neurotol. 31(6): 923-925, 2010

Y. Henkin, Y. Soffer, **C. Muchnik**, Auditory conflict processing: behavioral and electrophysiological manifestations of the stroop effect. J Am Acad Audiol. 21: 474-486, 2010

D. Ari-Even Roth, **C. Muchnik**, M. Hildesheimer, Y. Henkin. Auditory brainstem response in young children with autistic spectrum disorders. Devevelopmental Medicine and Child Neurology. 54 : 23-29, 2012

C. Muchnik, N. Amir, E. Shabtai, R. Kaplan-Neeman, Preferred listening levels to personal devices in young teenagers: self reports and physical measurements. International Journal of Audiology , 51:287-293, 2012

R. Kaplan-Neeman, **C. Muchnik**, M. Hildesheimer, Y. Henkin. Hearing aid satisfaction and use in the advanced digital era. Laryngoscope, 122: 2029-2036, 2012

N. Fink, M. Furst, **C. Muchnik**. Improving word recognition in noise of hearing impaired subjects with a single – channel cochlear noise reduction algorithm. Journal of the Acoustical Society of America, 132: 1718-1731, 2012

C. Muchnik, D. Ari-Even Roth, M. Hildesheimer, M. Arie, Y. Bar-Haim, Y. Henkin (2013) Abnormalities in auditory efferent activities in children with selective mutism. Audiology & Neurotology, 18:353-61, 2013.

May 24, 2014

Dr. Semyon Melnikov, Ph.D.

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Attitudes Toward Organ/Tissues Donation and Transplantation

Position

Lecturer, Sackler Faculty of Medicine

Research

Patients on organ transplant waiting lists continue to far exceed donor rates. Our research seeks to understand the barriers preventing people in Israel from donating organs/tissues for transplantation. The study tries to elucidate attitudes and perceptions regarding different sides of organ/tissues donation and transplantation. The research attempts to expound the understanding of emotional and ethical issues to which the transplant patients, organ donors and their family and health care professionals are exposed.

Publications

Melnikov S, Shor R, Kigli-Shemesh R, Gun Usishkin M, Kagan I. Closing an Open Psychiatric Ward: Organizational Change and Its Effect on Staff Uncertainty, Self-Efficacy, and Professional Functioning. *Perspectives in Psychiatric Care*. 2013, 49, 103-109.

Melnikov S, Itzhaki M, Kagan I. Israeli nurses' intention to report for work in an emergency or disaster. *Journal of Nursing Scholarship*. 2014, 46(2), 134-142.

Urinary organic anion transporter protein profiles in AKI. Kunin M, Holtzman EJ, **Melnikov S**, Dinour D. *Nephrol Dial Transplant*. 2012, 4, 1387-95

Melnikov S, Mayan H, Uchida S, Holtzman EJ, Farfel Z. Cyclosporine metabolic side effects: association with the WNK4 system. *European Journal of Clinical Investigation*, 2011, 41: 1113-20.

Farfel A, Mayan H, **Melnikov S**, Holtzman EJ, Pinhas-Hamiel O, Farfel Z. Effect of age and affection status on blood pressure, serum potassium and stature in familial hyperkalaemia and hypertension. *Nephrology Dialysis Transplantation*, 2011, 26, 1547-53

May 25, 2014

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Computational Biomechanics in Motor Rehabilitation

Position

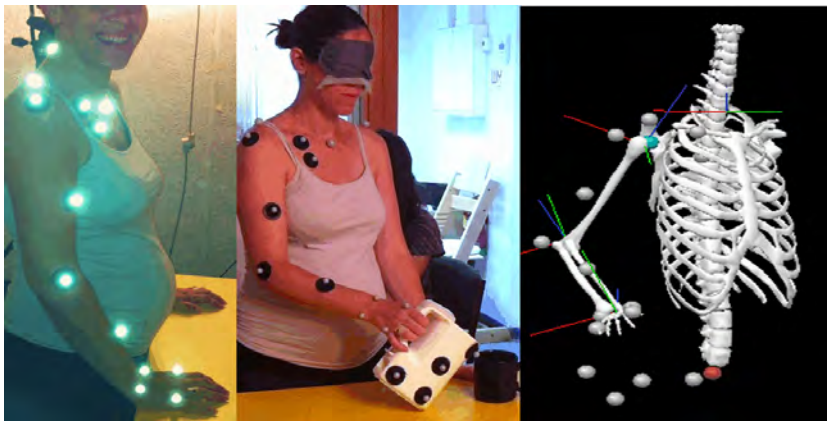
Lecturer, Sackler Faculty of Medicine

Research

The motor function and rehabilitation lab is dedicated to the study of motor mechanisms and rehabilitation strategies. The major research themes of the laboratory are:

1) Design of new evaluation and treatment tools for clinicians, based on state-of-the-art technologies.
2) Quantification, evaluation and feedback, provided to the motor-impaired patient by utilizing real-time data of the kinematics, kinetics and muscular activity patterns.
3) Development of innovative assistive technology and out-of-clinic rehabilitation solutions.

The work in the laboratory is highly interdisciplinary, combining aspects of biomedical engineering, rehabilitation medicine, physiotherapy, and occupational therapy.



3D kinematics of daily activities acquired using a passive-marker-based motion capture system

Publications

Portnoy S, van Haare J, Geers RPJ, Kristal A, Siev-Ner I, Seelen HAM, Oomens CWJ, Gefen A. Real-time subject-specific analyses of dynamic internal tissue loads in the residual limb of transtibial amputees. *Medical Engineering and Physics*, **32**, 312-323, 2010.

Elsner JJ, **Portnoy S**, Guilak F, Shterling A, Linder-Ganz E. MRI-based characterization of bone anatomy in the human knee for size matching of a medial meniscal implant. *Journal of Biomechanical Engineering*. 132:101008, 2010.

Elsner JJ, **Portnoy S**, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. *Journal of Biomechanical Engineering*. 132: 095001, 2010.

Portnoy S, Siev-Ner I, Shabshin N, Gefen A. Effects of sitting postures on risks for deep tissue injury in the residuum of a transtibial prosthetic-user: a biomechanical case study. *Computer Methods in Biomechanics and Biomedical Engineering,* 14:1009-19, 2011.

Portnoy S, Vuillerme N, Payan Y, Gefen A. Clinically-oriented real-time monitoring of the individual's risk for deep tissue injury. *Medical & Biological Engineering & Computing*, 49: 473-483, 2011. *Winner of the Nightingale Prize for best paper published in Medical and Biological Engineering and Computing in 2011.*

Portnoy S, Kristal A, Gefen A, Siev-Ner I. Outdoor dynamic subject-specific evaluation of internal stresses in the residual limb: hydraulic prosthetic foot compared to energy-stored prosthetic feet. *Gait & Posture*, 35:121-5, 2012.

Portnoy S, Schwartz I. Gait characteristics of post-poliomyelitis patients: standardization of quantitative data report, *Annals of Physical and Rehabilitation Medicine*. S1877-0657(13)00103-6. 2013.

Chapter

Portnoy S, Gefen A. Patient-specific modeling of subjects with a lower limb amputation, Patient-Specific Modeling in Tomorrow's Medicine, Studies in Mechanobiology, Tissue Engineering and Biomaterials Volume 09, 2012, pp 441-459.

May 25, 2014

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Gaming as a Means of Rehabilitation of Neurological and Geriatric Populations

Position

Senior Lecturer, Sackler Faculty of Medicine

Head of M.Sc. Program, Department of Occupational Therapy

Research

Our research focuses on achieving a better understanding of the factors hindering and facilitating recovery posts-troke. We have developed interventions aimed to improve the motor recovery and executive functions deficits that these individuals experience, in order to enhance function in daily living. The effectiveness of these novel interventions is assessed by conducting clinical trials.

Our current research project aims to assess the effectiveness of a 'Community' and 'Home' based VR therapy (using video games) as opposed to traditional therapy for enhancing daily function and participation of individuals with chronic stroke living in the community. The daily physical activity (daily walking and arm use) of these individuals is quantified by an innovative form of instrumentation technology (accelerometers). We are also investigating the use of Apps that run on Tablets for self-training of the impaired hand during rehabilitation of individuals following acquired brain injury.

Publications

Rand D, Givon N, Weingarden H, Nota, A., & Zeilig, G. Eliciting Upper Extremity Purposeful Movements Using Video Games A Comparison With Traditional Therapy for Stroke Rehabilitation. Neurorehabil Neural Repair, 2014, Feb 10. [Epub ahead of print]

Erez N, Weiss PL, Kizony R, **Rand D**. Comparing performance within a virtual supermarket of children with traumatic brain injury to typically developing children: a pilot study. OTJR. 2013, 33:218-227.

Tang A, Eng JJ, **Rand D**. Relationship between perceived and measured changes in walking after stroke. J Neurol Phys Ther, 2012, 36:115-121.

Neil A, Ens S, Pelletier R, Jarus T, **Rand D**. Sony PlayStation EyeToy elicits higher levels of movement than the Nintendo Wii: implications for stroke rehabilitation. Eur J Phys Rehabil Med, 2012, 48, 1-9.

Kam N, Struzik J, Jarus T, **Rand D**: Is the Nintendo Wii suitable for stroke rehabilitation? A pilot feasibility and usability study. IJOT, 2012, 21:E3-E25.

Rand D, Eng JJ. Disparity between functional recovery and daily use of the upper and lower extremities during subacute stroke rehabilitation. Neurorehabil Neural Repair, 2012, 26:76-84.

Rand D, Miller WC, Yiu J, Eng JJ. Interventions for addressing low balance confidence in older adults; a systematic review and meta-analysis. Age and Aging, 2012, 40:297–306.

Rand D, Eng J, Liu-Ambrose T, Tawashy A. Feasibility of a 6-month exercise and recreation program to improve executive functioning and memory of individuals with chronic stroke. Neurorehabil Neural Repair 2010, 24:722 –729.

Rand D, Eng J, Tang P, Hung C, Jeng J. Participation in physical activity and its contribution to the health-related quality of life of ambulatory individuals with chronic stroke. Health Qual Life Outcomes, 2010, 8: 80.

Rand D, Eng J. Arm-Hand Usage in Healthy Older Adults. AJOT, 2010, 64:877-885.

Book Chapters

Kizony K, Weiss PL, **Rand D**. Designing and adapting VR technology and VEs for rehabilitation: A multidisciplinary approach. In: Virtual Reality Technologies for Health and Clinical Applications P. Sharkey (Series Ed) Vol. 4: Design, Technologies, Tools, Methodologies & Analysis, S. Cobb and B. Lange (Eds). In press.

Weiss PL, Kizony R, Feintuch U, **Rand D**, Katz N. Textbook of Neural Repair and Rehabilitation Section: Technology of Rehabilitation. Chapter # 47: Virtual Reality Applications in, iNeurorehabilitation. In press.

Grants

2011-2015 EU, Marie Curie International Reintegration Grant (FP7-PEOPLE-2010-IRG) -

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Investigating the Ergonomics of Occupational Tasks and Driving Rehabilitation

Position

Associate Professor, Sackler Faculty of Medicine

Research

Our research focuses on the ergonomics of occupational tasks such as typing and playing musical instruments. Our current research integrates the usage of 3-dimensional advanced technologies to evaluate the movement of hands, specific devices to evaluate force, computerized technologies to evaluate sitting which enable to refer to dynamic situations and the change in risk factors while performing different tasks. These studies have provided essential information concerning risk factors for musculoskeletal disorders and have led to more recent investigations of the determinants of postural patterns amongst children that may contribute to risks in adolescence and adulthood. The anticipated outcomes of these programs of research are to develop training programs and/or contribute to workspace design to minimize these risks.

Driving rehabilitation is another major area of research. Research explores the impact of disease and disorder on driving with the aim of developing appropriate rehabilitation programs, reflecting the importance of 'driving' as a factor in independence as well as a marker of function for variety of populations.

Publications

Levanon, Y., Gefen, A., Lerman, Y., Givon, U., **Ratzon, N**.(2010). Validity and reliability of upper extrimity three dimensional kinematics during a typing task.*Gait & Posture,* 32, 469-474.

Ratzon, N., Schejter, T., Alon, E. and Schreuer, N. (2011). Are Young Adults with Special Needs Ready for the physical work demands? *Research in Developmental Disabilities,* 32, 371-376.

Kaufman-Cohen,Y., **Ratzon, N.** (2011). Correlation between risk factors and musculoskeletal disorders among classical musicians. *Occupational Medicine,* 61, 90-95.

Levanon, Y., Gefen, A., Lerman, Y., givon, U., **Ratzon, N.** (2012). Reducing musculoskeletal disorders among computer operators; a comparison between ergonomics interventions at the workplace. *Ergonomics,* 55, 1571-1585.

Green, D., Meroza, A., Edit-Margalita, A., **Ratzon, N.** (2012). A validation study of the Keyboard Personal Computer Style instrument (K-PeCS) for use with children. *Applied Ergonomics,* 43, *985-992.*

Ratzon, N., Ben Ari (Shevil), E., Froom, P., Friedman, S., Amit, Y. (2013). Functional capacity evaluation of work performance among individuals with pelvic injuries following motor vehicle

accidents. *Work: A Journal of Prevention, Assessment & Rehabilitation*, 45, 191-200.

Lipskaya-Velikovsky, L., Kotler, M., Weiss, P., Kaspi, M., Gamzo, S.,**Ratzon, N.** (2013). Car Driving in Schizophrenia: Can Visual Memory and Organization Make a Difference? *Disability and Rehabilitation, [Epub ahead of print]*

Ratzon, N., Zabaneh-Tannas, K., Ben-Hemo, L., Bart, O. (2010). The efficiency of the home parental program in visual-motor home activity among first grade children. *Child Care Health and Development*, 36, 249-254.

Ratzon, N., Futeran, R., Isakov, E. (2010). Identifying predictors of function in people with diabetes living in the community. *British Journal of Occupational Therapy,* 73, 277-283,

Bart O., Rosenberg L., **Ratzon N**., Jarus, T. **(**2010). Development and initial validation of the Performance Skills Questionnaire (PSQ). *Research in Developmental Disabilities,* 31, 46-56**.**

Rosenberg, L, **Ratzon. N**., Jarus. T., Bart, O. (2010). Development and initial validation of the Environmental Restriction Questionnaire, ERQ*. Research in Developmental Disabilities***,** 31**,** 1323-1331.

Rosenberg, L., Jarus, T., Bart O., **Ratzon, N.** (2011). Can personal and environmental factors explain dimensions of children participation? *Child: Care, Health & Development***,** 37, 266-275.

Soref. B., **Ratzon, N**., Rosenberg, L., Leitner, Y., Jarus, T., Bart, O. (2011). Personal and environmental pathways to participation in young children with and without mild motor disabilities. *Child: Care, Health & Development,* 38, 561–571.

Rosenberg, L., **Ratzon, N**., Jarus, T., Bart. O. (2012). Perceived environmental restrictions for the participation of children with mild developmental disabilities. *Child: Care, Health & Development,* 38, 836-843.

Liberman, L., **Ratzon, N**., Bart, O. (2013). The profile of performance skills and emotional factors in the context of participation among young children with Developmental Coordination Disorder. *Research in Developmental Disabilities,* 34, 87-94.

Lahav, O., Apter, A., **Ratzon, N.** (2013). Psychological adjustment and levels of self-esteem in children with visual-motor integration difficulties influences the results of a randomized intervention trial. *Research in Developmental Disabilities*, 34, 56-64.

Rosenberg, L., Bart, O., **Ratzon, N. Z**., & Jarus, T. (2013). Complementary contribution of parents and therapists in the assessment process of children. *Australia Occupational Therapy Journal*, *60*, 410-415.

Gat, S., & **Ratzon, N. Z**. (2014). Comparison of occupational therapy students' perceived skills after traditional and nontraditional fieldwork. *The American Journal of Occupational Therapy*, *68* , e47-e54.

Shichror, R., Sarid, A., **Ratzon, N.** (2014) Determining the Sampling Time Frame for In-Vehicle Data Recorder Measurement in Assessing Drivers. *Transportation Research Part C*, *42C*, 99-106.

Karni, S., Bentur, N., & **Ratzon, N.** (2014) Participation and Quality of Life of Cognitively Impaired Older Women in Israel Following Hip Fractures. *Occupational Therapy International.* Feb 10. doi: 10.1002/oti.1365.

<u>Grants</u>

2009-2013 National Road Safety Authority Grant

2012-2014 Office of Senior Citizens Grant

2013-2014 National Insurance Institute Grant

May 24, 2014

Prof. Dorit Ravid, Ph.D.

Department of Occupational Therapy
Stanley Steyer School of Health Professions
Sackler Faculty of Medicine

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Tel Aviv University
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Language Acquisition and Development of Linguistic Literacy

Position

Professor, School of Education and Sackler Faculty of Medicine

Vice-President, International Association for the Study of Child Language
Member, Academie Europea

Research

We study the ways Israeli infants, toddlers, children and adolescents acquire the structures, meanings and functions of spoken and written Hebrew (and Arabic). Empirical and theoretical exploration of linguistic phenomena are conducted against general models of language and cognitive acquisition, on the one hand, and the typological properties and constraints of Hebrew (and Semitic) verbal expression, on the other. Human development is taken as the critical context within which native language learning can take place in children. Specific areas of current investigation are (inter alia) acquisition of Hebrew verb structure (root and *binyan*) and semantics in mother-child dyads, children's peer talk and children's storybooks; linguistic input (maternal talk) to children and the relationship to their development in different socio-economic contexts; the emergence of syntactic constructions in children's development language; prepositions and prepositional phrases in spoken and written Hebrew development; the development of written text production abilities across the school years; narrative acquisition and narrative theory; morpho-syntactic constructions in learning to spell Hebrew.

Publications

Ravid, **D**. & R. Levie. 2010. Adjectives in the development of text production: Lexical, morphological and syntactic analyses. *First Language*, 30, 27-55.

Ravid, **D.** & R. Berman. 2010. Developing noun phrase complexity at school-age: A text-embedded cross-linguistic analysis. *First Language***,** 30, 3–26.

Berman, R.A. & **D. Ravid**. 2010. Interpretation and recall of proverbs in three pre-adolescent populations. *First Language*, 30, *155-173.*

DeKeyser, R., I. Alfi-Shabtay & **D. Ravid**. 2010. Cross-linguistic evidence for the nature of age effects in second language acquisition. *Applied Psycholinguistics*, 31, 413–438.

Berman, R.A., R. Nayditz & **D. Ravid**. 2011. Linguistic diagnostics of written texts in two school-age populations. *Written Language & Literacy,* 14, 161-187.

Schiff, R., **D. Ravid** & S. Levy-Shimon. 2011. Children's command of plural and possessive marking on Hebrew nouns: A comparison of obligatory vs. optional inflections. *Journal of Child Language*, 38, 433–454.

Bar-On, A. & **D. Ravid**. 2011. Morphological decoding in Hebrew pseudowords: a developmental study. *Applied Psycholinguistics*, 32, 553–581.

Ravid, **D.** 2012. Phono-morpho-orthographic construal: The view from spelling. Invited commentary on R. Frost's "A universal theory of reading". *Behavioral and Brain Sciences*, 35, 263–329.

Ravid, D. & R. Schiff. 2012. From dichotomy to divergence: Number/gender marking on Hebrew nouns and adjectives across schoolage. *Language Learning*, 62, 133-169.

Schiff, D. & **D. Ravid**. 2012. Linguistic processing in Hebrew-speaking children from low and high SES backgrounds. *Reading & Writing*, 25, 1427-1448.

Saiegh-Haddad, E., A. Hadieh & D. Ravid. 2012. Acquiring noun plurals in Palestinian Arabic: Morphology, familiarity, and pattern frequency. *Language Learning*, 62, 1024-1051.

Schiff, D. & **D. Ravid**. 2013. Morphological processing in Hebrew-speaking reading-disabled students. *Journal of Learning Disabilities*, 46, 220-229.

Ravid, D. & R. Schiff. 2013. Different perspectives on the interface of dyslexia and language: Introduction to the special LLD issue on Dyslexia and Language. *Journal of Learning Disabilities,* 46, 195-199.

Ravid, D., Bar- On, A. & E. Dattner. 2014. Linguistics in the service of communications disorders: New frontiers. *AILA Review*, 26, 79-99.

Abugov, N. & **Ravid, D.** 2014. The impact of Israeli Hebrew on Yiddish: noun plurals in Sanz Ultra Orthodox Yiddish. International Journal of the Sociology of Language, 226, 189–211.

Uziel-Karl, U., F. Kanaan, N. Abugov, R. Yifat, I. Meir, **& D. Ravid**. 2014. Hebrew and Palestinian Arabic in Israel: Linguistic frameworks and SLP services. Special issue on "Global issues in language disorders: Processes, frameworks and policies", *Topics in Language Disorders*, 34, 133–154.

Schiff, R. & **D. Ravid**. Morpho-syntactic load in judging adjective plural agreement: comparing adults with and without ADD. *Communication Disorders Quarterly.* In press.

Chapters and books

Ravid, D. 2012. *Spelling morphology: the psycholinguistics of Hebrew spelling*. New York: Springer.

Alfi-Shabtay, I. & **Ravid**, D. 2012. Adjective inflection in Hebrew: A psycholinguistic study of speakers of Russian, English and Arabic compared with native Hebrew speakers. In M. Leikin, M. Schwarts and Y. Tobin, (eds.). *Current Issues in Bilingualism. Cognitive and Socio-linguistic Perspectives* (pp. 159-178). New York: Springer.

Ravid, D. & Schiff, R. (Eds.) 2013. Journal of Learning Disabilities Special issue on Dyslexia and Language, 46.

Abugov, N. & **Ravid**, D. 2013. Assessing Yiddish plurals in acquisition: impacts of bilingualism. In Mueller Gathercole V. C (ed.) *Bilinguals and Assessment: State of the art guide to issues and solutions from around the world.* Bristol: Multilingual Matters, 90-110.

Ravid, D. 2013. Syntactic complexity in discourse production across different text types. In Catherine Bolly & Liesbeth Degand (eds), *Across the Line of Speech and Writing Variation*. Louvain-la-Neuve: Presses universitaires de Louvain, 51-66.

Ravid, D & G. Ginat-Heiman. 2014. L1 and L2 proficiency in Hebrew-English adolescent learners. In Adelheid Hu & Patrick Grommes (eds.), *Plurilingual Education: Policies – Practice – Language Development*. Amsterdam: Benjamins, 221-246.

Abugov, N. & **Ravid**, D. 2014. Noun plurals in Israeli Ultra-Orthodox Yiddish: a psycholinguistic perspective. In Aptroot, M. & Hansen, B. (eds.) *Yiddish Language Structures*. Berlin: Mouton De Gruyter, 9-39.

Grants

2013-2015 Discourse Syntax in Developing Text Production. Chief Scientist, Ministry of Education.

2013-2017 Verb structure and Semantics in Development. Israel Science Foundation.

May 28, 2014

Dr. Miriam Theilla, Ph.D.

Department of Nursing
Steyer School of Health Professions
Sackler Faculty of Medicine

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The Effect of Fish Oil Enriched Diet on Wound Healing Processes in ICU Patients

Positions

Lecturer, Sackler Faculty of Medicine

Research

Wound healing is the complex, multi-stage response to tissue injury. This physiologic repair response requires a dynamic temporal and spatial interplay of several cell types, including local parenchymal and mesenchymal cells as well as resident and recruited inflammatory cells. N-3 Fatty acids are recognized as influencing both wound healing and immunity .Our group studies the impact and the specific role of fish oil- and micronutrient enriched formulae on the healing of pressure ulcers and on immune function mediated through a modulation of expression of adhesion molecules in critically ill patients

Our results show a reduction in inflammation levels of C - reactive protein concentrations and increasing levels of adhesion molecules preceding the subsequent reduction in ulcer severity of critically ill patients.

The formulae may ameliorate the inflammatory response, both in magnitude and duration, probably mediated by an effect on adhesion molecule expression. by promoting the transition from an inflammatory to reparative stage of wound healing.

Publications

Theilla M, Schwartz B, Zimra Y, Shapiro H, Anbar R, Rabizadeh E, Cohen J, Singer P. Enteral n-3 fatty acids and micronutrients enhance percentage of positive neutrophil and lymphocyte adhesion molecules: a potential mediatorof pressure ulcer healing in critically ill patients. British Journal Nutrition. 1: 1-6, 2011

Theilla M, Schwartz B, Cohen J, Shapiro H, Anbar R, Singer P. Impact of a nutrition formula enriched in fish oil and micronutrients on pressure ulcer in ICU patients. American Journal of Critical Care. 21: 2-7, 2012.

Anbar R, Beloosesky Y, Cohen J, Madar Z, Weiss A, **Theilla M**, Koren Hakim T, Frishman S, Singer P. Tight Calorie Control in geriatric patients following hip fracture decreases complications: a randomized, controlled study. Clinical Nutrition 33:23-8, 2014

Frishman, S, **Theilla M**, Singer P, Avraham Z, Libman C, Kagan I. JCI Accreditation and its multiprofessional impact on nutrition care at Rabin Medical Center, Israel. Invited (peer-reviewed) paper, published 01 April 2014 on official site of Joint Commission International (JCI): http://www.jointcommissioninternational.org/new-study-jci-accreditation-and-nutrition-care-at-rabin-medical-center/

Chapter

Singer P, **Theilla M**, Cohen J. Intravenous lipids: what do the guidelines say. Institute for Nutrition Research and Critical Care Department. *In press*.

May 28, 2014

School of Public Health

Prof. Daniel I. Cohen, Ph.D.

Department of Epidemiology and Preventive Medicine
School of Public Health
Sackler Faculty of Medicine

Tel Aviv University
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Epidemiology of Infectious Diseases

Positions

Professor of Epidemiology and Preventive Medicine
Head, School of Public Health, Sackler Faculty of Medicine
Incumbent of Diana & Stanley Steyer Chair of Cancer Prevention and Control
Director, Stanley Steyer Institute for Cancer Epidemiology and Research
Director, Tel Aviv University Center for the Study of Bioterrorism

Research

Emerging Infectious Diseases, Vaccinology

(1) The study of risk and protective host factors against enteric diseases; identification of correlates of protection related to the immune response and host microbiota; development of enteric vaccines (2) Development of laboratory-based surveillance methods for enteric diseases (3) Seroepidemiology of vaccine-preventable diseases to monitor the immune status of the Israeli population (4) The study of the association between selected infectious agents (e.g. Helicobacter pylori, Human Papilloma Virus) and cancer.

Publications

Muhsen K, W. Na'amnah, Y. Lesser, I. Volovik, **D. Cohen**, T. Shohat. Determinates of underutilization of amniocentesis among Israeli Arab women. *Prenat Diagn*. 2010;30:138-43.

Muhsen K, A. Athamna, A. Spungin-Bialik, G. Alpert, **D. Cohen**. Presence of *H. pylori* in a sibling is associated with a long term increased risk of *H. pylori* infection in Israeli Arab children. *Helicobacter* 2010;15:108-13.

Cohen D, N. Gargouri., A. Ramlawi, Z. Abdeen, A. Belbesi, B. Al Hijawi, A. Haddadin, S. Sheikh Ali, N. Al Shuaibi, R. Bassal, R. Yishai, M.S. Green, A. Leventhal. 2009. A Middle East sub-regional laboratory-based surveillance network on foodborne diseases established by Jordan, Israel, and the Palestinian Authority. *Epidemiol Infect*. 2010;138:1443-8.

Rendi-Wagner, P., J. Tobias, L. Moerman, S. Goren, R. Bassal, M.S. Green, **D. Cohen**. The seroepidemiology of *Bordetella pertussis* in Israel – Estimate of incidence of infection. *Vaccine* 2010;28:3285-90.

Muhsen Kh, L. Shulman, E. Kasem, U. Rubinstein, J. Shachter, A. Kremer, S. Goren, I. Zilberstein, G. Chodick, M. Ephros, **D. Cohen** for the TAU-HCLV Rota Study Group. Effectiveness of rotavirus vaccines for prevention of rotavirus gastroenteritis-associated hospitalizations in Israel: a case-control study. *Hum Vaccin*. 2010;6:450-4.

Wiser, I., N. Orr, B. Kaufman, S. Segev, Z. Smetana, A. Bialik, N. Epstein, E. Mendelson, R. Catane, **D. Cohen**. Immunosupressive treatments reduce long term immunity to smallpox among breast cancer patients. *J Infect. Dis*. 2010;201:1527-34.

Cohen, D., J. Tobias, A. Bialik, T. Sela, R. Kayouf, Y. Volovik, M. Yavzori, M. Ephros. 2010. Phenotypic characteristics of enterotoxigenic *Escherichia coli* associated with acute diarrhea among Israeli young adults. *Foodborne Pathog Dis*. 2010;7:1159-64.

Muhsen K, Barak M, Henig C, Alpert G, Ornoy A, **Cohen D**. Is the association between Helicobacter pylori infection and anemia age dependent? *Helicobacter*. 2010;15:467-72.

Ziv T, Heymann AD, Azuri J, Leshno M, Cohen D. Assessment of the underestimation of childhood diarrhoeal disease burden in Israel. *Epidemiol Infect*. 2010 Nov 19:1-9.

Muhsen K, Chodick G, Goren S, Shalev V, **Cohen D**. The uptake of rotavirus vaccine and its effectiveness in preventing acute gastroenteritis in the community. *Vaccine*. 2010;29:91-4.

Wiser I, Orr N, Smetana Z, Spungin-Bialik A, Mendelson E, **Cohen D**. Alternative Immunological Markers to Document Successful Multiple Smallpox Revaccinations. *Clin Infect Dis*. 2011;52:856-61.

Bisharat, N, A. Bialik, E. Paz, C. Amaro, **D. Cohen**. Serum antibodies to Vibrio vulnificus biotype 3 lipopolysaccharide and susceptibility to disease caused by the homologous *V. vulnificus* biotype. *Epidemiol Infect*. 2011;139:472-81.

Muhsen K, Shohat T, Aboudy Y, Mendelson E, Algor N, Anis E, **Cohen D**. Sero-prevalence of mumps antibodies and vaccination coverage in subpopulations subsequently affected by a large scale mumps epidemic in Israel. *Vaccine*, 2011.

Muhsen K, Nir A, Spungin-Bialik A, Bassal R, Goren S, **Cohen D**. Interaction between ethnicity, socioeconomic status and Helicobacter pylori sero-prevalence among Israeli children and adolescents. *J Pediatr Gastroenterol Nutr*. 2011

Muhsen K, Jurban M, **Cohen D**. Incidence, age of acquisition and risk factors of Helicobacter pylori infection among Israeli Arab infants. *Journal Trop Ped*, 2011.

Muhsen K, Ornoy A, Akawi A, Alpert G, **Cohen D**. An association between Helicobacter pylori infection and cognitive function in children at early school age: a community-based study. *BMC Pediatr*. 2011 25;11:43

Levine H, Zarka S, Dagan R, Sela T, Rozhavski V, **Cohen D**, Balicer RD. Transmission of *Streptococcus pneumoniae* in adults may occur through saliva. *Epidemiol Infect*. 2012, 140:561-5

Muhsen K, Jurban M, **Cohen D**. Incidence, age of acquisition and risk factors of Helicobacter pylori infection among Israeli Arab infants. J Trop Pediatr. 2012, 58:208-13.

Bassal R**,** Reisfeld A, Andorn N, Yishai R, Nissan I, Agmon V, Peled N, Block C, Keller N, Kenes Y, Taran D, Schemberg B, Ken-Dror S, Rouach T, Citron B, Berman E, Green M.S, Shohat T, **Cohen D**. Recent trends in the epidemiology of non-typhoidal *Salmonella* in Israel (1999-2009). Epidemiology and Infection 2012; 140:1446-53.

Muhsen K, **Cohen D**, Spungin-Bialik A, Shohat T. Sero-prevalence, correlates and trends of *Helicobacter pylori* infection in the Israeli population. Epidemiology and Infection 2012, 140:1207-14.

Cohen D, O. Shoham, N. Orr, K. Muhsen. 2012. An inverse and independent association between Helicobacter pylori infection and the incidence of shigellosis and other diarrheal diseases. Clin. Infect. Dis. 54:e35-e42.

Muhsen K. Abed El-Hai R, Amit-Aharon A, Nehama H, Gondia M, Davidovic N, Goren S, **Cohen D.** Risk factors of underutilization of childhood immunizations in ultraorthodox Jewish communities in Israel despite high access to health care services. Vaccine. 2012;30:2109-15

Cohen D, Muhsen K. Association between Helicobacter pylori colonization and glycated hemoglobin levels: Is this another reason to eradicate Helicobacter pylori in adulthood? J Inf Dis; 2012;205:1183-5 (editorial).

Shulman LM, Hindiyeh M, Muhsen K, **Cohen D**, Mendelson E, Sofer D. Evaluation of Four Different Systems for Extraction of RNA from Stool Suspensions Using MS-2 Coliphage as an Exogenous Control for RT-PCR Inhibition. PLoS ONE 2012; 7: e39455.

Kotloff KL, Blackwelder WC, Nasrin D, Nataro JP, Farag TH, van Eijk A, Adegbola RA, Alonso PL, Breiman RF, Faruque ASG, **Cohen D** *et al*: The Global Enteric Multicenter Study (GEMS) of Diarrheal Disease in Infants and Young Children in Developing Countries: Epidemiologic and Clinical Methods of the Case/Control Study. *Clin Infect Dis* 2012, 55:S232-S245.

Di giovine P, Kafatos G, Nardone A, Andrews N, Olander, Alfarone G, Broughton K, **Cohen D**, Kriz B, Mikova I, O'flanagan D, Schneider F, Selga I, Valinsky I, Velicko I, Karacs I, Pebody R, Von hunolstein C. Comparative seroepidemiology of diphtheria in six European countries and Israel. Epidemiol Infect. 2013, 141:132-42.

Eriksen J, Davidkin I, Kafatos G, Andrews N, Barbara C, **Cohen D**, Duks A, Griskevicius A, Johansen K, Bartha K *et al*: Seroepidemiology of mumps in Europe (1996-2008): why do outbreaks occur in highly vaccinated populations? *Epidemiol Infect* 2013, 141:651-666.

Feldman N, Adler A, Molshatzki N, Navon-Venezia S, Khabra E, **Cohen D**, Carmeli Y: Gastrointestinal colonization by KPC-producing Klebsiella pneumoniae following hospital discharge: duration of carriage and risk factors for persistent carriage. *Clin Microbiol Infec* 2013, 19:E190-E196.

Levine H, Balicer RD, Zarka S, Sela T, Rozhavski V, **Cohen D**, Kayouf R, Ambar R, Porat N, Dagan R: Dynamics of Pneumococcal Acquisition and Carriage in Young Adults during Training in Confined Settings in Israel. *Plos One* 2012, 7: e46491.

Leventhal A, Ramlawi A, Belbiesi A, Sheikh S, Haddadin A, Husseini S, Abdeen Z, **Cohen D**: Enhanced surveillance for detection and management of infectious diseases: regional collaboration in the Middle East. *Emerging Health Threats Journal* 2013, 6.

Muhsen K, Kassem E, Rubinstein U, Schachter Y, Kremer A, Goren S, Zilberstein I, Ephros M, **Cohen D**, Shulman LM: Incidence and Characteristics of Sporadic Norovirus Gastroenteritis Associated with Hospitalization of Children Less Than 5 years of Age in Israel. *Pediatr Infect Dis J* 2013, 32:688-90

Weil M, Shohat T, Bromberg M, Bassal R, Dichtiar R, Mandelboim M, Sofer D, **Cohen D**, Mendelson E: The dynamics of infection and the persistence of immunity to A(H1N1)pdm09 virus in Israel. *Influenza and other respiratory viruses.* 2013, 7:838-46 .

Farag T, Faruque AS, Yukun Wu, Das SK, Hossain A, Ahmed S, Ahmed D, Dilruba N, Kotloff K, Panchilangam S, Nataro J, **Cohen D,** Blackwelder WC, Levine MM. Housefly Population Density Correlates with Shigellosis among Children in Mirzapur, Bangladesh: A Time Series Analysis. PLoS Negl Trop Dis 7: 2013 e2280.

Markovich MP, Shohat T, Riklis I, Avni R, Yujelevski-Rozenblit D, Bassal R, **Cohen D,** Rorman E: Seroepidemiology of Toxoplasma gondii infection in the Israeli population. *Epidemiol Infect*: 2014, 142:149-55.

Bassal R, Schejter E, Bachar R, Shapira H, Sandbank J, Supino Rosin L, Schvimer M, **Cohen D**, Keinan-Boker L: Cervical Pap screening among Israeli women, 2005-2010. Archives of Gynecology and *Obstetrics* 2014: 289:615-22

Cohen D, Bassal R, Goren S, Rouach T, Taran D, Schemberg B, Peled N, Kenes Y, Ken-Dror S, Vasilev V, Nissan I, Agmon V, Shohat T. Recent trends in the epidemiology of shigellosis in Israel *Epidemiol Infect*. 2014; Feb 20:1-12. [Epub ahead of print].

Reviews

Bassal R, Reisfeld A, Andorn N, Yishai R, Nissan I, Agmon V, Peled N, Block C, Keller N, Kenes Y, Taran D, Schemberg B, Ken-Dror S, Rouach T, Citron B, Berman E, Green M.S, Shohat T, **Cohen D.** Recent trends in the epidemiology of non-typhoidal *Salmonella* in Israel (1999-2009). *Epidemiol Infect* 2012, 140:1446-53.

Muhsen K, **Cohen D**, Spungin-Bialik A, Shohat T. Sero-prevalence, correlates and trends of *Helicobacter pylori* infection in the Israeli population. *Epidemiol Infect* 2012, 140:1207-14.

Grants

2011-2015 European Union, Development of vaccines against Shigella and enterotoxigenc *E. coli* enteric diseases. Leader of 2 WPs.

2013-2016 Israel National Institute for Health Policy and Health Services Research "Evaluation of the impact of the introduction of universal immunization with the rotavirus vaccine on the burden of severe childhood diarrhea associated with rotavirus in Israel"

May 24, 2014

Prof. Jiska Cohen-Mansfield, Ph.D.

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School of Public Health
Sackler Faculty of Medicine

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Aging and End of Life

Positions

Professor, Department of Health Promotion, Sackler Faculty of Medicine
Director, Minerva Center for the Interdisciplinary Study of End of Life

Research

Health and Mental Health Promotion in older persons:

- Preventing loneliness and social isolation in older persons
- Promoting physical activity in old age
- Age segregation and integration in society
- Methodologies for alleviating memory difficulties

End of Life

- Delineating end of life as a life stage
- Encountering the gap between the good death and the usual death
- Dementia
    - Understanding symptoms and behaviors in dementia
    - Improving dementia care
- Promoting dignity at the end of life

Publications

Shmotkin D, Lerner-Geva L, Cohen-Mansfield J, Blumstein T, Eyal N, Shorek A, Kave G, Hazan H. (2010) Profiles of functioning as predictors of mortality in old age: The advantage of a configurative approach. *Arch Gerontol Geriatr, 51*:68-75.

Cohen-Mansfield, J., Marx, M.S., Thein, K., & Dakheel-Ali, M. (2010) The impact of past and present preferences on stimulus engagement in nursing home residents with dementia. *Aging and Mental Health, 14*:67-73

Cohen-Mansfield J, Shmotkin D, Eyal N, Reichental Y, Hazan H. (2010) A Comparison of three types of autobiographical memories in old-old age: first memories, pivotal memories and traumatic memories. *Gerontology*, *56*:564-73.

Cohen-Mansfield J, Dakheel-Ali M, Frank JK. (2010) The impact of a Naturally Occurring Retirement Communities service program in MD, USA. *Health Promot Int*; 25:210-220

Cohen-Mansfield, J., Marx, M.S., Dakheel-Ali, M, Regier, N.G., & Thein, K. (2010) Can persons with dementia be engaged with stimuli? *American Journal of Geriatric Psychiatry, 18*, 351-362

Marx, M.S., Cohen-Mansfield, J., Reiger, N.G., Dakheel-Ali, M., Srihari, A., & Thein K (2010). The impact of different dog-related stimuli on engagement of persons with dementia. *American Journal of Alzheimer's Disease and other Dementias,* 25:37-45.

Cohen-Mansfield, J., Thein, K., Dakheel-Ali, M., & Marx, M.S. (2010) The underlying meaning of stimuli: Impact on engagement of persons with dementia. *Psychiatry Research, 177*, 216–222

Cohen-Mansfield J, Shmotkin D, Goldberg S. (2010) Predictors of longitudinal changes in older adults' physical activity engagement. *J Aging Phys Act*. 18:141-57.

Cohen-Mansfield J, Thein K, Dakheel-Ali M, Marx MS. (2010) Engaging nursing home residents with dementia in activities: the effects of modeling, presentation order, time of day, and setting characteristics. *Aging Ment Health*, 14:471-80.

Cohen-Mansfield, J., Marx, M., Regier, N.G., Dakheel-Ali, M., Thein, K., & Freedman, L. (2010). Can agitated behavior of nursing home residents with dementia be prevented with the use of standardized stimuli? *Journal of the American Geriatrics Society (JAGS)*. 58:1459-64.

Cohen-Mansfield, J., Thein, K., Dakheel-Ali, M., Regier, N.G., & Marx, M.S . (2010) The value of social attributes of stimuli for promoting engagement in persons with dementia. *Journal of Nervous and Mental Disease*, 198:586-92

Cohen-Mansfield J, Shmotkin D, Hazan H. (2010) The effect of homebound status on older persons. *J Am Geriatr Soc*, 58:2358-62.

Cohen-Mansfield J, Golander H. (2011) The measurement of psychosis in dementia: a comparison of assessment tools. *Alzheimer Dis Assoc Disord*. 25:101-8.

Vernooij-Dassen M, Vasse E, Zuidema S, Cohen-Mansfield J, Moyle W. (2010) Psychosocial interventions for dementia patients in long-term care. *Int Psychogeriatr*, 22:1121-8.

Cohen-Mansfield, J. (2010). The implications of the study of dementia on family members and caretakers. In Y.Brick & A.Levinstein (Eds), The old man and the family – Key issues in transgenerational relationships. Jerusalem: Eshel. (Hebrew)

Cohen-Mansfield J, Shmotkin D, Hazan H. (2010) The effect of homebound status on older persons. *J Am Geriatr Soc.,* 58: 2358-62.

Cohen-Mansfield J, Wirtz PW. (2011) Predictors of entry to the nursing home: Does length of follow-up matter? *Arch Gerontol Geriatr,* 53, 309-315.

Cohen-Mansfield J, Kivity Y. (2011) The relationships among health behaviors in older persons. *J Aging Health, 23*:822-842.

Cohen-Mansfield, J., & Perach, R. (2011). Is there a reversal in the effect of obesity on mortality in old age? *Journal of Aging Research*. 2011:765071.

Cohen-Mansfield J, Shmotkin D, Hazan H. (2012) Homebound older persons: Prevalence, characteristics, and longitudinal predictors. *Archives of Gerontology & Geriatric,* 54:55-60.

Cohen-Mansfield J, Marx MS, Thein K, Dakheel-Ali M. (2011) The impact of stimuli on affect in persons with dementia. *Journal of Clinical Psychiatry*, 72:480-6.

Cohen-Mansfield J, Jensen B, Resnick B, Norris M. (2012) Assessment and treatment of behavior problems in dementia in nursing home residents: a comparison of the approaches of physicians, psychologists, and nurse practitioners. *International Journal of Geriatric Psychiatry*, 27:135-45.

Cohen-Mansfield, J., Golander, H., Ben-Israel, J., Garfinkel D. (2011). The meanings of delusions in dementia: A preliminary study. *Psychiatry Research, 189*, 97-104.

Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M. (2012) What Are the Barriers to Performing Nonpharmacological Interventions for Behavioral Symptoms in the Nursing Home? *Journal of the American Medical Director's Assoc,* 13:400-5.

Cohen-Mansfield J, Jensen B, Resnick B, Norris M. (2012) Quality of nursing home care: perceptions of physicians, psychologists, and nurse practitioners. *Journal of Nursing Care Quality,* 27:70-6.

Cohen-Mansfield, J., Marx, M., Regier, N.G., Dakheel-Ali, M., Thein, K., Freedman, L., & Murad, H. (2011). The comprehensive process model of engagement. *American Journal of Geriatric Psychiatry, 19*: 859-870.

Cohen-Mansfield J, Jensen B, Resnick B, Norris M. (2012) Knowledge of and attitudes toward nonpharmacological interventions for treatment of behavior symptoms associated with dementia: a comparison of physicians, psychologists, and nurse practitioners. *Gerontologist,* 52:34-45.

Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Murad H, Freedman LS. (2012) The relationships of environment and personal characteristics to agitated behaviors in nursing home residents with dementia. *J Clin Psychiatry*, 73:392-9.

Cohen-Mansfield J, Marx MS, Freedman LS, Murad H, Thein K, Dakheel-Ali M. (2012) What affects pleasure in persons with advanced stage dementia? *J Psychiatr Res*, 46:402-6.

Cohen-Mansfield J, Dakheel-Ali M, Jensen B, Marx MS, Thein K. (2012) An analysis of the relationships among engagement, agitated behavior, and affect in nursing home residents with dementia. *Int Psychogeriatr*, 24:742-52.

Cohen-Mansfield J. (2012) Trends in health behaviors in the old-old population: results from a national survey. *Behav Med*, 38:6-11.

Cohen-Mansfield J, Golander H. (2012) Analysis of caregiver perceptions of "hallucinations" in people with dementia in institutional settings. *Am J Alzheimers Dis Other Demen*, 27:243-9.

Corbett A, Husebo B, Malcangio M, Staniland A, Cohen-Mansfield J, Aarsland D, Ballard C. (2012) Assessment and treatment of pain in people with dementia. *Nat Rev Neurol*, 8:264-74.

Cohen-Mansfield J, Perach R. (2012) Sleep duration, nap habits, and mortality in older persons. *SLEEP*, 35:1003–1009.

Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Freedman L. (2012) Efficacy of nonpharmacologic interventions for agitation in advanced dementia: a randomized, placebo-controlled trial. *J Clin Psychiatry,* 73:1255-61.

Cohen-Mansfield J, Juravel-Jaffe A, Cohen A, Rasooly I, Golander H. (2013) Physicians' practice and familiarity with treatment for agitation associated with dementia in Israeli nursing homes. *Int Psychogeriatr,* 25:236-44.

Cohen-Mansfield J. (2013) Smoking and mortality among persons aged 75-94. *Prev Med*, 56:185-9.

Cohen-Mansfield, J., Shmotkin, D., Malkinson, R, Bartur, L., Hazan, H. (2013) Parental bereavement increases mortality in older persons. *Psychological Trauma: Theory, Research, Practice, and Policy*. 5:84–92.

Husebo BS, Ballard C, Cohen-Mansfield J, Seifert R, Aarsland D. (2013) The response of agitated behavior to pain management in persons with dementia. *Am J Geriatr Psychiatry*, doi:pii: S1064-7481(12)00103-0. 10.1016/j.jagp.2012.12.006.

Cohen-Mansfield J. (2013) Even with regular use of an observational scale to assess pain among nursing home residents with dementia, pain-relieving interventions are not frequently used. *Evid Based Nurs*. 2013 May 1. [Epub ahead of print]

Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Jensen B. (2013) Sources of discomfort in persons with dementia. *JAMA Intern Med*, 173:1378-9.

Cohen-Mansfield J, Shmotkin D, Blumstein Z, Shorek A, Eyal N, Hazan H; CALAS Team. The old, old-old, and the oldest old: continuation or distinct categories? An examination of the relationship between age and changes in health, function,and wellbeing. Int J Aging Hum Dev. 2013;77(1):37-57.

Cohen-Mansfield J. Nonpharmacologic treatment of behavioral disorders in dementia. Curr Treat Options Neurol. 2013;15(6):765-85.

Cohen-Mansfield J, Garms-Homolová V, Bentwich M. Migrant home attendants: regulation and

practice in 7 countries. Am J Public Health. 2013;103(12):e30-9.

Cohen-Mansfield J, Golander H, Heinik J. Delusions and hallucinations in persons with dementia: a comparison of the perceptions of formal and informal caregivers. J Geriatr Psychiatry Neurol. 2013;26(4):251-8.

Cohen-Mansfield, J., Dakheel-Ali, M., Jensen, B. Predicting Service Use and Intent to Use Services of Older Adult Residents of Two Naturally Occurring Retirement Communities. *Social Work Research* 37(4) 313-326. 2013

Shmotkin, D., Eyal, N., Hazan, H., Shkolnik, T., Shorek, A., & Cohen-Mansfield, J. (2013). Between the Subjective and the Objective: How Informative Is Subjective Evaluation of Memory Among the Old-Old? *Clinical Gerontologist*, *36*(4), 294-315.

Cohen-Mansfield J, Marx MS, Thein K. What is discomfort in persons with dementia who are agitated?-Reply. JAMA Intern Med. 2014 1;174(2):292-3.

Cohen-Mansfield J, Golander H, Arnheim G, Cohen R. Reactions and Interventions for Delusions in Nursing Home Residents with Dementia. Am J Alzheimers Dis Other Demen. 2014 Feb 13. [Epub ahead of print]

Cohen-Mansfield J, Buckwalter K, Beattie E, Rose K, Neville C, Kolanowski A. Expanded Review Criteria: The Case of Nonpharmacological Interventions in Dementia. J Alzheimers Dis. 2014 Feb 27. [Epub ahead of print]

Cohen-Mansfield J, Perach R. Interventions for Alleviating Loneliness Among Older Persons: A Critical Review. Am J Health Promot. 2014 Feb 27. [Epub ahead of print]

Chapters

Cohen-Mansfield, J. & Martin, L. S. (2010) Assessment of Agitation in Older Adults. In P. A. Lichtenberg (Ed.), Handbook of Assessment in Clinical Gerontology (pp. 381-404). London: Elsevier.

Poon, L., W. & Cohen-Mansfield, J. (Eds.) (2011) Understanding Well-Being in the Oldest-Old. Cambridge University Press.

Poon, L., W. & Cohen-Mansfield, J. (2011) Toward New Directions in the Study of Well-Being among the Oldest-Old. In: L.W. Poon & J. Cohen-Mansfield, (Eds.) Understanding Well-Being in the Oldest-Old. (pp. 3-10) Cambridge University Press.

Cohen-Mansfield, J. (2011) The Shifting Baseline Theory of Well-Being: Lessons from across the Aging Spectrum. In: L.W. Poon & J. Cohen-Mansfield, (Eds.) Understanding Well-Being in the Oldest-Old.(pp. 46-62) Cambridge University Press.

Cohen-Mansfield, J. & Poon, L., W. (2011) Future Directions in the Study of Well-Being. In: L.W. Poon & J. Cohen-Mansfield, (Eds.) Understanding Well-Being in the Oldest-Old. (pp. 364-377) Cambridge University Press.

Margrett, JA, Mast, BT, Isales. MC, Poon, LW, & Cohen-Mansfield, J.(2011) Cognitive Functioning and Vitality among the Oldest Old: Implications for Well-Being. In: L.W. Poon & J. Cohen-Mansfield, (Eds.) Understanding Well-Being in the Oldest-Old. (pp. 186-211) Cambridge University Press.

Cohen-Mansfield, J. (2011). "Behaviour Management: Non Pharmacological" in M. T. Abou-Saleh, C. Katona & A. Kumar (Eds.) Principles & Practice of Geriatric Psychiatry, Third edition, John Wiley & Sons Ltd. Chapter 54, pps. 324-329.

Cohen-Mansfield, J. (2011). Loneliness in Older Persons: Correlates and Outcomes in S. Bährer-Kohler (Ed.) Social Determinants and Mental Health. Nova Publishing.

Cohen-Mansfield J Advances in Alzheimer's Disease Research: Implications for Family Caregiving In: Zarit, S. H., and Talley, R. C. (Eds.) (2013). Caregiving for Alzheimer's Disease and Related Disorders. New York: Springer. Chapter 12, pp. 181-202.

Prof. Yariv Gerber, Ph.D.

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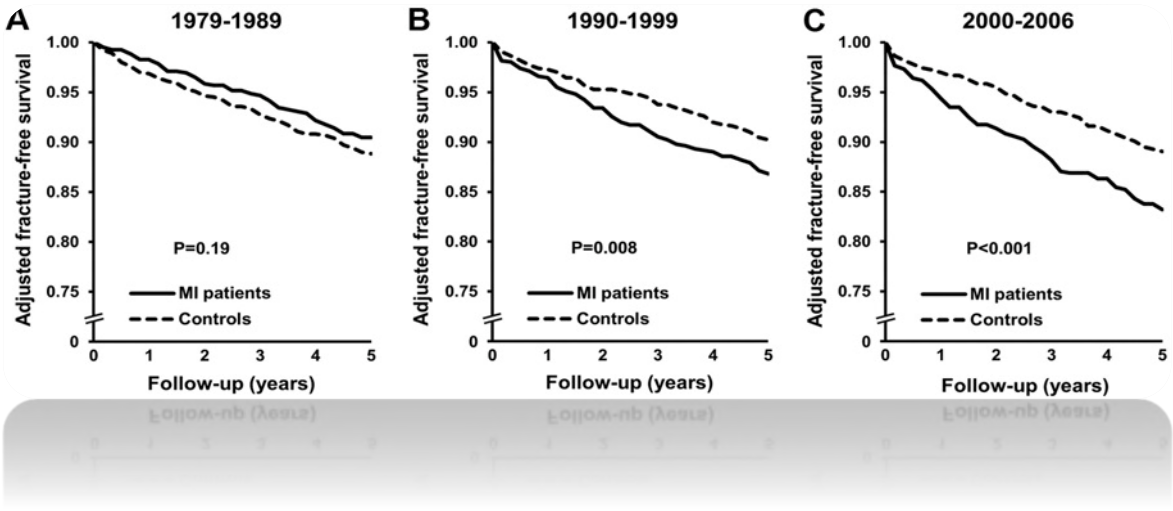
Cardiovascular Disease Epidemiology

Positions

Associate Professor, Sackler Faculty of Medicine
Adjunct Associate Professor of Epidemiology, College of Medicine, Mayo Clinic, Minnesota

Research

Our research covers a wide array of topics related to the epidemiology of cardiovascular diseases. These include risk factor and biomarker evaluation, secular trend analysis, and outcomes research. We have a particular interest in assessing long-term prognosis after acute myocardial infarction. This type of investigation usually combines data from multiple sources, including interviews and questionnaires, laboratory measurements involving blood specimens, and clinical details obtained through medical records and examinations. We are also interested in methodological aspects involved in conducting and interpreting observational studies.



Osteoporotic fracture-free survival curves by time period adjusted for age, sex, and prior fracture among Olmsted County, Minnesota, residents with incident myocardial infarction in 1979–1989 (A), 1990–1999 (B), and 2000–2006 (C) versus community control subjects.

Publications

Gerber Y, Benyamini Y, Goldbourt U, Drory Y. Neighborhood socioeconomic context and long-term survival after myocardial infarction. *Circulation* 2010;121:375-83.

Roger VL, Weston SA, **Gerber Y**, Killian JM, Jaffe AS, Kors J, Yawn BP, Bell MR, Jacobsen SJ. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation* 2010;121:863-9.

Gerber Y, Myers V, Broday DM, Koton S, Steinberg DM, Drory Y. Cumulative exposure to air pollution and long-term outcomes after first acute myocardial infarction: A population-based cohort study. Objectives and methodology. *BMC Public Health* 2010;10:369.

Gerber Y, Koton S, Goldbourt U, Myers V, Benyamini Y, Tanne D, Drory Y. Poor neighborhood socioeconomic status and risk of ischemic stroke after myocardial infarction. *Epidemiology* 2011;22:162-9.

Gerber Y, Myers V, Goldbourt U, Benyamini Y, Scheinowitz M, Drory Y. Long-term trajectory of leisure time physical activity and survival after first myocardial infarction: a population-based cohort study. *Eur J Epidemiol* 2011;26:109-16.

Gerber Y, Koren-Morag N, Myers V, Benyamini Y, Goldbourt U, Drory Y. Long-term predictors of smoking cessation in a cohort of myocardial infarction survivors: a longitudinal study. *Eur J Cardiovasc Prev Rehabil* 2011;18:533-41.

Gerber Y, Melton LJ 3rd, Weston SA, Roger VL. Heart failure and fractures: a community study. *Am J Med* 2011;124:418-25.

Molshatzki N, Drory Y, Myers V, Goldbourt U, Benyamini Y, Steinberg D, **Gerber Y**. Role of socioeconomic status measures in long-term mortality risk prediction post-myocardial infarction. *Med Care* 2011:49:673-8.

Gerber Y, Myers V, Goldbourt U, Benyamini Y, Drory Y. Neighborhood socioeconomic status and leisure time physical activity after myocardial infarction: a longitudinal study. *Am J Prev Med* 2011;41:266-73.

Gerber Y, Melton LJ 3rd, Weston SA, Roger VL. Association between myocardial infarction and fractures: an emerging phenomenon. *Circulation* 2011;124:297-303.

Myers V, Drory Y, **Gerber Y**. Sense of coherence predicts post-myocardial infarction trajectory of leisure time physical activity: a prospective cohort study. *BMC Public Health* 2011;11:708.

Myers V, **Gerber Y**, Goldbourt U, Benyamini Y, Drory Y. Post-myocardial infarction depression: Increased hospital admissions and reduced adoption of secondary prevention measures - a longitudinal study. *J Psychosom Res* 2012;72:5-10.

Koton S, **Gerber Y**, Goldbourt U, Drory Y. Socioeconomic risk factor aggregation and long-term incidence of ischemic stroke in patients after first acute myocardial infarction. Int J Cardiol 2012;157:324-9.

Gerber Y, Jaffe AS, Weston SA, Jiang R, Roger VL. Prognostic value of cardiac troponin T post-myocardial infarction: A contemporary community experience. *Mayo Clin Proc* 2012;87:247-54.

Gerber Y, Myers V, Goldbourt U. Smoking reduction at midlife and lifetime mortality risk in men: A prospective cohort study. *Am J Epidemiol* 2012;175:1006-12.

Koren A, Steinberg DM, Drory Y, **Gerber Y**. Socioeconomic environment and recurrent coronary events after initial myocardial infarction. Ann Epidemiol 2012;22(8):541-6.

Gerber Y, Melton LJ 3rd, McNallan SM, Jiang R, Weston SA, Roger VL. Cardiovascular and non-cardiovascular disease associations with hip fractures. Am J Med 2013;126:169.e19-26.

Gerber Y, Weston SA, Berardi C, McNallan SM, Jiang R, Redfield MM, Roger VL. Contemporary trends in heart failure with reduced and preserved ejection fraction after myocardial infarction: a community study. Am J Epidemiol 2013;178:1272-80.

Myers V, Broday DM, Steinberg DM, Yuval, Drory Y, **Gerber Y**. Exposure to particulate air pollution and long-term incidence of frailty after myocardial infarction. Ann Epidemiol 2013;2):395-400.

Koton S, Molshatzki N, Yuval, Myers V, Broday DM, Drory Y, Steinberg DM, **Gerber Y**. Cumulative exposure to particulate matter air pollution and long-term post-myocardial infarction outcomes. Prev Med 2013;57:339-44.

Myers V, Drory Y, **Gerber Y**. Clinical relevance of frailty trajectory post myocardial infarction. Eur J Prev Cardiol 2014: In press.

Gerber Y, Myers V, Broday DM, Steinberg DM, Yuval, Koton S, Drory Y. Frailty status modifies the association between air pollution and post-myocardial infarction mortality: a 20-year follow-up study. J Am Coll Cardiol. 2014; In press.

May 24, 2014

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Helicobacter pylori, Enteric Infections and Their Role in Health and Disease

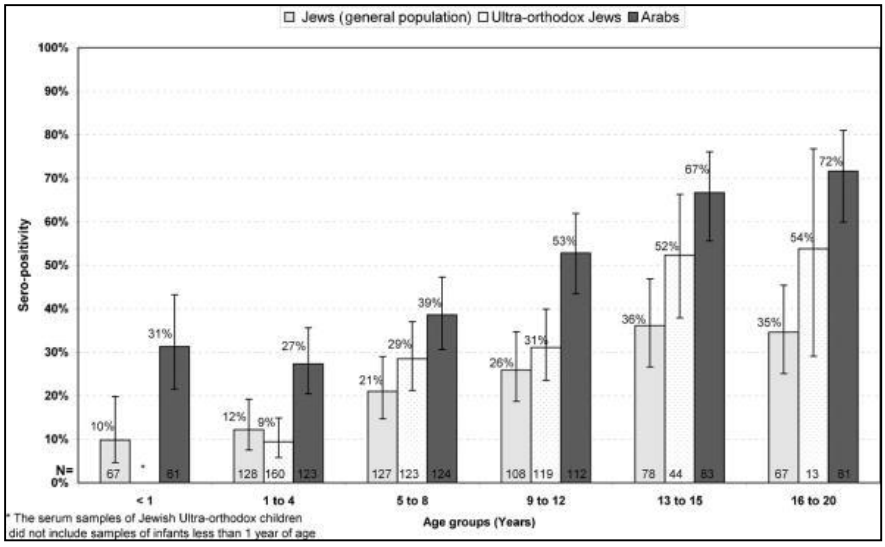
Positions

Senior Lecturer, Sackler Faculty of Medicine

Research

Helicobacter pylori infection is acquired during early childhood. It causes chronic gastritis which mostly remains asymptomatic; however in a small portion of the infected people *H. pylori* causes peptic ulcers and gastric cancer. My research focuses on the role of *H. pylori* in extragastric diseases such as iron deficiency anemia, cognitive function, and diabetes mellitus. Epidemiology of enteric infections in various populations consists an additional main research area in my group.

My research involves population-based studies in which I integrate various epidemiological and biostatistical methods, as well as biological markers assessed by immunological and microbiological tools.



Publications

Muhsen K, Athamna A, Spungin-Bialik A, Alpert G, Cohen D. Presence of *H. pylori* in a sibling is associated with a long term increased risk of *H. pylori* infection in Israeli Arab children. Helicobacter. 2010;15; 108-113

Muhsen K, Shulman L, Kasem E, Rubinstein U, Shachter J, Kremer A, Goren S, Zilberstein I, Chodick G, Ephros M, Cohen D for the TAU-HCLV Rota Study Group. Effectiveness of rotavirus

vaccines for the prevention of rotavirus gastroenteritis-associated hospitalization in Israel: a case-control study. Human Vaccines. 2010;6:450-454

Muhsen K, Barak M, Henig C, Alpert G, Ornoy A, Cohen D. Is the association between Helicobacter pylori infection and anemia age dependent? Helicobacter. 2010; 15: 467-472

Muhsen K, Chodick G, Goren S, Shalev V, Cohen D. The uptake of rotavirus vaccine and its effectiveness in preventing acute gastroenteritis in the community. Vaccine. 2010; 29:91-94

Muhsen K, Ornoy A, Akawi A, Alpert G, Cohen D. *Helicobacter pylori* infection is associated with diminished cognitive function in children at early school age. BMC Pediatrics. 2011;11(1):43.

Muhsen K, Nir A, Spungin-Bialik A, Bassal R, Goren S, Cohen D. Interaction between ethnicity, socioeconomic factors and *Helicobacter pylori* sero-prevalence among Israeli children and adolescents. J Pediatr Gastroenterol Nutr. 2011;53:524-7

Muhsen K, Jurban M, Goren S, Cohen D. Incidence, age of acquisition and risk factors of *Helicobacter pylori* infection among Israeli Arab infants. J Trop Pediatrics. 2012; 58:208-213.

Muhsen K, Cohen D, Spungin-Bialik A, Shohat T. Sero-prevalence, correlates and trends of *Helicobacter pylori* infection in the Israeli population. Epidemiol Infect. 2012; 140:1207-14.

Cohen D, Baida O, Orr N**, Muhsen K**. An inverse and independent association between *Helicobacter pylori* infection and the incidence of shigellosis and other diarrheal disease. Clin Infect Dis. 2012; 54(4):e35-42

Cohen D, **Muhsen K.** Association between *Helicobacter pylori* colonization and glycated hemoglobin levels: Is this another reason to eradicate *Helicobacter pylori* in adulthood? J Infect Dis. 2012;205(8):1183-5.

Muhsen K, Kassem E, Rubinstein U, Schachter Y, Kremer A, Goren S, Zilberstein I, Ephros M, Cohen D, Shulman ML. Incidence and characteristics of sporadic norovirus gastroenteritis associated with hospitalizations of children < 5 years of age in Israel. Pediatr Infect Dis J. 2013 Feb 13.

Muhsen K, Levine MM. A systematic review and meta-analysis of the association between *Giardia lamblia* and endemic pediatric diarrhea in developing countries. Clin Infect Dis. 2012;55 Suppl 4:S271-93.

Levine MM, Kotloff KL, Nataro JP, **Muhsen K**. The Global Enteric Multicenter Study (GEMS); Impetus, Rationale and Genesis. Clin Infect Dis. 2012;55 Suppl 4:S215-24.

Farag TH, Nasrin D, Wu Y, **Muhsen K**, Blackwelder W, Sommerfelt H, Panchalingan S, Nataro JP, Kotloff KL, Levine MM. Some epidemiological, clinical, microbiological and organizational assumptions that influenced the design and performance of GEMS-1. Clin Infect Dis. 2012;55 Suppl 4:S225-31.

Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, Wu Y, Sow SO, Sur D, Breiman RF, Faruque AS, Zaidi AK, Saha D, Alonso PL, Tamboura B, Sanogo D, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Ochieng JB, Omore R, Oundo JO, Hossain A, Das SK, Ahmed S, Qureshi S, Quadri F, Adegbola RA, Antonio M, Hossain MJ, Akinsola A, Mandomando I, Nhampossa T, Acácio S, Biswas K,O'Reilly CE, Mintz ED, Berkeley LY, **Muhsen K**, Sommerfelt H, Robins-Browne RM, Levine MM. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. Lancet. 2013 ;382(9888):209-22

Muhsen K, Cohen D, Levine MM. Can *Giardia lamblia* infection lower the risk of acute diarrhea among pre-school children? J Trop Pediatr. 2014, 60(2):99-103

Muhsen K, Lagos R, Reymann M, Graham DY, Pasetti MF, Levine MM. Age-dependent association among *Helicobacter pylori* infection, serum pepsinogen levels and immune response of children to live oral cholera vaccine CVD 103-HgR PLoS One. 2014, 15;9(1):e83999.

Muhsen K, Pasetti MF, Reymann MK, Graham DY, Levine MM. *Helicobacter pylori* infection affects immune responses following vaccination of typhoid-naïve U.S. adults with attenuated *Salmonella* Typhi oral vaccine CVD 908-*htrA*. J Infect Dis. 2014, 209(9):1452-8

Boyd MA, Tennant SM, Saague VA, Simon R, **Muhsen K**, Ramachandran G, Cross AS, Galen JE, Pasetti MF, Levine MM. Serum bactericidal assays to evaluate typhoidal and nontyphoidal salmonella vaccines. Clin Vaccine Immunol. 2014;21(5):712-21.

Chapter

Tennant SM, **Muhsen K**, Pasetti MF. Gut immunology and oral vaccination. In "Molecular Vaccines- From Prophylaxis to Therapy". 2013. Editor Matthias Giese M. Springer Vienna. ISBN: 978-3-7091-1418-6 (Print) 978-3-7091-1419-3 (Online)

Grants

MAOF award received from the Higher Council for Education- Israel (2013-2016).

2013-2016 - Israel National Institute for Health Policy and Health Services Research (Co-PI with Prof. D. Cohen)

May 25, 2014

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Epidemiology of Parkinson's Disease and Environmental Epidemiology

Positions

Senior Lecturer, Sackler Faculty of Medicine
Chair, School of Public Health Seminars

Research

Our research focuses on two main fields: 1. Neuro-epidemiology, and 2. Envirinmental epidemiology, with a special interest in methodological issues.

In neuro-epidemiology, we study the epidemiology of neuro-generative diseases. Specifically, we follow up and investigate a large cohort of patients with Parkinson's disease on disease burden, etiology, early-markers and co-morbidity. The cohort was derived through a drugs-purchased dataset that was linked to clinical and administrative databases.

In the area of environmental epidemiology, we study the short term effects of air pollution on adverse health outcomes such as birth-defects, emergency-room visits and mortality. We also evaluate vulnerability to air pollution hazards of specific sub-groups such as subjects with diabetes. In light of global climate changes, we study the short-term effects of ambient temperature on mortality and on the occurrence of food-borne diseases. These studies involve a temporal/spatial analysis.

Publications

Huber-Mahlin V, Giladi N, Herman T, **Perez C**, Hausdorff JM. Progressive nature of a higher level gait disorder: a 3-year prospective study. *J Neurol.* 2010; 257:1279-86

Zaidenstein R, **Peretz C**, Nissan I, Reisfeld A, Yaron S, Agmon V, Weinberger M. The epidemiology of extraintestinal non-typhoid Salmonella isolates in Israel: the effects of patient's age and sex. *Eur J Clin Microbiol Infect Dis.* 2010; 29:1103-9

Weinberger M, Yaron S, Agmon V, Yishi R, Andorn N, **Peretz C.** Curtailed short-term and long-term survival following infection with non-typhoid Salmonella in Israel. *Clin Microbiol Infec.* 2011; 17:278-84

Peretz C, Korczyn AD, Aharonson V, Birnboim S, Shatil E, Giladi N**.** Individualized computer-based cognitive training improves cognitive performance in elderly subjects: a randomized, prospective, double blind study with an active comparator *Neuroepidemiol.* 2011; 36:91-9.

Chillag-Talmor O, Giladi N, Linn S, Gurevich T, El-Ad B, Silverman B, Friedman N, **Peretz C.** Use of a refined drug tracer algorithm to estimate prevalence and incidence of Parkinson's Disease in a large Israeli population. *J Parkinson's Dis.* 2011; **1:** 35–47.

K. Agay-Shay, M. Friger, S. Linn, A.Peled, Y. Amitai, **C. Peretz.** Periodicity and time trends in the incidence of congenital malformations conceptions among Jews and Muslims in Israel, 1999-2006. *Birth Defects Res A.* 2012; 94: 438-48.

Chillag-Talmor O, Giladi N, Linn S, Gurevich T, El-Ad B, Silverman B, Friedman N, **Peretz C.** Estimation of Parkinson's disease survival in Israeli men and women, using health maintenance organization pharmacy data in a unique approach. *J Neurol.* 2012; 260:62-70.

Weinberger M, Agmon V, Yaron S, Nissan I, **Peretz C.** Geographical variations in Salmonella incidence in Israel 1997-2006: the effect of rural residency. *Epidemiol Infect.* 2012; 12:1-10.

Agay-Shay K, Amitai Y, **Peretz C,** Linn S, Friger M, Peled A. Exploratory spatial data analysis of congenital malformations in Israel, 2000-2006. *ISPRS Int J Geo-Inf.* 2013; *2*:237-255

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, **Peretz C.** Ambient temperature and congenital heart defects. *Hum Reprod.* 2013; 28:2289-97.

Leone M, D'Ippoliti D, De Sario M, Analitis A, Menne B, Katsouyanni K, De'donato FK, Basagana X, Salah AB, Casimiro E, Dörtbudak Z, Iñiguez C, **Peretz C,** Wolf T, Michelozzi P. A time series study on the effects of heat on mortality and evaluation of heterogeneity into European and Eastern-Southern Mediterranean cities: results of EU CIRCE project. *Environ Health*. 2013; 12:55.

Weinberger M, Lerner L, Valinsky L, Moran-Gilad J, Nissan I, Agmon V, **Peretz C.** Increased incidence of *Campylobacter* spp. infection and high rates among children, Israel. *Emerg Infect Dis J* 2013. 2013: DOI: 10.3201/eid1911.120900.

Grants

2013 - 2014 Teva National Network of Excellence (NNE) in Neurosciences, Student Scholarship

May 25, 2014

Dr. Laura (Leah) J. Rosen, Ph. D.

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School of Public Health
Sackler Faculty of Medicine

Tel Aviv University
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Improving Public Health, and Control Tobacco Use and Exposure

Positions

Senior Lecturer, Sackler Faculty of Medicine
Chair, Dept. of Health Promotion, School of Public Health
Affiliated Faculty, Harvard Global Center for Tobacco Control
Appointed Member, Israel Public Committee for Reduction of Tobacco Use and Damage
Temporary Adviser, European Advisory Council on Health Research (EACHr), World Health Organization,
C

Research

Our primary goal is to contribute to public health, at the national and global levels, through conducting research, advancing public health research methods and evidence-based health policy, and teaching and mentoring students. We focus on methodological issues of public health and health promotion research, including understanding and improving the evidence base for public health policy, systematic reviews, and rigorous evaluation of health promotion interventions.

Our main substantive research interest is tobacco, one of the major public health problems of our time. This includes the epidemiology of tobacco use, exposure, and harm, with a focus on the Israeli context; and development and evaluation of intervention programs and strategies to reduce tobacco use and exposure at the individual, local, and national levels. Specific research projects include: monitoring and evaluation of the recent governmentally-approved National Tobacco Control Plan; development of an intervention to protect young children from tobacco smoke exposure; understanding tobacco use initiation among youth; research on changes in tobacco use during Israeli military service, the study of smoking cessation among adults, research on the exposure of the Israeli public to tobacco smoke, and understanding public and policy-maker attitudes towards governmental intervention for tobacco control.

Publications

Ginsberg G, Rosenberg E, **Rosen L**. Issues in estimating smoking-attributable mortality in Israel. European Journal of Public Health 2010; 20: 113-119.

Rosen L, Zucker D, Rosen B, Connolly G. Secondhand smoke levels in Israeli bars, pubs, and cafes before and after implementation of smoke--free legislation. Eur J of Public Health 2011;21:15-20.

Rosen L, Ben Noach M. Systematic reviews on tobacco control from Cochrane and the Community Guide: Different methods, similar findings. Journal of Clinical Epidemiology 2010 63:596-606.

Rosen L, Brody D, Zucker D, Manor O, Meier M, Rosen B, Lev E, Engelhard D. Spreading the handwashing message: An alternative to traditional media campaigns. Am J of Infec Control 2010;38:562-4.

Rosen L, Ben Noach M, Rosenberg E. Missing the forest (plot) for the trees? A critique of the systematic review in tobacco control. BMC Medical Research Methodology 2010, 10:34.

Rosen L, Rosenberg E, McKee M, Gan-Noy S, Levin D, Mayshar E, Shacham G, Borowski J, Bin Nun G, Lev B. A framework for developing an evidence-based, comprehensive tobacco control program. Health Research Policy and Systems 2010, 8:17.

Rosen L, Zucker D, Brody D, Engelhard D, Meir M, Manor O. Enabling hygienic behavior among preschoolers: Improving environmental conditions through a multi-faceted intervention. Am J of Health Promotion 2011, 25:248-256 .

Rosen LJ, Guttman N, Hovell M, Ben Noach M, Winickoff J, Tchernokovski S, Rosenblum J, Rubenstein U, Seidmann V, Vardavas CI, Klepeis NE, Zucker D. Development, design, and conceptual issues of Project Zero Exposure: A program to protect young children from tobacco smoke exposure. BMC Public Health 2011, 11:508.

Rosen L, Ben Noach M, Winickoff J, Hovel M. Parental Smoking Cessation to Protect Young Children: A Systematic Review and Meta-analysis. Pediatrics 2012, 129:141–152.

Rosen L. Tobacco smoke exposure and children. Environment and Health. Fall, 2011. (Hebrew)

Ben Noach M, Steinberg D, Goldsmith R, Shimony T, Rosen L. Ethnic differences in patterns of secondhand smoke exposure among adolescents in Israel. Nicotine and Tobacco Research. 2012, 14:648-56.

Knishkowy B, Verbov G, Amitai Y, Stein-Zamir C, Rosen L. Reaching Jewish ultra-orthodox adolescents: results from a targeted smoking prevention trial. International Journal of Adolescent Medicine and Health. 2012, 24:173-9.

Rosen L, Rier D, Schwartz R, Oren A, Kopel A, Gevman A, Zeller M, Connolly G. Public support for smoke-free areas in Israel: A case for action. Health Policy. 2012, 106:161-8.

Rosen L, Rier D, Connolly G, Oren A, Landau C, Schwartz R. Do health policy advisors know what the public wants? An empirical comparison of how health policy advisors assess public preferences regarding smoke-free air, and what the public actually prefers. Israel Journal of Health Policy Research 2013, 2:20.

Rosen L. An intuitive approach to understanding the attributable fraction of disease due to a risk factor: the case of smoking. Int. J. Environ. Res. Public Health 2013, 10, 2932-2943; doi:10.3390/ijerph10072932

Rosen L, Myers V, Hovell M, Zucker D, Ben Noach M. Meta-analysis of Parental Protection of Children From Tobacco Smoke Exposure. Pediatrics 2014;133:698-714.

Ioscovich A, Davidson E, Orbach-Zinger S, Rudich Z, Ivry S, Rosen L, Avidan A Ginosar Y. Performance of aseptic technique during neuraxial analgesia for labor before and after the publication of international guidelines on aseptic technique. IJHPR 2014 3:9

Rosen L, Rozhavski V, Levine H, Sela T, Bar-Ze'ev Y, Molina-Hazan V, Zarka S. Smoking initiation among Israeli adolescents: A 24-year time-to-event analysis. Prev Med (In Press)

Grants

2008-2015 Intervention to prevent young child exposure to tobacco smoke. Flight Attendant Medical Research Institute. (PI)

School of Dental Medicine

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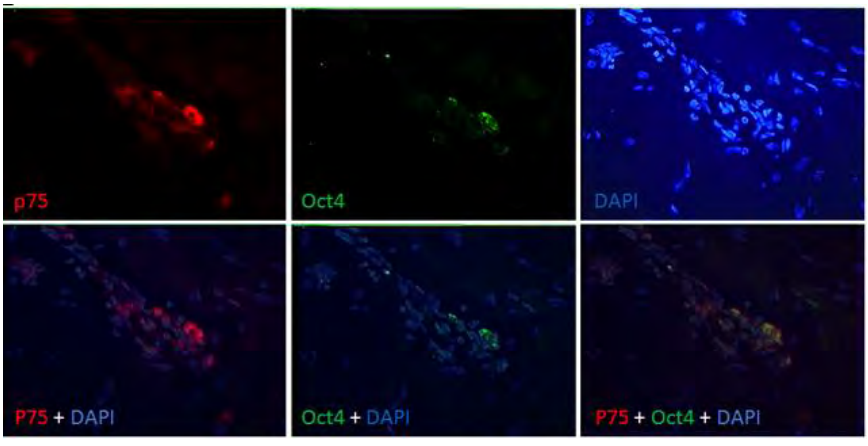
Novel Adult Oral Mucosa-derived Stem Cells - Basic and Translational Research

Positions

Professor of Oral Biology, Sackler Faculty of Medicine

Research

Our research focuses on the biology of a new stem cell population recently discovered in our laboratory. We found, that in contrast to other tissues, the oral mucosa of the adult and elderly organism harbors a **primitive neural crest-like stem cell population**, which is capable of expressing embryonic associated markers and of differentiating into cell lineages of the 3 germ layers – ectoderm, mesoderm and endoderm. We term this population "**oral mucosa derived stem cells – OMSC**". Using cutting edge technologies, we are investigating the genetic and epigenetic mechanisms that maintain such a fetal-like stem cell population in the adult and aging oral mucosa, and study how these mechanisms and OMSC are affected by chronic and neurodegenerative diseases as diabetes and Parkinson's Disease. By elucidating these mechanisms, we aim to develop new therapeutic approaches for treating chronic diseases associated with ageing.



Human OMSC co-expressing neural crest markers – p75 (red) and pluripotency associated markers – Oct4 (green) are located in specific niches within the lamina the lamina propria of the adult human oral mucosa.

Based on OMSC plasticity and stemness we are currently testing their therapeutic potential for the treatment of diabetic chronic wounds, Parkinson's disease, skeletal defects, inflammatory bowel disorders, retinal disorders and periodontal diseases. We have developed unique fibrin-based matrices for OMSC delivery and tissue engineering purposes.

Publications

Marinka K, Treves S, Yaffee M, Rachima H, Gafni Y, Cohen M, **Pitaru S.** The lamina propria of the oral mucosa harbors a novel stem cell population. Stem cells 2010;28:984–995.

Friedmann A, Gissel K, Soudan M, Kleber BM, **Pitaru S**, Dietrich T. Randomized controlled trial on lateral augmentation using two collagen membranes: morphometric results on mineralized tissue compound. J Clin Periodontol. 2011 Jul;38(7):677-85.

Gafni Y, Rachima H, Marynka-Kalmani K., Blatt A, Vered Z, Pitaru S. A new in vivo/in vitro model for assessing the capacity of human derived oral mucosa stem cells to colonize the infarcted myocardium. Stem Cell Studies. 2011;1:42-47.

Treves-Manusevitz S, Hoz L, Rachima H, Montoya G, Tzur E, Vardimon A, Narayanan AS, Amar S, Arzate H, **Pitaru S**. Stem cells of the lamina propria of human oral mucosa and gingiva develop into mineralized tissues in vivo. J Clin Periodontol 2013;40:73-81.

Ganz J, Ben Zur T, Nachum-Dadon M, Arie I, Poor S, Araidy S, **Pitaru S**, Offen Astrocyte-like cells derived from human oral mucosa stem cells provide neuroprotection in vitro and in vivo. Stem Cells Translational Medicine, 2014;375-386.

Grants

2013 - 2016 Does the diabetic state affect the stemness of the stem cell population in the lamina propria of the adult oral mucosa? Israeli Science Foundation

2012 - 2016 Oral mucosa stem cells for the generation of a primordial periodontium - The effect of aging and diabetes type 2. US-Israel Binational Science Foundation