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Although most of the cells in our body are normally in a differentiated state, they still retain the capacity to proliferate and invade. These properties, typically dormant in adult cells, are essential for many processes during embryonic development. And in the mature organism, too, these properties are often required for the daily maintenance of tissue integrity, such as replacing aged or dead cells. But when a cell loses control of these highly regulated capabilities, typically due to a genetic mutation, it enters a state of uncontrolled proliferation—cancer.

This initial change, however, is usually not sufficient to drive cancer growth beyond a few millimeters. To proliferate and metastasize, the newly born tumor must overcome many internal and external barriers. Although most cancers progress through specific steps, cells can follow multiple paths to reach each milestone. The multiplicity of mechanisms for tumor progression represents one of the main problems in combating cancer. This is because these various mechanisms provide bypass routes that allow tumors to evade therapy.

Many scientists at the Weizmann Institute are working to elucidate this complex, multi-stage progression process and reveal common cancer themes. They are also seeking to delineate the critical steps that enable specific cancers to evolve to the aggressive, metastatic version of the disease, which is so difficult to treat and cure. This booklet summarizes some of these most recent pursuits by Weizmann Institute scientists and their laboratory teams.

To proliferate, cancer cells must resist built-in cellular mechanisms put in place to induce the self-death of aberrant cells. They also gradually accumulate modifications that enhance their ability to progress and invade. Such changes can be found in many cellular processes, including gene expression, protein synthesis, and metabolism, as studied by Profs. Rivka Dikstein, Chaim Kahana, and Talila Volk.

The rise over the past decade of sophisticated technologies and analysis tools for the examination of genome-wide gene expression and whole-genome sequencing has made the DNA changes that accompany cancer progression more accessible for direct analysis than ever before. Weizmann Institute scientists such as Dr. Ido Amit and Prof. Eytan Domany are leaders in developing and applying these platforms to cancer research. These two scientists are using their innovations to reveal the changes that accumulate in the tumor genome as cancer progresses and how these modifications affect the tumor and its resistance to drug therapy.

Prof. Yardena Samuels exploits the ability to sequence the genome of cancer cells in order to identify the melanoma driver mutations—those directly responsible for the progression of the disease. Driver mutations provide important therapeutic targets, since inhibiting them could block tumor progression.

The rapid proliferation of cancer cells results in their exposure to a harsh environment where oxygen and nutrients are scarce. Under such conditions, the fittest cells have a clear advantage, resulting in the survival of the more aggressive, harder-to-treat cells. Prof. Menachem Rubinstein studies the response-to-stress mechanisms that tumor cells implement, critical for further expansion.

If that were not enough, a tumor must also overcome the suppressive activity of the surrounding tissue in order to induce the growth of new blood vessels that import the supplies it needs to thrive, a topic explored by Profs. Michal Neeman and Rony Seger. Another cancer concern is evading the search-and-destroy sentinels of the immune system, an issue addressed by Dr. Guy Shakhar.

The manifestation of cellular changes in cancer cells is not limited to the rate of proliferation alone. Profs. Avri Ben-Ze’ev and Benjamin Geiger study cellular adhesion and migration, both critically important for invasion and metastasis.

A breadth of research on cancer progression from a variety of approaches—like that conducted at the Weizmann Institute—is required to reach a comprehensive understanding of the complicated mechanisms that enable tumor progression and colonization of distant organs to form metastases. Only with such insight can science and medicine devise effective and targeted therapies and preventative tools.
Personalizing cancer treatment

Dr. Ido Amit’s genomics tools may one day be used by doctors to identify a patient’s exact cancer variant and state of tumor progression, allowing for accurate drug-patient matches.

What exactly do we do when we are asked to guess a person’s age? We typically check for height, wrinkles, the appearance of white hair, and so on. We do so because we know that, as we mature, our body undergoes predictable changes. This is also the case with cancer cells. As tumors expand and metastasize, their features evolve: Additional mutations are incurred, the DNA is structurally modified, the expression of proteins is altered, and the surrounding tissue is visibly affected. Being able to identify each stage’s unique signature is key to personalizing cancer treatment. This information will provide physicians with the knowledge they need to both pinpoint the exact disease variant and determine the best course of action based on the tumor’s exact degree of progression.

Reaching such a level of knowledge is a major endeavor; there are more than 200 types of known cancers, many of them with numerous molecular circuits driving the cancer phenotype. This line of research requires the development of advanced methods for profiling the genetic expression of cells and the creation of a set of reliable markers for the various stages of progression. This is exactly what Dr. Ido Amit is doing. The laboratory of Dr. Amit, who joined the Weizmann Institute in 2011, is creating next-generation sequencing platforms that can be used to profile malignant cells.

Genomic variation, however, does not refer only to sequence changes in the genome, i.e., mutations. Genomic output is also dependent on the way the DNA is folded and on the binding of structural and regulatory elements to it (a field called epigenetics). Dr. Amit’s team is also addressing the need to characterize such non-genomic modifications.

Dr. Amit’s study of the role of the immune system in cancer exemplifies his innovative research approach. The immune system is a double-edged sword when it comes to cancer. On the one hand, it protects healthy individuals from developing tumors; on the other hand, cancers manipulate the immune system in order to grow and incur additional mutations. Dr. Amit is applying his genomics methods to figuring out how cancers “convince” the immune system to change sides. This study entails profiling the global gene expression and epigenetic signatures of immune system cells derived from healthy animal models and those with liver cancer at different progression states. The idea is that the genetic and epigenetic changes revealed by the comparative analysis of the profiling results will lead to the identification of the key molecules and pathways that were altered in the immune cells. Every such modification is a potential point for medical intervention.

Dr. Amit’s research is supported by the M. D. Moross Institute for Cancer Research; the Abramson Family Center for Young Scientists; the Abisch Frenkel Foundation for the Promotion of Life Sciences; the Leona M. and Harry B. Helmsley Charitable Trust; Drs. Herbert and Esther Hecht; Sam Revsky; the Estate of Ernst and Anni Deutsch; the Estate of Irwin Mandel; the European Union Seventh Framework Programme for Research and Technological Development; the Human Frontiers Science Program; and the Israel Science Foundation.
Studies of inherited CRC revealed that in 85 percent of such patients the primary mutation targets a single signal-transduction pathway, the Wnt pathway. A key component in the Wnt pathway is β-catenin, a protein involved in the regulation of gene expression and the formation of cell-to-cell adhesions. When inappropriately activated, as is the case in various human cancers, β-catenin acts as an oncogene, activating genes that control cell growth and/or tumor cell invasion into new tissue. One of Prof. Ben-Ze’ev’s lines of research focuses on the β-catenin-mediated changes in gene expression and cell-to-cell adhesion in CRC.

A major goal in β-catenin-related cancer research is to identify and define the roles of its target genes that are activated during tumor development and metastasis. Detection of such genes might help in providing new markers for cancer diagnosis, and their targeted inactivation could suppress the formation and spread of cancer. In recent years, Prof. Ben-Ze’ev’s lab identified several β-catenin target genes in CRC cells, including the neuronal cell-adhesion receptor L1.

In the process of brain formation, L1 plays an important role in neuronal migration and guidance. Unexpectedly, this neuronal receptor was detected in a subpopulation of CRC cells at the invasive CRC tissue front. Interestingly, this subpopulation also displays highly active β-catenin signaling. When the scientists overexpressed the L1 gene in CRC cells, they observed an increase in the rates of cell growth and cell motility. L1 overexpression also promoted the metastasis of these CRC cells to the liver.

Additional studies from Prof. Ben-Ze’ev’s lab identified some of the signaling pathways that are unleashed when L1 is expressed in CRC cells. Of note, when his team disrupted the activity of these signaling pathways, the invasive and metastatic capacities conferred by L1 in CRC cells were essentially blocked. Prof. Ben-Ze’ev believes that unraveling the mode of action of these genes may provide further targets for therapy and early diagnosis of CRC.
Prof. Rivka Dikstein is studying the mode of operation of a protein that, when active, continuously contributes to tumorigenesis, metastasis, and the increased resistance of tumors to chemotherapy.

Prof. Rivka Dikstein investigates one of the most basic topics in biology—how genes are activated in order to produce proteins. Her study of the protein NF-kappaB highlights the importance of this research field to understanding cancer processes and to devising refined methods for treating the disease.

NF-kappaB oversees the expression of many genes needed for the smooth operation of the cell. When inactive, NF-kappaB resides outside the nucleus, in the cell’s cytoplasm. It is called into action only in response to specific extracellular signals, which prompt it to relocate to the nucleus, where it delivers its message to the DNA.

While the influence of NF-kappaB in healthy cells is transient, in cancer and inflammatory diseases involving NF-kappaB, its activity becomes permanent. Scientists have shown that this state of constant activation contributes to the spread of metastatic cells and the increased resistance of tumors to chemotherapy. NF-kappaB is also tightly linked to tumorigenesis, or tumor formation, through its ability to suppress cell death and to influence cellular processes that lead to uncontrolled growth. It is these findings that have made the NF-kappaB pathway an important target for cancer drug development.

While much of the research is focused on the stage of NF-kappaB activation, Prof. Dikstein is looking at the end point, that is, NF-kappaB’s effects on its more than 70 known target genes. Previous research in her lab determined how, in principle, the genes regulated by NF-kappaB are activated rapidly in response to extracellular signals, particularly those signals threatening cell survival. Subsequent studies by Prof. Dikstein revealed how NF-kappaB influences transcription, the first and most important stage of gene expression.

Transcription comprises three main stages—initiation, elongation, and termination. Prof. Dikstein showed that NF-kappaB primarily regulates the second stage, elongation. NF-kappaB functions as a foreman, “calling in from break” its crew of elongation factors. The fruits of their labor are genetic copies (i.e., mRNA molecules) of the genes NF-kappaB oversees, which are then used as templates for the synthesis of proteins.

Prof. Dikstein’s team recently revealed a previously unknown regulatory mechanism that offers a potential explanation for chronic NF-kappaB activation. One of the proteins in NF-kappaB’s elongation crew is DSIF. Together, NF-kappaB and DSIF promote the expression of a subset of genes specifically designed to shutdown NF-kappaB itself. Therefore, cells lacking DSIF or harboring a faulty variant have an increased chance of exhibiting chronic NF-kappaB activation, a state favorable for cancer cells.

Prof. Dikstein’s findings may have consequences for cancer therapy. Because NF-kappaB has a broad range of biological effects, impeding its activity directly would, most likely, engender significant unwanted side effects. However, indirect interference through a molecule such as DSIF, which modifies the actions of only a subset of NF-kappaB target genes, might ensure more specific targeting.
Prof. Eytan Domany | Department of Physics of Complex Systems

Identifying cancer signatures

Three decades of training and research in statistical physics enabled Prof. Eytan Domany to develop physics-based methods to cluster objects into well-defined groups. These methods have been applied, for example, to identifying areas with similar topographical characteristics on satellite maps. A chance encounter with a fellow physicist around 12 years ago, however, led to a complete shift in Prof. Domany’s research focus. That physicist noted that Prof. Domany’s clustering models can be extremely useful in the analysis of gene expression. Excited by the new frontiers waiting to be explored in biology, Prof. Domany redirected his attention to the mammalian cell.

There are around 20,000 genes in the human cell, each expressed under different conditions at different levels. Diseased cells, particularly cancerous ones, exhibit characteristic expression profiles. This is because a mutated gene will typically induce cellular events that increase, decrease, or altogether stop the expression of other genes. As a tumor progresses, it incurs additional mutations, further altering its expression profile. This is where Prof. Domany’s data analysis methods come into play.

Prof. Domany’s research tools are ideally suited to transforming the massive array of data generated by gene expression experiments into a clear readout that highlights the cell’s unique signature. His scientific approach is in high demand, denoted by the more than 30 collaborations he has struck with clinical and basic researchers from the Weizmann Institute and around the world, most of them focused on cancer (e.g., colon, breast, prostate and cervical tumors and leukemia).

One of the first biological issues Prof. Domany’s team tackled was the role of chromosomal instabilities in cancer. As tumors progress, they exhibit increasing deviation from the standard two-copies-per-chromosome profile. A heated scientific debate centered on whether this was an outcome or one of the actual causes of the disease. Prof. Domany and his collaborators studied chromosomal instability in patients with leukemia, glioblastoma, and colon cancer, as well as in artificially induced tumors. In all the cancer lines investigated, the results pointed to chromosomal instability as an event that occurs early on in cancer development, suggesting that it is a causative factor.

One of Prof. Domany’s exciting new directions is the development of sophisticated algorithms that determine the activities in which tumor cells deviate from normal ones. The algorithms split the genes into groups based on functionality—e.g., growth-promoting or DNA-repair genes—and assess, using the expression profiles of the genes of each group, the deviation of each functionality from normal. Prof. Domany believes that this line of research may form the basis for personalized medicine, where physicians enter a cell’s gene expression profile into a computer program and receive as output the pathways that are malfunctioning, as well as prognosis and guidance for effective therapy.

Prof. Domany’s research has been supported by the Leir Charitable Foundations; the Minerva Foundation; the Mario Negri Institute for Pharmacological Research-Weizmann Institute of Science Exchange Program; the Wolfson Foundation; the European Union Sixth Framework Programme for Research and Technological Development; the German-Israeli Project Cooperation; the Israel Ministry of Science and Technology; the Israel Science Foundation; and the National Institutes of Health, U.S. He is the Director of the Kahn Family Research Center for Systems Biology of the Human Cell and the incumbent of the Henry J. Leir Professorial Chair.

Prof. Eytan Domany is developing sophisticated algorithms capable of determining the activities in which tumor cells deviate from normal ones.
Halting cell migration in its tracks

Mapping the migration of tumor cells—the process that occurs in cancer metastasis—is a key step in finding drugs that can stop migration, and thus arrest the spread of cancer.

The most deadly aspect of cancer is its ability to spread, or metastasize. This highly complex process involves a cascade of critical events that affect cell behavior and fate. An early step in the process entails the loss of tight adhesions between the cancerous cells and the surrounding tissue that would normally hold them in place. Once “dislodged,” the cells are free to invade new tissue, and when they encounter blood or lymphatic vessels, they cross the vessel wall and are swept away in the flow to distant organs and tissues, into which they may infiltrate, then proliferate and form a new cancerous site.

Given the large number of cells within a primary tumor, it is not surprising that many new metastases develop, too numerous for surgical excision and, often, too many to be treated effectively with chemoradiotherapy. Considering the importance of the migratory process for the efficient dissemination of cancerous cells, it is rather surprising that attempts to develop migration blockers that act as anti-metastatic drugs are quite scarce.

In search of potential molecular targets for the development of such drugs, Prof. Geiger and his team initiated a study to pinpoint the genes and proteins involved in cell migration. The goal was to carry out a series of high-throughput screens in which the expression of candidate genes are modified and the effects of these modifications on cell migration are assessed. However, systematic screening of cell migration can be a painstaking, highly demanding process—seemingly incompatible with a high-throughput approach, which allows a researcher to quickly and simultaneously conduct thousands of chemical or genetic tests.

Prof. Geiger and his research team did not let this obstacle stand in their way, and skillfully developed a novel high-throughput screening platform especially suited for the tracking of cell migration. The method, created in collaboration with departmental colleague Prof. Zvi Kam, requires the use of advanced microscopy and special “home-made” quantitative image processing software. The experiments involve taking still images of the tracks formed by cells during their migration along a surface, which is uniformly covered with tiny beads. When cells move across such a surface, they push the beads aside, forming clear tracks that can be visualized. This platform is ideal for “capturing” cells that vary from the norm in their migratory pattern, suggesting the modified genes they contain are involved in cell movement regulation.

Using such screens to examine the migration of single cells, or of small groups of cells, also known as “collective migration,” the scientists identified novel genes that participate in either driving or hampering the migratory process, changing its speed, or altering its persistence. The discovery of such novel migratory mechanisms advances the search for specific drugs that could block metastatic cell migration, thereby reducing the risk of cancer metastasis.

Prof. Geiger’s research is supported by the Adelis Foundation, the Leona M. and Harry B. Helmsley Charitable Trust; IIMI, Inc.; the Mario Negri Institute for Pharmacological Research-Weizmann Institute of Science Exchange Program; the Estate of Alice Schwarz-Gardos; the European Union Seventh Framework Programme for Research and Technological Development; the Israel Science Foundation; and the National Institutes of Health, U.S. He is the incumbent of the Professor Erwin Neter Professorial Chair of Cell and Tumor Biology.
Prof. Chaim Kahana of the Department of Molecular Genetics discusses the role of polyamines in cancer research.

**Targeting cancer’s little helpers**

Prof. Chaim Kahana’s knowledge about chemicals that support cancerous growth—polyamines—may lead to innovative therapeutic strategies for selectively eradicating cancer cells.

When executing growth commands, all living cells call upon chemical assistants called polyamines, which are found everywhere: in the nucleus, in the cytoplasm, and also next to the membrane. It is not known how exactly these chemicals assist cellular growth, but whatever their precise role, the increased presence of polyamines in all vigorously dividing cells, including cancer cells, has turned them into prime suspects in supporting cancerous growth.

When cells are deprived of polyamines, they cease to proliferate, but how does polyamine depletion block cell growth and proliferation? Recent studies in Prof. Kahana’s lab revealed that this block is a result of the establishment of stress in the polyamine-depleted cells. Detailed investigations point to it being a yet-to-be-determined type of stress that, surprisingly, does not lead to cell death (i.e., apoptosis), which is usually the consequence of prolonged cellular stress. Rather, cells lacking polyamine enter a self-imposed state of growth arrest, halting all non-essential processes until the crisis is over.

His research has also provided clear evidence for the existence of a finely tuned, auto-regulatory circuit that governs cellular polyamine levels. In the center of this circuit are the antizymes. This family of proteins regulates polyamine transport across the cell membrane through a yet-unknown mechanism. Prof. Kahana has shown that antizymes also bind to ornithine decarboxylase (ODC), the first enzyme in the polyamine biosynthesis pathway targeting it for degradation, and thereby shutting down polyamine production. Just like the polyamines, ODC too has been linked to cancer: Its overexpression has been found to induce cellular transformation in some cases, and its activity is increased in a variety of malignancies.

In addition, the antizyme inhibitor (AzI) also regulates polyamine metabolism by negating antizyme functions. Since antizymes are more strongly attracted to AzI than to ODC, when AzI is present antizymes preferentially bind to AzI, thereby rescuing ODC from its pathway to destruction. Prof. Kahana is currently examining the effect of AzI overexpression on cell proliferation and transformation.

His data suggests that the ability of AzI to destroy antizyme function, which leads to increased ODC activity and polyamine uptake—indicates AzI’s growth-promoting and oncogenic potential. Conversely, the ability of antizymes to suppress cellular proliferation by inhibiting polyamine production and uptake infers that antizymes act as tumor suppressors.

Prof. Kahana is using his vast knowledge on polyamines to develop innovative therapeutic strategies that rely on the control of cellular processes in which these molecules are involved. One such experimental approach is geared toward selectively eradicating cancer cells while sparing healthy ones. This protocol is based on the differences between the polyamine metabolic activities of healthy versus cancer cells.

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Prof. Kahana’s research is supported by the Cure Foundation and the Israel Science Foundation. He is the incumbent of the Jules J. Mallon Professorial Chair of Biochemistry.
The cancerous side of sex hormones

Changes in the hormonal milieu that accompany menopause may lead to increased metastatic implantation of ovarian tumors on the abdominal cavity.

For many years, scientists were baffled by seemingly contradictory findings concerning ovarian carcinoma. On the one hand, studies suggested that ovulation is positively correlated with the disease. On the other hand, it was evident that the prevalence of ovarian cancer rises dramatically—by 50-fold—when ovulation ceases, i.e., once menopause sets in.

Prof. Michal Neeman’s research offers an elegant explanation for this discrepancy. She has postulated that while malignant transformations may arise during the reproductive period, the budding tumors remain dormant. This is because the menstrual cycles’ hormonal fluctuations do not allow for the formation of an environment conducive of cancer growth. Menopause, however, leads to the formation of a new stable hormonal milieu, one supportive of growth of latent tumor buds, if present.

So which hormones are responsible for this pro-cancer terrain? Prof. Neeman believes the two main culprits are the luteinizing and follicle-stimulating hormones (LH and FSH), both of which are present in the reproductive system at high levels post-menopause. It is these two hormones that, when surging in unison, induce ovulation in the menstruating female. But they also stimulate processes desirable for a budding tumor. For instance, Prof. Neeman has shown that these hormones promote the formation of new blood and lymph vessels, which a tumor needs in order to import supplies and remove waste, respectively.

Prof. Neeman has revealed that LH and FSH also assist ovarian tumors to overcome a major barrier to their metastatic spread—the adhesion of the malignant mass to the abdominal cavity, which frees the primary tumor to shed cells that can go on to penetrate the liver, colon, or stomach. Suppression of LH and FSH actually reduced the likelihood of both blood vessel formation (i.e., angiogenesis) and tumor adhesion and metastasis, resulting in protection from ovarian cancer.

Prof. Neeman is now working to characterize the mechanism by which the two hormones promote ovarian carcinoma progression. Using an innovative magnetic resonance imaging reporter probe developed in her laboratory, she was able to demonstrate that FSH and LH increase the expression of two types of proteins (i.e., HA synthases and hyaluronidases) that synthesize and degrade the massive polysaccharide hyaluronan. Found on the external surface of tissues, hyaluronan acts as a buffer, preventing organs from sticking to each other. The enhanced activation of HA synthases and hyaluronidases leads to the removal of this buffer, opening the way to ovarian cancer invasion. Interestingly, hyaluronan suppresses angiogenesis, but some of the products of its degradation produce the opposite effect. Therefore, by provoking a state of constant hyaluronan synthesis and degradation, FSH and LH not only contribute to tumor metastasis but also induce angiogenesis.
The stressful life of a tumor cell

What happens to tumor cells when they experience intense stress— which die and which live and continue to proliferate?

When we find ourselves in stressful situations there are different coping mechanisms that we tend to utilize. We sometimes try to find a solution to resolve the source of the stress, or we can eliminate or detach ourselves from its cause. Cancer cells too must find ways of coping with stress.

As solid tumors grow, they trigger extensive vascularization (blood vessel formation) to provide nutrients and oxygen and remove waste. Yet, because the tumor is constantly growing, there is a continuous shortage of supplies and accumulation of waste, leading to cell stress and subsequent death due to a lack of nutrients, a process termed necrosis. In other words, there is a constant balance between cell proliferation and cell elimination. Only if the rate of growth is greater than that of death will the tumor continue to expand.

Prof. Menachem Rubinstein is studying the regulation of stress in tumor cells, focusing on its effect on the endoplasmic reticulum (ER), a cellular organelle in which many of the cell’s proteins are synthesized. In one of his recent studies, Prof. Rubinstein set out to explain how melanoma tumor cells survive and proliferate despite extensive ER stress due to nutrient shortage and waste accumulation. His focus was on the proteins LAP and LIP. Prof. Rubinstein and his then PhD student, Dr. Ofir Meir, found that LAP promotes tumor progression, whereas LIP inhibits the progression. Of note, LAP is known to be over-expressed in many tumor types, including gastric, breast, prostate, non-small lung, Wilm’s, colorectal, prostate, ovarian, endometrial, and gliomas.

What Prof. Rubinstein and his research group discovered, to their surprise, was that while LAP promoted melanoma tumor progression, it did not do so by increasing the rate of cell division, nor did it reduce the rate of apoptosis—the two extensively studied mechanisms of cancer progression; in fact, LAP appeared to even slow down the rate of cell division. Rather, they found that LAP allowed tumor cells to withstand stress due to nutrient and oxygen shortage, thereby reducing the likelihood of death-by-necrosis. This finding reveals a third pathway that cancers utilize to overcome natural barriers in order to thrive.

Prof. Rubinstein believes that LAP’s protective capabilities are why it is over-expressed in many solid tumors. His research also suggests that, in normal cells, the LAP/LIP mechanism regulates the transition from the protective to the death-promoting phase initiated by ER stress. It is the hope that through the identification of the exact mechanisms activated by LAP, new potential targets for pharmaceutical intervention will be discovered.
Prof. Yardena Samuels is identifying genetic mutations that drive melanoma, the deadliest skin cancer.

Prof. Yardena Samuels uses the power of DNA sequencing to identify new groups of genetic mutation involved in the deadliest form of skin cancer, melanoma. Prof. Samuels joined the Weizmann Institute in January 2013 after establishing a successful research group at the National Institutes of Health (NIH) in Bethesda, Maryland. Melanoma is the most common fatal skin cancer. In the United States alone, its incidence has increased 15-fold over the last 40 years—faster than any other malignancy. Because it has such a high rate of mutation, melanoma is one of the most challenging solid cancers to study.

Prof. Samuels’ unique research approach entails the use of the most advanced DNA sequencing tools available to perform sophisticated functional genetics analyses of the mutations in late-stage melanoma. At the NIH, she and her team were the first to demonstrate that, contrary to previous beliefs, the metalloproteinases—enzymes that break down various proteins—may function as tumor suppressors rather than oncogenes, genes that have the potential to cause cancer. In a separate study, her team genetically surveyed the protein tyrosine kinase (PTK) family and determined that one PTK gene, ERBB4, is mutated in 19 percent of patients’ tumors, making it the most frequently mutated PTK gene in melanoma.

She also found that melanoma cells that harbor an ERBB4 mutation were dependent on the presence of that mutation for their growth. When the scientists exposed melanoma cells to the FDA-approved drug lapatinib, which inhibits ERBB activities, they observed a greater reduction in proliferation in the cells expressing the mutant ERBB4 than cells expressing normal ERBB4. Based on this study, Prof. Samuels has now initiated a clinical trial using lapatinib in melanoma patients harboring ERBB4 mutations. Patients for this clinical trial are being recruited from two different sites, the Surgery Branch of the National Cancer Institute and the Memorial Sloan Kettering Cancer Center.

As there remain a significant number of melanoma patients without a targetable mutation, further identification of alterations in new genes is urgently required. Therefore, at the Weizmann Institute Prof. Samuels plans to analyze the melanoma genome using whole genome and whole-exome sequencing (an approach that decodes the 1-2 percent of the genome that contains protein-coding genes) in order to identify the key genes that drive melanoma progression. She will then use this information to conduct in-depth, functional analyses of the deregulated pathways to gain further insight into the disease. Prof. Samuels will work closely with the Israel National Center for Personalized Medicine at the Weizmann Institute of Science to enable more personalized treatment for melanoma.
**Targeting cancer’s supply system**

Prof. Rony Seger is revealing some of the molecular mechanisms by which the protein PEDF is able to inhibit tumor growth.

The formation of new blood vessels is essential for the growth of tumors beyond a few millimeters. This process, called angiogenesis, is regulated by several natural compounds, including the protein PEDF. Many findings have revealed PEDF’s clear link to cancer. Most notably, the presence of PEDF inhibits tumor growth and metastatic potential. But how does PEDF actually promote tumor suppression? This is what Prof. Rony Seger is trying to find out. His group has already revealed some of the mechanisms affecting PEDF’s ability to keep tumors in check.

One of the common mechanisms by which proteins are controlled is phosphorylation: the addition of a phosphate unit to a specific site on a protein. There are, however, several sites to which a phosphate can attach, with each variation potentially causing a different change in the protein’s function—for instance, turning a particular activity on or off.

Previous research in Prof. Seger’s lab revealed that PEDF molecules can be phosphorylated on three sites. To decipher how phosphorylation contributes to PEDF’s anti-angiogenic function, the scientists created PEDF mutants with specific phosphorylation profiles, including no phosphorylation, as well as mono, double, and triple phosphorylation.

What Prof. Seger’s team found when comparing the mutants’ behavior was that the triply phosphorylated mutant serves as a much stronger anti-angiogenic factor than PEDF, with one of the doubly phosphorylated mutants coming in second. In line with this finding was the discovery that these two mutants inhibit tumor growth better than PEDF itself in breast, colon, and glioblastoma cancer models.

Prof. Seger and his group also showed that, aside from the anti-angiogenic activity, PEDF acts independently to alter the activity of the neurons with which it comes into contact. The scientists observed that while the triply phosphorylated variant also exhibited neurotrophic capabilities, the doubly phosphorylated mutant did not. The double mutant could be particularly useful in treating cancers that cause damage to the blood-brain barrier, which under normal conditions prevents most circulatory molecules from entering the brain. Since the double mutant has no effect on neurons, it will inhibit the tumor without influencing the function of the “exposed” brain.

As for the mode of impact, Prof. Seger’s research indicates that PEDF and its mutants specifically target the cells responsible for building the tumor’s vasculature, prompting them to commit suicide—a process called apoptosis—thereby preventing the formation of the supply system needed for cancer growth. However, they do not affect cancer cell survival, suggesting that PEDF and its mutants’ antitumor influence are indirect, achieved mainly through their anti-angiogenic activity.

These findings have implications for improving the properties of PEDF as a tumor suppressor and encouraging the development of PEDF mutants as specific, angiogenesis-targeting anticancer agents.
Dr. Guy Shakhar’s findings suggest that the treatment of melanoma can be improved by enhancing, rather than restricting, oxygen supply to tumors in patients undergoing immunotherapy.

The two faces of tumor vascularization

In order to survive and thrive in the body, a newly formed tumor must attract fresh blood vessels in a process known as angiogenesis. Without a constant supply of oxygen and nutrients from these vessels, the tumor will suffocate, starve, and wither away. It is not surprising, then, that the recent decade has witnessed a boom in research directed at stifling angiogenesis in cancer patients. This research has, in turn, produced tools which prolong the life of patients suffering from several forms of cancer, such as colorectal, lung, and breast tumors. It has failed, however, to impact other cancers, such as melanoma, the most dangerous type of skin cancer.

An alternative approach to treating cancer, which has recently gained momentum, is immunotherapy, in which cells of the immune system, typically cytotoxic T cells (CTLs), are recruited to fight cancer cells. Treatment with new drugs, which set CTLs loose, was shown to improve the prognosis of melanoma patients. However, CTL-mediated immunotherapy can only be carried out effectively if there is a constant source of oxygen—the very same ingredient necessary for angiogenesis and cancer growth. In other words, oxygen supply can simultaneously promote tumor growth and its destruction. Dr. Shakhar is trying to elucidate this interplay between CTL-mediated tumor destruction and tumor proliferation.

While studying tumors resected from melanoma patients, Dr. Shakhar’s group discovered that CTLs first concentrate around the tumor’s periphery and only later spread through the entire tumor to remove the target cells. To fully characterize this dynamic process, Dr. Shakhar’s group adapted a novel microscopic technique called two-photon imaging to monitor—in real time—the interactions between CTLs and tumor cells in mice. Using this method, Dr. Shakhar’s group discovered how the architecture of blood vessels dictates the pattern of tumor elimination by therapeutic CTLs delivered into the mice.

The process evolves in the following manner: Initially, the injected CTLs enter the tumor through blood vessels in its periphery; they then start crawling vigorously at their entry areas, never traveling far from flowing blood vessels. With time, CTLs form dense swarms that spread through the tumor and clear it by ganging up on individual tumor cells. Once they have identified their target, CTLs physically attach to it and release molecules that perforate its membrane in a highly-specific manner. Interestingly, tumor cells that cannot be molecularly recognized by the CTLS, even if located only micrometers away, are spared. The entire process is highly dependent on oxygen supply, as CTLs located too far from a flowing blood vessel cannot perform their duties.

Dr. Shakhar’s findings suggest that the treatment of melanoma can be improved by enhancing, rather than restricting, oxygen supply to these tumors in patients undergoing immunotherapy.
Scientists have found the protein Sam68 to be intimately associated with cellular transformation and cancer initiation and progression; its irregular forms or expression have already been linked to breast cancer, prostate cancer, and renal cell carcinoma. Understanding how Sam68 exacts its role and how it can be controlled may lead to novel therapeutic options for treating these and other cancers. Prof. Volk’s research on Sam68’s fruit fly counterpart, the protein HOW, could potentially offer this insight.

Just like Sam68, HOW regulates RNA metabolism in many tissues, and it has been found to be critical for fruit fly tissue differentiation and other embryonic development processes. Prof. Volk and her team are working to identify the RNA molecules to which HOW binds, reveal the nature of the binding process, and map HOW’s activity during embryonic development.

Her team has already successfully characterized the exact sequence on the RNA molecule to which HOW binds. Using this code as an identity badge, the scientists screened the RNA output of the various tissue cells during development to find all the other RNA molecules that are targets of HOW. They identified more than 30 such RNA variants, each with its own distinct tissue and temporal expression profile. This study led Prof. Volk to suggest that the differential RNA expression pattern enables the same regulatory protein—HOW—to control a wide range of processes at many locations. This is a convenient mechanism for an organism that needs to coordinate among various processes at a time of expedited growth.

One of Prof. Volk’s most recent findings is that adding a phosphorus atom to the HOW protein promotes its association with another HOW protein. This interaction enhances HOW’s RNA-binding capabilities. If Sam68 behaves in a similar fashion, targeting the process of Sam68-to-Sam68 association may offer an effective means of modifying Sam68’s activities in cancer cells.
In Appreciation

The Weizmann Institute of Science gratefully acknowledges the invaluable assistance of generous donors worldwide. These friends have contributed to cancer research and have joined us on this extraordinary journey of discovery for the benefit of mankind. As so many have participated in this endeavor, we list here only the institutes, centers, and major funds providing support for cancer research.

The M. D. Moross Institute for Cancer Research, directed by Prof. Yoram Groner of 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 benefiting from the support of the Moross Institute have generated valuable insights into cancer diagnostics and therapies.

Additionally, a network of institutes and centers support Weizmann Institute research on specific aspects of cancer research:

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