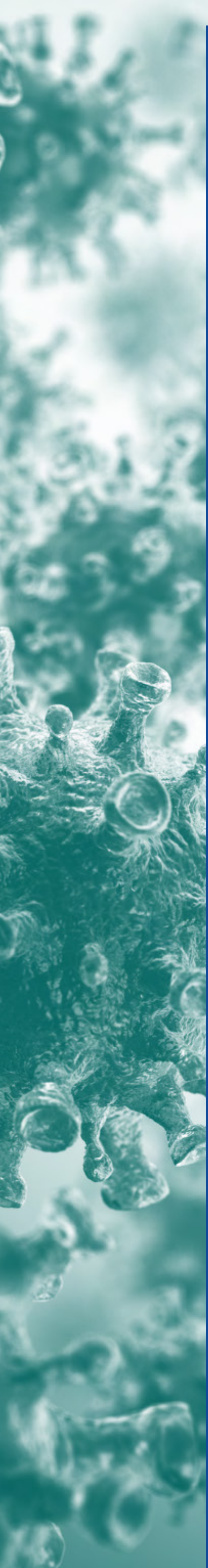


The Rappaport Technion Integrated Cancer Center

Annual Report

February 2023

TECHNION
AUSTRALIA

TECHNION
Israel Institute of Technology

Produced in partnership with the Technion Division of Public Affairs and Resource Development

Contents

I. A Multidisciplinary Center for Cancer Research at the Technion

What are the characteristics of a truly world-class cancer research center? Globally renowned scientists; pioneering research programs; and a steady record of publications appearing in prestigious journals. The Rappaport Technion Integrated Cancer Center (RTICC), currently in its eighth year of operations at the Technion, embodies this ideal.

Led by Professor Yuval Shaked, the RTICC is distinguished by its cross-pollination of 55 collaborative Technion principal investigators working in 11 Technion faculties, and an additional 13 principal investigators working at four of the Technion's affiliated hospitals. The academic affiliation of physicians in these health care units encourages clinical research and furthers the mission of the RTICC. The activities being conducted by investigators at the Technion itself, as well as at the university's affiliated hospitals, ensures the breadth of RTICC work encompasses both pure research and clinical aspects of cancer care.

RTICC Principal Investigators By the Numbers

Technion Faculty	Number of Principal Investigators
Ruth and Bruce Rappaport Faculty of Medicine	23
Faculty of Biology	11
Faculty of Biomedical Engineering	6
Faculty of Biotechnology and Food Engineering	5
Andrew and Erna Viterbi Faculty of Electrical and Computer Engineering	2
Schulich Faculty of Chemistry	2
Wolfson Department of Chemical Engineering	2
Faculty of Physics	1
Faculty of Mechanical Engineering	1
Faculty of Computer Science/Biology	1
Faculty of Materials Science and Engineering	1
Total PIs at the Technion	**55**
Technion-Affiliated Hospitals	
Rambam Medical Center	8
Carmel Medical Center	2
Emek Medical Center	2
Bnai Zion Medical Center	1
Total PIs at Hospitals	**13**

Prof. Ilana Chefetz-Menaker of the University of Minnesota speaks at “Live RTICC Club,” a special guest seminar series hosting international and national academic speakers specializing in various cancer-related topics.

The result of this diversity of scientific backgrounds is an environment in which researchers academically prosper while pursuing exciting ideas within three major areas: basic cancer research; translating research into practical therapies; and innovating new technology that allows therapies to be applied in the clinic. The focus of RTICC researchers’ activities might include everything from tumor metastasis, to drug resistance, to personalized medicine, to novel drug design, and beyond.

This report focuses on a range of advances in cancer research achieved by RTICC members over the past year, highlighting an impressive range of innovations, including new insights into how cancer evolves, advances in cancer drug delivery, and developments in the treatment of cancer pain. Additional breakthroughs, showcased below, address advances in cancer testing, the prevention of metastasis, and improvements in selecting optimal cancer treatments.

The Technion once again offers thanks to the Bruce and Ruth Rappaport Foundation, whose generous gift led to the renaming of the former Technion Integrated Cancer Center as the Rappaport Technion Integrated Cancer Center.

II. The Biology of Cancer

Developing New Tools to Analyze Cancer Evolution

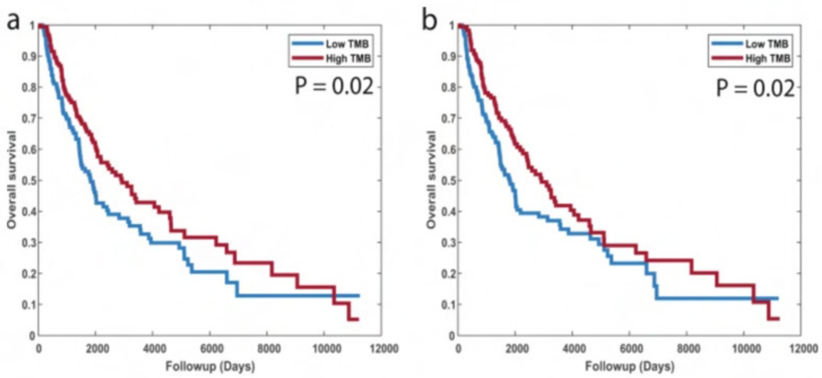
Assistant Professor Yossi Maruvka, a member of the Faculty of Biotechnology and Food Engineering, joined the RTICC in 2022. Asst. Prof. Maruvka and his research team are developing tools to analyze the evolution of cancer, and studying how their findings can be applied as therapies.

Recent technological developments in generating biological data, such as DNA and RNA sequencing, have led to an exponential growth of information. This is particularly true of cancer data, as DNA sequencing is routine at many medical centers. The main bottleneck for research, therefore, is not generating data but interpreting it. The Technion's Cancer Evolution Laboratory, led by Asst. Prof. Maruvka, is developing new tools for analyzing cancer data with the goal of generating new biological insights and medical diagnostic tools. Although his interest spans many areas of cancer data analysis, his current focus is on the genomics of tumors.

In one project, Asst. Prof. Maruvka's team is developing computational methods to help detect and analyze traces of cancerous DNA in the blood. These methods might be useful both for the early detection of cancer and for monitoring the relapse of previous tumors. In a second project, the team is analyzing lesions from patients with Lynch Syndrome, a condition that can lead to colon cancer, with the aim of seeking a preventive vaccine against tumor development.

Estimating the Number of Mutations in Cancer Cells

Assistant Professor Keren Yizhak is a member of the Ruth and Bruce Rappaport Faculty of Medicine and head of the Technion's Computational Cancer Genomics Laboratory. In the past year, Asst. Prof. Yizhak and two colleagues — one from the Technion and one from the University of Maryland — published research discussing a novel technique for estimating the number of gene mutations inside cancer cells — an important number that can determine how likely those cancer cells are to be attacked by the body's immune system. Asst. Prof. Yizhak's study was published in the journal *Nature Communications* on June 2, 2022.



Left: Association between tumor mutational burden and patient survival.

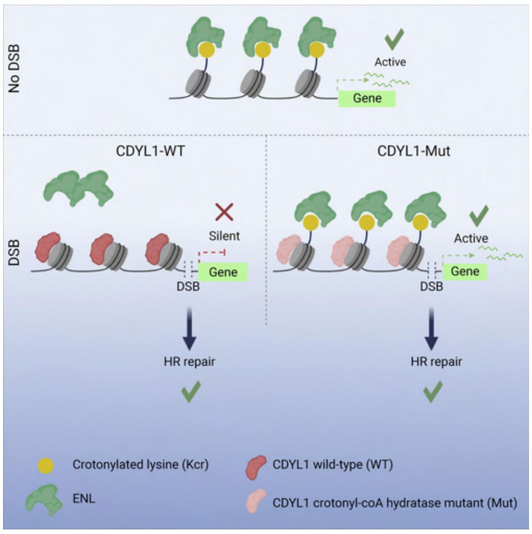
The research involves a concept called "tumor mutational burden," which is a measure of the number of gene mutations present within cancer cells. The cancer cells with a high tumor mutational burden might be more likely to be recognized as abnormal by the body's natural defenses. Studying tumor mutational burden is also important for developing new cancer therapies. In the research study, Asst. Prof. Yizhak and her team developed a new model for detecting mutations in a patient's cancer cells with the help of RNA sequencing techniques. The team has shown how this technique can be used to compute the tumor mutational burden.

To date, Asst. Prof. Yizhak and her colleagues have studied the potential for applying this technique in skin cancer, lung cancer, and colon cancer in a clinical setting.

Uncovering Mechanisms That Fix Cancer-Causing Mutations in DNA

Associate Professor Nabieh Ayoub is a member of the Faculty of Biology. In the past year, Assoc. Prof. Ayoub helped discover a new mechanism that our cells use to repair broken DNA — an important safeguard against the development of cancer.

Our DNA contains the genetic instructions that allow our bodies to function. Every day, each cell in our bodies might experience various types of damage to the DNA it contains. Fortunately, our cells have evolved a sophisticated set of mechanisms — called the DNA damage response — to detect damaged DNA, facilitate its repair, and protect our genes. If this DNA damage response were faulty, it would lead to the accumulation of genetic mutations (i.e., the specific type of cell damage) that could, in turn, contribute to cancer, as well as premature aging, developmental disorders, and neurodegenerative diseases. (For example, damage to the BRCA1 or BRCA2 genes might lead to the development of breast or ovarian cancer.)



In a recent research study, Assoc. Prof. Ayoub and his team discovered how a certain protein, known as CDYL1, not only participates in the repair of damaged DNA inside our cells, but also helps ensure that broken genes are prevented from being copied, thus avoiding the damage caused by dangerous mutations. The study was published in the journal *Molecular Cell* on April 20, 2022. The team's ultimate goal is to translate discoveries like this one into new approaches for eradicating cancer cells.

Left: Schematic of the CDYL1 protein.

Developing Unique Chemical Tools with Anti-Cancer Potential

Professor Ashraf Brik is a member of the Schulich Faculty of Chemistry. Last year, he and several of his colleagues published research on a unique variety of molecules known as peptides that may have potential use as an anticancer therapy. Prof. Brik worked with postdoctoral fellows Dr. Ganga Vamisetti and Dr. Abbishek Saha from the Schulich Faculty of Chemistry, along with Associate Professor Nabieh Ayoub from the Technion's Faculty of Biology and Professor Hiroaki Suga from the University of Tokyo.

In their most recent work, Prof. Brik and his colleagues found that when peptides attach to a certain kind of protein known as ubiquitin, the peptides disrupt the protein's ability to repair the DNA of cells that harbor it. This leads to the accumulation of damaged DNA within those cells, and eventually to the death of those cells. When this process occurs in cancer cells, it destroys these cancer cells. The researchers believe this therapeutic strategy could be more effective than existing anticancer drugs, against which patients gradually develop a resistance. The team's work was published in the journal *Nature Communications* on October 18, 2022.

Focusing on a Protein Playing a Key Role in Ovarian Cancer

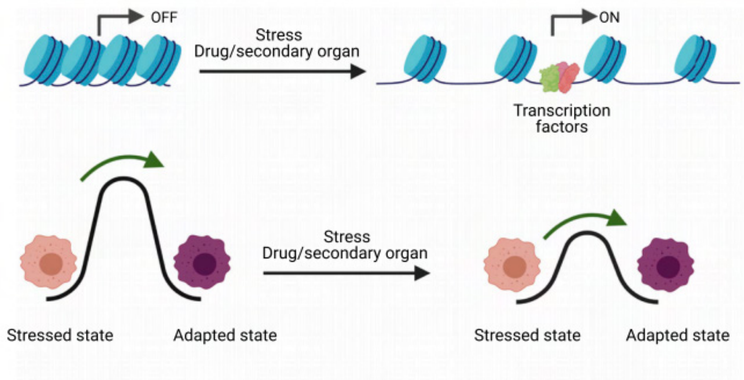
Dr. Ruth Perets is deputy director of the Division of Oncology, director of Phase 1 clinical trials in oncology, and head of the Women's Cancer Research Lab at Rambam Health Care Campus. Her lab is focused on gynecologic cancers, and especially ovarian cancer. In recent years, it has been shown that the most common type of ovarian cancer actually does not arise from the ovary but rather from the fallopian tubes. This understanding prompted Dr. Perets' research group to study the role of fallopian tube proteins in ovarian cancer.

Specifically, she and her colleagues are focused on PAX8, a protein important in the embryonic development of the fallopian tubes, and also found in adult fallopian tubes and in ovarian cancer. Dr. Perets' group has discovered that PAX8 is essential to ovarian cancer cells, and removing it from cells leads to death of the cancer cells. They have also showed how PAX8 performs this essential role. In their latest research, Dr. Perets's group has shown that PAX8 is also important for the ability of cancer cells to migrate, a trait essential for tumors to metastasize. This research lays the groundwork for understanding critical processes that drive ovarian cancer progression and metastasis, and the development of drugs targeting these processes.

Left: Structural organization of the PAX8 protein.

Exploring How Cancer Cells Learn

Associate Professor Omri Barak is a member of the Ruth and Bruce Rappaport Faculty of Medicine and the Technion's Network Biology Research Laboratory. This past year, he and his colleagues have investigated drug resistance and metastasis, two major complications associated with cancer. When a cancer cell is exposed to a brand new drug or travels to a new environment within the human body, it puts the cancer cell under a great deal of stress. How do cancer cells nevertheless manage to overcome these challenges and cause damage to the body?



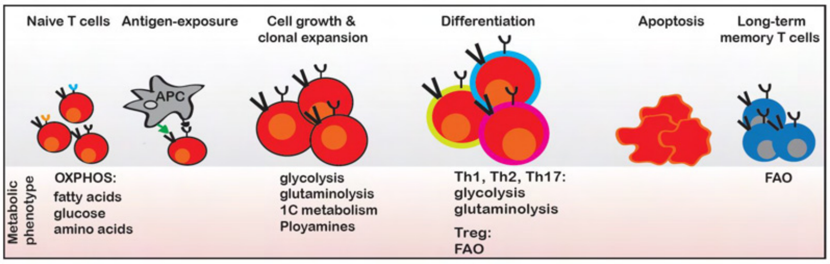
Left: Chromatin remodeling: (top) Stress induced by the secondary organ or the drug can reshape the chromatin landscape, making it more permissive. (bottom) This endows the cells with higher plasticity to explore alternative states by lowering the barriers of transition.

Assoc. Prof. Barak, along with Dr. Aseel Shomar and Professor Naama Brenner of the Technion's Faculty of Chemical Engineering, suggest that cancer cells evolve drug resistance and handle the challenges of metastasis through a type of learning. In effect, a primitive form of learning takes place within individual cancer cells — learning that is characterized by random self-modification guided by feedback from outside the cell. This learning process potentially provides cancer cells with the flexibility to survive and thrive when faced with extreme challenges, such as novel cancer drugs and foreign tissue. Assoc. Prof. Barak and his team published their findings in the journal *iScience* on March 18, 2022.

Enhancing Cancer Therapy for Older Patients

Assistant Professor Noga Ron-Harel is a member of the Faculty of Biology. This past year, Asst. Prof. Ron-Harel and her research team studied the challenges of developing effective cancer treatments in older patients. Cancer disproportionately affects the elderly, and older patients are less tolerant to the detrimental side effects of traditional therapies like chemotherapy and radiation. Therefore, older patients could greatly benefit from more specific treatments, like immunotherapy, that use the patient's own immune cells to attack tumors. Unfortunately,

TECHNION AUSTRALIA



the immune system is negatively impacted by aging as well, so cancer immunotherapy must therefore account for age-related changes within the body.

Above: Metabolic regulation of T lymphocytes.

Asst. Prof. Ron-Harel has focused on a potential treatment in which certain white blood cells, called T lymphocytes, are collected from a patient and genetically modified in a way that allows those cells to recognize and attack tumors.

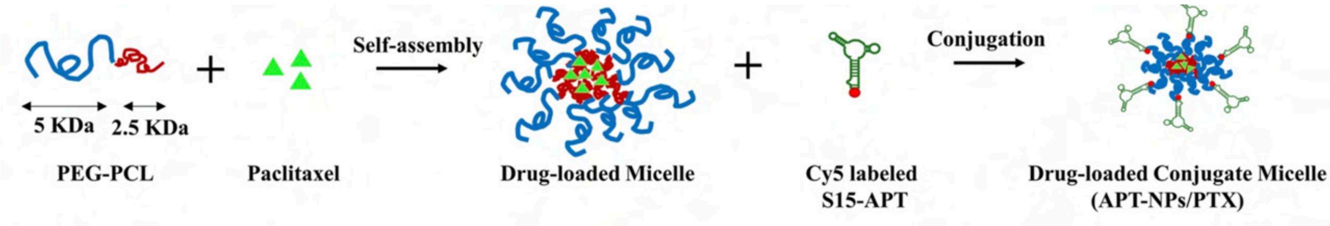
These modified white blood cells would then be returned to the patient to fight off the disease. Her studies of older mice have suggested ways in which a patient's age could negatively affect the success of this type of treatment; for example, she has found that attempting to genetically modify older cells does not succeed to the same extent as with younger cells. Asst. Prof. Ron-Harel continues to study various ways to enhance cell function in older patients.

III. Cancer Drug Delivery

Creating Anti-Cancer Drug Delivery Systems for Chemotherapy

Professor Yoav Livney, a member of the Faculty of Biotechnology and Food Engineering, joined the RTICC in 2022. Prof. Livney and his team are focused on developing anti-cancer drug delivery systems for chemotherapy.

In one of Prof. Livney's projects, he and his team in the Technion's Laboratory of Biopolymers for Food and Health have developed a system of tiny capsules — known as nanoparticles — that can be filled with cancer drugs and that can be swallowed by patients with gastrointestinal cancers. (In recent years, nanoparticles have emerged as important players in modern medicine, with a range of clinical applications including use as carriers for drug and gene delivery into tumors.) Administered by mouth rather than intravenously, this system may be able to help cancer patients with multidrug resistance, a major roadblock to alleviating cancer. Since it is an oral therapy, it could also help patients avoid some of the risks of hospitalization, including exposure to drug-resistant pathogens. Avoiding intravenous therapy administered in the hospital additionally alleviates patients' discomfort and stress, boosting their quality of life.

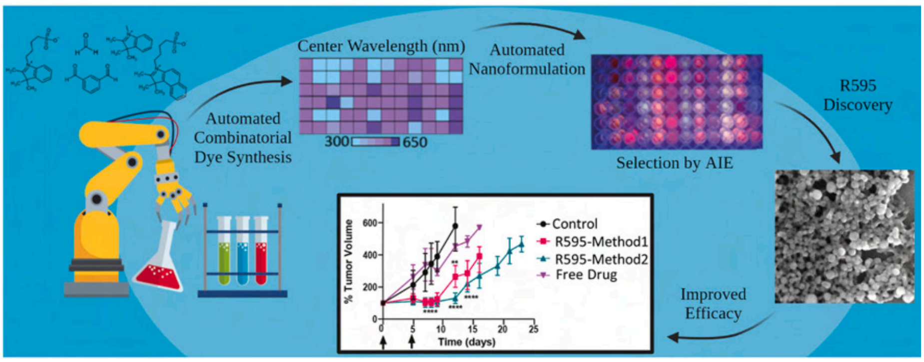


Above: Schematic structure of nanoparticles.

In another project, Prof. Livney's team devised nanoparticles that can deliver cancer drugs to patients with ovarian cancer. Specifically, this drug delivery technique targets a molecule called CD44, which exists in ovarian cancer cells and contributes to tumor growth, metastasis, cancer recurrence, and drug resistance. In a third study, Prof. Livney and his team are studying the potential of nanoparticles to deliver cancer drugs to patients with lung cancer. So far, their findings suggest their nanoparticles hold great promise in selectively targeting and eradicating human non-small cell lung cancer cells without harming normal tissues.

Enhancing the Delivery of Cancer Drugs to the Body

Assistant Professor Yosi Shamay is a member of the Faculty of Biomedical Engineering. This past year, Asst. Prof. Shamay, along with Technion doctoral student Yuval Harris and lab manager Dr. Hagit Sason-Bauer, published research describing a method of enhancing the ability of anti-cancer drugs to target tumors. Their research, which was published in the journal *Biomaterials* in October 2022, shows how drugs that kill cells in solid cancers can be packaged into nanoparticles that are easily transported to the exact site of cancer in the body.



Left: Automated discovery of nanomaterials via drug aggregation induced emission.

Asst. Prof. Shamay and his team developed a system that makes it possible to determine which substances will serve as the ideal building blocks of nanoparticles to deliver specific cancer drugs within the body. The team discovered a new material, named R595, whose physical properties represent an improvement over other existing materials used in the creation of nanoparticles. In preclinical trials, Asst. Prof. Shamay and his team showed that the nanoparticles created from this new material were effective in the treatment of solid tumors associated with lung cancer, pancreatic cancer, and intestinal cancer.

IV. Clinical Advances

Determining the Value of Medical Cannabis to Treat Cancer Pain

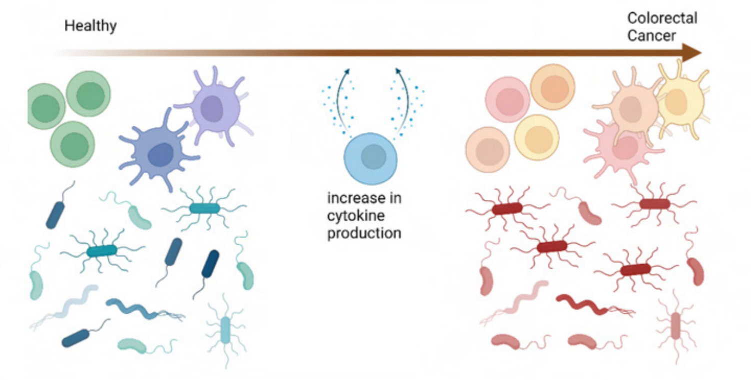
Assistant Professor David Meiri, a member of the Faculty of Biology, leads the Technion's Laboratory of Cancer Biology and Cannabinoid Research. In the past year, research he conducted has suggested that medical cannabis is highly effective in the battle against cancer pain. A paper reporting this finding was published in the journal *Frontiers in Pain Research* on May 20, 2022.

This study, which was noted in numerous news outlets including *Newsweek*, *U.S. News*, and the *Jerusalem Post*, found that for most cancer patients, pain levels improved significantly, and other symptoms also decreased, with the use of medical cannabis, which was administered via two routes: inflorescences (for smoking or inhaling) and/or oil extracts (under the tongue). For the study, the research team followed 324 cancer patients who used medical cannabis for six months. Asst. Prof. Meiri told the *Jerusalem Post* that cancer-related pain is traditionally treated primarily by opioid painkillers; however, most oncologists perceive opioid treatment as hazardous, so alternative therapies are required.

Upon analyzing the patient data collected for the study, researchers found the patients' self-reporting of pain after they commenced use of medical cannabis was reduced; the patients experienced an average 20% reduction in pain symptoms, an average 22% drop in anxiety, and an average drop in depression severity of 12%. Critically, their opioid use was significantly reduced as well. Nearly half of the patients ceased use of all other pain medication after six months of treatment with medicinal cannabis.

Providing an Alternative to an Intrusive Cancer Exam

Assistant Professor Naama Geva-Zatorsky is a member of the Ruth and Bruce Rappaport Faculty of Medicine and head of the Technion's Microbiome Laboratory. She is also the co-founder and chief scientist of an Israeli startup named Biotax. The company is now pursuing the development of a test that could potentially do away with clinical exams, the current method for colon cancer screening, whose invasiveness and unpleasantness lead many patients to forego them. The solution, which involves the use of a simple stool test that can be performed at home and advanced computing tools, is based on research performed by Asst. Prof. Geva-Zatorsky. Patients wishing to test themselves for colon cancer would collect a stool sample and send it to a laboratory, where a machine-learning algorithm developed by Biotax would test the sample to identify bacterial signatures that potentially indicate the development of precancerous polyps in patients.

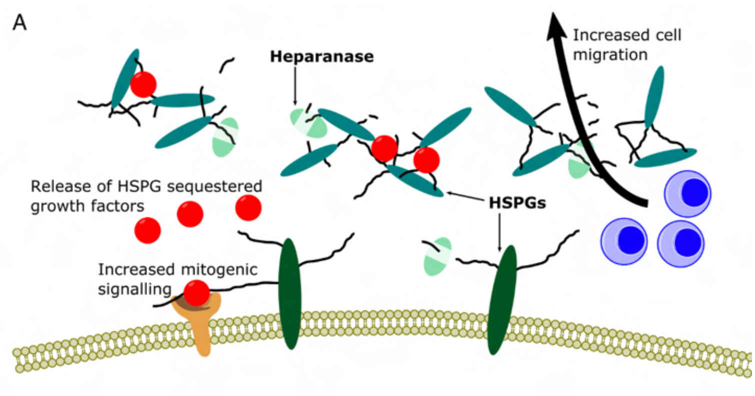


Left: Influence on the increase in cytokine production on the development of colorectal cancer.

Biotax is now completing the development of its computational and diagnostic platform, built with the help of information gathered from clinical trials the company conducted as well as public medical data. If all goes well, in a few years Biotax may have developed a home screening test that can be performed on populations at risk for colon cancer as well as adults over age 50. Colon cancer is responsible for one-fifth of all cancer-related deaths, according to the World Health Organization.

Preventing Tumor Cells from Spreading

Professor Israel Vlodavsky is an emeritus professor in the Ruth and Bruce Rappaport Faculty of Medicine. In the past year, in partnership with colleagues at Leiden University (Netherlands) and the University of York (UK), Prof. Vlodavsky helped discover a molecule with a notable property: it can maintain the integrity of tissue surrounding a tumor, preventing tumor cells from spreading from a primary cancer site to other locations in the body. The team published its research in the journal *Proceedings of the National Academy of Sciences* on July 26, 2022.



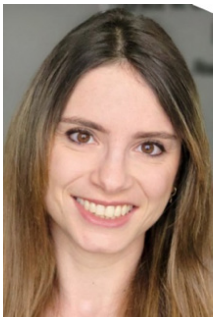
Left: Biological effects of the enzyme heparinase overexpression in the extracellular space.

As noted by the news website Phys.Org in an article on this discovery, metastasis — the spread of cancer cells to distant sites in the body — is what makes cancer so lethal. In metastasis, molecules called enzymes break down spaces surrounding cancer cells, allowing them to travel. In Prof. Vlodavsky's research, a new sugar-like molecule was developed and tested that fuses with an enzyme known for playing a major role in metastasis. Once combined, the enzyme is no longer able to break down the tissue surrounding cells, confining the tumor to its original site.

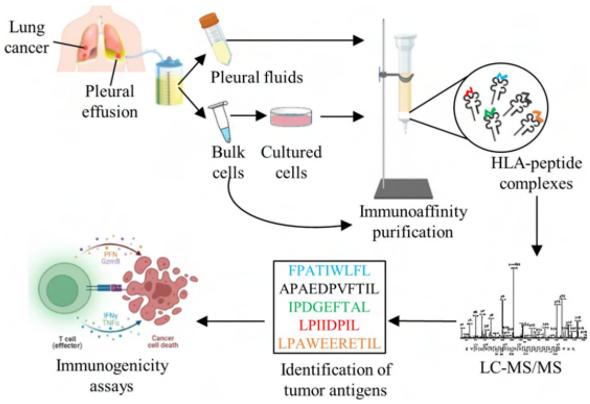
TECHNION AUSTRALIA

Prof. Vlodavsky and his colleagues are investigating ways to enhance the activity of their molecule; Prof. Vlodavsky has already studied the molecule's efficacy in lung cancer, breast cancer, and blood cancer, using lab mice. It is still too early to determine if the new molecule will be tested in human clinical trials.

Harnessing Lung Fluid to Develop New Cancer Therapies



Professor Arie Admon is an emeritus professor and head of the Proteomics Center in the Technion's Faculty of Biology. This past year, Prof. Admon, along with Dr. Sofia Khazan-Kost, his former student, published research suggesting that fluid from human lungs could be used in new methods for diagnosing and possibly treating lung cancer. Their research study — an initiative of Dr. Michael Peled, a senior physician at Sheba Medical Center in Ramat Gan — was published in the *Journal for Immunotherapy in Cancer* on May 17, 2022.



Left: Collection and analysis of lung fluid in research for cancer immunotherapy.

In the research study, led by Dr. Khazan-Kost, it was found that a certain class of molecules found in lung fluid — known as peptides — might serve as a powerful tool for detecting some types of lung cancer. The researchers identified a method of purifying and analyzing lung fluid to detect these molecules. In addition to detecting cancer, the study suggests these molecules might also be a rich source of antigens — i.e., molecular tools that trigger an immune response — that can be harnessed to diagnose and fight lung cancer and other diseases.

Dr. Khazan-Kost and her team believe the lung fluid molecules they have studied might one day form the basis of a novel therapeutic vaccine, and have expressed the hope that drug developers will use their findings as the groundwork for a new form of immunotherapy.

Helping Oncologists Choose the Best Cancer Therapy for Their Patients

Professor Yuval Shaked is the director of the Rappaport Technion Integrated Cancer Center and a member of the Department of Cell Biology and Cancer Science at the Ruth and Bruce Rappaport Faculty of Medicine. This past year, OncoHost — an Israel-based startup whose technology is based on research conducted by Prof. Shaked, and for which he is chief scientific advisor — continued the development of a "prediction platform" whose goal is to help oncologists choose the most appropriate type of chemotherapy or immunotherapy for specific cancer patients. OncoHost's efforts were spotlighted by the news site ISRAEL21c.

Traditionally, doctors have been unable to predict reliably which medications are most likely to work in each individual cancer patient. OncoHost's approach begins by taking a blood sample. Then the company's platform harnesses machine learning and AI to analyze molecular patterns in the blood sample, and attempts to assess how a patient will respond to a particular drug. This approach is also designed to inform doctors if patients appear to be resistant to the effects of specific cancer drugs.

The overall goal of OncoHost's work is to enable an enhanced form of personalized medicine in cancer care, providing improved treatment on a patient-by-patient basis. OncoHost is currently conducting clinical trials in patients with lung cancer and melanoma at sites in Israel, Europe, and the UK, and the company plans additional studies in patients with breast, pancreatic, and colorectal cancer.

It is important to note that although the research currently being conducted at the RTICC is very exciting, it might take months or years for these breakthroughs to be further developed and translated into practical therapies that are available for healthcare providers treating cancer patients. As a result, these innovations should be appreciated as a preview of what cancer care might encompass at some point in the future.

During an era in which understanding the fundamental science and treatment of cancer is ever more important, the RTICC is distinguishing itself as a preeminent site for discovery.

In addition, the link for donations is: https://app.etapestry.com/onlineforms/TechnionAustraliaIncorporated/donations.html

From Visionary Education to a World of Impact

Technion Australia supports visionary education and world-changing impact through the Technion - Israel Institute of Technology. We support various activities to engage donors, alumni, and stakeholders who invest in the Technion's growth and innovation to advance critical research and technologies that serve the State of Israel and the global good. Since the 1960's, our nationwide supporter network has funded Technion scholarships, research, labs, and facilities that have helped deliver world-changing contributions and extend Technion education to campuses in three countries.

For more than a century, Technion has pioneered in science and technology education and delivered world-changing impact. Proudly a global university, the Technion has long leveraged boundary-crossing collaborations to advance breakthrough research and technologies. Now with a presence in three countries, the Technion will prepare the next generation of global innovators. Technion people, ideas, and inventions make immeasurable contributions to the world, innovating in fields from cancer research and sustainable energy to quantum computing and computer science to do good around the world.

TECHNION AUSTRALIA

CONTACT: CEO YOASH DVIR
0410 390 176
yoash.dvir@austechnion.com