תכנית מחקר ברפואה ממוקדת אישית
برنامج الطب الشخصي
Israel Precision Medicine Partnership

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PRESS RELEASE

16 RESEARCH PROPOSALS CHOSEN BY THE ISRAEL PRECISION MEDICINE PARTNERSHIP FEATURING UNPRECEDENTED COLLABORATIONS BETWEEN SCIENTISTS AND CLINICIANS, ACADEMIC INSTITUTIONS AND HEALTH CARE ORGANIZATIONS

NIS 60 million in grants awarded in the current application cycle; Total for the first two cycles: NIS 120 million

- The 16 research proposals were selected out of 75 submitted in a wide range of topics related to human biology as applies to medicine.
- The Israel Precision Medicine Partnership (IPMP), launched in Summer 2018, enables the expansion of personalized Precision Medicine research in Israel and will support excellent studies that are expected to lead to major breakthroughs in this field.
- The winning proposals were selected via a competitive process, based on their scientific excellence, by an international committee chaired by the 2006 Nobel Prize laureate in Chemistry, Professor Roger Kornberg of Stanford University.
- The grants for the projects are among the largest ever awarded to Israeli researchers by an Israeli funding body.
- The research will lead to a deeper understanding of human diseases and will advance the implementation of new healthcare approaches.
- The overall IPMP budget, some NIS 210 million, enables funding of four application cycles. The duration of each project is up to four years.
- The research partnership relies on pooled resources from the Council for Higher Education's Planning and Budgeting Committee, the Ministry of Health, the Ministry of Social Equality's Digital Israel Initiative, and philanthropic organizations Yad Hanadiv, and the Klarman Family Foundation (Boston).
- The IPMP program is administered and operated by the Israel Science Foundation.

Professor Yuval Dor, Head of ISF's Life Sciences and Medicine division: "In IPMP's second program cycle, we have witnessed a wealth of outstanding research programs that reflect the scientific depth and spirit of collaboration among researchers and physicians in Israel, and among universities, hospitals, and health funds. We were pleased to have been able to conduct the competitive evaluation process without delay, in spite of disruptions caused by the coronavirus pandemic. The winning proposals are from a range of universities and medical institutions,

address fundamental questions in human health, and are expected to generate important scientific insights and medical applications."

Professor Yaffa Zilbershats, Chair of the Council for Higher Education's Planning and Budgeting Committee: "The IPMP program is a source of pride and satisfaction. By the end of the first cycle, it emerged that the program had exceeded all expectations. The second cycle reinforces this understanding. I am excited to see the content of the winning projects, their scientific quality, and the collaborations between scientists from academia and physicians and researchers from health organizations. There is no doubt that the program will make a huge contribution to advancing research and medicine in Israel and around the world. I thank the members of the Israel Science Foundation (ISF), who rose up to the challenge of evaluating the proposals within the timetables, despite the coronavirus outbreak."

Shai-Lee Spigelman, CEO, Digital Israel, Ministry of Social Equality: "The IPMP program is a significant part of the Digital Health initiative as an engine of growth, positioning Israel at the forefront of the digital health revolution. It demonstrates the tremendous value of the medical information generated in Israel. The outstanding research studies that won the second cycle of the program will expand our understanding of a variety of diseases, and help prevent and treat them. Equally important, they will strengthen the excellent existing collaboration between Israel's academia and health system. This collaboration underpins Israel's excellence in health, and is one of the reasons for Israel's success in battling the first wave of the coronavirus pandemic."

Research in the field of Precision Medicine is based on broad interdisciplinary collaborations, which integrate scientific and medical knowledge, theory, in-depth analysis of medical big data, and extensive experimental work. The winning research projects utilize data from the Israeli healthcare institutions' tissue banks and unique databases, while meticulously protecting patient privacy. Of note is Israel's considerable relative advantage in this field, due to these databases' vast scope and high reliability.

Background and Core Mission of the IPMP Program

Numerous studies conducted in recent years point to the fact that different people suffering from the same disease (such as diabetes, various types of leukemia, breast cancer, Crohn's disease, and others) may have different disease manifestations, including the disease's rate of development, severity, and variability in response to treatment. The Israel Precision Medicine Partnership program focuses on achieving in-depth understanding of the mechanisms responsible for this variations in disease phenotypes among individuals, and strives to advance innovative research that will lead to novel preventive, diagnostic and therapeutic approaches.

The substantial heterogeneity among patients has long been recognized in the medical world, but the understanding of the reasons underlying this variability is still limited. The lack of validated data about the key factors influencing it has made it more difficult to provide an optimal, personalized care for each and every patient.

The IPMP program seeks to address these challenges, by utilizing a wide range of technologies, by multidisciplinary research teams, including physicians, basic researchers, theoreticians, experimentalists, computational biologists, computer scientists and data scientists, engineers, statisticians, epidemiologists, and others.

The program's funding partners are: The Council for Higher Education's **Planning and Budgeting Committee** (PCB), the **Ministry of Health**, the Ministry of Social Equality's **Digital Israel** initiative, and two philanthropic foundations – **Yad Hanadiv** (Israel) and the **Klarman Family Foundation** (USA). The partnership is operated and administered by the **Israel Science Foundation**.

The program will enable Israeli researchers to advance large-scale research projects in fields of human health, which draw extensively on new collaborations between researchers in Israeli institutions of higher education and healthcare institutions, on populations of healthy and ill volunteers, and on big data depositories in hospitals and HMO databases in Israel.

Collaborations between researchers in universities and healthcare institutions significantly advance research capabilities in the field in Israel, and help accelerate the rate of discovery and the potential for implementing new therapeutic approaches, **while positioning Israel as a trailblazer at the forefront of global precision medicine science.**

In September **2019**, the second call for proposals was sent to researchers in the field and **75** research proposals, based on collaborations of exceptional scope and covering a wide range of topics in the areas of human medicine, were submitted. The proposals underwent a comprehensive judging process by international experts and **16** were selected for funding.

In September **2020**, the next call for proposals will be published for the third of the four planned submission cycles.

Due to the Covid-19 pandemic, another grant program was approved in April 2020, for expedited funding of studies focused on curbing this contagious disease. The NIS 14 million program is funded by the PBC and several philanthropic foundations: Yad Hanadiv, the Klarman Family Foundation, the Russell Berrie Foundation and the Wolfson Foundation. The program will be administered by the Israel Science Foundation. Through this dedicated budgeting, the intention is to fund some 30 projects at NIS 180,000–720,000 per study, which will take six months to two years.

New Projects that Received Funding

Following is a list of the 16 selected research proposals, with the researchers' names and specializations, the research topic, and the grant amount:

1. **Research team: Professor Eli Pikarsky**, School of Medicine, The Hebrew University of Jerusalem (Immunology and Cancer Research and Department of Pathology), **Professor Itamar Willner**, The Hebrew University of Jerusalem (Institute of Chemistry), **Dr. Oren Parnas**,

The Hebrew University of Jerusalem (Immunology and Cancer Research), **Professor Rachel Nechushtai**, The Hebrew University of Jerusalem (Plant and Environmental Sciences)

Grant Amount: **NIS 4.2 million**

Project: Nano code – finding the right drug for treating cancer using nano-particles in a patient: A key objective in personalized oncology is identifying the drug-sensitivity profile of a patient's cancer to a wide spectrum of different drugs. In this project, a new method will be developed for the rapid identification of the drug-sensitivity profile of a specific type of ovarian cancer to numerous drugs. The multidisciplinary team brings together scientists from diverse fields, including nanoparticles, nanochemistry, cancer biology, pathology, and systems biology. Using smart, stimulus-responsive nanoparticles, the team will simultaneously screen the ability of multiple drugs to kill cancer cells in vivo.

2. **Research team: Professor Eyal Gottlieb**, Technion – Israel Institute of Technology (Ruth and Bruce Rappaport Faculty of Medicine), **Dr. Yaacov Richard Lawrence**, Sheba Medical Center (Radiation Oncology), **Dr. Keren Yitzhak**, Technion – Israel Institute of Technology (Faculty of Medicine), **Dr. Talia Golan**, Sheba Medical Center (Oncology Institute)

   Grant Amount: **NIS 4.9 million**

   Project: Defining sensitivity and overcoming resistance to PARP inhibition in pancreatic ductal adenocarcinoma using combined genomics and metabolomics tools

   Pancreatic cancer is a malignant disease that typically does not respond well to conventional therapy. Recently, a sub-group of pancreatic cancer patients, in whom the tumors are deficient in a genetic repair mechanism, was characterized. Consequently, these tumors respond better to DNA-damage-inducing drugs. Nevertheless, these tumors also rapidly develop resistance to treatment. By combining genetics and biochemistry, the research will map the metabolic profile of these tumors, in order to decipher mechanisms of resistance to therapy and identify ways to overcome them.

3. **Research team: Dror Sharon**, Hadassah-Hebrew University Medical Center (Ophthalmology), **Eyal Banin**, Hadassah-Hebrew University Medical Center (Ophthalmology), **Shay Ben-Aroya**, Bar-Ilan University (Faculty of Life Sciences), **Shai Carmi**, The Hebrew University (School of Public Health)

   Grant Amount: **NIS 4.2 million**

   Project: Inherited retinal diseases – from the identification of genes and risk factors to a new method of personalized medicine

   Inherited retinal diseases are a group of blinding conditions that lead to drastic reduction in the quality of life of those affected, and also impose a substantial socioeconomic burden on society. While currently there is no effective treatment for the majority of these diseases,

novel therapies, including gene- and cell-based approaches, are now emerging in this field. The research aims to leverage national epidemiological resources and recent developments in personalized medicine to better characterize, diagnose, and treat these diseases. The researchers' hope and expectation is that the results of this initiative will contribute to our understanding of the biology and epidemiology of IRDs, and will open new avenues for improved screening, diagnosis, genetic counseling, prevention, and treatment of inherited retinal diseases.

4. **Research team: Dr. Michael Berger**, The Hebrew University of Jerusalem (Immunology and Cancer Research, School of Medicine), **Dr. Dinorah Friedmann-Morvinski,** Tel Aviv University (Biochemistry and Molecular Biology)

   Grant Amount: **NIS 1.75 million**

   Project: Immunotherapy of glioblastoma with metabolically superior bi-specific CAR T-cells
   Chimeric antigen receptor (CAR) T-cell therapy of glioblastoma has limited success due, in part, to two issues: Antigen escape through a molecular change and metabolic exhaustion of the CAR T-cells due to nutrient insufficiency in the glioblastoma microenvironment. To overcome these obstacles, the researchers will develop bi-specific and metabolically superior CAR T cells that will target two different molecules, and which will be genetically programmed to overcome glucose and oxygen insufficiency. The study is expected to provide a novel approach and practical tools for precision therapy of glioblastomas, and therefore is crucial for the transitioning of CAR T-cells from a promising treatment – to an effective one. The study is conducted in cooperation with the **Sheba Medical Center**.

5. **Research team: Professor Talma Hendler**, Tel Aviv University (School of Psychological Sciences and Sagol Brain Institute, School of Medicine) and the Tel Aviv Sourasky Medical Center (Ichilov), **Professor Noam Shomron**, Tel Aviv University (Edmond J Safra Center for Bioinformatics and Sagol School for Neuroscience, Faculty of Medicine), **Professor Malka Gorfine**, Tel Aviv University (Department of Statistics and Operations Research, School of Mathematics), and **Professor Lior Wolf**, Tel Aviv University (School of Computer Science, Facebook AI Research)

   Grant Amount: **NIS 3.5 million**

   Project: Dynamic risk prediction model for post-trauma psychopathology, based on multi-scale and multi-layered profiling of stress response

   Ubiquitous in our lives, stress affects physical and mental wellbeing. The stress response is multi-layered biological and psychological, and changes through time. Individuals differ in how they react to stress, and there is no way to predict who is going to develop long-term psychopathology. Combining expertise in neuroscience, psychiatry, genetics, statistics, and artificial intelligence, the research team plans to develop a dynamic risk-prediction model for

psychopathology, closely following a traumatic event, and for the development of psychological problems over time. The model will also guide early personalized interventions and improve long-term prognosis. It will provide the basis for similar developments in other psychopathologies in which unfolding in time is critical for characterization and treatment improvement.

6. **Research team: Professor Gil Ast**, Tel Aviv University (Human Molecular Genetics), **Professor Roded Sharan**, Tel Aviv University (School of Computer Science)

   Grant Amount: **NIS 4.9 million**

   Project: Elucidating epigenetic mechanisms that drive autism spectrum disorder and tailoring a personalized treatment

   Autism spectrum disorder (ASD) is highly heritable, but ASD-related variants are often found in unaffected individuals. The researchers identified two genes, highly expressed in ASD, which may modify ASD penetrance since their over-expression in cell line causes? generated genome-wide epigenetic changes, notably of ASD-candidate genes sentence doesn't quite make sense to me; seems to be missing a word] In this study, the researchers will characterize cells from affected and unaffected individuals who share the same ASD variant, and compare epigenetic parameters, splicing patterns, and gene expression profiles. Finally, they will develop a diagnostic tool for ASD using a machine learning approach, and implement a system that modifies DNA methylation of selected targets. The study is conducted in cooperation with the **Ben-Gurion University Autism Research Center**.

7. **Research team: Professor Benjamin Dekel**, Sheba Medical Center (Head, Pediatric Stem Cell Research Institute and Division of Pediatric Nephrology), **Dr. Tomer Kalisky**, Bar-Ilan University (Bioengineering), and **Professor Yair Anikster**, Sheba Medical Center (Head, Metabolic Disease Unit)

   Grant Amount: **NIS 1.75 million**

   Project: Modeling tubulopathies using patient-specific kidney organoids for renal precision medicine – mitochondrial disease-associated Fanconi syndrome as proof of concept

   In this study, urine will be collected from patients, and stem cells isolated from the urine will be expanded and built into kidney micro tissues (termed spheres or organoids) which simulate kidney function in a petri dish. The researchers aim to study mitochondrial diseases that damage the kidneys, by generating organoids from patients' urine, studying defective pathways, and determining which specific drugs can enhance mitochondrial functions and potentially cure mitochondrial disease.

8. **Research team: Professor Ido Amit**, Weizmann Institute of Science (Immunology), **Dr. Moshe Gatt**, Hadassah Hebrew University Medical Center (Hematology), **Dr. Chamutal Gur**, Hadassah

Medical Center, Ein Kerem (Department of Medicine), **Dr. Yael Cohen**, Tel-Aviv Sourasky Medical Center (Hematology) and Tel-Aviv University (Sackler Faculty of Medicine).

Grant Amount: **NIS 4.2 million**

Project: Personalizing multiple myeloma prognosis and treatment: advanced single-cell genomics analysis of the dynamics of tumor-immune crosstalk

Multiple myeloma is the second most prevalent blood cancer worldwide, which, despite tremendous improvement in treatment, remains incurable. The research study will provide clinicians with new and powerful molecular tools for early disease detection, predicting treatment response, and for developing novel treatments for multiple myeloma.

9. **Research team: Professor Yoram Reiter**, Technion – Israel Institute of Technology (Biology), **Professor Myriam Ben-Arush,** Rambam Health Care Campus (Pediatric Hemato-oncology), and **Dr. Adi Shapira**, Rambam Health Care Campus (Pediatric Hemato-oncology)

   Grant Amount: **NIS 1.925 million**

   Project: Overcoming Resistance to CAR-T cell Therapy due to Antigen Loss or Modulation by New Chimeric Receptors Targeting Intracellular-derived HLA Peptidome

   The use of autologous engineered T cells carrying a chimeric antigen receptor (CAR) directed against surface antigens expressed on cancer cells has shown marked efficacy in patients with refractory hematological malignancies. However, resistance to CAR T therapy with subsequent relapse attributable to antigen loss was observed in 60% of patients and remains an unmet challenge. The approach of this study is to exploit another pool of targets, which is naturally utilized by the immune system to differentiate between self and non-self; specific peptides bound to class I major histocompatibility complex (MHC) proteins to generate peptide-MHC complexes presented on the cell surface. Disease-specific class I MHC/peptide targets will be targeted with TCR-like antibodies, which mimic the TCR specificity. The TCR-like antibody approach combines two main advantages of the immune system: The fine specificity of T cells, which use the MHC internal surveillance mechanism to detect cells that express any foreign or abnormal protein, and the biological and pharmacological properties of an antibody that is not susceptible to most of the tumor regulatory influences that limit T cells. The new strategy with TCR-like antibody-based targeting CD19-derived peptide-HLA complex (pCD19) will be tested as a proof-of-concept and evaluated for the potential of this approach to restore functional outcome in CD19 negative relapse. The research may lead to a new family of therapeutic methods for cancer and additional diseases.

10. **Research team: Dr. Ori Avinoam**, Weizmann Institute of Science (Biomolecular Sciences), **Dr. Neta Regev-Rudzki**, Weizmann Institute of Science (Biomolecular Sciences), **Professor Ziv Gil**, Rambam Health Care Campus, Rappaport Institute, Technion – Israel Institute of Technology, **and Dr. Amnon Bar-Shir**, Weizmann Institute of Science (Organic Chemistry)

Grant Amount: **NIS 1.75 million**

Project: The Delivery Mechanism of Tumor-Derived Extracellular Vesicles

The research will focus on understanding the delivery mechanism of tumor-derived extracellular vesicles, which are membrane-bound compartments that are secreted from cancer cells to carry out a number of functions that support tumorigenesis, such as invasion, metastasis and suppression of the immune response. The information gained will be used to develop methods for early diagnosis, and to design a synthetic drug delivery system.

11. **Research team: Professor Shai Shen-Orr**, Technion – Israel Institute of Technology (Faculty of Medicine), **Professor Valery Krizhanovsky**, Weizmann Institute of Science (Molecular Cell Biology), and **Professor Michal Paul**, Rambam Health Care Campus (Institute of Infectious Diseases)

    Grant Amount: **NIS 4.2 million**

    Project: Understanding the relation of cellular and immuno-senescence in aging and their relevance to the dynamics and clinical outcomes of severe infections

    Disease-causing infections are preventable and curable. Unfortunately, much is not known on the risk for infections and the risk for developing a severe or lethal infection. The study will examine how variation between individuals in two fundamental processes of aging – that of the immune system and that of cells of other organs – play out in infection. Ultimately, the research is expected to lead to predictive markers for infection severity and clinical outcomes. The study is conducted in cooperation with the **Maccabi Health Data Science Institute.**

12. **Research Team: Professor Rotem Karni**, The Hebrew University of Jerusalem (Faculty of Medicine), **Professor Erez Levanon**, Bar-Ilan University (Faculty of Life Sciences), **Professor Batsheva Kerem**, The Hebrew University of Jerusalem (Department of Genetics, Life Sciences Institute), and **Professor Eitan Kerem**, Hadassah Medical Center (Pediatric Department)

    Grant Amount: **NIS 4.9 million**

    Project: A computational and experimental personalized medicine approach for the diagnosis and treatment of rare genetic diseases

    Thousands of different rare diseases are known, which affect the lives of some one hundred million people around the globe, but for most of them there is no dedicated treatment. This multidisciplinary project employs new approaches to translate patient-specific genomic data into guides for intervention and development of novel, tailored therapies for the specific mutation. The study is conducted in cooperation with **MIDGAM – the Israeli Biorepository Network for Research.**

13. **Research team: Professor Zvi Livneh,** Weizmann Institute of Science (Biomolecular Sciences), **Professor Moshe Oren**, Weizmann Institute of Science (Molecular Cell Biology). **Professor Baruch Brenner**, Rabin Medical Center – Beilinson Hospital (Davidoff Center for the Treatment and Research of Cancer), and **Dr. Tamar Paz-Elizur**, Weizmann Institute of Science (Biomolecular Sciences)

    Grant Amount: **NIS 4.9 million**

    Project: Personalized risk assessment of colorectal cancer based on natural anti-cancer defense mechanisms: a potential tool for prevention and early detection

    The team plans to develop markers for personal risk assessment of colorectal cancer, one of the most common and deadliest cancer types. The markers will be based on our body's natural defenses against cancer, and will include DNA repair, suicide of pre-cancerous cells, and our immune system. These markers and the risk assessment will be used for prevention and early detection of colorectal cancer, with the goal of reducing its incidence and mortality.

14. **Research team: Dr. Ronen Hazan**, The Hebrew University of Jerusalem (Institute of Dental Sciences and Faculty of Dental Medicine), **Dr. Daniel Barkan**, The Hebrew University of Jerusalem (School of Veterinary Medicine, The Robert H. Smith Faculty of Agriculture), **Professor Ran Nir-Paz**, Hadassah Medical Center (Clinical Microbiology and Infectious Diseases), **Professor Michal Baniyash**, The Hebrew University of Jerusalem (Lautenberg Center for Immunology, Faculty of Medicine)

    Grant Amount: **NIS 4.2 million**

    Project: Towards precision therapy in infectious diseases – personalizing bacteriophage and antibiotic treatments

    The Covid-19 crisis has somewhat overshadowed the existence of other threats, such as the alarming emergence of antibiotic-resistant bacteria, which results in a daily death toll of about 20 people in Israel. The research team focuses on the use of bacteriophages – viruses that kill bacteria efficiently and precisely. A significant advantage in using bacteriophages is the researchers' ability to change and adapt them when a bacterium develops resistance. In addition, because they accurately target bacteria, they do not cause damage to the "beneficial" microbiome bacteria. Furthermore, their accuracy ensures that the treatment is personally tailored to each patient.

15. **Research team: Professor Eli Sprecher**, Tel Aviv Sourasky Medical Center (Dermatology), **Dr. Ruby Shalom-Feuerstein**, Technion – Israel Institute of Technology (Developmental Biology and Genetics), **Dr. Or Zuk**, The Hebrew University of Jerusalem (Statistics)

    Grant Amount: **NIS 3.5 million**

Project: Genetic and epigenetic modifiers of disease phenotypes – skin diseases as a paradigm

The need for tailoring medical treatments to the patient is because the course and manifestations of diseases, as well as the responses to treatment, often differ significantly between individuals. Those differences are, to a large extent, genetically and epigenetically determined. The study attempts to delineate the genetic basis for clinical disease variations in the context of single-gene skin diseases. The characterization of factors modulating clinical behavior will lead to the identification of novel biomarkers, actionable drug targets, and innovative therapeutic strategies to improve disease management of simple and complex traits alike.

16. **Research team: Professor Aharon Blank**, Technion – Israel Institute of Technology (Chemistry), **Professor Mogher Khamaisi**, Rambam Health Care Campus (Internal Medicine D and Endocrinology), **Professor Marcelle Machluf**, Technion – Israel Institute of Technology (Biotechnology and Food Engineering), and **Dr. Yaron Fuchs**, Technion – Israel Institute of Technology (Biology).

    Grant Amount: **NIS 4.2 million**

    Project: A personalized 3D oxygen-sensing skin graft for the diagnosis and treatment of chronic wounds in patients with diabetes

    The study's main aim is to develop new approaches for personalized diagnoses and treatments of chronic diabetic wounds. More specifically, the researchers plan to offer a radical new way of treating wounds by means of a personalized, wound-specific, artificial skin graft combined with personalized oxygen therapy. The oxygen therapy will be based on a novel magnetic-resonance methodology for wound-specific non-invasive monitoring of oxygen levels.