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Update on Cancer Research
Causes and Prevention
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The history of medicine teaches us that the best way to fight disease is to prevent it altogether. A prime example is heart disease; there was a dramatic decrease in death from heart disease in the second half of the 20th century, half of which was due to prevention. Unfortunately, there is very little in way of prevention when it comes to cancer—a global health concern, with an estimated 13 million people diagnosed with cancer worldwide every year and eight million deaths annually. So what can we do to avoid the onset of cancer?

Weizmann Institute scientists are looking for answers. By conducting in-depth basic research into the processes that transform healthy cells into cancerous ones and the genes and mechanisms involved, researchers at the Weizmann Institute seek to identify ways to target the mutated genes and faulty mechanisms as a means to curing cancer. Their findings are likely to enable risk assessment and preventive strategies, as well as methods for early detection of cancer, which will greatly help increase the success rate of therapy.

The Weizmann Institute has a long-standing record as a major contributor to scientific understanding of cancerous transformations. First on the list is one of the world pioneers of cancer research, the late Prof. Isaac Berenblum, whose studies at the Weizmann Institute in the first decades following Israel’s independence formed the foundation for cancer research in Israel. It was Prof. Berenblum who formulated the two-stage theory of cancer development in the late 1940s. Although it is clear today that cancer progresses in multiple stages, Prof. Berenblum was the first to demonstrate that for cancer to develop, certain events must occur in an ordered manner.
In the early 1960s, Prof. Leo Sachs found that irradiation and certain chemicals can induce the transformation of healthy cells into cancerous ones in a petri dish, paving the way to new in vitro experimental approaches to study the cellular changes that allow tumor growth. He also found that leukemia cells can be made to behave again like normal cells and stop multiplying by adding a key regulator of development. This insight showed that cancer cells can be “reprogrammed,” and also led to the formation of a new method for treating leukemia.

Like chemical carcinogens and irradiation, viruses too can induce cancer, but they may also have therapeutic uses. Prof. Ernest Winocour found that some viruses selectively kill cells in the early stages of the malignant transformation. Understanding the basis of this selectivity may lead to the exploitation of “good” viruses for ridding the body of cells at high risk of becoming cancerous.

With the dawn of the era of DNA cloning in the 1980s, Profs. David Givol and Eli Canaani revealed that rearrangements in the structure of the genome due to chromosomal translocations play an important role in cancer development. Most impressive, it was Prof. Canaani who demonstrated that chronic myelogenous leukemia (CML) was the outcome of a particular chromosome translocation that leads to the faulty fusion of two parts from different chromosomes and results in the expression of a new fused cancerous protein. This fused protein is the target for Imatinib (Gleevec/Glivec), a drug that treats the disease and is now commonly prescribed to cancer patients throughout the world. Since Prof. Canaani’s discovery, 400 more chromosomal translocations and fused
genes were identified in various cancers and are now the subjects of intense research.

Weizmann Institute researchers have also shed light on the regulatory processes that play a role in cancer induction. One such line of research involves the growth factors, hormone-like proteins that facilitate cell growth and are critical in tumor progression. It was Prof. Sachs that, in the 1960s, discovered the family of growth factors known as colony stimulating factors, responsible for inducing the growth and differentiation of specific types of blood cells. In later years, Prof. Yosef Yarden uncovered the family of growth factors called Neuregulins (NRGs) and further showed that one of the cellular proteins that mediate the activities of the Neuregulins, the HER2 protein, which is typically over-expressed in relatively aggressive breast tumors, acts as an amplifier of growth activity in breast cancer cells. Another contribution to the field of growth factors came from the research of Prof. Givol, who cloned the fibroblast growth factor receptors (FGFRs), known to be involved in lung and bladder cancer. Of note, Prof. Michael Sela pioneered the synergy concept in cancer therapy, in which an antibody that inhibits an epidermal growth factor receptor’s growth-promoting signals is used in combination with chemotherapy. This led to the drug Erbitux, used in the treatment of colon cancer, as well as head and neck cancers.

Another important step in understanding cancer induction came from the research on the major tumor suppressor p53, the most studied protein in cancer research. This effort includes the seminal work of Profs. Givol, Moshe Oren, and Varda Rotter in the 1980s. They were among the first researchers to clone and characterize the p53 gene, with Prof. Givol successfully cloning the active full-length human variant. This protein, suggested earlier by Prof. Rotter to be a general tumor cell marker, was shown by Profs. Oren and Rotter to actively prevent cancer. It has since been found that p53 is dysfunctional in almost all cancer types.

Another major contribution to the field of tumor suppressors came from the research of
Prof. Adi Kimchi, who discovered the prominent family member DAP-kinase and showed that when it is inactive in cancer cells, they are unable to undergo programmed cell death. Her studies on the regulation and molecular mode of action of DAP-kinase established the current use of this gene as a prognostic tool in many types of human cancers.

The cell’s main mechanism to prevent genetic mutations is the DNA repair system. It was the research of Prof. Zvi Livneh and Dr. Tamar Paz-Elizur on this system that revealed that low activity of OGG1, an enzyme involved in the repair of oxidative DNA damage, is a risk factor for lung cancer and head and neck cancers. This insight led them to develop tests for measuring the level of DNA repair enzymes in human cells, which can be utilized as a preventative diagnostic measure.

An additional diagnostic tool came from the laboratory of Prof. Hadassa Degani. Her research of hormonal regulation of blood vessel growth in breast cancer led to the development of a magnetic resonance imaging (MRI) technique for the early detection of breast tumors, now in common practice worldwide. These examples represent only a fraction of the scientific contributions of the Weizmann Institute to the understanding of the basic processes that underlie cancerous transformations. This booklet showcases some of the recent findings of a selection of Weizmann scientists in this field, who, in many cases, are using their new insights to devise innovative therapies and preventative tools.
From Inflammatory Lung Disease to Lung Cancer

Prof. Ronen Alon
Department of Immunology

The lungs, which are among the most immunologically active organs, maintain the body’s first line of defense against numerous pathogens and air-borne particulates, including dust and tobacco smoke. However, this organ can only withstand so much ill treatment before succumbing to the induced immunological responses that contribute to the development of health problems such as inflammation and lung cancer.

The latter can be induced directly by carcinogens, such as tobacco smoke, or indirectly during the onset of various inflammatory processes, primarily those associated with chronic obstructive pulmonary disease (COPD). One possibility by which COPD instigates cancer is by “switching off” tumor suppressor genes, essential in the prevention of tumor formation and metastasis.

Prof. Ronen Alon’s research focuses on how immune cells respond to pathogens and migrate out of the blood stream to induce inflammation and eradicate infectious agents. In one of his latest collaborative studies, focused on the interplay between tobacco smoke and COPD, he has shed new light on the activities of the tumor suppressor DAP-kinase. This protein, which prompts damaged cells to commit suicide, is missing in many tumor cell lines, including certain lung cancers.

As part of this joint study with Prof. Adi Kimchi from the Department of Molecular Genetics, Prof. Alon and his colleagues designed an experiment to explore how animal models that lack DAP-kinase cope in a COPD environment, induced by either bacterial insult or tobacco smoke. They found that these animal models

DAP-kinase, and possibly other tumor suppressors, may have both a direct and indirect role in lung cancer prevention.
exhibit profoundly higher sensitivity to both tobacco smoke and bacterial insults. It appears that DAP-kinase helps protect various types of lung cells from COPD-like inflammation. The scientists have further suggested that DAP-kinase's protective effect is achieved in the following manner: In response to a local insult, both the lung airways and white blood cells populating the lung express DAP-kinase, which inhibits the pro-inflammatory factors released by these various lung cells on site.

Thus, DAP-kinase, and possibly other tumor suppressors, may have both a direct and indirect role in lung cancer prevention: It can drive newly mutated cells to commit suicide; and it can suppress inflammation of non-mutated neighboring cells and immune cells, thereby preventing the formation of the supportive environment cancers need to develop into aggressive tumors. Prof. Alon's findings further emphasize that restraining lung inflammation can protect lung cells from incurring cancerous mutations and, once transformed, from developing into aggressive tumors.

This research avenue will help in the identification of risk factors that predispose humans to COPD and specific lung cancers, as well as assist in the elucidation of the links between inflammation and cancer. Defining these factors is essential for pinpointing novel targets for early diagnostics and therapeutic intervention, first in animal models and later on in humans.

Prof. Alon's research is supported by the Flight Attendant Medical Research Institute grants. He is the incumbent of the Linda Jacobs Professorial Chair in Immune and Stem Cell Research.
Fusion Genes as Leukemic Agents

Prof. Eli Canaani
Department of Molecular Cell Biology

Prognosis of childhood acute leukemia has improved dramatically over the past half a century. However, for 20 to 25 percent of these cases the projection is still quite dismal. Among that group are a significant number of infants from birth to one year of age. The vast majority of these infants carry in their leukemia cells a fused gene caused by erroneous switching of DNA segments between two chromosomes. It is this new fusion gene that produces a cancer-causing hybrid protein. One of the genes that have been found in such fused constructs is MLL.

Prof. Eli Canaani, who was the first to prove the link between hybrid proteins and cancer, has been investigating the role of the MLL gene in acute leukemias. He has shown that the MLL gene may fuse to at least 50 partner genes, each scenario leading to a potent oncogene. MLL fusions have been found in approximately 10 percent of human leukemias and account for more than 70 percent of childhood acute leukemias; they are also prevalent among patients that develop acute leukemia after being previously treated for other malignancies.

Intensive investigations in Prof. Canaani’s laboratory and others have established the mode of operation of the MLL-fusion oncogenes: Gene expression comprises three main steps—initiation, elongation, and termination. The fused proteins interfere with the stage of elongation during the process of transcription, changing the recruitment of elongation factors to target genes, thereby leading to excessive expression.

Prof. Canaani and his group have moved one step closer to understanding the nature of MLL-related leukemias by identifying all of the approximately 170 primary gene targets of MLL-AF4, the predominant MLL fusion protein in infant acute leukemia. They have
shown that among MLL’s targets are at least four genes that are strongly expressed in the majority of MLL-associated leukemias. The scientists have further revealed that the proteins expressed by these target genes are essential for the proliferation and spread of the leukemic cells in the bone marrow of animal models transplanted with the cells. These results offer new targets for therapeutic intervention in MLL-associated acute leukemias.

In the 1980s, Prof. Canaani isolated a fused protein that triggers chronic myelogenous leukemia (CML), the first discovery of cancer produced by protein fusion. This finding provided the foundation for the development of Imatinib (known as Gleevec in the U.S. and Glivec in Europe), the first drug based on the molecular understanding of a specific cancer. Produced by Novartis, it was approved in 2001 by the FDA and is now routinely prescribed around the world to patients with CML.

Prof. Canaani’s research is supported by the Kirk Center for Childhood Cancer and Immunological Disorders; the Sergio Lombroso Award for Cancer Research; the Spitz Family Philanthropic Fund; and the U.S.-Israel Binational Science Foundation. He is the incumbent of the Harry Kay Professorial Chair of Cancer Research.
Three Pathways to Breast Cancer Diagnosis

**Prof. Hadassa Degani**
Department of Biological Regulation

Prof. Hadassa Degani has dedicated the last 25 years to characterizing hormonal regulation of breast cancer and developing mechanisms of endocrine therapy. Among her many contributions to science and medicine are three breast cancer diagnostic tools, all based on magnetic resonance imaging (MRI).

In the late 1990s, Prof. Degani showed that MRI, in combination with the injection of a contrast agent, can be used to construct a 3D image of blood flow in breast tissue to detect regions with heightened activity, caused by the formation of new blood vessels—a marker of cancer growth. In 2003, her method, nicknamed “3TP,” received U.S. Food and Drug Administration clearance for use in the detection of breast cancer, as well as prostate cancer. It is now employed by doctors worldwide to detect cancer and distinguish between malignant tumors and benign lumps.

Prof. Degani has now gone one step further by developing a completely non-invasive, sensitive breast cancer screening method. Her new invention relies on the fact that breast tumors decrease the natural diffusion of fluid in the mammary ductal tubes. This is because the vast majority of breast tumors form on the inner lining of the tubes, obstructing fluid movement in the tubes as they grow. Prof. Degani’s new MRI-based technique provides a 3D map of the self-diffusion of water in the ductal trees, with clogged regions pointing to the location of tumors. Since cell growth obstruction of the ductal tubes occurs at an early stage of tumor development, this detection method raises the possibility of...
increasing the probability of curing the disease.

To test the new method, Prof. Degani and Dr. Edna Furman-Haran, head of the Weizmann Institute’s functional MRI (fMRI) unit, are now conducting a clinical study, taking place on campus, in collaboration with the breast imaging unit at Meir Medical Center, Israel, headed by Dr. Myra Feinberg-Shapiro. The study involves more than 120 female volunteers, split into three groups: with no known lumps, with a benign lump, and with a malignant tumor. The initial results indicate that the MRI method accurately distinguishes between the three tissue types.

To complement the two abovementioned tools, Prof. Degani, in collaboration with Prof. David Milstein (Department of Organic Chemistry) and Prof. Joel Sussman (Department of Structural Biology), is also developing a molecular imaging method for detecting the “estrogen receptor,” a cellular protein that, in cancer cells, interacts with the hormone estrogen to promote growth. This receptor is over-expressed in many breast tumors and serves as a marker for endocrine therapy. Using this method, doctors will be able to better characterize the type of cancer a patient has, knowledge needed to personalize treatment to ensure the best possible medical outcome.
Chemical communication between cells and transfer of information inside them are essential for cell survival and function. It is by these means that cells receive instructions from their surroundings. In the absence of such communication, important processes such as cell division, secretion of certain substances, or even cell death would not occur. A major hallmark of cancer is the ability of individual cells to free themselves from having to abide by the instructions they receive.

Prof. Ari Elson’s studies examine the molecules that participate in this flow of information in cells. In particular, his team focuses on the enzymes that add or remove small phosphorous-containing chemical groups from proteins, thus affecting their structure and function. Irregularities in these processes are among the best-known and most intensively characterized causes of disease, including cancer. One of the molecules that Prof. Elson is studying is called PTPe, which, in the context of breast cancer, helps tumor cells survive.

Almost all instances of breast cancer originate in the lobules or ducts of the mammary glands. In one study, Prof. Elson’s group described how PTPe contributes to the ability of another protein to transform healthy mammary cells into tumor cells. Interestingly, absence of PTPe resulted in mammary cancers that were less destructive, indicating that its function is important for the malignant process.

Advanced breast cancer often causes metastases in bone that lead to a decrease in bone mass and an increase in the susceptibility for fractures, as well as an imbalance in various metabolic processes. A recent study by Prof. Elson’s group has led him to believe that PTPe also plays a role in this type of metastasis. This study relates to the activity of osteoclasts, bone cells whose function is to remove bone tissue.
Prof. Elson’s team found that, in mice that lack PTPe, the osteoclasts do not receive their orders to remove the bone tissue and, as a result, these mice exhibit increased bone mass. Based on these findings, his group has suggested that mice lacking PTPe might be protected from bone loss caused by bone metastases of breast cancer. The scientists now aim to provide more precise quantification of this result and to examine the possibility that inhibiting PTPe in osteoclasts can be used as a method for combating metastatic breast cancer in bone.

Lacking PTPe may also be good for your figure. Prof. Elson’s studies show that female mice lacking PTPe are relatively resistant to weight gain when fed a high-fat diet, revealing that PTPe participates in the signals that regulate body weight. Therefore, in addition to breast cancer and bone loss, pharmacological inhibition of PTPe may also be useful for combating obesity.
Down Syndrome and Leukemia

Prof. Yoram Groner
Department of Molecular Genetics

Down syndrome, also called Trisomy 21, is the most common cause of human birth defects. This severe developmental disorder results from an extra copy of chromosome 21 in the cells’ genetic makeup. Unfortunately, it appears that Trisomy 21 patients are also 500 times more likely to contract childhood **acute megakaryoblastic leukemia** than the general population. This leukemia is characterized by the uncontrolled proliferation of megakaryoblasts, the forefathers of platelets. In many cases, it strikes in infancy and then passes, but it can return later on with much harsher consequences.

What causes acute megakaryoblastic leukemia to be particularly prevalent among Down syndrome patients? Previous research in Prof. Yoram Groner’s lab had pointed to a possible culprit: the protein Runx1. This regulatory protein binds to DNA segments and, thereby, controls the expression of a large number of genes. The damning evidence against Runx1 included its location on chromosome 21 and the fact that quantities of an “abridged” version of Runx1, which muddles the normal function of this protein, are found in many leukemias.

Prof. Groner’s working hypothesis is that when an extra copy of the Runx1 gene is present in megakaryoblasts, as is the case in Down syndrome patients, its expression levels are not regulated correctly, leading, in turn, to faulty expression of its target genes, a change that brings about a shift from regulated differentiation to uncontrolled proliferation.

The first step to proving this hypothesis was to verify Runx1’s role in megakaryoblast differentiation. And, indeed, in a collaborative study with the group of Dr. Amos Tanay from the Department of Computer Science and Applied Mathematics, Prof. Groner’s team was able to show that Runx1 is a key player in
differentiation, binding to over 10,000 sites on the genome at various stages in the process.

To play so many different roles, Runx1 teams up with other regulators of gene expression, including one called GATA1, which is often faulty in Down syndrome patients with leukemia. The scientists now believe that mishaps in the cooperation between the two regulators might contribute to the development of leukemia. This hypothesis has gained strength in a recent study in Prof. Groner’s lab, which entailed the creation of transgenic animal models with faulty versions of both the Runx1 and GATA1 genes. The scientists observed that these animal models display the symptoms of Down syndrome and leukemia. The researchers now plan to further explore how the two proteins interact and, it is hoped, to finally clear up the mystery of the disappearing-recurring leukemia in Down syndrome.

Prof. Groner’s research is supported by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; the Irving B. Harris Foundation; the Leona M. and Harry B. Helmsley Charitable Trust; the European Union Seventh Framework Programme for Research and Technological Development; Foundation Jerome Lejeune; and the Israel Science Foundation. He is the Director of the M.D. Moross Institute for Cancer Research, the Kekst Family Institute for Medical Genetics, and the David and Fela Shapell Family Center for Genetic Disorders Research, and is the incumbent of the Dr. Barnet Berris Professorial Chair of Cancer Research.
A Molecular Link between Cell Death, Cancer, and Diabetes

Prof. Atan Gross
Department of Biological Regulation

Prof. Gross’s research may help in the design of drugs that induce mitochondria apoptosis in cancerous cells or correct mitochondria fat/sugar metabolism in obese or diabetic individuals.
When cells incur too much damage, reaching the point where repair is no longer an option, they make the fatal decision to “commit suicide,” a process known as “programmed cell death” or “apoptosis.” This process is one of the body’s safeguards against disease, as it ensures that malignant cells are removed from the general population. Apoptosis is particularly important when it comes to cancer: Cells must circumvent it to ensure uncontrolled proliferation.

Apoptosis is brought about either by closing down central command—the nucleus—or by shutting off the energy plants—the mitochondria, specialized cellular organs entrusted with the important task of converting nutrients into the chemical energy required for the cell’s ongoing operations. The mitochondrion is also the place where cellular respiration, i.e., the conversion of oxygen into carbon dioxide, takes place.

Prof. Atan Gross is mapping the activities of key apoptotic factors and their role in other cellular processes. He has shown that one such factor, a protein called “BID,” plays a critical role in inducing apoptosis in the mitochondria. His exploration of BID’s activities has also led to the discovery of a novel mitochondrial protein, “mitochondrial carrier homolog 2,” or “MTCH2” for short. This protein acts as a receptor for BID; from its post on the mitochondria membrane, it recruits passing BID molecules and enables them to execute apoptosis in the mitochondria.

It seems, however, that MTCH2 has other qualifications listed in its resume. Prof. Gross believes that assisting in mitochondria apoptosis is only MTCH2’s “night job,” and that its primary occupation may be transporting metabolites—molecules involved in cellular metabolism, such as sugars and fats—across the mitochondria membrane. This hypothesis is very plausible given the great similarity between the structure of MTCH2 and that of other mitochondrial transporters.

Prof. Gross and his team’s investigation of MTCH2’s “day job” has already yielded interesting results; they have unraveled an intriguing connection to the metabolism of fats and sugars in the mitochondria. For example, they found that when the MTCH2 gene is silenced in obese animal models, the animals remain slim even when on a high-fat diet. This finding provides new insight into obesity and metabolic diseases such as Type II diabetes.

Prof. Gross’s research has potential biomedical implications. If clinicians could regulate the production and activity of MTCH2, they would be able, for instance, to induce mitochondria apoptosis in cancerous cells or correct mitochondria fat/sugar metabolism in obese or diabetic individuals.

Prof. Gross’s research is supported by the Dr. Josef Cohn Minerva Center for Biomembrane Research; the Jeanne and Joseph Nissim Foundation for Life Sciences Research; the Pearl Welinsky Merlo Foundation; the Victor Pastor Fund for Cellular Disease Research; the German-Israeli Cooperation Program in Cancer Research; the German-Israeli Foundation for Scientific Research and Development; the Israel Cancer Association; the Israel Science Foundation; and the U.S.-Israel Binational Science Foundation.
Programmed cell death is the principal mechanism by which cells are physically eliminated in our body. Cancer cells must turn off this internal system in order to proliferate, and that is why finding a way of turning it back on only in these cells represents the most attractive means of combating tumor growth.

A cell has several end-of-life options from which to choose. It can “commit suicide” (i.e., apoptosis), resort to “self-cannibalism” (i.e., autophagy), opt for immune system-assisted suicide (i.e., programmed necrosis), or initiate a combination thereof. The cell’s decision is dependent on the external and internal stimuli it receives. Each death module is characterized by a specific set of morphological features and signaling pathways.

Prof. Adi Kimchi is studying the molecular mechanisms underlying these programmed cell death options. Her research is providing critical knowledge about how cell fate decisions are made and the way by which specific alterations in these mechanisms promote cancer development. Her group’s investigations have already led to the identification and comprehensive characterization of several new components of the cell death network in mammalian cells, namely, the “Death Associated Proteins” (DAPs).

Among the newly identified DAPs is “DAP-kinase,” which Prof. Kimchi’s team exposed as a potent tumor suppressor. DAP-kinase is typically missing or inactive in many tumors, including various hematological cancers such as B-cell lymphomas and many types of carcinomas and sarcomas. This scientific development highlights the importance of investigating the programmed cell death machinery in understanding cancer.

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Following her discovery of DAP-kinase, Prof. Kimchi and her team have taken a leading role in exposing the nature of the cell death pathways in which it is involved. In one recent
study, the scientists revealed that another tumor suppressor, “Beclin-1,” is, in fact, a direct target of DAP-kinase. Beclin-1 is an essential autophagy component, but it is usually inhibited by its regulator, the protein Bcl-2. DAP-kinase prevents Beclin-1 from associating with Bcl-2, thereby freeing Beclin-1 to activate autophagy.

In parallel to investigating specific cell death pathways, Prof. Kimchi’s group has also been developing a novel holistic approach for analyzing the complexity of the entire programmed cell death network. By applying this approach to cells exposed to chemotherapeutic drugs, Prof. Kimchi’s team discovered several novel principles delineating the structural and functional organization of the programmed cell death machinery, including specific links between apoptosis and autophagy. These findings open exciting future directions in personalized cancer therapy where it will be possible, through model simulations, to identify ways of overcoming a specific cancer’s resistance to cell death by switching to alternative pathways still operational inside the tumor.

Prof. Kimchi’s research is supported by the European Union Seventh Framework Programme for Research and Technological Development; the Flight Attendant Medical Research Institute grants; the German-Israeli Cooperation Program in Cancer Research; and the Israel Science Foundation. She is the incumbent of the Helena Rubinstein Professorial Chair in Cancer Research.
Arresting Cancer Growth

Dr. Valery Krizhanovsky
Department of Molecular Cell Biology

Cellular senescence, which occurs when cells keep functioning but stop reproducing, is one of the natural mechanisms that limits the proliferative potential of cells and can be a potent barrier to tumorigenesis. Dr. Valery Krizhanovsky was one of the leading scientists in the research group that showed that it occurs as part of a number of responses to stress or injury, and that senescent cells are eliminated by the immune system to limit cancer and tissue damage.

One of Dr. Krizhanovsky’s scientific interests is the interplay between senescence, the p53 tumor suppressor protein, and cancer. Mutations that inactivate the p53 network occur in most human cancers. The p53 protein protects against cancer by inducing cells to “commit suicide” (i.e., apoptosis); by preventing damaged cells from reproducing; or by promoting senescence. In his postdoctoral work, Dr. Krizhanovsky and a team of researchers set out to discover how p53 works to control liver cancer. He helped create an ingenious “reversible” gene knockout that enabled them to turn the p53 gene’s output off and on. Not surprising, they found that liver tumors with their p53 suppressed grew quickly when transplanted into mice, and that the tumors receded dramatically when the p53 functions were turned on, even for a short time. But they were surprised to find that tumors were cleared not by apoptosis but through cells becoming senescent and subsequently being removed by the immune system, revealing a previously undescribed tumor suppression mechanism.

Another cancer research avenue focuses on induced pluripotent stem cells (IPS cells). Dr. Krizhanovsky and other researchers have pointed out the striking similarities between cancer cells and IPS cells. Just like embryonic
Dr. Krizhanovsky's research is supported by the Abisch Frenkel Foundation for the Promotion of Life Sciences; the Henry S. and Anne Reich Family Foundation; the Simms/Mann Family Foundation; the Estate of David Arthur Barton; the European Union Seventh Framework Programme for Research and Technological Development; the Israel Science Foundation; and the U.S.-Israel Binational Science Foundation. He is the incumbent of the Carl and Frances Korn Career Development Chair in Life Sciences.

stem cells, IPS cells can self-renew and are able to give rise to all tissue types of the body, but they can be produced from adult cells, which could eliminate the need for embryonic stem cells and immunologically matched transplant donors.

IPS cells were first produced by controlling four transcription factors, but recent studies have shown that inhibiting p53 enables the production of IPS cells with only two of the four factors. This finding led Dr. Krizhanovsky and his colleagues to suggest that, perhaps, the route to converting an ordinary cell into either a cancerous or IPS cell requires bypassing two important checkpoints: p53-mediated apoptosis and senescence.

Dr. Krizhanovsky is currently working to understand the role of cellular senescence in tissue damage, cancer, various diseases, and aging.
When our cars break down, we visit the mechanic, and when the water pipes clog up, we phone the plumber. Our cells too have a repair crew, entrusted with the important job of fixing damaged DNA. This complex, multi-layered system is vital for ensuring the integrity of the genetic material, which is “attacked” about 20,000 times a day—one hit every four seconds—by sunlight, tobacco smoke, metabolic byproducts, and other environmental agents. It also assists in the correct duplication of the entire 3 billion “letters” of the human genome during cell replication.

It is, therefore, not surprising that the DNA repair system is essential for protecting genes from incorporating disease-causing mutations, particularly cancerous ones. This fact is highlighted by the finding that mutations in the DNA repair system are implicated in many hereditary cancers. And this is also true of non-hereditary ones. Prof. Zvi Livneh and Dr. Tamar Paz-Elizur, for example, have shown that reduced activity of one of the members of the DNA repair apparatus, the enzyme “8-oxoguanine DNA glycosylase,” is a risk factor for lung and head and neck cancers, and may therefore be used as a biomarker for predisposition of these cancers.

Prof. Livneh and Dr. Paz-Elizur are now using their extensive knowledge on DNA repair enzymes to pioneer a method that will assist physicians in the risk assessment and early detection of lung cancer, one of the deadliest forms of the disease. The idea behind the detection method is straightforward: An imbalance in the activity of the enzymes that repair DNA damage associated with lung cancer in a blood sample will indicate an increased risk of the disease.

Prof. Livneh, Dr. Paz-Elizur, and their team have already completed the development of assays that accurately measure the levels of three such enzymes in blood samples. These assays are being tested in clinical trials to determine their efficacy in predicting lung cancer risk.

Title: Novel Risk Biomarkers for Early Detection and Prevention of Lung Cancer

Author: Prof. Zvi Livneh

Department of Biological Chemistry

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DNA repair enzyme biomarkers. To adapt the method to a clinical setting, they switched from a manually operated procedure to an automated one, which has greatly increased the scope of analysis, testing efficiency, and measurement accuracy. One great benefit of the new setup is that it is now possible to simultaneously test for a number of DNA repair enzymes using the same blood sample without significantly affecting the overall throughput—a major step forward in translating the findings from the lab to the public health arena.

The novel risk assessment method is currently being used in a study involving 200 blood samples—100 from lung cancer patients and 100 from healthy subjects—collected for the purpose of examining the involvement of the DNA repair system in lung cancer. The scientists are also in the process of examining the relation between the novel DNA repair biomarkers and early detection of lung cancer using spiral CT imaging.

Prof. Livneh’s research is supported by the M.D. Moross Institute for Cancer Research; the J & R Center for Scientific Research; the Helen and Martin Kimmel Institute for Stem Cell Research; the Leona M. and Harry B. Helmsley Charitable Trust; the Flight Attendant Medical Research Institute grants; the Israel Science Foundation; and the National Institutes of Health, U.S. He is Dean of Biochemistry, the Director of the Y. Leon Benoziyo Institute for Molecular Medicine, and is the incumbent of the Maxwell Ellis Professorial Chair in Biomedical Research.
The Many Faces of the p53 Tumor Suppressor

Profs. Moshe Oren and Varda Rotter
Department of Molecular Cell Biology

Profs. Moshe Oren and Varda Rotter are pioneers of research into the molecular mechanisms of cancer and the p53 tumor suppressor gene. This gene is known as the “guardian of the genome,” because it puts the “brakes” on cancer when the cell’s DNA is damaged. However, when these brakes are not functioning properly, the road to cancer remains open, and there is nothing to stop a normal cell from transforming into a full blown cancerous one. Most alarming, scientists have found that p53 is mutated in over half of all cases of human cancer, making it the most frequently altered gene in tumors.

After 30 years of rigorous research and numerous discoveries into this enigmatic protein, there is still much more to learn regarding p53’s cancer-related activities. One example relates to the association between inflammation and cancer. This link was discovered long ago; yet, recent research implies that the contribution of chronic inflammation to tumor growth is more than previously estimated. Using genetically engineered mouse models, Profs. Oren and Rotter found that the presence of p53 mutations greatly accelerates the emergence of inflammation-associated cancer in the gut—the tumors that arise are more invasive in comparison with those that lack p53 mutations. This finding may have future practical implications in view of ongoing attempts by several pharmaceutical companies to develop drugs that abolish the unwelcome activities of mutant p53.

New revelations have put forward the idea that p53 also plays a role in the life of stem cells. It is well accepted that p53 is central for the maintenance of genomic stability, and the expression of the deregulated or mutant p53 gene leads to tumor development. However, recent findings have suggested that mutated
p53 may also cause normal stem cells to transform into cancer stem cells. Indeed, by using in vitro models of stem cell generation, Prof. Rotter’s team has found that stem cells with defective p53 diverted into aggressive cancer cells. This observation further highlights the notion that p53 must commence its vigilant status as protector of the cells from the time of their earliest emergence as stem cells and remain attentive throughout the life cycles of the body’s countless cell population.

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Prof. Rotter’s research is supported by the Leir Charitable Foundations; the Centre Leon Berard; the Jeanne and Joseph Nissim Family Foundation for Life Sciences; the Estate of John M. Lang; Donald Schwarz, Sherman Oaks, CA; the European Union Seventh Framework Programme for Research and Technological Development; the Flight Attendant Medical Research Institute grants; and the Israel Science Foundation. She is the director of the Women’s Health Research Center, and is the incumbent of the Norman and Helen Asher Professorial Chair of Cancer Research.
As an organism grows and develops, its cells must divide to allow for this growth. However, in order for the organism to function properly, its cells must also know when to stop growing. For example, when an organ has reached what is considered its “normal size,” the growth must cease. The ability to stop growing is particularly pertinent when it comes to cancer, which can be viewed as the outcome of cells that have lost this function.

Scientists have recently identified a new regulatory system that controls cell growth and organ size. This pathway consists of cellular proteins, beginning with those located on the cell surface that receive messages from other cells, continuing with proteins within the cell that receive the messages and relay them onward, and ending with the “Yap” effector—a protein entrusted with the important job of turning on and off genes that regulate cell growth.

Prof. Yosef Shaul’s interest in the regulatory activities involving cell growth has led him to take a closer look at the new pathway. His team’s investigation revealed the intricate nature of Yap’s activities: It seems that the Yap protein can actually change its role. In response to DNA damage, Yap is modified in a way that, instead of inducing cell growth in cancerous cells (and healthy ones), it starts promoting the complete opposite—cell death (i.e., apoptosis). In doing so, Yap helps protect the body from cancerous growth.

Interestingly, Prof. Shaul’s team has shown that Yap’s conversion to an inducer of apoptosis can be stimulated by irradiation (i.e., radiotherapy), a method commonly used in cancer treatment. This finding opens the way to the possibility of adjusting cancer radiotherapy protocols so as to increase Yap-mediated tumor cell death. The research team is now analyzing the
various genes that are induced by Yap under DNA damage due to radiation therapy and, in addition, is working to further reveal the molecular mechanisms behind Yap’s “switching” phenomenon. They are also studying another effector in the pathway, a protein called “Taz,” to determine how its modification may also result in a role shift.

Prof. Shaul believes that once his team determines the molecular mechanisms underlying Yap’s activities, they will be able to further sensitize tumor cells to radiotherapy, and maybe even formulate new approaches for switching tumor cells off.

Prof. Shaul’s investigation revealed that, in response to DNA damage, the Yap protein is modified in a way that, instead of inducing cell growth in cancerous cells (and healthy ones), it starts promoting cell death.

Prof. Shaul’s research is supported by the M.D. Moross Institute for Cancer Research; the Y. Leon Benoziyo Institute for Molecular Medicine; the J & R Center for Scientific Research; the Phyllis and Joseph Gurwin Fund for Scientific Advancement; the Leona M. and Harry B. Helmsley Charitable Trust; the Israel Cancer Research Fund; and the Minerva Foundation. He is the Director of the Leo and Julia Forchheimer Center for Molecular Genetics and the incumbent of the Oscar and Emma Getz Professorial Chair.
A Holistic Approach to Studying Tumorigenesis

Dr. Amos Tanay
Department of Computer Science and Applied Mathematics

Tumor cells often proliferate by suppressing the expression of the body’s normal cancer-fighting genes. Since the completion of the Human Genome Project, scientists such as Dr. Amos Tanay and his interdisciplinary group of computer scientists, biologists, mathematicians, and physicists have begun to concentrate on understanding the intricate relationship between genes, the mechanisms that interpret them, and the physical processes governing how they are expressed, a field of research known as epigenetics.

Dr. Tanay and his team combine extensive computational work with the development of new experimental systems to study genomes and epigenomes as they change in cancer. They are particularly interested in the dynamics of DNA methylation: the addition of a methyl group (one carbon and three hydrogen atoms) to a gene, which is associated with the reduction, or even silencing, of the gene’s expression. The importance of DNA methylation in cancer was highlighted in Dr. Tanay’s recent in vitro study of prostate cancer cells. He and his team found that silent accumulation of changes in DNA methylation may be progressively eroding the cell’s capability to respond to signals, thereby impairing the natural defense program of the cell against malignant processes. Interestingly, they obtained similar results when studying another epigenetic “silencing” feature, called polycomb repressive complexes, which set prostate cancer cells apart from their normal counterparts. The team’s data suggests that the two silencing mechanisms act in parallel to reprogram the cancer epigenome and provide researchers with a mathematical model by which such reprogramming can be understood and challenged.

Dr. Tanay and his group are also shedding light on how genetic regions that lie outside the known protein-coding regions contribute to tumorigenesis. In a recent study with researchers
and cancer specialists at Harvard, MIT, and UCLA, Dr. Tanay’s lab explained how a particular genomic region that is far from any known protein coding gene can genetically increase the risk for many cancers, including prostate, breast, and colon tumors. Modern genetic studies have revealed numerous regions that are associated with increased risk for cancer but are remote from classical cancer-related genes. The mechanisms associating these regions with target genes are rarely understood and so the ability to develop new therapies and diagnosis based on such genetic studies remained limited. The team is now developing high throughput DNA sequencing methods for globally measuring and modeling the physical proximity among remote genetic elements, allowing interpretation of results from genetic studies and better understanding of the many faces of cancer genomes and epigenomes.

Dr. Tanay’s research is supported by Pascal and Ilana Mantoux, Israel; the European Union Seventh Framework Programme for Research and Technological Development; and the Israel Science Foundation.
The group of related proteins known as the “tumor necrosis factor” (TNF) family plays an important role in keeping us healthy. These natural immune hormones are crucial in the inflammatory process and other immune defense mechanisms. As their name implies, some TNF family members have the ability to destroy tumors. When functioning normally, the TNF family members execute their role by recognizing infected or tumor cells and initiating a number of immune mechanisms that act to induce the cells’ destruction, thereby restricting the spread of diseased cells.

Prof. David Wallach was not only one of the first researchers to isolate TNF; he was also the first to isolate the TNF receptors, proteins located on the cell membrane that transfer TNF’s cell death messages into the cell. The receptors isolated by Prof. Wallach are now used in medication for effective treatment of chronic inflammatory diseases to which TNF contributes.

One of Prof. Wallach’s research aims is to elucidate the mechanisms that regulate the function of two cellular molecules activated by TNF: caspase-8 and NIK. Both an absence of caspase-8, which plays a crucial role in the initiation of cell death, and excessive activity of signaling molecules like NIK are known to contribute to the emergence of tumors.

In addition to mediating cell death, caspase-8 was found to be frequently deficient in certain kinds of cancer, including neuroblastoma and small cell lung carcinoma. The studies of Prof. Wallach’s group suggest that caspase-8 deficiency contributes to the development of these cancers both by its effects on cells,
resulting in enhanced mutations, and by facilitating the production of inflammatory mediators. Further clarification of the irregularities of cell cancer function resulting from caspase-8 deficiency will, it is hoped, indicate ways to supplement for its absence.

In regard to NIK, Prof. Wallach’s group found that it is involved with the activation of proteins that control cell growth, cell survival, and inflammation. Mutations resulting in NIK over-activation lead to enhanced cellular activities that greatly contribute to the development of several cancers, including multiple myeloma and pancreatic carcinoma. Prof. Wallach’s current NIK studies are aimed at exploring the mechanisms of NIK action and developing drugs that will inhibit the function of NIK.
In Appreciation

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The **M. D. Moross Institute for Cancer Research**, directed by Prof. Yoram Groner from the Department of Molecular Genetics, serves as the central and primary entity in facilitating collaborations among the more than 50 research groups at the Weizmann Institute working on cancer-related topics, and fostering expansion into clinical research efforts and applications. Many of the studies benefitting from the support of the Moross Institute have generated valuable insights into cancer diagnostics and therapies.
Additionally, a network of institutes, centers, and research schools support Weizmann Institute research on specific aspects of cancer research:

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