Sackler Faculty of Medicine
Clinical Research 2017
Cover images (from bottom left, clockwise):

**Image 1:** Staining of a novel anti-frizzled7 monoclonal antibody directed at tumor stem Cells. Credit: Benjamin Dekel lab.

**Image 2:** Growing adult kidney spheroids and organoids for cell therapy. Credit: Benjamin Dekel lab.

**Image 3 & 4:** Vibrio proteolyticus bacteria infecting macrophages. Credit: Dor Salomon.

**Image 5:** K562 leukemia cells responding to complement attack (red-complement C9, green-mitochondrial stress protein mortalin) Credit: Niv Mazkereth, Zvi Fishelson.

**Image 6:** Cardiomyocyte proliferation in newborn mouse heart by phosphohistone 3 staining (purple). Credit: Jonathan Leor.
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 (TAU) 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. The Faculty of Medicine includes 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. This network of preclinical and clinical teams helps realize the ultimate goals of the research: the basic understanding of human pathophysiology and the prevention, diagnosis and treatment of disease. The research of clinical faculty members from the Sackler School of Medicine are featured in this research brochure.

The Faculty of Medicine engages in joint teaching and research programs with nearly every faculty at TAU, including the Wise Faculty of Life Sciences, the Sagol School of Neuroscience, the Edmond J. Safra Bioinformatics Center, the TAU Center for Nanoscience and Nanotechnology, and the Edmond J. Safra Center for Ethics, 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 limited 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 TAU. 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 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 260 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, Prof. Ehud Grossman; Vice Deans Prof. Karen Avraham, Prof. Iris Barshack, Prof. Moshe Phillip, Prof. Anat Lowenstein, Prof. Meir Lahav, Prof. Ami Fishman, Prof. Moshe Kotler, and Assistant to the Dean, Michal Gilboa.
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K562 leukemia cells responding to complement attack
(red-complement C9, green- Rab11, blue- mitochondria mitotracker)
Credit: Niv Mazkereth, Zvi Fishelson
The Integrated Cancer Prevention Center (ICPC) has diverse and broad experience in translational research focused on early detection, prevention and therapy of cancer, particularly in tumors of the gastrointestinal (GI) tract. The team is highly experienced in clinical studies, molecular epidemiology as well as in molecular and cell biology studies of cancer. Currently, on-going researches at the ICPC focus on translational research, bridging between basic researches in the lab and clinicians and patients in the clinical center. The center has a long history of planning, developing, and conducting clinical trials, with a main focus on investigator-initiated and cooperative group trials investigating the activity of...
drugs for the prevention and treatment of colorectal cancer (CRC).

Basic research takes place at the Laboratory of Molecular Biology, headed by Dr. Shiran Shapira, a senior scientist and member of the academic staff at Tel Aviv University. Dr. Shapira devotes herself to cancer research in the fields of early detection, prevention, and cancer therapy. She possesses extensive experience in wide range of biology areas with focusing on cancer research, biochemistry, molecular biology, signal transduction, antibody engineering, protein expression and purification and gene delivery.

Research Team
Prof. Nadir Arber, MD, MSc, MHA, Head of ICPC; Dr. Shiran Shapira, PhD, Head of Laboratory; Dina Kazanov, MSc; Dr. Eliezer Liberman, MD; Ilana Bostenai, PhD student; Ahmad Fokra, PhD student; Sally Zigdon, MSc; Lina Tiklan

Projects
1. Early detection – development of new methods for the early detection of CRC and colorectal adenomas as well as other types of solid and hematological cancers. The tested samples taken from humans, blood and urine.

2. Prevention – Serving as the PI of several international, multicenter trials in the prevention of GI tumors, and in particular sporadic and familial CRC.

3. Identifying high risk subjects through molecular epidemiology – We have identified a new polymorphism in the APC gene (E1317Q), which is more common in Sephardic Jews and Arabs and is associated with a HR of ~4. When it is combined with another polymorphisms in the CD24 gene (V248A) the OR is 7.8.

4. Detection of new oncogenes that play a role in the multistep process of CRC carcinogenesis.

The research team at the Laboratory of Molecular Biology has been exploring, for several years, the hypothesis that CD24 is a potential oncogene in GI malignancies and may serve as a biomarker and target for the treatment of cancer and cancer-related chronic inflammatory disorders such as, inflammatory bowel diseases (IBD).

5. Treatment - Development of novel therapeutic strategies for cancer treatment with a main focus on immunotherapy using humanized anti-CD24 monoclonal Abs, immunotoxin and bi-specific

6. Design of novel therapeutic agents targeting Ras and Wnt pathways that play an important role in GI carcinogenesis, based on gene therapy using adenoviruses and highly sophisticated viral vectors such as adenoviruses, lentiviruses and adeno-associated viruses.

7. Wound healing- CD24 may represent a novel clinical intervention strategy to accelerate the healing of wounds both acute and chronic injuries for patients. The proposed treatment may enable faster recovery from injuries while reducing the risk of infection, toxicity and other possible side

Publications


Kraus S, Sion D, Arber N. Can We Select Patients for Colorectal Cancer Prevention with Aspirin? Curr Pharm Des. 2015;21(35):5127-34.


Grants

2016-2018 Kamin Grant, The Industry Academy Programs of the Chief Scientist (OCS), Israeli Ministry of Industry and Trade, Delayed wound healing heat stabke (HSA/CD24) knockout mice

2014-2017 ERA-Net on translational cancer research (TRANSCAN), Personalized prevention of colorectal neoplasia by use of genetic variability for the prediction of efficacy and toxicity of treatment with COX-2 inhibitors and aspirin", PREDICT

2016-2017 Dotan, The Varda and Boaz Dotan research center in Hemato-Oncology, Tel Aviv University, Lentiviral gene-based therapy for hematological malignancies

2016 – 2017 CBRC, Cancer Biology Research Center, Selective targeting of aberrant Cyclin D1-expressioning cancer by a novel gene therapy approach

2015-2017 ICRF, Israel Cancer Research Fund, Humanized anti-CD24 antibody; a potential biology tool for cancer immunotherapy

2016 – 2017 Djerassi Elias for oncology, Development of a novel drug delivery strategy to treat lung cancer

2017-2018 The Varda and Boaz DOTAN Research Center in Hemato-Oncology, Tel Aviv University, Targeting lymphoma with bispecific antibodies that simultaneously engage CD30 and CD24
Investigating Hormone Metabolism in Cancer

Positions
Senior Lecturer, Sackler Faculty of Medicine

Research
Our research deals with the role of thyroid hormones in cancer progression and on the development of a novel class of targeted cancer therapy. A set of small molecules that specifically block the thyroid-cancer axis were developed. Our research group is the first to show the potent elimination of various cancer types by these novel drugs.

Publications


Ashur-Fabian O, Blumenthal DT, Bakon M, Nass D, Davis PJ and Hercbergs A. Long-term disease response in glioblastoma multiforme treated with medically induced hypothyroidism and chemotherapy:

Ovarian cancer cell proliferation and migration is enhanced by thyroid hormones


Prof. Iris Barshack, M.D.
Department of Pathology
Sheba Medical Center, Tel-Hashomer

Investigating Markers of Inflammation and of Neoplastic Processes for Diagnosis and Treatment

Positions
Professor of Pathology
Vice Dean, Head of School of Medicine, Sackler Faculty of Medicine, Tel Aviv University
Head, Department of Pathology
Co-director, Tumor Tissue Bank, Molecular Diagnostic Service, Precision Medicine Project (diagnostic service), Digital Pathology Project, Sheba Medical Center, Tel Hashomer

Research
The profession of Pathology encompasses three main constituents: diagnostics, teaching and research. Within the department, description, processing and examination of the macroscopic specimen is performed by the doctors of the department. The specimens undergo histochemical staining. If necessary for the sake of diagnosis, additional specialized histochemical and immunohistochemical stains are carried out. Furthermore, the department executes other techniques that enable precise diagnosis such as: FISH, PCR, In-situ hybridization and Electron Microscopy visualization. The department delves in a large array of research projects with the cooperation of other departments within and outside of the hospital, and intrinsic research of the department itself.

The department encompasses a laboratory specific for histochemical staining, a laboratory for immunohistochemical staining that performs in-situ hybridization, as well as a laboratory for PCR, Electron Microscopy, FISH and for Molecular Pathology. Moreover, we are leading the tumor tissue bank of the Sheba Medical Center, and the Molecular Diagnostic Service of the Sheba Medical Center, using an advanced NGS platform for diagnostic and research purposes. We also perform on a routine and research basis immunohistochemical stainings and molecular methods for precision medicine and immunotherapy. Furthermore, the department includes an advanced system for photographing and processing both macroscopic and microscopic constituents, and leads the Digithal Pathology Project of the Sheba medical Center.

Another branch is that of independent research. One of the great accomplishments has been the conceptual implementation of the use of microRNAs to aid in the identification of different tissues and the application of this knowledge to identify metastases of unknown origin. In situ hybridization of microRNAs is an important methodology used in our research for studying the pathogenesis of inflammatory and non-neoplastic processes. Another area of research in which the department is leading is the development of the technology of tissue microarrays. The department leads the investigation of inflammatory processes and lymphoproliferative tumors according to the production and study of heavy chain B lymphocytes within the tissue. In light of this investigation, the department received a number of important research grants.

**Publications**


Weiss B, **Barshack I**, Onaca N, Goldberg I, Berkovich Z, Melzer E, Jonas A, Reifen R. Vitamin A deficiency is associated with enhanced proliferation of bile duct epithelial cells in the rat. *IMAJ* 12(2):82-86 (2010) *both authors contributed equally to the manuscript


*Both authors equally supervised the manuscript.


stomach - from gastritis to gastric lymphomas. Front Immunol. 2014 Jun 3;5:264. * Both authors equally supervised the manuscript.


**Grossman C**, **Barshack I**, Bornstein G, Ben-Zvi I. Is temporal artery biopsy essential in all cases of suspected giant cell arteritis? Clin Exp Rheumatol. 2015;33(2 Suppl 89):84-9.* both authors contributed equally to the manuscript


Investigating the Microenvironment Interactions and B-cell Receptor Signaling in Chronic Lymphocytic Leukemia

Positions
Senior Lecturer, Sackler Faculty of Medicine
Head, CLL Service, Tel Aviv Sourasky Medical Center
Secretary, Israeli CLL Study Group
Committee Member, Israel Society of Hematology

Research
We study interactions between the CLL cells and the tissue microenvironment and explore new aspects of the B-cell receptor (BCR) signaling in CLL cells. Our previous work characterized distinct in vivo gene expression signatures of CLL cells derived from the different compartments of blood, bone marrow and lymph nodes. Recently, we have shown that SLP76, an adaptor protein of the T-cell receptor pathway, is ectopically expressed in CLL cells and mediates alternative signaling downstream of the BCR (Figure). Our research is aimed to discover novel targets of therapy of CLL. Our group is well experienced in performing cell biology assays, flow cytometry and image analysis, protein analysis and gene silencing in primary CLL cells, and is highly skillful in studying signaling in CLL cells.

Publications


Cohen S, Shoshana OY, Zelman-Toister E, Maharshak N, Binsky- Ehrenreich I, Gordin M, Hazan-Halevy I,


Grants

Basic and Translational and Research of Childhood Malignancies and Leukemia

Positions
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.

Carboxypeptidase E (CPE), a novel Wnt inhibitor, is excluded from the colonic crypt bottom.
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 consisting of 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


Elhasid, R., T. Tohami, N. Moustafa-Hawash, J. Ben-Ezra, S. Izraeli, and D. Sayar. Spontaneous remission of childhood acute marrow fibrosis and


**Reviews**


**Grants**

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

2014-2018 BSF Functional analysis of ERG GATA1

2014-2018 ISF Modelling T-lympho-myeloid leukemia

2014-2017 ISF-NSFC Hematopoietic transcription factors in leukemia – mouse models and human leukemias

2014-2017 The Israel Science Foundation (ISF) and the National Natural Science Foundation of China (NSFC), PIs Izraeli, Shai (Israel) Chen, Sai-Juan (China)

2014-2017 Israel Ministry of Health ERA-NET EU programs, PIs Izraeli, Shai (Israel), multiple Europeans PIs

2014-2017 Israel Science Foundation

2014-2017 USA-Israel Bi-National Scientific Foundation, PIs Izraeli, Shai (Israel); Crispino, John (USA)

2015-2018 DOD USAMRMC

2016-2018 Children With Cancer UK, PI Enver, Tariq (UCL), co-PI Izraeli, Shai

2016-2019 German Israel Foundation
Dr. Ben Zion Katz, Ph.D.
The Hematology Laboratory
Tel Aviv Sourasky Medical Center

Development of B-Cell Malignancies

Positions
Senior Lecturer, Sackler Faculty of Medicine
Deputy Director, The Hematology Laboratory, Tel Aviv Sourasky Medical Center

Research
The focus of the research in the laboratory is on B-cell malignancies, their developmental processes, and the clinical significance of the malignant B-cells physiological and molecular phenotypes. We utilize a wide range of both clinical and basic research laboratory techniques, and study tissue culture model systems, as well as primary patient-derived samples.

Specific research programs
A) The role of microenvironmental interactions in the pathogenesis of chronic lymphocytic leukemia.
B) The function of CD19 and CD38 in the physiology of malignant B-cells.
D) Development of novel laboratory methodologies to study B-cell malignancies
The complexity of the B-cell receptor.

Publications


Herishanu, Y., Katz, B.-Z. Cryoglobulins mimicking platelet recovery in a mantle cell lymphoma patient

Sackler Faculty of Medicine Research 2017
Cancer


Grants

Tumor-Microenvironment Cellular Interactions in Cancer Progression and Metastasis

Positions
Chair, Department of Surgery A
Senior Lecturer, Sackler Faculty of Medicine

Research
The surgical oncology research lab was established in order to conduct clinical and basic science research in order to further understand disease patterns and mechanisms, thus, trying to improve diagnosis and treatment outcomes of the patients we operate on. Moreover, the lab is a platform for the development of future academic surgeons, passionate about both research and the field of surgery. We focus on patient-driven translational research, studying the molecular basis of various soft tissue sarcoma (STS) tumors, and gastrointestinal malignancies. We aim to explore distinct signaling pathways and molecules that may play a role in cancer progression and metastasis. Specifically, we investigate the cross talk between metastatic GI cancer cells and the omentum. We also investigate the potential role of miRNAs as molecular biomarkers for staging, prognosis, and pattern of future spread. For these purposes we frequently utilize in-vitro and in-vivo models, human cancer specimens from our clinically annotated tissue bank, as well as various advanced molecular and bioinformatic approaches.

Tumor growth is promoted by omental fat in vivo. PANC-1 pancreatic cancer cells were initially pretreated in vitro with human omental fat conditioned medium (CM) or control regular medium (RM) for 24h. The tumor cells were then injected subcutaneously into the flank of nude mice. (A) Tumor growth and weight of PANC-1 tumors was facilitated in mice following pre-treatment with omental fat CM (n=15); (B) Representative mice and tumor images; (C) Marked increase in proliferation (Ki-67) and microvessel density (CD31) by human omental fat CM.
Uptake of omental fat exosomes by cancer cells. PKH67-labeled omental fat exosomes were incubated with PANC-1 pancreatic cancer cells (upper panel) and AGS gastric cancer cells (lower panel), reaction was stopped at different time points (1, 3, 5 and 7 hours) and cells were analyzed by confocal microscopy. The nucleus of PANC-1 and AGS cells was stained with dapi. Negative control- PANC-1 and AGS cells with no addition of labeled exosomes.

Publications


Immunotherapy of Brain Tumors: From Basic Mechanisms to Clinical Translation

Positions – Zvi Ram
Chairman, The Neurosurgery Section, Tel Aviv Sourasky Medical Center
Full Professor, Sackler Faculty of Medicine
Former Chairman, Tumor Section of European Association of Neurosurgical Societies

Positions – Ilan Volovitz
Lab Head, Cancer Immunotherapy Lab, Neurosurgery Department, Tel Aviv Sourasky Medical Center

Research
Our laboratory studies the unique immunology of brain tumors by combining basic-science with clinically-applied investigation. Utilizing the discrepancy between the relatively weak immune surveillance inside the brain and the potent one outside it, the lab has developed a novel method to treat brain tumors utilizing a concept we termed ‘Split Immunity’. The concept was recently translated from rats to human glioblastoma (GBM) patients. To monitor the post-therapy changes in the anti-tumor immune response, the lab has developed a unique set of high resolution immune assays that follow the peripheral (outside the tumor) and the intratumoral immune response.

Main research interests
• Development of scientific and clinical insights into the concept of ‘Split Immunity’ and how it affects the treated patients.
• Mapping of the entire adaptive and innate cellular immune milieu found inside human brain tumors.
using advanced multicolor (up to 12-color) flow cytometry.

- Using a cell-centered approach called "Immune Cytomics" to study the network of interactions formed between the different intra-tumoral immune cells and between immune and tumor cells.
- Evaluating how novel, non-immune-based, treatments for brain tumors affect the anti-tumoral immune responses.

Publications


Grants (Ilan Volovitz and/or Zvi Ram)

2014-2017 – Joint Project – Barrow Neurological Institute – Immunotherapy of recurrent GBM patients using ‘Split immunity’ (Ilan Volovitz and Zvi Ram)


2015-2018 – Novocure - Evaluating the effects of tumor treating fields (TTFields) on immune responses. (Ilan Volovitz and Zvi Ram)

2013-2018 – European FP7 grant- Microbubble driven multimodal imaging and heranostics for gliomas. (Zvi Ram)
Radiation Biology: Translating Biological Insights from the Lab to Impact Cancer Patient Care

**Positions (Dr. Lawrence)**
- Director, Center for Translational Research in Radiation Oncology
- Senior Lecturer (regular track), Sackler Faculty of Medicine
- Assistant Professor (adjunct), Dep. Radiation Oncology, Thomas Jefferson University

**Research**
Radiation therapy is a cornerstone of modern cancer care. Ionizing radiation kills cancer cells by generating reactive oxygen species, damaging DNA, and inducing chromosomal damage. Yet many aspects of radiation biology remain unknown. The lab focusses on understating cells’ ability to survive ionizing radiation, a phenomenon known

**Dr. Yaacov Richard Lawrence, MBBS, MA, MRCP**
Dept. of Radiation Oncology, Sheba Medical Center

**Dr. Uri Amit, M.D., Ph.D.**
Dept of Radiation Oncology, Sheba Medical Center
as radioresistance. We seek to answer the question of how some tumors are able to withstand very large doses of radiation. We hypothesize that cells withstand the intense onslaught of DNA damage by adapting their metabolic processes, diverting biosynthesis pathways to nucleotide synthesis and REDOX management. Another explanation of why cells in-vivo appear to resist radiation is the result of the interaction between tumor cells and the microenvironment. Ongoing projects in the lab are challenging and developing both these concepts.

The research center also performs clinical research, initiating and running clinical trials. Hence, a particular strength of the lab is the ability for our findings to impact patient care through the performance of clinical trials.

**Publications**


**Grants**

2014–2017 Rosetree’s Foundation

2014–2017 NATO Science for Peace and Security Programme

2017–2018 Israel Cancer Association
Dr. Raya Leibowitz-Amit, M.D, Ph.D.
Sheba Medical Center
Department of Oncology
Sackler Faculty of Medicine

miRNAs in Solid Malignancies / Immunotherapy Research / Clinical Cancer Research

Positions
Senior Lecturer, Sackler Faculty of Medicine
Senior Medical Oncologist, Clinician-investigator, Oncology Institute & Cancer Research Center, Sheba Medical Center, Tel Hashomer

Research
As a clinician-investigator and a practicing medical oncologist, our lab is engaged in basic, translational and clinical cancer research.

Basic research: Our lab at the Cancer Research Center at the Sheba campus studies the role of microRNAs in solid malignancies. We were the first to show that a large micro-RNA cluster on chromosome 14q32 is silenced in melanoma. This cluster was later dubbed ‘the larger tumor suppressor miRNA cluster’ and was shown to be down-regulated in a wide range of malignancies. We showed the involvement of three miRNAs from this cluster in melanoma progression, and continue to study the role of this cluster in the pathogenesis of this disease. In the last year, we have also studied the involvement of miRNAs in bladder cancer; specifically, preliminary results suggest that a family of miRNAs are associated with the development of resistance to chemotherapy in bladder cancer; research is currently ongoing.

Translational research: Immunotherapy, namely the activation of the immune system against cancer, is revolutionizing cancer treatment, yet not all cancers, and not all patients within a given cancer, respond to immunotherapy. Currently, the biomarkers associated with response to immunotherapy are unknown. In collaboration with Dr. Irit Gat-Viks from the Faculty of Life Sciences at TAU, we are embarking on a clinical trial in which we will prospectively search for immune cell populations within the systemic circulation that are associated with response to immunotherapy. We will perform RNA sequencing of immune cells before and following immunotherapy treatment and analyze the cell populations using deconvolution algorithms developed at the Gat-Viks lab.

Clinical research: Whereas the list of anti-neoplastic treatments is constantly growing across the cancer spectrum, currently there are almost no proven predictive biomarkers of response to treatment with any of these agents, and clinical decisions are generally empirical and based on ‘trial and error’. We are interested in finding associations between lab variables/plasma biomarkers and response to anti-neoplastic treatment in genito-urinary malignancies; specifically, we recently addressed the following clinical questions:
1. We described clinical and laboratory variables associated with response to the hormonal agent abiraterone in prostate cancer.
2. We showed that the neutrophil-lymphocyte ratio is associated with response to chemotherapy in bladder cancer, and that a high lymphocyte count is associated with pathological complete response at cystectomy following neo-adjuvant treatment.
3. We described the patterns of change of several plasma biomarkers following treatment with the biological agent cabozantinib in prostate cancer.
4. We summarized our clinical experience with the immunotherapeutic anti-PD1 antibody pembrolizumab, showing that low lymphocyte counts are associated with lack of response.

These clinical works, taken together, show that the adaptive arm of the immune response is imperative in amounting response to both chemo and immunotherapy.

Publications
Leibowitz-Amit R, Shapira-Frommer R, Golan T, Israel A, Shacham-Shmueli E, Gluck I, Aderka D, Onn...


Grants

Israel Science Foundation (ISF): The role of micro-RNAs from the 14q32 locus in the transformation, progression and drug sensitivity of malignant melanoma.


Tel Aviv University ‘Djerassi Dream Idea grant’: Potentiating the anti-neoplastic effects of the immune system by disrupting exosomal communications.
Hematological Malignancies

Positions
Prof. Raanani, Clinical Full Professor in Hematology, Sackler Faculty of Medicine

Research
Our primary field of interest is finding new therapies or better therapies for the treatment of incurable hematological malignancies. Our projects focus on exploring the effect of new agents on different leukemia and lymphoma cell lines and patient samples. We study the molecular pathways involved in the initiation and maintenance of hematological tumorigenesis and try to understand the effect of the different agents on these molecular pathways. We apply cutting-edge technologies including, molecular protein and cellular biology, microarray and NGS analysis. Understanding normal hematological development and understanding the molecular effect of different chromosomal abnormalities.

Deferasirox is a rationally-designed oral iron chelator used to reduce chronic iron overload in patients who receive long-term blood transfusions. We showed that this agent can induce apoptosis in mantle cell lymphoma.
(translocations, deletion, etc.) is essential for understanding the processes leading to the induction and maintenance of hematological malignancies and for designing targeted treatments for these malignancies.

Publications


Reviews


Grants

2016-2017 Delivery of miR-15/16-enriched exosomes to treat CLL, Research Authority, Tel Aviv University


2016-2017 Pathogenesis of Tyrosine Kinase Inhibitors (TKIs) Associated Vascular Disease in Chronic Myeloid Leukemia (CML), Pfizer Pharmaceuticals Israel Ltd.
Investigating Mechanisms of Hepatitis B Virus Persistence and Its Link to Liver Cancer

Dr. Amir Shlomai, M.D., Ph.D.
Department of Medicine D and the Laboratory of Liver Research
Felsenstein Medical Research Center
Rabin Medical Center, Beilinson Hospital

Positions
Head, Department of Medicine D and the Laboratory of Liver Research
Senior Lecturer, Sackler Faculty of Medicine

Research
Current research interests focus on the role of the innate immune system in HBV infection and the role of HBV infection in liver carcinogenesis.

1. Studying the molecular mechanisms by which HBV confers resistance to sorafenib in order to get a deeper understanding of HBV oncogenicity and to gain insight into possible molecular targets for HCC interventions.
2. Characterizing the molecular signature of type I interferon induction and response following HBV infection.
3. Characterizing the interferon-response genes (ISGs) induced by HBV and their effect on HBV life cycle.
4. Investigating the mechanism(s) of HBV inhibition by the innate immune response.

Publications


**Grants**

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<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2016-2020</td>
<td>Israeli Science Foundation (ISF)/Physician-Scientist Grant</td>
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<tr>
<td>2016-2020</td>
<td>US-Israel Binational Science Foundation (BSF) Grant (with CM Rice)</td>
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Professional Research, Hematology Division, Sackler School of Medicine
Pediatric Hemato-Oncology Department
Chaim Sheba Medical Center, Tel-Hashomer

Pediatric Brain Tumors, Leukemias and Lymphomas

Research
Targeted therapies aimed at new targets identified by in-house analysis of genetic panels studying pediatric cancer patients’ DNA.

Immunotherapy with new bispecific antibodies.

Incorporation of checkpoint inhibitors.

T-CARS for patients with relapse/refractory ALL. This innovative treatment has been performed in only a few centers in the USA and was successfully given to 5 patients. Pediatric brain tumors and neuroblastoma studies in the lab including pathogenesis, innovative therapies, discovery of new molecular aberrations, new biomarkers, new therapeutic targets the effect of new drugs on cell lines, primary cells and xenografts, studying the influence of changes in the levels of non-coding RNA’s (mirs and link-RNA) on the tumor. Improvement of the activity of cytokine induced killer cells stemming from alfa/beta depleted T cells left over after haploidentical transplantations. Studying the effects of phytocannabinoids, synthetic cannabinoids and endocannabinoid-like substances on pediatric glioblastomas and neuroblastoma.

Main research areas:
1. T-CARS therapy for relapsed/resistant CD19 expressing leukemias and lymphomas
2. The effects of cannabinoids on pediatric tumors
3. Cytokine induced killer cells against pediatric tumors
4. Pediatric brain tumors research

Publications


Mehrian-Shai R, Freedman S, Shams S, Doherty J, Slattery W, Hsu NY, Reichardt JK, Andalibi A, Toren...
A. Schwannomas exhibit distinct size-dependent
gene-expression patterns. Future Oncol. 2015.

Goldstein G, Shemesh E, Frenkel T, Jacobson JM,
Toren A. Abnormal body mass index at diagnosis in
patients with Ewing sarcoma is associated with

Goldstein G, Keller N, Blik R, Bielorai B, Toren A. Do
immunocompromised children benefit from having
Cardiovascular System

Macrophage accumulation at site of myocardial injury.
Credit: Tal Konfino, Dalia Palevski, Jonathan Leor lab
Investigating Hypertension, Diabetes Mellitus and Metabolic Syndrome

Positions (Prof. Grossman)
Head, Internal Medicine D and Hypertension Unit, Chaim Sheba Medical Center, Tel-Hashomer
Professor of Medicine, Sackler Faculty of Medicine, Tel Aviv University
Dean, Sackler Faculty of Medicine, Tel Aviv University

Research
Our research concentrates on the impact of coronary calcifications on cardiovascular morbidity and mortality in hypertensive patients. We showed that the presence of coronary calcifications is associated with increased mortality and that diabetic patients without coronary calcifications have a good prognosis. Our team also studied the effect of blood pressure control and stroke outcomes. We showed that elevated systolic blood pressure in acute stroke is associated with poor outcome and that change in BP during the first week after stroke has no effect on outcome. Our main basic research is on metabolic syndrome. How can we improve metabolic syndrome? We also studied the effect of melatonin on the cardiovascular system. Our recent paper in *J Pineal Res* showed that melatonin prevents kidney injury in a high salt diet-induced hypertension model by decreasing oxidative stress.

Publications
**Grossman E.** Blood pressure: The lower, the better: The con side. Diabetes Care. 2011;34 Suppl 2:S308-312


Rationale and design of a randomized controlled trial. Am Heart J. 2014;168:830-837 e1.


Cardiovascular Regulatory Systems Focusing on the Autonomic Nervous System in Human (Translational Science)

Position
Associate Professor, Medicine and Physiology

Research
Recanati Autonomic Dysfunction Center
The effect of adrenoceptors activation on the coagulation system
Insight into the regulatory mechanisms of mesenteric flow
Organ-specific flow regulation, e.g. cerebral and penile blood flow
Autonomic nervous system dysregulation in CVD
Autonomic nervous system and pain regulation, including fMRI studies
Postural tachycardia Syndrome (POTS)
Collaborations: Vanderbilt University, Nashville, TN, USA, Milano University, Italy, and Eurospace Center, Germany.

Publications


Atherosclerosis – Research, Treatment and Prevention

Positions
Professor of Medicine, Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine
Acting Vice President of Research and Development and Academy and Chairman, IRB Committee
President, The Bert W. Strassburger Lipid Center, Sheba Medical Center
Chairman, IRB Committee of the Sheba Medical Center
CEO, Vascular Biogenics Ltd (VBL)

Research
We investigate lipid metabolism, atherosclerosis and vascular biology. In our research, we apply advanced research tools, utilizing in-vitro and in-vivo models and performing clinical trials. In our studies, we focus on basic aspects in atherosclerosis progression and developing new treatments for prevention of the disease.

The current research projects are:

- The effect of carotenoids and their cleavage products on the activation of the nuclear receptor RXR and atherosclerosis in mouse models.
- The effect of carotenoids on Retinitis Pigmentosa.
- The effect of carotenoids on Alzheimer in transgenic mice.
- The role of the coagulation Factor XI in early and advanced atherosclerosis by using apolipoproteinE/FactorXI double knock-out mice.
- The role of apoA5 in atherosclerosis development by using apolipoproteinE/apoAVI transgenic mice.

Publications


**Grants**

2014-2017
Nikken-Shohonsha, 9-cis retinoic Acid-Lipid Metabolism & Atherogenesis

2014-2017
Regeneron, A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of an every four weeks treatment regimen of Alirocumab in patients with primary hypercholesterolemia

2014-2017
Sanofi , Open label extension study of EFC12492, R727-CL-1112, EFC12732, & LTS11717 studies to assess the long-term safety and efficacy of Alirocumab in patients with Heterozygous FH

2015-2017
Pfizer, Phase 3, multi-center, double blind, randomized, placebo-controlled, parallel group evaluation of the efficancy, safety and tolerability of Bococizumab (PF 04950615), in reducing the occurrence of major cardiovascular events in high risk subjects-SPIRE-2

2015-2017
Pfizer, Phase 3, multi-center, double blind, randomized, placebo-controlled, parallel group evaluation of the efficancy, safety and tolerability of Bococizumab (PF 04950615), in reducing the occurrence of major cardiovascular events in high risk subjects-SPIRE-1
Elucidating the Molecular & Pathophysiological Mechanisms Leading to the Initiation and Progression of Cardiovascular Diseases

We study the molecular networks leading to the initiation and progression of acute versus chronic presentation of various cardiac diseases. Currently we mainly focus on studying the following cardiac pathologies: 1. Acute myocardial infarction leading to left ventricular dysfunction; 2. cardiac volume overload- a prominent pathology in valvular diseases and chronic heart failure; 3. the prevalent presentation of cardio-renal syndrome. Utilizing the appropriate in vivo models as well as various molecular and cellular techniques, we have been trying to identify novel therapeutic targets for attenuating disease progression and to improve the clinical presentation of these devastating conditions.

Captures of transmitted electron microscopy demonstrating the organized structure of cardiac mitochondria in sham-operated control rats (A) compared to the swollen unorganized structure of the mitochondria in the heart tissue of animals with chronic kidney disease (B).
Main ongoing research topics

The potential involvement of the cation channel TRPV2, which is highly abundant on peri-infarct immune cells, in the recovery processes following an acute myocardial infarction.

Elucidating the therapeutic potential of anti-metalloproteinase antibodies as well as reagents holding anti- histone deacetylase activity for the treatment of cardiac volume overload.

Cardiac mitochondria as a promising target for attenuation of cardiac dysfunction and progression to cardiorenal syndrome in patients with chronic kidney disease.

Publications


Grant
2015-2018 Medical treatment in old age, Ministry of Science, Technology & Space
Positions
Full Professor, Sackler Faculty of Medicine
Rena Favaloro Chair for Heart Surgery and Interventional Cardiology
Chairman, Division of Cardiology and Cardiac Catheterizations, Rabin Medical Center
President, Israeli Society of Cardiology

Research
Prof. Kornowski has been involved in multiple technology developments and innovative treatment techniques in cardiology. The research activities include:

Development of new techniques geared towards catheter valve interventions, examining feasibility, safety and treatment outcomes.

Innovative imaging techniques of the coronary arteries and physiology.

Study of the cardiac effects of caloric restriction and neuro-hormonal pathways of weight reduction.

Translational studies of coronary thrombosis and progenitor endothelial cells.

Translational cardiovascular research of stem cells and gene therapy.

Development of new medications during and after cardiac catheterizations.

Research of novel drug-eluting stents and biodegradable scaffolds implanted within the coronary arteries.

Development of methods of “hybrid” cardiac interventions combined with minimal invasive cardiac surgery to treat structural and coronary diseases.

Mentoring and guiding students and young cardiologists in the early stage of their career.

Publications


Cardiovascular Regenerative Medicine and Targeting of Inflammation and Fibrosis

Positions
Professor of Cardiology, Sackler Faculty of Medicine
Director, Neufeld Cardiac Research Institute, Tel Aviv University
Director, Tamman Cardiovascular Research Institute, Sheba Medical Center
Director, Sheba Center of Regenerative Medicine, Stem Cells and Tissue Engineering

Research
Our lab is focused on translational research. Specifically, we study cardiovascular regenerative medicine, stem cells and tissue engineering. In addition, we aim to target cardiovascular inflammation and fibrosis using novel nano-medicine and a theranostic (therapy + diagnosis) approach. We use a combination of gene profiling, new biomaterials, liposomes, tissue engineering, physiological testing, and molecular imaging technologies, to understand heart cell biology in vitro and in vivo. Particularly, we work on the development of novel nano-therapies for cardiovascular disease.

Publications


Myocardial regeneration in a neonatal heart of a mouse, 3 days after apical resection. We used the heart of a newborn mouse to study the mechanism of myocardial regeneration and repair. The regenerating myocardium is characterized by cardiomyocyte (cardiac actin, red) dedifferentiation, and proliferation. Phospho-histone 3 immunostaining detects dividing nuclei (blue) and mitotic activity. Nuclei are stained green with DAPI.


Klempfner R, Leor J, Tenenbaum A, Fisman EZ and Goldenberg I. Effects of a vildagliptin/metformin


**Grants**

2014-2019 Israel Science Foundations, Role of macrophages in myocardial regeneration
Intracellular Regulation of Cholesterol Homeostasis

Positions
Senior Lecturer, Department of Human Genetics and Biochemistry, Sackler School of Medicine
Laboratory Director, Bert W. Strassburger Lipid Center, Sheba Medical Center

The levels of cholesterol in mammalian cells are tightly regulated by cholesterol itself via multitude of negative feedback mechanisms that coordinate its uptake from plasma lipoproteins and endogenous production in the mevalonate pathway. The major rate-limiting step in the mevalonate pathway is catalyzed by the enzyme HMG-CoA reductase, the target of statins class of cholesterol-lowering drugs.

The intracellular abundance, hence activity, of HMG-CoA reductase is strictly controlled by cholesterol and intermediates of the mevalonate pathway, and the research in our laboratory is aimed to unravel the molecular events and cellular factors that operate in the degradation of HMG-CoA reductase protein.

Our studies have wider implications to our understanding of atherosclerosis and neoplastic processes, and afford new perspectives for devising novel therapeutic modalities to combat these diseases.

Publications

Stress and Inflammation in the Cardiovascular System

Positions (Prof. Shapira)
Deputy Director General and Director, Rehabilitation Hospital
Associate Dean, Tel Aviv Sourasky Medical Center
Full Clinical Professor

Research
- Cholinergic regulation of stress and inflammation.
- Exercise-induced urinary protein secretion as a risk for metabolic syndrome.
- Determination of new set of control limits for the identification of patients at risk.
- The influence of work characteristics (burnout and stress) on physical health.

The Tel Aviv Medical Center Inflammation Survey (TAMCIS) is a long-term, ongoing cardiovascular cohort study evaluating stress and inflammation in 22,000 apparently healthy working adults admitting to our medical center for routine annual medical check-ups. It is designed to evaluate the association between physiological and psychological measures of stress, inflammatory profile and their additive effect on cardiovascular risk.

Our database includes more than 50,000 visits with more than 600 parameters per visit; including medical history and medication, laboratory tests (Metabolic profile, Blood chemistry, blood count and Urine tests), ophthalmologist examination, exercise test and spirometry, psychological comprehensive questionnaire consisting of socio-demographic variables, personal and family medical history, health behaviors, among them dietary and sports habits, objective as well as subjective work conditions and various psychological scales such as depression, fear of terror, burnout, perceived control and social support. Research methods include basic molecular biology as well as sophisticated statistical models. The study team includes multidisciplinary researchers and physicians, from internal medicine, cardiology and neurology departments, biology and the School of Management.

Publications


S Shenhar-Tsarfaty, I Shapiro, S Toker, O Rogowski, S Berliner, Y Ritov, H Soreq. Weakened cholinergic


Positions

Associate Professor, Senior Lecturer, Sackler Faculty of Medicine
Chair, Israel Working Group on Cardiac Pacing and Electrophysiology, Israel heart Society
Associate Editor – Circulation
Past Associate Editor – *Heart Rhythm*
Past Associate Editor – *Europace*

Research

We perform clinical studies on cardiac arrhythmias, particularly related to long QT syndrome, Brugada syndrome and early repolarization. We have several ongoing studies on long QT syndrome caused by atrioventricular block, drug induced long QT syndrome, empiric quinidine therapy for Brugada syndrome.

Publications


Antzelevitch C, Yan GX, Ackerman MJ et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge: Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), and the Latin American Society of Cardiac Pacing and Electrophysiology (Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología [SOLAECE]). Europace 2016.


Hu D, Barajas-Martinez H, Pfeiffer R et al. Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome. J Am Coll Cardiol 2014;64:66-79.


Belhassen B, Viskin S. Near fatal ventricular fibrillation in Brugada syndrome despite presence of an implanted implantable cardioverter defibrillator. Can J Cardiol 2014;30:1460 e3-5.


Adler A, van der Werf C, Postema PG et al. The phenomenon of “QT stunning”: the abnormal QT prolongation provoked by standing persists even


Immunofluorescence of PAR-4 expression in human mucosal biopsy from normal pouch. Credit: Sarit Hoffman, Ilya Borovok, Iris Dotan, Nitsan Maharshak
Basic and Translational Research of Liver Diseases

Positions
Director, Liver Disease Center

Research
Our lab is part of the Liver Disease Center at the Chaim Sheba Medical Center. We focus our studies on basic and applied liver disease research to better understand and improve the diagnosis and treatment of different liver diseases. We utilize various methods such as molecular biology, biochemistry, genetics, tissue culture and in-vitro and in-vivo models. The proximity between the Liver Disease Center and the lab creates a unique and highly successful dynamic relationship where the unsolved clinical needs are immediately translated into research for achieving better solutions.

The research in our lab is divided into two main projects:

1. Molecular mechanisms in the development of liver fibrosis

   Fibrosis is the excess accumulation of extracellular matrix (ECM), resulting from chronic, non-resolving inflammation. Multiple etiologies underlie development of liver fibrosis, such as chronic viral hepatitis B or C, autoimmune and biliary diseases, alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). Fibrosis progression toward cirrhosis is the major cause of liver-related morbidity and mortality. Patients with cirrhosis are more prone to develop liver failure, portal hypertension or infection and are at higher risk of developing hepatocellular carcinoma (HCC). In the normal liver, hepatic stellate cells (HSCs) constitute quiescent, vitamin A–storing cell. Following activation by specific stimuli released by an injured liver, HSCs undergo "activation" or transdifferentiation, yielding a myofibroblast-like cell. We are currently investigating the interactions between hepatocytes and HSCs in healthy and fibrotic livers in the different chronic liver diseases listed above. Our goal is to advance the research in this field and to establish resolution of liver fibrosis.

2. Microbiome and liver diseases

   The human gastrointestinal tract hosts a large number of microbial cells, which exceeds their mammalian counterparts by approximately 3-fold. The genes expressed by these microorganisms constitute the gut microbiome and participate in diverse and essential functions, including digestion, regulation of energy metabolism and modulation of inflammation and immunity. The liver, due to its critical functional relationship with the gastrointestinal (GI) tract, is continually exposed to multiple harmful and beneficial microorganisms derived from the small and large intestines. We study the microbiota signature of patients with different liver diseases (Primary Sclerosing cholangitis (PSC), PSC-IBD, Hepatocellular carcinoma and cirrhosis) and compare...
them to healthy control. Moreover, we investigate the correlation between environmental lifestyle and diet patterns, the host microbiome and disease etiologies.

Publications


Grants

2016 Gut Microbiome signature in Patients with Primary Sclerosing Cholangitis (PSC) with/without IBD and the Impact of Lifestyle patterns, The Israel Society for Liver Research

2015 The role of ADAR1 as a regulator in the development of liver fibrosis and hepatocellular carcinoma. Israel Cancer Association
Drug Mechanisms and Immunogenicity in IBD

Positions
Director, IBD Service, Gastroenterology Dept. Sheba Medical Center
Associate Professor of Medicine, Sackler Faculty of Medicine
Member, Organization Committee, European Crohn' & colitis Organization (ECCO)

Research
We focus on translational science, aiming to study drug mechanisms in IBD. Specifically, we study mechanisms whereby immune-modulating and biologic drugs exert their cellular effects and/or cause unwanted adverse events, as well as immunogenicity of biologic drugs, i.e. the eliciting of immune hyperresponsiveness in the recipient towards the biologic drug. We are interested also in studying novel herbal compounds for possible synergistic effects with conventional immune-modulators.

Completed projects include:
1. A study to decipher the delay in onset of action of thiopurine related to gradual depletion of antigen-specific memory T-cells
2. Development of novel and one of the first available assays to measure anti-drug antibodies against infliximab, and later adalimumab and currently vedolizumab
3. Identifying the Fab fragment as the immune-dominant fragment of infliximab, responsible for eliciting anti-drug antibodies
4. Study of cross-immunogenicity of infliximab and its bio-similar drug, CT-P13

Ongoing projects include:
1. Studying cellular mechanisms responsible for B-cell lymphoproliferation under immune-modulating drugs
2. Studying the decay in immune-suppression following azathioprine withdrawal
3. Studying herbal Chinese compounds effects on cells propagating inflammation

Publications
Ben-Horin S, Yavzori M, Katz L, Kopylov U, Picard O, Fudim e, Coscas D, Goldstein I, Chowers Y. The immunogenic part of infliximab is the F(ab')2 fragment, but measuring antibodies to the intact infliximab molecule is more clinically useful. Gut 2011;60:41-8

Grants
2015–2020 Horizon 2020 Immunogenicity of infliximab, within the SPARE trial (BioCycle consortium)
2017 Takeda Exploring mechanisms for TB induced by anti-TNFs
2014–2017 Celltrion Cross-immunogenicity of infliximab and CT-P13
Host: Microbial Interactions - Translational Research in Gastrointestinal Diseases

**Positions**
Physician-Scientist, Sheba Medical Center
Adjunct Assistant Professor, Division of Pediatric Gastroenterology, Hepatology, & Nutrition, Cincinnati Children’s Hospital Medical Center, OH, USA.

**Research**
We aim to investigate the pathogenesis of pediatric gastrointestinal disease, with a specific focus on inflammatory Bowel Disease (IBD) and congenital gastrointestinal manifestations. Our main research uses state-of-the-art sequencing approaches and patients’ samples to detect the widest range of microbial shifts and changes in host genes, present in the actual lining of the gut. These analyses are used to better characterize disease phenotype and pathogenesis with an ultimate goal to use this data in the future to better tailor therapy for a specific patient based on gut gene expression, microbial data and genetics.

Within our IBD research we focus on characterizing the role of non-coding elements (non-coding RNAs and GWAS significant non-coding SNPs) and we try to elucidate if and how these non-coding regions take part in the host:microbial interactions.

Another interest of the lab is to elucidate genotype:phenotype associations in patients with congenital gastrointestinal manifestations. Using high throughput genotypic analyses, we aim to explore connections between abnormal gastrointestinal metabolism and development with genetics. We hope that by understanding the genetics underlying those pathologies, we will be able to better understand the phenotype and tailor treatment.

**Publications**


*Equal contribution.


Book chapters


Investigating the Microbiome-Human Interactions

**Positions**
Senior Lecturer, Sackler Faculty of Medicine  
Head of Bacteriotherapy Clinic  
Deputy Chief, Department of Gastroenterology and Liver Diseases

**Research**
We study the role of enteric bacteria in inflammatory and metabolic related disease conditions in humans and in-vitro. Specifically, we study how bacterial proteases impact the epithelial barrier function and how enteric microbial alterations are related to diseases. Clinically, we study the implication of fecal microbial transplantation in disease conditions.

**Publications**
Maharshak N, Packey CD, Manick S, Siddle JP, Ellermann M, Plevy SE, Sartor RB, Carroll IM. Altered

Fecal supernatants from pouchitis patients have increased proteolytic activity, disrupt epithelial tight junctions and increase epithelial permeability. Fecal supernatants isolated from pouchitis patients compared to healthy controls and normal pouch (NP) patients caused: (A) disruption of tight junction proteins (ZO-1, occludin) as assessed by Western blot. (B) Decrease ZO-1 immunofluorescence (white arrows) of Caco-2 cells monolayers. Alexa anti mouse 488 was used as the secondary antibody (green). Nuclei were counterstained with DAPI and are shown in blue.


**Grants**
2012 – present Adalimumab for post operative Crohn’s disease patients. Abbvie LTD.
Studying Biliary Atresia Pathogenesis

The etiology remains unknown and there is no effective treatment. We identified an isoflavonoid toxin, biliatresone, that causes BA outbreaks in Australian livestock and we showed that it causes lumen obstruction of neonatal mouse bile duct (NBD) explants. This is a novel tool for the study of BA and allows us to study the primary event in the disease, providing new potential for identifying therapeutic interventions. We found that biliatresone acts by inducing a rapid and transient decrease in reduced glutathione (GSH) and a decrease in SOX17.

**Figure: Biliatresone induces ductal fibrosis.** Neonatal mouse bile duct explants were incubated with DMSO or biliatresone for 24 h and stained for the cholangiocyte marker K19 (green) or the myofibroblast marker smooth muscle actin (SMA) or collagen I or the EIIIA splice variant of fibronectin (all red). Scale bars 100 μm.
in cholangiocytes and that cholangiocyte injury can be mimicked using DL-buthionine sulfoximine (BSO) to reduce GSH or by knocking down Sox17. NBD cultured ex vivo and treated with either biliatresone or BSO showed disruption of the cholangiocyte monolayer, lumen obstruction, and subepithelial myofibroblast differentiation and fibrosis. Both obstruction and fibrosis could be prevented using GSH-protective agents, and were reversible with biliatresone wash out. In this proposal, we aim to define mechanistically the relationship between biliatresone, decreased GSH and downstream signaling molecules (Hey2, Hes1, RhoU, DAAM1 and other WNT signaling pathway genes) in the disruption of cholangiocytes and bile duct integrity. We will study the relationship between changes in cellular tubulin, loss of apical polarity, epithelial permeability and fibrosis and mechanism of repair of cholangiocyte damage and fibrosis. Understanding potential mechanisms of initial injury in BA may lead to new treatments.

Publications


Mononuclear Phagocytes in Digestive Tract Diseases

Positions
Senior Lecturer, Sackler Faculty of Medicine, Department of Clinical Microbiology and Immunology
Director, Research Center for Digestive Tract & Liver Diseases

Research
We are studying the role of mononuclear phagocytes in the pathogenesis of IBD, liver diseases, metabolic diseases and colorectal cancer. We utilize transgenic murine systems as well as human patient tissues to mechanistically unravel the involvement of these cells in the pathophysiology of these diseases. Among our main research topics:

- The interplay between immune cells and extracellular matrix (ECM) remodeling in the pathogenesis of IBD, colorectal cancer and liver fibrosis
- Monocytes and macrophage type of immune cells as pivotal drivers of inflammation and resolution during drug-induced liver injury, liver fibrosis and IBD
- The incretin hormone GIP as key linker between metabolism and immunity in type II diabetes

Publications
Ehud Zigmond*, Chen Varol*, Julia Farache, Elinor Elmaliah, Gilgi Friedlaender; Nahum Shpigl, Ivo G Boneca, Guy Shakhar, Zamir Halpern, Steffen Jung. Ly6Chi monocytes give in the inflamed colon

Tumor associated macrophages (TAMs) are pivotal constructors of the colorectal tumor collagenous matrix (Afik et al., JEM, 2016). (A) Confocal imaging showing the co-localization of TAMs (green) with collagen matrix (red). (B) Scanning electron microscopy (SEM) images of decellularized ECM scaffolds extracted from WT and TAM-deficient colorectal tumors. TAMs instruct collagen crosslinking and linearization processes, which are essential for tumor development, expansion and invasion. (C) Murine colonoscopy images showing the impaired colorectal tumor development in the absence of TAMs.


Fernanda Dana Mantelmacher, Sigal Fishman, Keren Cohen, Metsada Pasmanik Chor, Yuichiro Yamada, Isabel Zvibel, **Chen Varol**. Glucose-dependent insulinotropic polypeptide (GIP) receptor deficiency leads to impaired BM hematopoiesis. 2017. *Journal of Immunology*. 198: 000.


**Grants**

2016 – present Endogenous-like inhibitors for ADAM17 and ADAM8 – novel therapeutic agents for Inflammatory bowel diseases (IBD), Azrieli Foundation

2016 - 2019 Glucose-dependent insulinotropic polypeptide (GIP) improves adipose tissue inflammation and metabolism through direct regulation of adipose tissue macrophage function, Israel Science Foundation (ISF)
Investigating the Mechanisms of Liver Steatosis, Obesity and Cholestatic Injury

Positions
Principal investigator, Research Center for Digestive Tract and Liver Diseases
Tel Aviv Sourasky Medical Center
Senior Lecturer, Sackler Faculty of Medicine

Research
Our lab is investigating two main diseases, liver steatosis in models of diet-induced obesity and insulin resistance and cholestatic liver injury. Obesity and the metabolic syndrome accompanying it affect a large percentage of Western world population and the obesity epidemic is only expected to increase, therefore it's of the utmost importance to understand the mechanisms involved.

Cholestatic liver injury can be caused by various factors that impair bile flow and result in accumulation of bile in the liver, such as genetic defects, structural/mechanical obstruction of bile ducts impairing bile flow (e.g., common bile duct stones), toxins, and dysregulated function of the immune system. The two main cholestatic disorders in adult human patients are primary biliary cholangitis and primary sclerosing cholangitis for which liver transplantation is the only treatment as the disease progresses to liver failure. Specifically, we are investigating the roles played by sortilin, a trafficking molecule and a co-receptor, in both obesity and cholestatic liver damage, since we have found that sortilin deficiency has a protective role in diet-induced obesity and in murine models of primary sclerosing cholangitis. We are using both isolated liver cells (hepatocytes, cholangiocytes) as well as the cre-flox model where sortilin is deleted in various liver cells in order to further elucidate the mechanisms and signals regulating the protective roles of sortilin.

Publications


Endocrine Disease

The epiphyseal growth plate.
Credit: Galia Gat-Yablonski
Investigating the Molecular Basis of Linear Growth in Children and Animal Models

Positions – Moshe Phillip, M.D.
Professor, Sackler Faculty of Medicine
Director, Institute for Endocrinology and Diabetes
National Center for Childhood Diabetes
Schneider Children’s Medical Center of Israel
Vice Dean for Research and Development, Sackler Faculty of Medicine

Positions – Galia Gat-Yablonski, Ph.D.
Senior Lecturer, Sackler Faculty of Medicine
Committee Member, Israel Endocrine Society

Research
Children’s growth is regulated by both genetic and environmental factors. The most effective environmental factor is nutrition; however, the
mechanisms connecting nutrition and longitudinal growth are still not fully understood. Deciphering these mechanisms both in children and in animal models of rats and mice, has been the focus of our research, as currently means to improve growth in short stunted children are very limited.

We have identified several novel and important factors that are involved in regulation of this process, including growth factors that are produced and secreted from adipocytes such as leptin and GDF5, transcription factors such as hypoxia inducible factor (HIF)-1, and epigenetic factors such microRNAs and histone deacetylases including SIRT1, HDAC10. We have also studies extensively the effect of nutritional manipulation on bone quality in young rats. We may now exploit these findings as targets of new treatment strategies for children with growth disorders as well as children with special nutritional needs like premature babies, infants and children with chronic diseases associated with nutritional problems.

Publications


Shlomit Shalitin, Moran Gal, Yacob Goshen, Ian Cohen, Isaac Yaniv, Moshe Phillip. Endocrine Outcome in Long-Term Survivors of Childhood Brain Tumors. Hormone Research in Paediatrics 2011; 76:113-122


Alon Liberman, Bruce Buckingham, Moshe Phillip. Diabetes technology and the human factor. The International Journal of Clinical Practice, 2012; 66(Suppl. 175), 79-84

Rakefet Pando, Naomi Even Zohar, Biana Shtaif, Liat Edry, Noam Shomron, Moshe Phillip and Galia Gat-Yablonski. MicroRNAs in the growth plate are responsive to nutritional cues: Association between miR-140 and SIRT1. The Journal of Nutritional Biochemistry 2012; 23:1474-1481


Peter Adolfsson, Riitta Veijola, Celine Huot, Helle Doré Hansen, Jacob Bo, Moshe Phillip. Safety and patient perception of an insulin pen with simple memory function for children and adolescents with type 1 diabetes – the REMIND study. Current Medical Research & Opinion 2012; 28(9): 1455-1463


Rakefet Pando, Biana Shtaif, Moshe Phillip, Galia Gat-Yablonski. A Serum Component Mediates


Liat de Vries, Galia Gat-Yablonski, Nitsan Dror, Amihood Singer, Orly Elpeleg, Moshe Phillip. A Novel MKRN3 Missense Mutation Causing Familial
Precocious Puberty. Hum Reprod. 2014; 29:2838-43. doi:

**G. Gat-Yablonski, M. Phillip.** Nutritional Induced Catch-Up Growth. Nutrients 2015; 7:517-551


Tadej Battelino and **Moshé Phillip.** Technologies in Diabetes—the Sixth ATTD Yearbook. Diabetes Technol Ther 2015; 17 Suppl1: S-2


Tadej Battelino, Jasna Šuput Omladič, **Moshé Phillip.** Closed loop insulin delivery in diabetes. Best Practice & Research Clinical Endocrinology & Metabolism 2015; 29:315-325

Natasa Bratina, Shlomit Shalitin, **Moshé Phillip** and Tadej Battelino. Type 1 diabetes in the young: organization of two national centers in Israel and Slovenia. Zdrav Var 2015: 54: 139-


Biana Shtaif, Nitzan Dror, Meytal Bar-Maisels, **Moshé Phillip & Galia Gat-Yablonski.** Growth without Growth Hormone: Can growth and Differentiation Factor 5 be the mediator? Growth Factors 2015;33(4):309-18


Stacey M Anderson, Dan Raghinaru; Jordan E. Pinsker; Federico Boscari; Eric Renard; Bruce A. Buckingham; Revital Nimri; Francis J. Doyle III, Sue A. Brown; Patrick Keith-Hynes; Marc D Breton; Daniel Chernavvsky; Wendy C. Bevier, Paige K. Bradley; Daniela Bruttomesso, Simone Del Favero; Roberta Calore; Claudio Cobelli; Angelo Avogaro, Anne Farret; Jerome Place; Trang T. Ly; Satya Shanmugham; **Moshe Phillip**; Eyal Dassau; Isuru S. Dasanayake; Craig Kollman; John W. Lum; Roy W. Beck; Boris Kovatchev; for the Control to Range Study Group. Multinational Home Use of Closed-loop Control is Safe and Effective. *Diabetes Care.* 2016;39(7):1143-50.

Avital Adler, Michal-Yackobovitz Gavan, Riva Tauman, **Moshe Phillip**, Shlomit Shalitin. Do children, adolescents, and young adults with type 1 diabetes have increased prevalence of sleep disorders? *Pediat Diabetes.* 2016 Aug 3. [Epub ahead of print]


**Chapters & Editorials**


**Galia Gat-Yablonski, Moshe Phillip**. Nutritional induced longitudinal catch up growth: a focus on the growth plate, growth related genes, autophagy, mTOR and microRNAs. V.R. Preedy (ed.), *The Handbook of Growth and Growth Monitoring in Health and Disease,* Springer Science+Business Media LLC2012, 1029-1043

Investigating Lipid Metabolism and Atherosclerosis

Positions
Senior Lecturer, Medicine, Sackler School of Medicine

Research
Our research interests are within the fields of metabolic inflammation that contributes to the derangements of fat accumulation in atherosclerosis, fatty liver disease and diabetes. Specifically, we study the role of the inflammatory cytokine IL-1α and the ubiquitin-like protein HLA-F Adjacent Transcript 10 (FAT10) in these diseases. We recently discovered that the inflammatory cytokine IL-1α has an important role in early and advanced stages of atherosclerosis and fatty liver disease. We also discovered an unexpected role of IL-1α in determining ovarian lifespan and fertility.

We apply advanced technologies including genetically modified mice (Cre/loxP), molecular and cellular biology and microarray analysis to identify and functionally characterize genes that regulate atherosclerosis with the ultimate aim to prevent and treat this deadly disease.

Publications


Positions
Associate Professor, CAMEA, Sackler Faculty of Medicine
Researcher at the Bert Strassburger Lipid Center, Sheba, Tel Hashomer

Research
We study the effect of maternal dietary fatty acids quality during pregnancy and lactation on the gene networks that are involved in lipogenesis and thermogenesis in the offspring. Obesity-associated chronic metabolic diseases such as Cardiovascular, Type 2 diabetes and Non-Alcoholic Steatohepatosis are purported to have an early in utero origin. The nutrigenetic impact of fatty acids quality in normcaloric diets and healthy mothers during development is almost unknown. We are exploring this question by studying the metabolic and genetic evolution of the offspring from birth to adult age in our animal nutritional model and in humans. We apply the latest methodologies including biochemistry, lipidomics, molecular biology, and microarray analysis to identify and functionally characterize genes that regulate the lipogenic and thermogenic processes that determine the energetic balance leading to obesity or its absence. Understanding the normal or obesity prone gene programming during development and characterizing the associated fingerprint in the offspring at birth is essential for the early diagnosis and design of treatments to prevent long-term metabolic obesity-associated disorders that are leading causes of disease in almost 40% of world population and death.

Protein interaction between products of genes upregulated (red full) or down-regulated (blue full) by ω3 essential fatty acid (ALA) or saturated fatty acids (SFA). Enriched functions are marked using open colored circles.
**Publications**


L Shomonov Wagner, A Raz, A Leikin-Frenkel. 2015. Alpha linolenic acid in maternal diet halts the lipid disarray due to saturated fatty acids in the liver of mice offspring at weaning Lipids Health Dis. 26:14-14.


**Review**

Reproductive Endocrinology and Infertility- From Basic Science to Clinical Application

**Positions**
Professor, Obstetrics and Gynecology, Sackler Faculty of Medicine.

Incumbent, Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Sackler Faculty of Medicine

Director, Division of Reproductive Endocrinology and Infertility, Sheba Medical Center

Co-Editor-in-Chief, Reproductive Biology and Endocrinology

**Research**
Our research includes:

- Various aspects of controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).
- The role of GnRH-analogues, and specifically GnRH agonist versus antagonist in COH for IVF.
- The different modes of triggering final follicular maturation.
- Endometrial preparation for frozen-thawed embryo transfer.
- Obesity and IVF outcome.
- Fragile X Associated Premature Ovarian Insufficiency (FXPOI) in FMR1 premutation carriers.
- Pre-implantation genetic screening (PGS) and diagnosis (PGD).
- Several aspects of ovarian hyperstimulation syndrome (OHSS): pathophysiology, prediction, prevention and its relation to the inflammatory response.

**Publications**

**Manuscripts**


Elizur SE, Lebovitz O, **Orvieto R**, Dor J, Zan-Bar T. Reactive oxygen species in follicular fluid may serve as biochemical markers to determine ovarian aging


Haas J, Zilberberg E, Kedem A, Yerusalmi G, Dar S, Orvieto R. Do poor-responder patients benefit from increasing the daily gonadotropin dose from 300 to 450 IU during controlled ovarian hyperstimulation for IVF? Harefuah 2015;154(2):118-121


Reviews


Elizur SE, Orvieto R, Cohen Y. Are we Close to Solve the Mystery of Fragile X Associated Premature Ovarian Insufficiency (FXPOI) in FMR1 Premutation Carriers? Austin J In Vitro Fertili 2015;2(1): 1012.

Orvieto R. Triggering final follicular maturation-hCG, GnRH-agonist or both, when and to whom? J Ovarian Res 2015;8:60.


Orvieto R, Seifer DB Biosimilar FSH preparations- are they identical twins or just siblings? Reprod Biol & Endocrinol 2016;14:32


Dr. Amir Tirosh, M.D. Ph.D.
The Endocrinology and Diabetes Research Center
Institute of Endocrinology, Sheba Medical Center
Sackler Faculty of Medicine, Tel Aviv University

Mechanisms for the Development of Obesity and Diabetes – Molecular and Translational Aspects

Position
Associate Professor of Medicine, Sackler Faculty of Medicine

Research
With the worldwide epidemic proportions of obesity, its related morbidities such as cardiovascular disease and diabetes have become an emerging threat for public health. While the strong genetic predisposition for these conditions is a subject of intense research, less is known about the strong influence of various environmental factors on the pathophysiology of obesity and diabetes. We have recently established the Endocrinology and Diabetes Research Center at the Institute of Endocrinology at Sheba Medical Center with the vision to promote all aspects of research in the field of obesity, insulin resistance and diabetes.

Our group has focused on the following aspects of the pathophysiology of obesity and diabetes:

a. The role of food preservatives as ‘metabolic disruptors’: Some environmental and nutritional factors have been demonstrated to act as ‘endocrine disruptors’, with the ability to act as agonists or antagonists to certain receptors in a wide variety of biological systems. We have identified a common food preservative, with distinct metabolic effects. We were able to demonstrate that this food preservative results in an increase in hepatic glucose production as well as in changes in glucagon and insulin levels leading to liver insulin resistance. Chronic exposure results in weight gain, increase adiposity and systemic insulin resistance in mouse models. We are currently working on translating our pre-clinical results to humans in a series of randomized controlled trial. In addition, we continue to work using in-vitro and in-vivo animal models to assess the effects of micronutrients in modern nutrition on the development of obesity and diabetes.

b. Cellular mechanism linking over-nutrition with inflammation, insulin resistance and diabetes: Previous studies have clearly demonstrated that chronic inflammation and cellular stress is a central feature of obesity and its associated metabolic disease cluster. This inflammatory response is distinct, appears to respond to intrinsic cues, and does not resemble the classical inflammatory paradigm. Significant data have emerged in recent years on the molecular mechanisms leading to the development of these inflammatory and stress responses and how they are linked to metabolic homeostasis. Our research is focused on the regulation and adaptation to inflammation and stress within the tissue milieu in metabolically relevant tissues such as liver and adipose tissue. More specifically, we study cell-cell communication and the propagation of inflammatory and stress signals between cells within a tissue and the potential role of such communication in mediating insulin resistance and metabolic abnormalities.

c. In addition to utilizing basic research tools to promote our understanding on the mechanisms leading to insulin resistance and diabetes, we involve in clinical studies assessing novel risk factors and potential therapeutic approaches for these conditions. We are currently involved in several studies looking at the potential role of the novel adipokine FABP4 (fatty acid binding protein 4) in the insulin counter-regulatory response to hypoglycemia and as a potential contributor to the pathophysiology of gestational diabetes.

Publications


**Grants**

2012-2017 National Institute of Health (NIH)/National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), Characterization of the role of gap junction proteins in ER stress and obesity

2015-2018 The Research Projects and Fellowships Fund on Food and Nutrition with Implications of Public Health. Israel Ministry of Health, An unexpected role for propionic acid, a commonly-used food preservative, in mediating insulin resistance and weight gain

2016-2019 Innovative Clinical or Translational Science Award. The American Diabetes Association, Acute effects of the food preservative propionic acid on glucose metabolism in humans
Genetic Diseases & Genomics

Credit: Viktor Koen
Deciphering the Molecular Basis of Inborn Errors of Metabolism and Rare Genetic Disorders

Positions
Professor, Sackler Faculty of Medicine
Director, Metabolic Disease Unit, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Tel-Hashomer
Chairman, Israeli Society for Metabolic Diseases (ISMD)

Research
At the Metabolic Disease Unit and the Molecular Biochemistry laboratory at the Sheba Medical Center, we strive to identify and characterize the molecular basis of an array of inborn errors of metabolism (IEM) and other rare inherited disorders. As a referral center for patients with a wide array of IEMs, we take a “bedside to bench to bedside” approach, studying the biochemical pathways and genetic basis of their disease, delineating the functional effects of the disease-causing variants, and aiming our efforts at the exciting possibilities for novel therapeutic approaches.

In the past few years, we were the first to identify a causative association between variants in several genes and a number of new neurometabolic disorders, as published in the New England Journal of Medicine, American Journal of Human Genetics, Brain, Journal of Biological Chemistry, among others. This was the case, for instance, of an autosomal recessive subtype of Polyarteritis Nodosa vasculopathy, caused by

Clinical Features of Polyarteritis Nodosa Associated with Adenosine Deaminase 2 (ADA2) Mutations. Clinical manifestations of polyarteritis nodosa included digital necrosis of the toes in Patient B-III-3 (Panel A) and Raynaud’s phenomenon and livedo reticularis in Patient B-III-6 (Panel B). Angiography of the celiac artery in Patient B-III-3 revealed an aneurysm (Panel C, arrow). Periarteritis, fibrinoid necrosis of the media, and destruction of the elastic laminae were revealed in a biopsy specimen of the superior mesenteric artery in Patient A-III-1 (Panel D, hematoxylin and eosin).
variants in the CECRT1 gene, encoding Adenosine Deaminase 2 (ADA2). Since the publication of our results [Navon Elkan P et al. N Engl J Med 2014], this disorder, manifesting with early-onset cerebral infarctions (among others), has been diagnosed in numerous families worldwide.

Most recently, we identified and characterized a newly recognized inherited neurotransmitter deficiency, caused by mutations in DNAJC12 [soon to be published in the American Journal of Human Genetics]. This disorder was found to manifest in hyperphenylalaninemia, dystonia and intellectual disability. Interestingly, patients with the DNAJC12-associated phenotype showed dramatic clinical improvement following early treatment with BH4 and/or neurotransmitter precursors, and thus this unique disorder is a new treatable and preventable cause of intellectual disability.

Publications


Genomics and Epitranscriptomics

**Positions**
Professor, Sackler Faculty of Medicine
Djerassi Chair in Oncology, Tel Aviv University
Head - Cancer Research Center, Sheba Medical Center, Tel Hashomer
Head - The Wohl Institute of Translational Medicine, Sheba Medical Center, Tel Hashomer

**Research**
Our main interest lies in the deciphering of novel genetic and epigenetic mechanisms affecting global gene expression and their implication in cancer and neuronal disorders.

Our research interests are:
- The deciphering of the role of RNA epigenetics, including RNA editing and RNA methylation in the regulation of gene expression and cell fate.
- The study of transposable genetic elements in cancer and development
- Genetic and genomic studies relevant to cancer and genetic diseases
- Genetically non-identical tumors

**Publications**

**Manuscripts**


Reviews


Grants
2013-2017 Israel Centers of Research Excellence (I-CORE)
2013-2018 Ernest and Bonnie Beutler Research Program
2014-2017 CRBC Hematological Research Grants Program
2014-2019 Flight Attendants Medical Research Institute FAMRI
2016-2018 ISF-Joint Israel-Canada Health Research Program
Rare Diseases Diagnosis and Research

Positions
Pediatrician - Medical Geneticist, Sheba Medical Center
Director, Institute for Rare Diseases
Associate Professor, Sackler Faculty of Medicine
National Coordinator, Orphanet Israel
National Coordinator, Rare Diseases National Registry

Research
There are more than 6000 rare diseases affecting more than 60 million people in Europe and the US alone. Most of these diseases are affecting children, are chronic and are of genetic etiology.

Advances in rare disease research are very quickly changing the pediatric care for children affected with these non identified diseases which are very often complex. Research is one of the basics stones for building an accurate care of patients and families. Here, we wish to incorporate research to awareness, diagnosis, treatment and health policy. Our goals include identification of rare diseases causing genes, study the function of the abnormal protein, and finally deciphering new protein pathways in order to establish new therapies. Since the laboratory is in a clinical setting the results of the work is translated into genetic counseling and clinical care and sometimes treatment (MPS II-MPS IV-Fabry disease). With this in mind we are performing cellular studies and drug screens targeted to rare diseases in collaboration with other laboratories, aiming to better understand pathways such as the one linked to mucolipin 1 involved in the mucolipidosis IV clinical symptoms with the goal to provide a specific therapy.

In the field of clinical research, we focus on different subjects that include different topics such as: Natural history of MPS III (Hetz project; Understanding of the practical aspects of the medical genetics (Genet Med. 2016;18(4):372-7); Ongoing project on how the patients are dealing with the information linked to the results of the use of new technologies such as CNV and Exome sequencing.
**Publications**


Reviews


New Gene Identification and Genotype-Phenotype Correlation

Positions
Associate Professor of Pediatrics and Human Molecular Genetics and Biochemistry, Sackler School of Medicine
Committee Member, Israel Medical Association, Israeli Board of Medical Genetics, American Society of Human Genetics, American Board of Medical Genetics, Institutional Review Board (Helsinki) Assaf Harofeh
Member, Research and Development Committee, Tel Aviv University

Research
We study genetically undefined families using homozygosity mapping and EXOME analyses, in collaboration with other leading centers, to define disease causing genes. Once a causative mutation is defined, further functional studies are carried out. We identified at least five new genes in the last decade that enabled counseling patients and prenatal diagnosis.

We investigate the genotype-phenotype correlation of newly defined mutations to expand the disease spectrum and impact of genetic disorders.

Publications

NEB gene schematic presentation. The gene contains several transcripts ranging from 149-183 exons. The arrows point at specific exons where variants were detected in patients with prenatal AMC.


Prof. Eli Sprecher, M.D., Ph.D.
Laboratory of Molecular Dermatology, Department of Dermatology, Tel Aviv Medical Center; Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine

Dr. Ofer Sarig, Ph.D.

Investigating the Molecular Genetics of Skin Diseases

Positions
Chair, Department of Dermatology, Tel Aviv Medical Center
Professor, Sackler Faculty of Medicine, Tel Aviv university

Research
Our laboratory has been investigating the genetic basis of skin disorders for the past 15 years. Monogenic skin disorders are known to be prevalent among Middle Eastern populations, and at this regard, our laboratory is ideally situated to carry research in that field. These efforts have led to the deciphering of the molecular basis of more than 20 genetic diseases by members of our group. The deciphering of the molecular basis of a monogenic disorder invariably reveals a novel pathway whose importance is exemplified by the disease resulting from its malfunction. We systematically explore the mechanistic aspects of these new pathways using almost exclusively humanized models such as three-dimensional skin equivalents, hair organ cultures and chimeric mouse models. Once the function of a novel gene product is established, this new knowledge can be translated in the form of new treatments for rare and more common diseases alike. For example, we have found that defective expression of P-cadherin causes hair loss due to disrupted Wnt signaling. We are now developing small inhibitors for this new pathway as a new treatment for conditions associated with excessive hair growth. Based on a similar paradigm we are now also investigating the genetic basis of complex skin traits including psoriasis and pemphigus, a dreadful autoimmune disorder associated with 90% mortality if left untreated.

Artificial human skin grown in vitro
Ex vivo culture of human hair follicles
Publications


Mohamed J, Malchin N, Shalev S, Sarig O, **Sprecher E**. ARCI7 revisited and re-positioned. J Invest Dermatol, in press, 2017


**Review**


**Grants**

2014-2017 Israel Science Foundation-National Science Foundation of China Joint Scientific Research Program: “The genetic foundations of pemphigus vulgaris”. Investigators: Eli Sprecher (PI), Xuejun Zhang (PI), Ofer Sarig (co-PI), Xianfa Tang (co-PI), Xianbo Zuo (co-PI), Hui Chen (co-PI), Fusheng Zhou (co-PI)

2014-2018 Binational Science Foundation: “Modulation of IGFBP7 expression as a new therapeutic approach in psoriasis”. Investigators: Eli Sprecher (PI) and Peter Marinkovitch (PI)

2017-2020 COST: “A European Network for Connective Tissue Calcifying Diseases”. Investigators: PI Ludovic Martin (PI); Eli Sprecher et al (co-PIs)

The Lab for microRNA Research

microRNAs in human disorders: Psoriasis

One of the main research subjects in the lab is the involvement of miRNAs in the psoriasis. We found that the miRNAs’ expression differs between psoriatic and normal skin. Some of these miRNAs are involved in biochemical cycles which regulate skin development and others regulate the interplay between immunocytes and keratinocytes. We are exploring how the expression of these miRNAs is regulated and how they affect the pathogenesis of the disease.

Skin cancer squamous cell carcinoma (SCC)

Skin carcinogenesis, as in most other cancer types, is believed to be a multi-step process with several steps along its malignant evolution: Solar elastosis (SE), actinic keratosis (AK or KIN1-2), a more advanced stage of AK (KIN3) and CSCC. Using high-throughput deep sequence analysis of five stages along the malignant evolution we clearly see that miRNAs expression is distinct in each of the predefined five stages of malignant progression, a typical signature characterizes each stage. Currently we are investigating the biochemical pathways regulated by these miRNAs and their role in the malignant transformation of keratinocytes.

The lab researchers and students
Parasites exosomal miRNAs as diagnostic tool and their effect on host immune cells

Parasitic infections are responsible for considerable human suffering. Currently, diagnosis and management of parasitic infections is challenging in many settings. We hypothesize that pathogen-specific miRNA can be utilized to understand, diagnose and manage parasitic infections. We have undertaken a pilot study of schistosomiasis as preliminary proof-of-concept for need and feasibility of miRNA-based diagnosis for parasitic infections. Schistosomiasis is a parasitic disease caused by helminthes (blood-flukes) of the genus Schistosoma that affects more than 200 million people, mostly in the developing world. Infection in returning travelers has received increasing attention, including among Israeli travelers. We were able to detect the presence of schistosomal miRNAs in the micro-vesicles fraction harvested from the patient sera. The Schistosoma parasites have developed multiple mechanisms for modulating or suppressing host immunity. We hypothesize that the adult Schistosoma utilizes secreted exosomes as a mechanism to manipulate and escape the immune system. Currently, we have data suggesting this hypothesis.

The lab researchers and students. PhD students: Mizrahi Adi, Masalha Moamen (MD/PhD student); Postdoc fellow: Dr Layani Adi; Former lab members - PhD students: Dr Lerman Galya, Dr Zehavi Liron, Dr Bonen Hamutal; M.Sc students: Vestin Assaf, Volman Ella, Weinstein Jonathan; Scientist: Dr Elharrar Einat. Location: Sheba Medical Center.

Publications


Molecular and Cellular Studies of Rare Disorders of Hematopoiesis

Positions
Professor of Pediatrics, Sackler Faculty of Medicine
Director, Hematology Unit, Schneider Children’s Medical Center of Israel

Research
We study rare hematological disorders, using different cellular model systems. The roles of codanin-1 in normal hematopoiesis and in the pathogenesis of congenital dyserythropoietic anemia type I (CDA I). CDA I is a rare disorder causing anemia and bone abnormalities. We have identified CDAN1, the gene causing CDA I, in 2002, by linkage analysis. Codanin-1, encoded by CDAN1, is ubiquitously expressed and necessary for early embryonic development. However, its roles in hematopoiesis are not known. We generated erythroid tissue specific KO mice, and identified early anemia and embryonic lethality caused by a complete lack of codanin-1. We are also utilizing other model systems for the disease, including K562 cell line, murine fetal liver erythroid differentiation system, and primary human erythroid cultures. Understanding the roles of codanin-1 in red blood cells development may shed light on specialized processes involved in erythropoiesis. Even more significant, elucidating the role of codanin-1 in CDA I may help develop novel therapeutic approaches to alleviate the anemia in these patients.

The pathomechanisms of severe congenital neutropenia and cyclic neutropenia through patients will be understood by using derived induced pluripotent stem cells. We use the cutting edge technology of induced pluripotent stem cells generated from patients with congenital neutropenia as a model system for severe congenital neutropenia and cyclic neutropenia, caused by ELANE mutations. We aim to define the granulopoietic defects caused by these mutations, establish a genotype-phenotype correlation of iPSC lines carrying ELANE mutations causing both diseases, and study novel potential therapies by pharmacological correction of the granulopoietic defects detected.

Publications


Grants
- 2016-2018 Understanding the pathomechanisms of severe congenital neutropenia and cyclic neutropenia through patients derived induced pluripotent stem cells. Germany Israel Foundation (GIF)
- 2016-2019 The European Diamond-Blackfan Anemia Consortium. E-Rare
Primary Immunodeficiencies (PIDs) – From Bed to Bench and Back

Positions
Head, Pediatric Department, Immunology Services

Research
Our research focuses on:
1. Primary immunodeficiencies - finding and characterizing novel diseases
2. Newborn screening for immunodeficiency
3. Investigating fetal immunity in health and diseases
4. Next generation sequencing to illustrate and understand for T and B cell receptor repertoires

Our pediatric immunology clinic and laboratory are dedicated to the diagnostic evaluation, treatment, monitoring and research of patients with disorders of the immune system, including congenital immunodeficiencies and autoimmune diseases. In addition, we are leading Israel in the field of newborn screening for severe immunodeficiency and recently became the national laboratory for validating results obtained from this program. We are acknowledged as a “Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiency” (www.jmfworld.org) – which is the “gold standard” benchmark for excellence in this field. Part of our service is in-house laboratory which is well-experienced in the most advanced immunological and molecular assays that are used world-wide to assess immune function. We are interested in thymus functions in health (embryonic development and neonates) and in PIDs, as reflected by V(D)J rearrangement and thymic output of T cells, as well as B cell development, using advanced molecular methods, such as TREC and KREC analyses and next generation sequencing (NGS). We use whole exome sequencing (WES) to discover new PIDs. This approach led us to identify to date several novel mutations that cause inherited PIDs. We found that mutations in two of these mutated novel genes, VPS45 (New England Journal of Medicine, 2013) and STN1 (Journal of Experimental Medicine, 2016) cause syndromic PIDs, i.e. severe congenital neutropenia (SCN5) and Coats plus, respectively. In our large PID cohort of patients some mutations were found in genes that have not been known until now to be involved in the development of the immune system. We continue to find such mutations in novel genes that cause PIDs.
with atypical clinical characteristics and study their pathophysiology mechanisms, using also a zebra fish model. Characterization of proteins encoded by the activity of these genes in immune cells of patients compared with those of healthy individuals enable us a better understanding of the development and function of the immune system, as well as designing new targeted drugs or gene therapy to the immune deficiency the patients suffer from. Another interest in our lab is to investigate T and B cell development and repertoire productions in health and disease including the development of the immune system in fetal life (Science Translational Medicine, 2015). We have used traditional methodologies (e.g. flow cytometry or PCR analysis) to illustrate cell repertoire in patients with immunodeficiency, autoimmunity and in developing human embryos. Yet the recent development of next generation sequencing (NGS) techniques enabled analysis of these immune repertoires to a depth that was unreached before. This was already used by us in various pathologic conditions including immunodeficiencies, autoimmune disorders and infections. One of the advantages of the NGS technology over the traditional methodologies for investigation of the expanded clones and for clinical follow-up is that it ensures finding of the clonal receptor rearrangements in every patient due to the enormous depth of sequencing. It allows for the detection of multiple sub-clones, specific preferential usage of V, D and J gene segments and complementarity determining region 3 (CDR3) characteristics and to look for clonotypic sharing in patients with a similar disease. In addition, with the use of the CRISPR-Cas9 genome editing platform, we are modeling relevant primary immunodeficiency causing genes, such as RAG1/2, DCLRE1C (artemis) and ATM in wild type human lymphocytic cell-lines, and are using this ‘bed to bench and back’ approach to correct these mutated genes as a strategy to develop innovative curative gene correction therapy in patients’ cells.

Publications


**Reviews**


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**Sackler Faculty of Medicine Research 2017**

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**Immunology & Hematology**

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Vibrio proteolyticus bacteria infecting macrophages.
Credit: Dor Salomon
Mechanisms of Virulence and Drug Resistance in Pathogenic Fungi

**Positions**
Senior Lecturer, Sackler School of Medicine  
Head, Infectious Diseases Unit, Tel Aviv Sourasky Medical Center  
Director, Molecular Mycology Laboratory, Tel Aviv Sourasky Medical Center

**Research**
We study the pathobiology and epidemiology of medically important fungi. Fungal infections are encountered with increasing frequency in advanced medical settings, and are associated with high mortality rates. Specifically, *Candida* species are frequent causes of hospital-acquired bloodstream infection, particularly in the intensive care setting, whereas *Aspergillus* species and other pathogenic filamentous fungi cause sinopulmonary and disseminated infections in immunocompromised patients.

Our work has outlined the incidence, drug resistance patterns, geographic distribution, risk factors and outcomes of *Candida* bloodstream infections in Israeli hospitals. A multicenter effort is currently underway to study the epidemiology of invasive mold infections in Israel.

We are specifically interested in *Candida glabrata*, an opportunistic pathogen notable for its limited susceptibility to antifungal agents and its tendency to rapidly evolve resistance following exposure to antifungalazole drugs. Using population analysis techniques, we showed that clinical strains of *C. glabrata* are often heterogenous at the cell-population level with respect drug resistance. This phenomenon, termed heteroresistance, facilitates the expansion of drug-resistant subpopulations during antifungal treatment. We discovered that heteroresistance is associated with over-expression of efflux transporters, and that heteroresistant strains can persist *in vivo* despite high-dose azole treatment. Heteroresistance is not captured by standard susceptibility tests performed at clinical laboratories, and may explain the mismatch between susceptibility data and treatment outcomes.

**In vivo assay for angiotropism and angioinvasion:** Matrigel plugs implanted subcutaneously induce the formation of endothelial cell networks (black arrowheads). *A. fumigatus* forms hyphae (white arrowheads) that invade neovessels. Genetic manipulation is used to dissect *A. fumigatus* genes responsible for angiotropism and angioinvasion.
Additional work has focused on the emerging species *Candida auris*. Unknown until recently, *C. auris* is a multidrug resistant organism that has caused simultaneous outbreaks of invasive infections in multiple countries in Europe, North and South America, Africa and Asia. We characterized the drug resistance and pathogenicity traits of *C. auris* isolates. Ongoing work at our lab aims to define optimal treatment strategies for *C. auris* infection using in vitro and animal models.

Invasion of host blood vessels is characteristic of invasive Aspergillus fumigatus infection. We have previously shown that angioinvasive *A. fumigatus* produces gliotoxin, a secondary metabolite which down-regulates host angiogenesis. We hypothesized that angioinvasion is essential for *A. fumigatus* virulence. Research conducted at the Tel Aviv Medical Center Mycology laboratory and at the laboratory of Prof. Nir Osherov at the Sackler School of Medicine aims to understand the genetic underpinnings of angiotropism and angioinvasion. We predict that this line of research will uncover novel targets for the treatment and prevention of invasive aspergillosis.

**Publications**


**Grants**

2014-2017 Israeli Science Foundation 1347/14
Investigating Infectious Diseases

Positions
Head of Department, Medicine E, Rabin Medical Center, Beilinson Hospital
Sackler Faculty of Medicine
Editor-in-Chief, Clinical Microbiology and Infection
Director, Infectious Diseases University Research Center, Rabin Medical Center, Beilinson Hospital

Research
Our research focuses on improving the treatment and management of patients with severe infections and at the same time, focusing on interventions that will reduce the rise of resistance to antibiotics in microorganisms. Our main goal is to reduce mortality and suffering caused to patients by these infections.

Together with partners in Denmark, we have developed a computerized decision support system for antibiotic treatment in patients with moderate to severe infections. It was tested in a multi-center trial in three countries, and was shown to improve the outcome of patients, while at the same time reducing unnecessary use of antibiotics and hospital stay.

Our studies, systematic reviews and meta-analyses and clinical studies, served to change international guidelines and improve patient’s management. For example:

- Study that stopped the use of single-dose antibiotics for urinary tract infection.
- A clear evidence on the benefit of appropriate empirical antibiotic treatment
- Antibiotic prophylaxis for neutropenic patients.
- Discontinuing the use of beta-lactam/aminoglycoside combinations.
- Proof that some antibiotics (tigecycline and cefipime) are less effective than others.
- Current projects

- Optimizing diagnosis, treatment and outcome definitions in elderly patients with bacterial infections (Ministry of Science, Technology and Space).
- The impact of a decision support system for antibiotic decisions on appropriateness of treatment, morbidity and mortality, consumption of antibiotics and resistance to antibiotic drugs (The Israeli national institute for health policy research).
- Combating Bacterial Resistance in Europe – Molecules against Gram Negative Infections (IMI – COMBACTE-MAGNET).

Publications


Farbman L, Avni T, Rubinovitch B, Leibovici L, Paul M. Cost-benefit of infection control interventions targeting methicillin-resistant Staphylococcus aureus


Infectious Diseases


Johnson AP, Leibovici L. An essential requirement for the licensing of new antibiotics is the provision of data on efficacy and safety obtained from clinical trials in which patients are randomized to receive either the experimental drug or a comparator antibiotic regarded as a standard treatment option. Preface. J Antimicrob Chemother. 2013 Jul;68 Suppl 2:i1.


Reviews

Leibovici L. Ethical considerations in research published in the CMI. Clin Microbiol Infect. 2016 Dec;22(12):957.


Yahav D, Leibovici L, Goldberg E, Bishara J, Paul M. Time to first antibiotic dose for patients


**Grants**

2015-2017 The Israel National Institute for Health Policy Research: The impact of a decision support system for antibiotic decisions on appropriateness of treatment, morbidity and mortality, consumption of antibiotics and resistance to antibiotic drugs


2016-2021 IMI – COMBACTE-MAGNET: Combatting Bacterial Resistance in Europe – Molecules Against Gram Negative Infections

Functional MRI results, scanned at the Strauss Computational Neuroimaging Center, Tel Aviv University
Credit: Tom Schonberg
Dr. Yuval Bloch, M.D.
Cognitive and Emotion Research Lab
Shalvata Mental Health Center
Sackler Faculty of Medicine

Investigating Cognitive and Emotional Difficulties that Typify Different Psychopathologies in Life Span: Therapeutic Brain Stimulation

Positions
Senior Lecturer, Sackler Faculty of Medicine
Co-Cordinator, Course of Continuing Medical Education in Psychiatry, TAU
Head, Child and Adolescent Outpatient Clinic “Shalvata”

Research
Our research work is embedded in our clinical dilemmas and difficulties. Our studies have focused on: Cognitive and emotional domains in the course and development of different pathologies, especially depression and ADHD. We are interested in the interplay between anxiety and ADHD and a differential effect of Methylphenidate on state anxiety. We were able to show effects of depression on cognition in depressed adolescents with some cognitive domains related to state the depressive episode and others to the trait. In recent years, our studies have focused on brain stimulation, especially deep transcranial magnetic stimulation (rTMS), effects of pharmacotherapy and psychotherapy and placebo on emotions and cognition.

Publications

Segev A, Spellun J, Bloch Y. Anxiety as a central outcome measure in an adolescent with major...


**Grants**

The Israel National Health Policy (NIHP) grant “Collecting routine outcome measures” in the mental health system”. 2014-present
Investigating Chronic and Acute Pain Mechanisms and New Ways for Pain Modulation and Relief

Positions
Head, Institute for Pain Medicine, Sourasky Medical Center

Research
Chronic pain is a complex physiological condition affecting around 17% of the population. While acute pain, following noxious stimuli or tissue damage, is useful as a warning sign and usually disappears when the trauma is over, chronic pain persists even though the tissue has been healed. Moreover, chronic pain often triggers an array of neurologic, immunologic, physical and psychological changes that worsen the patient’s situation and are not related to the original cause of the pain.

Figure: (Top panel) Mean pain and unpleasantness scores. Mean pain (A, left panel) and unpleasantness scores (B, right panel) following: a painful cold stimulus (baseline); natural meditation; meditation after placebo administration; and meditation after naloxone administration, respectively. Bars represent standard error. (Bottom panel) The differences in pain scores following naloxone vs placebo and participants’ mindfulness meditation (MM) experience. The positive correlation of the response to intervention with years of experience suggests reduced response to placebo with increasing experience.
At the Institute for Pain Medicine, we focus on the biochemical basis of pain transmission and pain relieving treatments. For example, in a recent study we showed, for the first time, that meditation involves endogenous opioid pathways, mediating its analgesic effect. In another study, we investigated gender effect on the relationships between parasympathetic activity and pain modulation. We found that women demonstrated higher parasympathetic activity compared to men, which resulted in a subsequent lower pain perception. In a third study, we showed that many patients suffering from complex regional pain syndrome (CRPS), are diagnosed with alexithymia which can be regarded as an outcome of CRPS, highlighting the importance of early CRPS diagnosis and support. These and additional research findings hold promising therapeutic implications and further elucidate the fine mechanisms involved in human pain modulation.

Future research/programs: TMS TDCS Biofeedback, Pain rehabilitation programs, Cannabis database

Publications


The Pathophysiology and Development of Movement Disorders and Specifically Parkinson’s Disease

Positions
Full Professor, Sackler Faculty of Medicine  
Chairman, Tel Aviv Institute of Neurology, Tel Aviv Medical Center  
Director, Department of Neurology and Neurosurgery, Sackler School of Medicine  
Incumbent, Sieratzki Chair in Neurology, Sackler School of Medicine  
Sagol School of Neuroscience

Research
We have been leading a large-scale research endeavor to clinically and epidemiologically characterize the Ashkenazi Jewish Parkinson’s Disease (PD) population in Israel and to identify genes that influence the risk of developing the disease in this population. In recent years our group has conducted groundbreaking research on the influence of mutations in two major genes - LRRK2 and GBA. The research was first aimed at identifying the prevalence of mutations in these genes in patients with PD and explores differences in phenotype. Our research then evolved to include first degree relatives of these patients to explore early markers of disease in healthy asymptomatic carriers. In addition to examining the contribution of risk mutations, the existence of protective haplotypes or genes was also investigated. For example, recent work has shown that immune system B cells may contribute to protection from the disease or influence its progression. The above described research has opened new avenues of exploring disease identification, progression and even prediction and could potentially impact treatments in PD.

We are also keenly interested in understanding the relationship between cognitive functions and quality of gait, as well as the risk of falling and the neurophysiological basis of the phenomenon of Freezing of Gait (FOG) in Parkinsonism. Our early work on identifying and quantifying FOG resulted in a standardized validated and widely used questionnaire (FOGQ). In addition, our group makes use of accelerometers and gyroscopes to record gait during usual activities, in both the laboratory setting and in the home environment, to better understand changes in performance during daily activities, medication cycles, habits and behavior. Using specified indices, the importance of the variance between different steps was identified, as a measure of fall risk and as a sensitive measure of sub-clinical changes, susceptibility to cognitive loads and perhaps a marker of disease.

In recent years, we have also been involved in exploring new interventions for the patients with PD. These include exploring the effects of tDCS stimulation and virtual reality to improve motor-cognitive function and functional abilities of patients with PD. This work builds on the study of movement disorders, on the one hand, and on examining ways to ameliorate motor symptoms in patients with PD.

Publications


**Giladi N**, Asgharnejad M, Bauer L, Grieger F, Boroojerdi B. Rotigotine in Combination with the MAO-B Inhibitor Selegiline in Early Parkinson’s


Rosenberg-Katz K, Herman T, Jacob Y, Mirelman A, Giladi N, Hendler T, Hausdorff JM. Fall risk is associated with amplified functional connectivity.


Giladi N, Ghys L, Surmann E, Boroojerdi B, Jankovic J. Effects of long-term treatment with rotigotine transdermal system on dyskinesia in patients with


Giladi N, Horak FB, Hausdorff JM. Classification of gait disturbances: distinguishing between continuous and episodic changes. Mov Disord. 2013 .73-1469:(11)28;15


Kedmi M, Bar-Shira A, Gurevich T, Giladi N, Orr-Urtreger A. Decreased expression of B cell related...


Grants

2013 - 2018 National Parkinson Foundation, USA (PI), NPF Center of Excellence, Support Care and Outreach

2013-2018 Michael J Fox Foundation, USA (PI), PPMI – Biological Markers in Asymptomatic carriers of G2019s mutations in the LRRK2 gene

2016-2021 Biogen, USA (PI), Identifying markers of disease in a population at risk for developing Parkinson’s disease.
Using Functional Imaging to Investigate Affective Neuroscience

Positions
Professor, Sackler Faculty of Medicine, Sagol School of Neuroscience
Director, Tel Aviv Center for Brain Function, Tel Aviv Sourasky Medical Center
Clinical Director, Presurgical Brain Mapping Service, Tel Aviv Sourasky Medical Center

Research
Our group has been applying advanced brain imaging techniques, including functional magnetic resonance imaging (fMRI), Diffusion Tensor imaging (DTI) intracranial and scalp electroencephalography (EEG) and magnetic encephalography (MEG) to study mental processing in the healthy and diseased human brain. Our research theme has focused on portraying the neural underpinnings of individual emotional experience and expression. The accumulative work in affective neuroscience in the last two decades has paved the way for promising translations of imaging technologies for the cure to mental suffering. For example, the lab has pioneered the development of a new real-time imaging approach for the non-invasive identification of "neural finger-prints" that can reliably depict deep limbic areas through trans-modalities’ learning computation (e.g. from fMRI to EEG). This new method enables accessible bed-side Brain Computer Interface procedures aimed to alleviate and/or prevent stress related psychopathologies.

Publications


and sufficient for transition into pre-sleep induced by EEG neurofeedback. *NeuroImage*, 97, 19-28.


Grants

2011-2018 Representative of TAU for the competition on Israel-Centers of Excellence Program in Advanced Cognitive Science. Awarded the joint center (with the Weizmann Inst and Bar Ilan University): The Recursive Mind: From Perception to Memory and Back

2013-2016 BRAINTRAIN: FP7 Health Program (Consortium partner, leader of a WP), Taking Imaging into the Therapeutic Domain: Self-regulation of the brain systems for mental disorders

2016-2018 Israeli Ministry of Science and Technology. A specific, non-invasive, closed loop neuromodulation system for treatment of chronic pain in a natural environment

Investigating the Vestibular and Ocular Motor Systems

Positions
Professor, Department of Neurology, Sackler Faculty of Medicine.
Director, Dizziness and Balance Disorders Service, Department of Neurology, Meir Medical Center
Head, Machado-Joseph Disease (MJD) Clinic (recognized by the Israel Ministry of Health)

Research
The vestibular system stabilizes gaze during head movements, ensuring clear vision of the seen world. This is mainly accomplished by the vestibulo-ocular reflex (VOR), which produces compensatory (opposite) eye movements for head rotations. Then, eye position in space is held steady and images do not slip on the retina. During everyday life activities, the vestibular system acts with the optokinetic and visual fixation systems to hold images of the seen world steady on the retina; while saccades, smooth pursuit and vergence eye movements obtain and hold images of objects of interest on the fovea. Moreover, in everyday life activities, the vestibular, visual, ocular motor, proprioceptive and motor systems work together to reach exquisite balance, equilibrium and perform accurate motor tasks. Interaction between sensory (vestibular, visual, proprioceptive) and motor (eye movement, locomotion) systems; i.e sensory-motor integration is essential to maintain balance, equilibrium and perform accurate motor tasks including locomotion. Our Vestibular and Eye Movement Laboratory is fully equipped with modern systems for measuring vestibular function, all type of eye movements and balance and gait function.

Our three major ongoing interest and research projects include:
1. Vestibulo-Ocular Reflex (VOR) and eye movement abnormalities as possible biomarkers of Spinocerebellar Ataxia Type 3.
Spinocerebellar Ataxia Type 3 (SCA-3), also known as Machado-Joseph Disease (MJD), is an autosomal dominant neurodegenerative disorder for which genetic testing can reveal those at risk for developing the disease. Quantitative measures that would identify pre-symptomatic gene carriers at the threshold of clinical diagnosis would be extremely valuable in early diagnosis, tracking disease progression, and assessing treatment. This is a crucial subject of investigation not only in SCA-3 but also in other neurodegenerative diseases. Eye movement abnormalities have been reported as reliable neurophysiologic biomarker and even proposed as “a window into disease prevention.” By using bedside vestibular tests and laboratory recording of eye movements, we have described severe VOR deficit and different saccadic abnormalities in patients with SCA-3. Our specific aim is to investigate if VOR and eye movements can be used as biomarkers to quantify the appearance and progress of SCA-3 even pre-symptomatically.

2. Dizziness, vertigo, balance: Clinical and basic research
Dizziness, vertigo and problems with balance are among the most frequent complaints at all ages. Our current research focuses on the following topics:
The contribution of VOR impairment to the perceptual and emotional experience of blurred vision, dizziness and oscillopsia (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).
The relationship between vestibular pathology and the development of anxiety, balance impairment and spatial disorientation (in collaboration with the School of Psychological Sciences, Psychobiology Research Unit, Tel Aviv University).
The evaluation of a novel specs device with stabilizing marks on the peripheral visual field to alleviate dizziness.
The search for novel physical and virtual reality strategies to improve balance and alleviate dizziness.
3. Cerebellar Disorders

As our Neurology Department at the Meir Medical Center houses the only Machado-Joseph Clinic in Israel recognized by the Ministry of Health, we therefore have access to most MJD sufferers and many other cerebellar patients in the country and focusing on the following research topics:

Respiratory function in cerebellar degeneration.

Autonomic nervous system function and emotional features in cerebellar diseases.

Cognitive and behavioral changes in cerebellar degeneration.

Physical and pharmacological treatment of cerebellar disorders.

Language and reading difficulties in cerebellar diseases (in collaboration with the School of Education, Tel Aviv University).

The role of the cerebellum in the hedonic experience of music (in collaboration with the Functional Brain Center, Wohl Institute for Advanced Imaging, Tel Aviv Sourasky Medical Center).

The mutational origins of Machado-Joseph Disease in the Jew Yemenite subpopulation in Israel (in collaboration with the IBMC - Institute of Molecular and Cell Biology, and IPATIMUP – Institute of Pathology and Molecular Immunology of University of Porto, Portugal).

Publications


Caspi A, Zivotofsky AZ, Gordon CR. Multiple saccadic abnormalities in spinocerebellar ataxia type 3 (SCA-3) can be linked to a single deficiency in velocity feedback. Invest Ophthalmol Vis Sci 2013; 54: 731-738.


Neurogenetics Syndromes

Positions
Professor, Psychiatry & Sagol School of Neuroscience
President, Israel Society of Biological Psychiatry
Director, The Behavioral Neurogenetics Center
Director, The Child Psychiatry Division, Sheba Medical Center

Research
We have been studying neurogenetics syndromes - 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome for two decades. 22q11.2DS is the most common known microdeletion syndrome. The 22q11.2DS phenotype consists of cleft and cardiovascular anomalies and immunological abnormalities. Additionally, all individuals with 22q11.2DS cope with cognitive deficits and one-third of the patients develop schizophrenia-like psychotic disorders and many manifest with autism spectrum disorder. We study the pathways leading to psychosis, autism and cognitive deficits in 22q11.2DS. Our focus is identifying cognitive, behavioral and psychiatric risk factors associated with the evolution of psychosis in 22q11.2DS. We also study molecular and immunological pathways to psychosis and to the behavioral and cognitive phenotype of the syndrome using blood samples and animal models. We collaborate with many centers from US and Europe under the umbrella of the International Brain and Behavior Consortium funded by the NIMH.

Publications


Reviews


Grants
2013–2017 NIMH
2017–2020 National Institute of Psychobiology
Investigating the Association between Drug Use and Psychiatric Disorders

Positions
Senior Lecturer, Sackler Faculty of Medicine
Physician-in-Chief, Lev Hasharon Medical Center

Research
We study the association between drug use and psychiatric disorders. We harness epidemiological and clinical approaches aimed at improving the understanding of mental health related aspects of drug use.

Specifically, much of our current research focuses on psychiatric outcomes of cannabis use. In recent decades, there has been a significant increase in the prevalence of cannabis use, as well as in the potency of cannabis consumed. This holds several medical and social implications, some of which are yet unclear. We focus on exploring mental-health related outcomes of cannabis use by conducting epidemiological research using large population-based samples and analysis of “big-data” based on internet-based sources. In addition, we explore specific neuro-biological and neurocognitive aspects of heavy cannabis use by utilizing advanced functional technologies such as Transcranial Magnetic Stimulation (TMS). Our studies regarding the effects of cannabis on depression and anxiety are commonly cited in World Health Organization publications, and our reports on mental-health related aspects of medical marijuana and prescription opioids have served as a basis for national policy papers.

Publications


Functional Neuroimaging Laboratory

Positions
Head, Functional Neuroimaging Laboratory, Department of Diagnostic Imaging, Sheba Medical Center, affiliated to Sackler Faculty of Medicine
Researcher, Sagol Neuroscience Center, Sheba Medical Center.

Research
The Functional Neuroimaging Lab Studies brain pathologies, in particular the way the brain reorganizes due to brain injury (TBI). We use various tools including: advanced structural MRI and fMRI protocols using tailor-made fMRI tasks to examine the deficits after TBI. We apply also extensive neuropsychological batteries in order to investigate cognitive impairments. Furthermore, we examine symptoms and emotional status using validated questionnaires and scales. This data is integrated and analyzed to identify networks and patterns which will further our understanding of neuropathology and neuronal reorganization. Our research aims to improve the prediction of brain pathology’s progression, to plan medical and rehabilitative interventions for the well-being of patients with brain diseases and head injuries.

Publications

The relation between severity of TBI and working-memory brain activation during an n-back task. Maximum intensity projections in three orthogonal views of the brain (from left to right: sagittal, coronal and axial) depict areas of significant activation (p<0.005, k>100) in a one-tailed-t statistic contrasting MR signal increases. The color scale shows t-values to the right. a, c: 2->0-back= high WM load; b, d: 2->1-back= WM load increase; CTRL= controls; mTBI= mild TBI; msTBI= moderate-severe TBI. mTBI patients further activated bilateral prefrontal and left parietal regions. msTBI patients revealed greater activation than controls in frontal, parietal and limbic regions.

Grants

2016-2017 Monitoring brain changes following a traumatic brain injury in structure and functioning through clinical testing, neuropsychological, anatomic and functional MRI and EEG analysis; Principal-Investigator; Magneton Grant.

The Role of Neuroinflammation and Neurocoagulation in the Pathophysiology of Neurological Disorders

Positions
Senior Lecturer, Sackler Faculty of Medicine
Senior Neurologist and Neurophysiologist, Department of Neurology, Chaim Sheba Medical Center, Tel HaShomer

Research
Our research focuses on the understanding of the role of coagulation factors, as well as their interaction with neuroinflammation in the physiology and pathophysiology of the nervous system. We have recently discovered that thrombin, the factor that ignites the coagulation cascade, is synthesized in the brain and has a fundamental role in regulating synaptic plasticity. However, we have also shown that high concentrations of thrombin (that reach the brain upon haemorrhage) can cause seizures and epilepsy. Our research has contributed in designing novel compounds that are currently being tested in order to counteract the pathogenic actions of thrombin in the brain. We apply cutting-edge technologies including mouse genetic tools, behavioural analysis, electrophysiology and molecular and cellular biology.

Publications

The coagulation pathways play fundamental roles in the physiology and pathophysiology of the nervous system. Immunofluorescence analysis reveals the expression pattern of thrombin in the hippocampus.


Schuldt G., Galanis C., Strehl A., Schiener S., Hick M., Lenz M., Deller T., **Maggio N**, Vlachos (2016) Inhibition of Protease-Activated Receptor 1 (PAR1) does not affect dendritic homeostasis of cultured...


Lenz M., Ben Shimon M., Vlachos A.* and Maggio N.* (2016) Pilocarpine- induced status epilepticus is associated with changes in the actin-modulating protein synaptopodin and alterations in long term potentiation in the mouse hippocampus. Neural Plasticity, accepted, in press. *Equal contributors and last authors.


Grants

2016 – 2018 German Israeli Foundation (GIF), Role of Thrombin and Protease-Activated Receptor (PAR-1) in hyperexcitable neuronal networks: from seizures to maladaptive plasticity

2016-2018 Israeli Ministry of Economy – The Office of Chief Scientist – Kamin Grant Program, Development of novel peptides for the therapy of neuroinflammation
Prof. Shimon Rochkind, MD., Ph.D.
Research Center for Nerve Reconstruction (RCNR)
Division of Peripheral Nerve Reconstruction
Department of Neurosurgery
Tel Aviv Sourasky Medical Center

Positions
Associate Professor, Sackler Faculty of Medicine
Director, Division of Peripheral Nerve Reconstruction, Tel Aviv Sourasky Medical Center

Research
The research group is involved in projects targeting improvement in nerve reconstruction and rehabilitation from several aspects, aiming at the creation of innovative treatments to both peripheral nerve (PN) and spinal cord (SC) injuries. RCNR major projects include:

Creation of artificial nerve for nerve reconstruction using the innovative Guiding Regenerative Gel (GRG) to improve and accelerate regeneration of peripheral nerve injury (PNI) with massive defect. The GRG is a special milieu that was developed in collaboration with Prof. Zvi Nevo from Tel-Aviv University, Israel. The unique composition of GRG has recently been shown to be as efficient as autologous nerve graft, promoting axonal growth and sprouting without dependence on the addition of any external growth factors. In a short-term in vivo study it was shown that GRG loaded into a conduit promoted axonal sprouting of nerve cells and enabled the regeneration of a 15mm long nerve gap in rats,
which is not possible when bridging with an empty conduit (regeneration of up to 7mm). Therefore, the GRG allows a simpler procedure with less side effects, since its implantation does not involve other nerve origin, sensation loss or cosmetic defect as the "gold standard" treatment, therefore, GRG can provide a promising simple off the shelf solution for clinical use for complete PNI.

Based upon our encouraging results with the GRG, which shed light on the utilization of this innovative composite implant to bridge a gap, we postulate to improve this approach and attempt reconstruction of experimental complete SCI. Since astroglial scarring is one of the main obstacles for axonal growth and therefore spinal cord recovery, we have developed an Antigliotic Guiding Regenerative Gel (AGRG) which contains Guiding Regenerative Gel (GRG), and was proven to promote axonal sprouting and survival as well as antgliotic agents, which presented in vitro highly significant antgliotic activity, while reducing the amount of GAGs by more than 84%, thus inhibiting scar growth barrier formation in the site of injury.

The effect of laser phototherapy (low power laser irradiation) was explored on neuronal cells and peripheral nerve. In nerve cell cultures, laser irradiation significantly accelerated axonal sprouting (Rochkind et al., Lasers Surg Med, 2009). Animal studies in a model of incomplete peripheral nerve injury showed that laser phototherapy has an immediate protective effect, maintains functional activity of the injured nerve, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord and significantly increases axonal growth and myelination. In a model of complete peripheral nerve injury with segmental loss, the laser-treated group showed more intensive axonal growth and morphological reconnection compared with the control group (Rochkind. Neurosurgical Focus, 2009). Recently, we found that in early stages of muscle atrophy, laser phototherapy may preserve the denervated muscle by maintaining creatine kinase activity and the amount of acetylcholine receptors. (Rochkind and Shainberg, Photomed Laser Surg, 2013). The current projects are intended to test and validate the beneficial effect of laser phototherapy on severely injured PN with a view to move forward to clinical study.

Publications


Rochkind S, Nevo Z. Recovery of peripheral nerve with massive loss defect by tissue engineered guiding regenerative gel. BioMedical Research International; 2014:327578; 2014.


<table>
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<th>Grants</th>
<th>Description</th>
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<tbody>
<tr>
<td>2017-2018 The Colton Family Next Generation Technological Institute</td>
<td>Advanced Reviving Matrix – Anti-Gliotic Guiding Regenerative Gel (AGRG) for Reconstruction of Severely Injured Spinal Cord.</td>
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<td>and The Miles Nadal institute for Technological Entrepreneurship</td>
<td></td>
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<tr>
<td>2017-2019 German Israeli Foundation</td>
<td>Development of GRG advanced chitosan nerve guides – NerveMatrix.</td>
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<tr>
<td>2017-2018 Israeli Ministry of Defense</td>
<td>On-site treatment of crushed muscle due to prolonged pressure, aimed at decreasing damage extent and rapid regaining of physical competence.</td>
</tr>
<tr>
<td>2016-2017 Dr. Herman Schauder Memorial Endowment Fund, the Sackler</td>
<td>Innovative Guiding Regenerative Gel (GRG) for Functional Recovery following Peripheral Nerve Injury with Massive Nerve Loss.</td>
</tr>
<tr>
<td>Faculty of Medicine, Tel Aviv University;</td>
<td></td>
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<tr>
<td>2016-2017 Israeli Ministry of Defense</td>
<td>Improvement and acceleration of muscle and nerve recovery after peripheral nerve injury.</td>
</tr>
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The Neuronal Encoding of Human Speech

Positions
Senior Lecturer, Sackler Faculty of Medicine and Sagol School of Neuroscience
Senior Researcher and Neurophysiologist, Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center (“Ichilov”)

Research
We study the neuronal representation of speech production, perception and imagery in the human brain. We explore the acoustic, phonetic and phonological levels, and the deterioration in speech due to neurological disorders, for example in Parkinson’s disease. Our main focus is the encoding of speech features by single neurons (for example, see Figure 1). We also aim to develop brain-machine interfaces for restoring speech faculties in completely paralyzed persons by decoding their neuronal activity (i.e., inferring speech contents solely from spiking activity).

We take advantage of a unique clinical “opportunity” to work with neurosurgical patients undergoing implantation of electrodes for clinical reasons. Experiments are conducted intra-operatively with awake patients with movement disorders or in the ward, with epilepsy patients. Understanding the neuronal representation of human speech is essential for understanding the underlying mechanisms of speech disorders, for the development of new

Medial–frontal units that we have discovered, with high specificity to vowels. Raster plots and peri-stimulus time histograms of five units (rows) during the articulation of the five vowels a, e, i, u and o (columns). The response of each unit is specific to one or two vowels only. Red vertical dashed lines indicate speech onset. All vertical scale bars correspond to firing rates of 20 spikes/s (from: Tankus et al., Nature Communications, 2012).
therapeutic procedures, and for restoration of the ability to speak. The research thus bears enormous potential to greatly improve the quality of life of millions of people around the globe.

**Publications**


**Grants**


Rabbit retinal section following intravitreal injection of ziv-aflibercept.
Credit: Prof. Anat Lowenstein
Investigating Age-Related Macular Edema and Diabetic Retinopathy

Positions
Professor of Ophthalmology, Sackler Faculty of Medicine
Assistant Dean, Sackler Faculty of Medicine
Head, Department of Ophthalmology
Incumbent, Sydney A. Fox Chair in Ophthalmology
Editorial board member: Retina, European Journal of Ophthalmology, Ophthalmologica, Graefes for Archives and Research in Ophthalmology
Associate editor, International Journal of Retina and Vitreous
Editor in Chief, Case Reports in Ophthalmology
Chairperson, National Ethics Review Board Committee, State of Israel Ministry of Health
Board member, Israeli Council of Surgery and Anesthesia
Chair, Academia Ophthalmologica Internationalis
General Secretary of the Board, Euretina Society
International Committee Member, Macula Society

Research
Prof. Loewenstein’s main research area is early detection of macular degeneration, including development of novel technology, which is approved and used now in the USA, as well as development of automated techniques for interpretation of ophthalmic imaging. She has vast interest in toxicity to the retina of drugs. In addition, she is developing devices for slow release devices for drug administration in the retina. One of the latest toxicity studies was that of the toxicity of ziv aflibercept, a drug that can be potentially used for the treatment of ascular retinal disease was evaluated and shown to have local toxicity. This is one example of a toxicity study with significant clinical correlation.

Publications


Neurodegeneration in the Eye

Positions
Dr. Ygal Rotenstreich, M.D.
Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer
Senior Lecturer, Sackler Faculty of Medicine, Tel Aviv University
Member, Sagol School of Neuroscience, Tel Aviv University

Dr. Ifat Sher, Ph.D.
Lab Manager & Senior Researcher

Chair, Association for Research in Vision & Ophthalmology (ARVO) Ethics and Regulations in Human Research Committee
Founder and Medical Director, Epitech-Mag Inc. Israel
Founder and Medical Director, EVERADS Inc. Israel
Medical Advisor, Accutome, Halma Inc. USA
Member, Sheba Medical Center Patent Committee

Immunofluorescence analysis (A), histopathology analysis (B) and MRI (C) for monitoring stem cell therapeutic effects in animal models. Multicolor OCT imaging (D) and chromatic multifocal pupilloperimetry (E) for objective structure & function clinical assessment. Nanotherapy for stem cell modulation (F).
Research

We lead basic science, translational medicine and clinical studies in an attempt to solve the unmet needs in neurodegenerative diseases in the eye and brain. The research focuses on clinical trials, basic science and translational medicine aimed at development of novel treatments and diagnostic tools for retinal degeneration and brain pathologies (such as Alzheimer disease and increased intracranial pressure) using a multidisciplinary approach in an attempt to discover treatments and develop drug delivery and diagnostic platforms for studying these leading incurable diseases.

Current research projects include:

- Development of novel treatments for neuroretinal degeneration
- Development of innovative diagnostic tools for macular, retinal degeneration and optic nerve diseases
- The eye as a window to the brain – using retinal structure and function measurements as novel early and objective biomarkers for brain neurodegeneration diseases (e.g. Alzheimer’s disease and multiple sclerosis), brain injuries and brain tumors.

Publications


Rotenstreich Y, Tzameret A, Kalish SE, Belkin M, Meir A, Treves AJ, Nagler A, Sher I. A novel system for minimally invasive transplantation of bone marrow derived stem cells as a thin layer in the subretina and...


**Grants**

2015-2017 Drug delivery of advanced therapies into the posterior pole, Moxie Foundation

2015-2017 Microglia-targeted pharmacotherapy - a new therapeutic strategy for treating neuro-retinal degeneration, National Network of Excellence in Neuroscience, TEVA

2016-2017 A Novel Portable Chromatic Multifocal Pupillometer for objective triage & assessment of head injuries, Israel Defense Force Health Research Grant

2016-2017 Determination of Physical Parameters Relevant to Ophthalmic Lasers, Israel Defense Force Health Research Grant

2016-2018 The association between retinal and medial temporal lobe structure and function in people with high risk for Alzheimer disease National Network of Excellence in Neuroscience, Israeli Science Foundation (ISF)

2016-2018 Retinal structure and vasculature measures as novel objective biomarkers for Alzheimer diseases, National Network of Excellence in Neuroscience, TEVA
Public Health
Positions
Head, Epidemiology & Database Analysis Department, Maccabi Institute for Research & Innovation, Maccabi Healthcare Services
Associate Professor, Epidemiology & Preventive Medicine Division, School of Public Health, Tel Aviv University
Adjunct Investigator, Radiation Epidemiology Branch, Division of Epidemiology and Genetics, National Institute of Cancer, National Institutes of Health, Bethesda (MD), USA
Head, Academic Department of Public Health, Medical Division. Maccabi Healthcare Services

Research
Our primary research interests focuses on the use of Maccabi’s large database to examine multiple dimensions of health care quality, including safety (e.g. adverse effects of IVF, renal effects of chronic medications), efficacy and effectiveness of healthcare technologies (e.g. glycemic control and outcomes in patients treated with new generation therapies for diabetes), medical and economic burden of chronic diseases and health events (e.g. congestive heart failure, hepatitis C infections) as well as pharmacoepidemiology studies such as medication adherence studies (e.g. tamoxifen in breast cancer patients) and pleiotropic effects (e.g. statins). Our other interests include health effects of low dose ionizing radiation and specifically cancer and cataract.

Publications


Lutski M, Shalev V, **Chodick G**. Continuation With Statin Therapy and the Risk of Primary Cancer: a Population-Based Study Preventing Chronic Diseases. 2012;9:E137.


Rabinowich L, Steinvil A, Leshem-Rubino E, Berliner S, Zeltser D, Rogowski O, Shalev V, Raz R, Chodick G. Adherence to Statins is associated with reduced incidence of idiopathic venous thromboembolism: real-life data from a large healthcare maintenance organization 8:1817-1821


Eshel N, Raz R, **Chodick G**, Shalev V, Guindy M. The Invisible Patient: Characteristics of Elderly People


Simon Tuval T, Triki N, Chodick G, Greenberg D. Determinants of cost-related non-adherence to medications among chronically ill patients in Maccabi Healthcare Services, Israel. Value in Health Regional Issues 2014; 4: 41-46


Chodick G, Almog M, Ashkenazi A, Sella T. Rotavirus Immunization and Type 1 Diabetes Mellitus: A Nested Case-Control Study. Pediatric Infectious Diseases 2014; 6:147-149.


Leibovitz E, David N, Ribitzky-Eisner H, Abo Madegam M, Abuabed S, Chodick G, Maimon M, Fruchtmann Y. The Epidemiologic, Microbiologic and Clinical Picture of Bacteremia among Febrile Infants and Young Children Managed as Outpatients at the Emergency Room, before and after Initiation


Grants
2016–2017 Co-PI, Israel Cancer Society, Adherence with breast cancer therapies
2016–2017 Co-PI, Israel Ins. Health Policy, Effectiveness of generic med
2016–2017 Co-PI, BSF, CT in testicular cancer
Using Medical Databases for Personalized Medicine

Positions
Head, Maccabi Institute for Research & Innovation, Maccabi Healthcare Services
Associate Professor, Epidemiology & Preventive Medicine Division, School of Public Health, Tel Aviv University
Independent family practice partnership clinic, Rosh Haayin

Research
The emergence of precision medicine technologies has allowed medical scientists to address complex questions which necessitate very large datasets and patients’ numbers. Unlike traditional methods such as randomized trials, the richness of very large sets of data enables more rapid advance toward personalized medicine. At the Maccabi Institute for Research & Innovation, we utilize large real-world databases to investigate clinical issues for better provision of care and improved outcomes. In addition to traditional and pragmatical clinical trials, we conduct multiple observational analysis using advanced data platform to enable data science studies based on Maccabi’s database of 2.5M members’ medical files. One example for personalized medicine is our newly developed method for identifying individuals at increased risk of harboring colorectal cancer by analyzing their complete blood counts records. We have developed a computational model using a large derivation dataset of over 450,000 Israeli individuals and validated it on 2 separate and independent datasets of primary care patients, consisting of over 139,000 Israeli and over 25,500 UK individuals. Our approach applies novel methods both in feature generation (where we use a set of linear models to handle sparse and irregular measurements along time) and in model construction (where we combined 2 tree-based models – RF and Gradient Boosting). We showed that our approach can detect 50% of CRC cases 3–6 months before diagnosis at 88% specificity in the Israeli dataset and 94% specificity in the UK dataset. The system is already successfully implemented in routine practice at Maccabi.

Publications


young children following the introduction of universal rotavirus vaccination in Israel. Eurosurveillance 2015;20


Goldstein D, Chodick G, Shalev V, Thorsted BL, Elliott L, Karasik A. Use of Healthcare Services Following Severe Hypoglycemia in Patients with Diabetes: Analysis of Real-World Data. Diabetes Therapy


Archives of Osteoporosis 2015;10:
Mouse oocyte (Fyn – green), Actin – red). Credit: Mattan Levi, Ruth Shalgi
Folliculogenesis and Ovulation in the Human Ovary – Fertility Treatments and Control

Positions
Associate Professor, Obstetrics and Gynecology, Sackler Faculty of Medicine
Senior Physician, IVF Unit
Director Reproduction Laboratory, Sheba Medical Center
Lab Director
Dr. Yuval Yung, Ph.D.

Email: yuval.yung@sheba.health.gov.il

Research
Our laboratory’s aim is the molecular characterization of the ovulatory cascade in the human ovary. We undertook to systematically identify novel ovulation-associated genes. Differentially expressed candidate genes (n = 1746) were identified by comparing the transcriptome of cumulus granulosa cells from compact pre-ovulatory germinal vesicle (GV) cumulus oocyte complexes with those of expanded post-ovulatory Metaphase II COCs. We assumed that differentially expressed genes likely serve as regulators of ovulation, cumulus expansion, and/or oocyte maturation. To complete the identification of factors involved in the ovulatory process, we generated a library of global miRNAs involved in this process, and by bioinformatics tools link the ovulatory miRNA library with the mRNA library. The bioinformatics analysis enables us to identify new regulatory mechanisms responsible for the oocyte maturation process and ovulation.

The resulting database provides unprecedented insight into the processes and pathways involved in follicular maturation and ovulation. This effort led us to identify and characterize several new genes involved in the human ovulatory process such as sFRP4, ADAMTS-1, Decorin and Lumican. Recently, prompted by the observation that prostaglandin transporter (PGT) constitutes a highly expressed peri-ovulatory transcript, we set out to investigate the physiological role of this key transporter protein in the ovulatory process. We were able to show that PGT is an indispensable mediator of ovulation, the inhibitors of which may constitute potential novel candidates for non-hormonal contraception (Science Translational Medicine, 2016).

These studies will contribute significantly to the understanding of the complex process of ovulation in

![Diagram](image-url)
human which is central to the reproductive processes. The implications of improved understanding of this process may contribute to further development of strategies for in vitro maturation of oocytes and follicles, improve IVF success rates especially in difficult clinical conditions. Genes that their expression levels correlate with oocyte clinical outcome may contribute to our understanding of infertility conditions such as anovulation, and development of novel strategies for fertility control.

Publications


Fertility Preservation Research and Clinical Center

Positions
Fertility Preservation Center, Reproduction IVF, Division of Obstetrics and Gynecology, Sheba Medical Center and Tel Aviv University.

President, International Society for Fertility Preservation (ISFP) http://www.isfp-fertility.org/

Research
Our research center is specialized in fertility preservation. We have a fully equipped basic research laboratory, together with a large clinical database with a significant number of incoming patients. This makes our research center unique for high quality basic research with clinical relevancy. Our research focuses on:

- Ovarian follicle research and the biological clock.
- Cryopreservation / transplantation of ovarian tissue and IVF.
- The effects of toxic agents and chemotherapy on reproduction and gametes.
- Modalities and agents that protect the gametes and prevent toxic damage.
- Genetic injury to the gametes.
- Methods to detect cancer cells in tissue.
- Endometrial receptivity.
- Interpreting cancer patients’ information regarding endocrine, reproductive and psychological effects.

Publications


An artist’s view of how single-cell clones represented by a specific color emerge during kidney development, maintenance, and regeneration. Credit: Dekel Lab, Pediatric Stem Cell Research Institute, Sheba Medical Center.
Prof. Benjamin Dekel, M.D., Ph.D.
Division of Pediatric Nephrology, Pediatric Stem Cell Research Institute, Edmond and Lily Safra Children’s Hospital, Sheba Medical Center, Sackler Faculty of Medicine

From Developmental Biology to Normal and Cancer Stem Cells to Novel Therapeutics

Positions
- Head, Pediatric Stem Cell Research Institute, Sheba Medical Center
- Director, Division of Pediatric Nephrology, Sheba Medical Center
- Associate Professor, Dept. of Pediatrics, Sackler Faculty of Medicine
- Adjunct Faculty, Dept. of Human Molecular Genetics & Biochemistry, Sackler Faculty of Medicine
- Member, American Society of Clinical Investigation
- President, Israel Stem Cell Society

Research
Our laboratory takes a multi-disciplinary approach including genetics, genomics, molecular biology, biochemistry, and the development of preclinical human-mouse models to cast light on fundamental problems of kidney developmental biology, tissue regeneration, and cancer; while, at the same time, holding promise for novel disease therapies. Our central hypothesis is that normal and transformed tissue stem cells drive these processes and therefore we aim to discover such cells and study their molecular mechanisms. In the field of human kidney development and pediatric renal cancer (Wilms tumor), we have pioneered the identification and isolation of normal and malignant renal stem/progenitor cells and have shown how these novel cell types are of relevance to human disease; on one hand utilization of the normal stem cells in tissue repair and regeneration and on the other hand development of targeted therapy against cancer stem cells and tumor eradication. These bench discoveries have been fundamental to translation to bedside; our approach for tumor stem cell eradication has already sparked a multicenter clinical trial for the treatment of patients with relapsing Wilms’ tumors.

Publications


The cover illustration shows how single-cell clones emerge during development, maintenance, and repair to generate a multicolored kidney. Dekel and colleagues report that continued growth of the mammalian kidney in adulthood is performed by lineage-restricted clonal progeny that continuously add new epithelial cells to each segment of the kidney and are responsive to Wnt signaling. Lineage-restricted progenitors are also observed in development after renal epithelial induction and during acute renal injury. Rainbow mice, which express one of four alternative fluorescent reporters in each cell, allow genetic lineage tracing of individual clones.
Harari-Steinberg O, Pleniceanu O, Dekel B. Selecting the optimal cell for kidney regeneration: fetal, adult or reprogrammed stem cells. Organogenesis 2011;7(2).


Reviews and chapters


Laboratory for the Research of Skin Disease

Positions
Senior Lecturer, Sackler Faculty of Medicine
Director, Pediatric Dermatology Service, Lili Hospital, Sheba Children’s Edmond Safra & Medical Center
Lab Manager
Dr. Gil Leichner Ph.D.

Research
We study skin diseases with a focus on angiogenesis and lymphangiogenesis. Deficiency in development or function of the vascular or lymphatic vasculature causes various anomalies in humans, and active angiogenesis and lymphangiogenesis play a significant role in tumor metastasis. The presence of vascular anomalies can cause emotional and social problems. Moreover, some malformations are painful or even life-endangering. Current treatments for these diseases do not achieve optimal results. The goal of my research is to isolate and characterize the endothelial cells, the major cellular component of the vascular malformations in order to develop targeted therapy for these lesions. We apply cutting-edge technologies including molecular biology, and microarray analysis to characterize the molecular paths that regulate the endothelium development. Other areas studied in the lab are editing in psoriasis and Cutaneous graft versus host disease.

Isolation and characterization of endothelial cells from lymphatic malformations. FACS (A) and immunofluorescence analyses shows pure lymphatic endothelium phenotype with reduced expression of the differentiation marker CD31.
Publications


hESCs in Development, Genetic Disorders and Cell Therapy

**Positions**

Dalit Ben Yosef  
Director, IVF Lab and Wolfe PGD-Stem Cell Lab, Tel Aviv Sourasky Medical Center  
Professor, Department of Cell and Developmental Biology, Sackler Faculty of Medicine

**Research**

The Wolfe PGD-Stem Cell Lab focuses on studying issues related to early embryonic and developmental processes, genetic disorders and different aspects of cell therapy using our unique collection of PGD-derived human embryonic stem cells (hESCs).

We derive hESCs directly from affected embryos, which are obtained as a by-product of the preimplantation genetic diagnosis (PGD) procedure. PGD is performed for couples at high risk of transmitting a genetic defect and who wish to ensure the birth of a healthy child. It requires in vitro fertilization (IVF), which makes the pre-implantation embryos available for biopsy and single-cell molecular analysis. Following IVF-PGD, embryos diagnosed as being disease-free are transferred into the uterus for implantation, whereas the affected embryos that would be otherwise discarded are used to establish hESC lines that carry the naturally inherited mutations. This setup provides the benefit of efficient coordination between the generously donated affected embryos and the stem cell lab that focuses on researching these very unique samples. By means of these capabilities, we have already established >50 mutant hESC lines associated with 18 different inherited disorders.

These lines make it possible for us to study the molecular and pathophysiological mechanisms underlying the genetic disease of which they were diagnosed. In addition, since we have a large collection of hESC lines derived under the same conditions, we are able to perform different studies on the pluripotent, genetic and epigenetic properties of these cells.

**Publications**

enables determination of the timing and origin of mutational events. Cell Rep 4, 1288-1302.


Grants
2017-2018 Leo Mintz Faculty Grant
2015-2017 Or Shapira Fund
2015-2017 Israel Cancer Research Foundation (ICRF)
2014-2017 Israel Ministry of Health