WHAT THE WEIZMANN INSTITUTE IS DOING

about Cancer

מכון ויצמן למדע

WEIZMANN INSTITUTE OF SCIENCE

M.D. Moross Institute for Cancer Research

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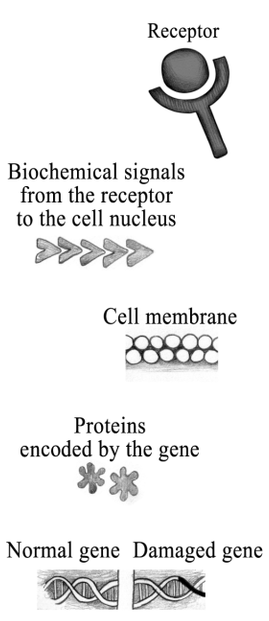
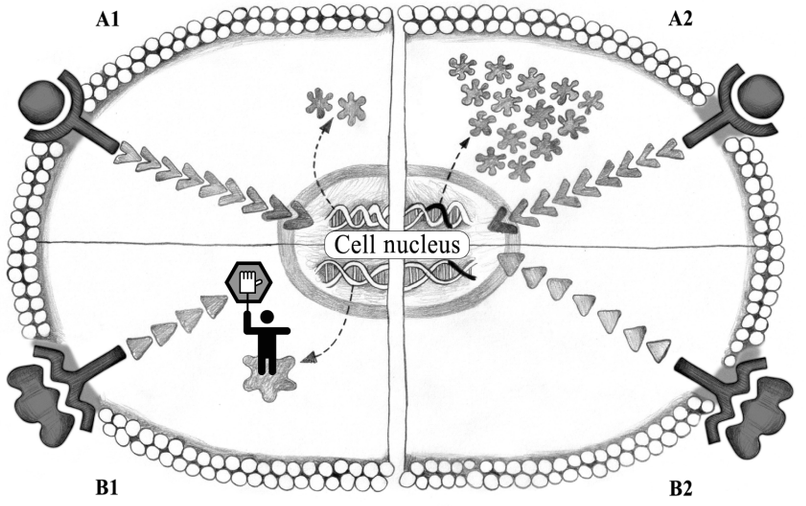
HOW CANCER DEVELOPS

STEP 1 Malignant Transformation





NORMAL GENES - CONTROLLED CELL GROWTH

A1
Proto-oncogenes (unmutated) trigger normal cell growth

B1
Tumor suppressor genes block growth signals as needed

DAMAGED GENES - ABNORMAL CELL GROWTH

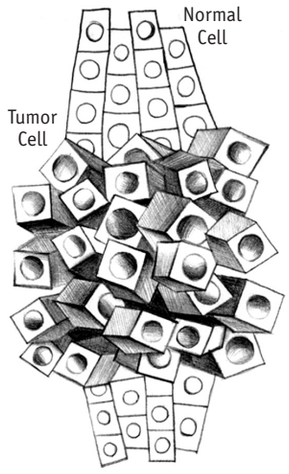
A2
Mutated oncogenes issue abnormal growth commands

B2
Mutated tumor suppressor genes fail to block growth signals

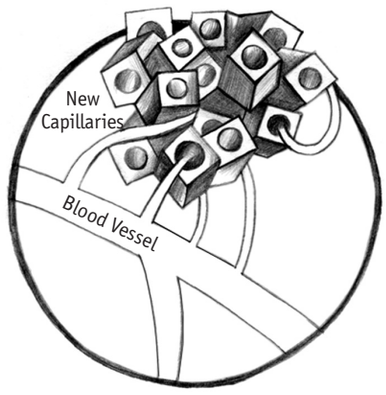
and how the weizmann institute

IN THE BODY

STEP 2 Tumor Growth

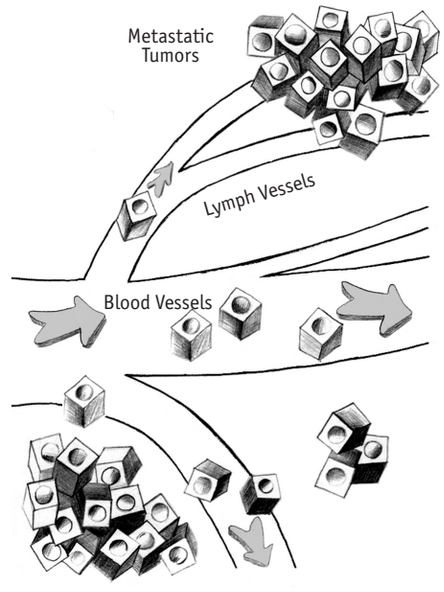


Abnormal growth is promoted. "Good neighborhood"/adhesion rules are ignored. Cells "forget" to commit suicide and live forever.



The tumor feeds itself by promoting an abnormal development of blood vessels.

STEP 3 Metastasis



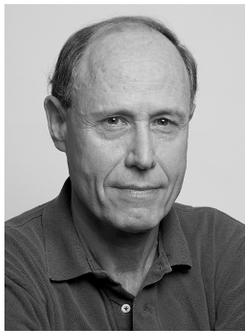
Malignant cells travel to distant locations via lymph and blood vessels. Metastatic tumors form at the new sites.

is working to prevent it

TAKING ACTION AT STEP 2

TAKING ACTION AT STEP 3

Introduction



Prof. Yoram Groner
Director, M.D. Moross Institute
for Cancer Research

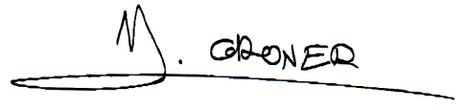
A new era is dawning in the battle against cancer. In the more than 30 years that have elapsed since U.S. President Richard Nixon "declared war" on cancer in 1971, scientists have made gigantic strides in charting the course of this affliction. We now know that cancer is a disease of damaged genes. We also know that it develops in multiple stages and takes many years, even decades, to unfold. We have learned moreover that there are hundreds of different cancers, each caused by a specific set of genetic defects, which is one of the major reasons that malignancy is so difficult to treat.

Thanks to this new understanding, the entire management of cancer promises to change. Genetic testing will make it possible to identify groups of people who are most prone to develop cancer and who must therefore take preventive measures. Non-invasive DNA analysis and improved imaging techniques will allow physicians to detect and diagnose cancer earlier. Finally, therapies will become more selective and precise. Rather than destroying tissues in bulldozer fashion as do the traditional chemotherapy and radiation treatments, they will serve as finer tools, carving out the tumor while sparing healthy tissues. It may even become possible to design tailor-made treatments to suit the patient's individual traits and genetic profile.

Cancer is a healthcare issue of vast scope. In the United States, for example, the various cancers combined claim more than half a million lives annually, a death toll second only to that caused by heart disease. Globally, cancer kills some six million people every year, according to the World Health Organization. Ironically, the rise in the incidence of cancer stems indirectly from our progress in science and technology: people in modern society live longer lives, but this prolonged life expectancy increases the risk of developing cancer. Fortunately, scientific progress also offers brighter prospects for beating cancer.

At the Weizmann Institute, several dozen research teams are attacking the problem from different directions; their studies are conducted within the framework of several research centers whose activities are coordinated by Weizmann's M.D. Moross Institute for Cancer Research. Important achievements are already on record: Weizmann scientists were the first to clone p53, a gene involved in more than half of all human cancers; basic research conducted at the Institute provided the foundation for the development of Glivec, the first in the upcoming generation of molecular drugs; and a number of cancer therapies developed at Weizmann are currently being tested in clinical trials.

In this publication, we describe the Institute's multi-faceted cancer research targets. Our ultimate goal: to understand what causes cells to become cancerous and what can be done to intervene in the progression of malignancy at its different stages.



Taking Action at Step 1

Malignant Transformation

Contrary to popular belief, getting cancer is not so easy. Although genes constantly sustain damage, in most cases this damage does not lead to malignancies: many mutations – ”spelling mistakes” in the letters of the genetic code – are successfully repaired; if the repair fails, the defective cell is often commanded to self-destruct. For a cell to undergo a malignant transformation – in other words, start dividing uncontrollably – up to 10 mutations must accumulate in the genetic code. That's why cancer is mostly a disease of old age: it may take several decades for the necessary number of mistakes to add up in the genes of a single cell. Most people die of other causes before cancer has a chance to unfold.

But how do spelling mistakes occur in the genetic code in the first place? Some are copying errors, “typos” that appear when a cell duplicates its genes before dividing into two daughter cells. Others occur when the cell suffers abuse from the environment, such as that inflicted by viruses, chemical carcinogens or radiation; or from internal aggressors, such as the highly reactive molecules called free radicals. Mutations can also be inherited; a parent can pass on to offspring a mutated form of a gene. Such unfortunate inheritance explains why cancer sometimes runs in families: several family members may carry the mutation that predisposes them to the disease. It also explains why some cancers occur early in life: the presence of inherited mutations speeds up malignant transformation.

Two types of genes play a major role in malignant transformation: oncogenes and tumor suppressor genes. When present in their normal form, these genes escort the cell through the healthy processes of growth and division. But when both these gene types contain fatal mistakes, the cell can embark upon a malignant course: a destructive, unchecked growth.

Environmental and Lifestyle Factors

Cancer is largely a preventable disease. Hundreds of thousands of lives could be saved annually if people avoided risky behaviors and exposure to carcinogens that push cells toward malignancy. Smoking tops the list, accounting for one-third of all cancer deaths in developed countries. A high proportion of fatal cancers can be blamed on dietary practices and lack of exercise. About 15 percent of cancers worldwide are caused by known infectious agents, including viruses, bacteria and parasites. Exposure to radiation and to cancer-causing chemicals can also damage genes, thus contributing to malignant transformation.

Viruses

Viruses account for a relatively small percentage of malignancies, but it was largely thanks to these infectious organisms that the roots of cancer were first uncovered. In the 1970s, scientists studying cancer-causing viruses showed that a virus could trigger tumor growth by turning normal genes into cancer-causing genes. This research touched off a hunt for latent cancer genes that continues to this day. Currently, research into the viral origins of cancer holds potential in two major areas: prevention of malignancies caused by viruses and, on a broader scale, gaining a better understanding of cancer mechanisms.

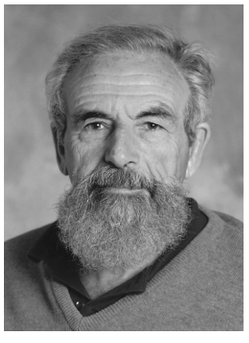
How does a virus manage to evade a cell's defenses against foreign invaders? What strategies does it use to take over the cellular machinery? These questions are addressed in the laboratory of **Prof. Yosef Shaul** of the Molecular Genetics Department. Shaul has discovered how hepatitis B virus, a major contributor to liver cancer, sabotages a cell's growth machinery: the virus has a regulatory gene that acts as a "molecular bridge" allowing it to reproduce inside the cell. The same mechanism may explain how hepatitis B triggers malignancy: this gene apparently allows the virus to shut down tumor suppressor genes in liver cells, causing these cells to undergo a malignant transformation. While Shaul continues to study the link between hepatitis B and liver cancer, his research has already led to the development of a hepatitis B vaccine tested in clinical trials by an Israeli biotechnology company. An estimated 350 million people in Africa and Asia suffer from hepatitis B, making this ailment a health problem of global proportions. If these infections were eradicated, a significant proportion of liver cancers could be prevented.

More recently, the study of viruses has led Shaul to the discovery of an important tumor suppressor mechanism. He focused his attention on one of the genes with which hepatitis B interacts – a major regulator of cell growth called c-Abl. Working with other Weizmann Institute researchers, Shaul found that c-Abl normally safeguards the cell against cancer: when DNA damage occurs, c-Abl recruits a tumor suppressor gene, and together they either prevent the cell from dividing or command it to commit suicide. But when either gene is mutated – by, say, exposure to a virus or to radiation – the risk of cancer soars.

Viruses can wear two hats when it comes to cancer. While some contribute to malignant transformation, others exert an opposite, protective effect, selectively destroying cancer cells but leaving healthy cells untouched. Veteran Weizmann Institute researcher **Prof. Emeritus Ernest Winocour** of the Molecular Genetics Department spent more than three decades studying the connection between viruses and cancer. He has clarified important aspects of viral behavior in malignancy while focusing his attention on members of the parvovirus family. In particular, he has been studying the adeno-associated virus, or AAV, which is unique in its ability to bind to a specific site on a human chromosome rather than, as other viruses do, simply invading the host cell in a general way. Winocour has clarified the mechanism by which AAV targets its specific site and suggested a way for incorporating this mechanism into gene therapy, including gene therapy of cancer. ●

If hepatitis B infections were eradicated, a significant proportion of liver cancers could be prevented

Prof. Yosef Shaul holds the Oscar and Emma Getz Professorial Chair



Prof. Ernest Winocour

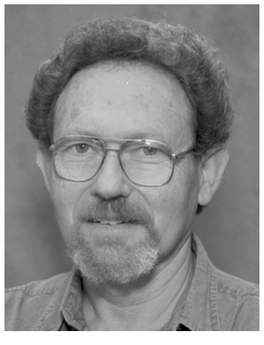
Radiation

Medical X-rays can detect small cancerous tumors, improving the patient's chances for survival. But excessive radiation can itself cause cancer by damaging the DNA. What are the healthy limits of medical screening? And what should be the standards for maximum radiation exposure in the workplace? Weizmann Institute researchers led by **Prof. Amos Breskin** of the Particle Physics Department, working with colleagues from the United States, have designed a novel radiation detector that makes it possible to address these questions. The detector, which is 100 to 1,000 times more accurate than any previous system, has for the first time allowed scientists to assess radiation effects on the living cell, down to the scale of DNA. At this level of accuracy, scientists can predict how much radiation will severely damage a cell's genetic material.

In addition to setting more precise limits to radiation exposure, this research may help improve radiation therapy for cancer, in which a tumor is destroyed by streams of protons, or gamma rays. The difficulty here is to deliver just the right amount of radiation without exposing the person to unnecessary tissue damage. Breskin's research may enable physicians to adjust radiation to levels at which it is just sufficient to do its job.

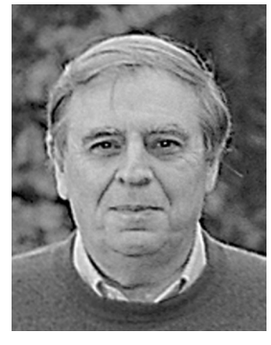
Another Institute study, performed with the help of X-ray crystallography, has furnished a tool for developing pharmaceuticals that would protect the body against high-dose radiation. A team led by **Prof. Joel Sussman** of the Structural Biology Department and **Prof. Israel Silman** of the Neurobiology Department, working with scientists from the Netherlands and France, has for the first time produced a three-dimensional "movie" revealing how molecules break apart when exposed to X-rays. The Weizmann team and its European collaborators plan to examine the anti-radiation potential of various substances that could be applied on a conventional basis or in an emergency such as the Chernobyl nuclear power plant failure. ●

This research may help improve radiation therapy for cancer, in which a tumor is destroyed by streams of protons



Prof. Amos Breskin holds the Walter P. Reuther Professorial Chair of Research in Peaceful Uses of Atomic Energy

Prof. Joel Sussman holds the Morton and Gladys Pickman Professorial Chair of Structural Biology



Prof. Israel Silman holds the Bernstein-Mason Professorial Chair of Neurochemistry

DNA Repair

Every cell in the human body daily sustains thousands of attacks, yet cellular DNA survives the assaults relatively intact. The secret of this resilience: DNA is being regularly patrolled by vigilant "maintenance crews" responsible for its integrity. These crews are molecular repair mechanisms that correct or erase DNA damage, preventing it from perpetuating mutations during cell division. If it weren't for DNA repair, cancer would be rampant; in fact, if DNA repair ceased completely, life on earth would be impossible because the DNA would sustain severe damage and mutations would eventually go haywire.

Boosting natural defenses

Prof. Zvi Livneh of the Biological Chemistry Department studies DNA repair mechanisms and their role in cancer. In most cases, DNA repair systems operate on an all-or-nothing basis: when unable to precisely correct the damage, they stop working. The stoppage leads to gaps in the DNA, which prevent genetic replication from being completed. Livneh, however, identified a new group of enzymes that endow DNA repair systems with the ability to compromise: they are able to fill in the gaps in the DNA, but while doing so they may introduce mutations. Thus these enzymes, called bypass DNA polymerases, ensure the cell's continued existence but also pose a certain risk; imbalances in their activity may increase mutations to a level at which they cause cancer.

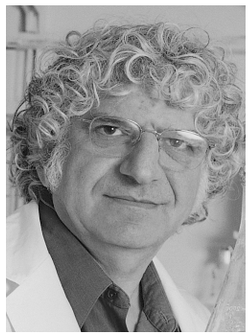
Livneh has also discovered a mechanism that restrains the mutational activity of the new enzymes. It involves ”heroic” proteins that throw themselves on the damaged sites in DNA, preventing them from being copied, much like demonstrators throwing themselves down on the road to block traffic. Livneh is currently studying various aspects of this protein valor, which provides a second line of defense against the mutation and gives the cell a crucial second chance at healthy growth.

In addition, Livneh's team is studying the possibility of identifying people whose bodies aren’t as effective at repairing DNA as those of others. One day scientists may be able to warn people who are more susceptible to genetic defects induced by a particular exposure: for example, people more susceptible to damage caused by ultraviolet radiation may be warned against excessive exposure to sunlight.

An important study conducted by Livneh and his colleagues has already made it possible to identify people who are predisposed to lung cancer due to reduced capacity to repair DNA damage caused by, among other factors, tobacco smoke. (Only 10% of heavy smokers develop lung cancer, suggesting a personal genetic susceptibility.) The scientists focused on a DNA repair enzyme called OGG1 (8-oxoguanine DNA glycosylase 1); it repairs DNA parts damaged by toxic molecules called oxygen radicals, which are found in tobacco smoke. When OGG1 is not sufficiently active, the person's ability to repair DNA is decreased. The researchers discovered that low OGG1 activity results in high susceptibility to cancer, increasing the risk 5- to 10-fold compared with normal OGG1 activity. Smoking further escalates the risk, since it causes more damage for DNA repair enzymes, including OGG1, to fix. Smokers who have a low level of OGG1 activity were estimated to be around 120 times more likely to get lung cancer than non-smokers with regular levels of OGG1 activity. A simple blood test based on these findings will be able to detect smokers who are at an especially high risk of developing lung cancer.

Apart from providing personalized guidelines for avoiding risky exposures, understanding DNA repair may one day help prevent cancer on a molecular level. If we can fully clarify how DNA repair occurs, we may be able to turn it on as required in order to avert malignant transformation. ●

A simple blood test will be able to detect smokers who are at an especially high risk of developing lung cancer



Prof. Zvi Livneh holds the Maxwell Ellis Professorial Chair in Biomedical Research

Oncogenes

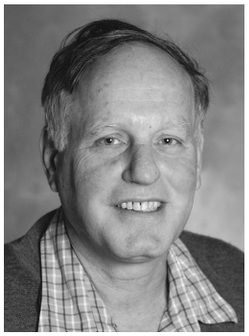
Healthy, unmutated oncogenes (also known as proto-oncogenes) take part in stimulating normal cell growth and division. But when an oncogene contains one or more mutations, it may stay in the ON position too long, continuously commanding the cell to proliferate. (A cell with activated oncogenes is sometimes compared to a car with a jammed accelerator.) Future therapies would block abnormal cell proliferation by shutting down the misbehaving oncogenes.

Perilous partnerships

Several types of leukemia – acute lymphocytic and acute myeloid leukemia in babies, and many cases of therapy-related acute leukemia in older children and adults – are characterized by an abnormality at a particular site on chromosome 11. **Prof. Eli Canaani** of the Molecular Cell Biology Department has succeeded in identifying and cloning the gene at this site. This gene, called ALL-1, normally plays a key role in establishing the correct body pattern of a developing embryo by activating a series of regulatory genes involved in this process. In a normal cell, ALL-1 works by forming an unusually large complex with some 30 other proteins, and together they activate target genes. But Canaani found that in acute leukemia, ALL-1 is defective; it abnormally fuses to any of its more than two dozen partner genes, resulting in the production of anomalous fused proteins that are oncogenic. Canaani now seeks to establish how these unnatural fused proteins convert the normal cell into a malignant one. In one series of experiments, he is conducting comparisons between proteins that are physically associated with the normal as opposed to leukemic ALL-1. His aim is to reveal the features of the abnormal ALL-1 protein complex responsible for the malignant transformation. Another research direction is to try to pinpoint the critical genes activated by the abnormal ALL-1 protein. Canaani pursues this goal by comparing the entire repertoire of genes activated in acute leukemias with and without defective ALL-1, in order to identify the genes that are active only in leukemias with the ALL-1 abnormality.

In the meantime, Canaani's basic research from the 1980s provided the foundation for the development of Glivec (known as Gleevec in the United States), the drug that has won unusual praise and attention as the first therapy based on the molecular understanding of a specific cancer. Canaani had isolated two genes that abnormally swap pieces of genetic material and lead to the production of a fused protein that triggers chronic myelogenous leukemia (CML). It was the first discovery of cancer initiated by protein fusion. Using these findings, the pharmaceutical company Novartis developed a molecule that works by seeking out and destroying cancer cells making the fused protein. Glivec was approved in 2001 by the U.S. Food and Drug Administration for the treatment of CML and is now routinely prescribed around the world to patients with this malignancy. ●

Institute research from the 1980s provided the basis for the development of Glivec, the first drug stemming from an understanding of the genetic origins of cancer

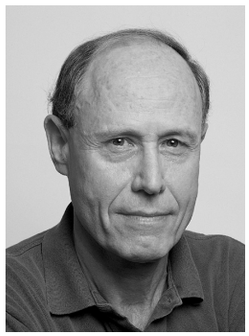


Prof. Eli Canaani holds the Harry Kay Professorial Chair of Cancer Research

Down with leukemia

The study of Down syndrome, which is caused by an extra copy of chromosome 21, has led to the discovery of a gene responsible for acute myelogenous leukemia, or AML. Children with Down syndrome run an unusually high risk – up to 20 times higher than average – of developing this type of leukemia. **Prof. Yoram Groner** of the Molecular Genetics Department has explained the reason. His team has identified a gene, called AML-1, which is located on chromosome 21 and is normally involved in a wide range of growth-related processes, from embryonic development to blood cell production. In Down syndrome, an extra copy of this gene results in the production of altered proteins, which may trigger malignancy. Groner's team is developing genetically modified mice that carry extra copies of the AML-1 gene and therefore serve as a research model for the AML-1 involvement in Down syndrome. Studying these animals provides clues about the molecular mechanisms underlying the malignant transformation induced by the altered activity of AML-1. Groner's findings suggest that defects in AML-1 may also trigger leukemia in children without Down syndrome and in adults. ●

The study of Down syndrome has led to the discovery of a gene responsible for acute myelogenous leukemia



Prof. Yoram Groner holds the Dr. Barnet Berris Professorial Chair of Cancer Research

Reversing malignancy

Pioneering steps

Prof. Leo Sachs holds the Otto Meyerhof Professorial Chair of Molecular Biology

In the 1960s, **Prof. Leo Sachs** of the Molecular Genetics Department was the first to show that cancer cells – in tissue cultures and in living organisms – can be made to revert to normal behavior. This finding led to the development of a new treatment, differentiation therapy, for restoring the ability of cancer cells to grow and develop in a benign fashion. This approach is now being used clinically in human promyelocytic leukemia and is being tested in other types of cancer. Differentiation therapy grew out of Prof. Sachs' landmark discovery of proteins that control the growth and differentiation of blood cells. These proteins, now called colony-stimulating factors and interleukins, signal stem cells to multiply and differentiate to different cell types, and they also prevent blood cells from dying prematurely; in fact, one of the proteins that Sachs identified, the granulocyte colony-stimulating factor, is now used to boost the production of disease-fighting white blood cells in cancer patients undergoing irradiation or chemotherapy. This colony-stimulating factor also induces migration of stem cells from the bone marrow to the peripheral blood, so that peripheral blood rather than bone marrow can now be used for stem cell transplantation. Sachs is currently carrying out studies aimed at fine-tuning the use of colony-stimulating factors and interleukins in cancer. In parallel, he is studying the genetic and biochemical changes that make cancer cells outlive normal cells. ●

Outwitting a brainy gene

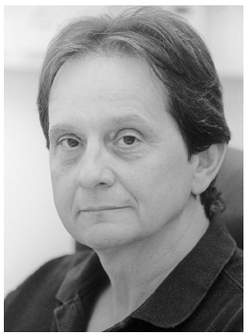
The very first in the series of mutations causing colon cancer occurs in the beta-catenin gene; this gene is abnormally activated in about 90 percent of colorectal cancer patients, and in a much smaller percentage of people with almost every other type of cancer. Beta-catenin plays a dual role in the cell: it promotes adhesion, or stickiness, between cells, and regulates the expression of genes in the nucleus.

Research conducted in the laboratory of **Prof. Avri Ben-Ze'ev** of the Molecular Cell Biology Department suggests that in cancer, beta-catenin functions as an oncogene: when aberrantly activated, it spurs malignant transformation and causes the cell to proliferate abnormally. In one collaborative project with Institute colleagues, Ben-Ze'ev discovered that in normal cells, the p53 tumor suppressor gene keeps beta-catenin in check, but in malignant cells p53 loses its grip on beta-catenin. In another collaborative project, a team led by Ben-Ze'ev isolated a short peptide (protein fragment) that blocks a vital portion of the beta-catenin molecule; the protein may thwart the development of cancer by preventing beta-catenin from acting as an oncogene.

More recently, Ben-Ze'ev's team unraveled several crucial elements in the signaling chain unleashed by the corrupt beta-catenin. One of these elements is Nr-CAM, a cell adhesion molecule not previously known to play a role in cancer. In healthy people, the protein made by the Nr-CAM gene is present only in the brain and not at all in other tissues of the body, but the Weizmann scientists showed that the Nr-CAM levels are dramatically elevated in colon cancer and melanoma cells; in fact, the more advanced the tumor, the higher the Nr-CAM level. These findings could lead to the screening of large populations and early detection of cancer, based on the detection of the protein made by the Nr-CAM gene: this protein is likely to be present only in people with cancer caused by overly activated beta-catenin. Moreover, since the protein made by the Nr-CAM gene sticks out from the surface of cells, it is a convenient target for cancer therapy: by inactivating Nr-CAM, it may be possible to interrupt the chain of signals released by beta-catenin, thereby suppressing the development of prevalent malignancies such as melanoma and colon cancer.

Ben-Ze'ev's laboratory has also revealed that beta-catenin is involved in a key mechanism leading to the metastasis of colon cancer. By manipulating this mechanism, Ben-Ze'ev's team succeeded in reversing the metastatic properties of colon cancer cells in vitro. This research raises hopes that a target-specific therapy might be devised to prevent, or reverse, the invasive behavior of metastatic colon cancer cells. ●

Protein that sticks out from the cell surface is a convenient target for cancer therapy



Prof. Avri Ben-Ze'ev holds the Samuel Lunenfeld-Reuben Kunin Professorial Chair of Genetics

Tumor Suppressor Genes

In healthy cells, tumor suppressor genes keep the cell's growth machinery in check, releasing their grip on growth-promoting chemicals in a controlled manner, only as needed. In cancer, however, these genes are not working, allowing the tumor to grow without restraint. (To continue the automobile metaphor, a cell without properly working tumor suppressor genes is like a car without brakes.) In fact, when cancer runs in families, the hereditary defect is often in the suppressor genes. Therapies compensating for the lack or malfunction of these genes would be equivalent to fixing the brakes in order to stop the developing cancer.

The cancer killer

The most "glamorous" of all tumor suppressor genes is p53. Several years ago, it was pronounced Molecule of the Year by *Science*; it has also been the subject of a *Newsweek* cover story headlined "The Cancer Killer." The p53 gene owes its celebrity status to the fact that defective copies of it are found in more than half of all human cancers, including such major killers as cancers of the breast, lung, colon and prostate. A therapy compensating for a lack of properly functioning p53 copies would therefore have enormous potential for combating cancer. In fact, a gene therapy that delivers active p53 to tumor cells is already being tested in clinical trials in the United States and Europe.

Weizmann Institute scientists have made seminal contributions to understanding the role of p53 in normal and cancerous cells. It is now known that p53 acts as the cell's damage control and as a "guardian of the genome." When genes are damaged by radiation, chemicals or other means, threatening to set the cell on a course toward malignant transformation, p53 senses the damage and its supply builds up. The p53 protein activates numerous genes that prevent tumors from forming; by so doing it either blocks the growth of damaged cells, allowing for the correction of DNA damage, or commands these cells to commit suicide. But if the cell has no healthy p53, the road to cancer remains open.

Prof. Moshe Oren of the Molecular Cell Biology Department, together with the Weizmann Institute's Prof. Emeritus David Givol and Prof. Arnold Levine, then of Princeton University, was the first to clone p53 – in other words, to isolate the gene and determine the sequence of its genetic letters – in 1983. The p53 clone and its genetic sequence provided laboratories around the world with one of the most frequently used tools for studying cancer. Subsequently, Oren was the first to show that reactivation of p53 in cancer cells can prompt them to self-destruct, a principle that underlies the ongoing p53 gene therapy trials. Oren is now focusing on elucidating the biological processes that allow this gene to function as a tumor suppressor. Among the questions studied in his lab: How does p53 interact with other genes? How are the levels of p53 regulated in a cell? Usually, p53 is present in minute amounts, but its levels soar in response to DNA damage and other types of stress. Oren has discovered the role of a major regulator of p53 activity, called MDM2. He found that MDM2 is responsible for the elimination of p53, and he now seeks to clarify how exactly MDM2 achieves this. Oren predicts that interfering with MDM2 will strengthen p53, thereby boosting the natural anti-cancer defense mechanisms.

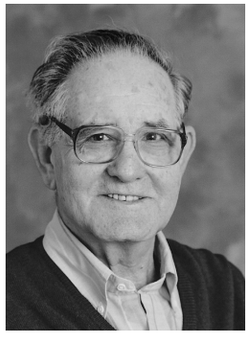
Prof. Varda Rotter of the Molecular Cell Biology Department was the first to develop antibodies against p53, laying the foundations for the study of this gene's function. She also provided some of the earliest evidence that p53 is a tumor suppressor. At present, Rotter is working toward two major goals: to decipher the function of p53 in the normal cell and to clarify the behavior of mutant p53 in tumor cells. In particular, she seeks to understand how p53 can induce three different processes: blockage of growth, cell differentiation or cell death. She is working to clarify whether all three processes can occur in a single cell, or whether different cells respond differently to p53.

The state of a patient's p53 may determine whether conventional cancer treatments are likely to be effective. Several years ago, oncologists made a surprising discovery: radiation therapy and some chemotherapies, rather than directly killing cells as had previously been thought, in fact work by activating p53, which in turn orders cells to self-destruct. Therefore, patients with intact copies of p53 are more likely to be helped by these treatments. In the absence of p53, the cancer is resistant to chemotherapy. **Prof. Emeritus David Givol** of the Molecular Cell Biology Department has conducted several studies exploring the effects of p53 on different chemotherapies.

Givol is now using DNA chips to determine which other genes are activated by p53. He discovered new cell suicide genes that are turned on by p53 in response to DNA damage. If p53 is defective, alternative means may be used to activate such genes. ●

Weizmann scientists were the first to clone the p53 gene and have made seminal contributions to understanding its function

Prof. Moshe Oren



Prof. David Givol

Prof. Varda Rotter holds the Norman and Helen Asher Professorial Chair of Cancer Research

Making history

Pioneering steps

The late Prof. Isaac Berenblum

In the 1950s, Weizmann Institute scientists were among the first to demonstrate that certain types of cancerous growths develop in a two-stage process and that cancer depends on the presence of multiple factors. Until then, it was believed that a single factor was sufficient for cancer to develop. The discovery – by the late **Prof. Isaac Berenblum**, a foremost cancer researcher – improved the understanding of various scenarios that might lead to malignancy. It also provided an explanation for the time lapse, sometimes several decades, between exposure to carcinogenic substances and the development of a tumor. ●

Death benefits

Finding a defective gene can be likened to locating a burnt-out lightbulb somewhere in North America while having no idea where to begin the search. **Prof. Adi Kimchi** of the Molecular Genetics Department has developed a fast and convenient method for identifying tumor suppressor genes, which until recently were particularly difficult to isolate. The method, called Technical Knockout, or TKO, works by selectively disabling various genes and monitoring the effect of this disabling on the cell. In this manner, scientists can isolate out of 30,000 genes a single gene that possesses a particular function.

Kimchi and her team have successfully used this method to discover several completely new genes called DAP (death-associated proteins) that are connected to death-inducing processes in cells. One of these genes, called DAP-kinase, falls into the category of tumor suppressor genes; it is responsible for destroying cells that have begun converting to a cancerous state.

In a recent discovery, Kimchi found that DAP-kinase is the trigger that activates the p53 gene, leading to the destruction of cells intent on undergoing a malignant transformation. A malfunction of DAP-kinase interferes with this destruction program, allowing a cancerous growth to develop. Another stage in cancer development controlled by DAP-kinase is metastasis: loss of this gene or a malfunction of its protein promotes the formation of metastatic tumors. DAP-kinase abnormalities have been detected in human cancers of the lung, breast, head and neck, as well as in type B cell lymphoma. ●

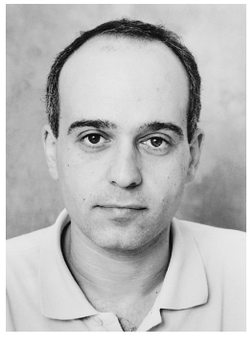
Institute scientists have developed a fast and convenient method for identifying tumor suppressor genes

Prof. Adi Kimchi holds the Helena Rubinstein Professorial Chair in Cancer Research

Controlling the switch

Dr. Doron Ginsberg of the Molecular Cell Biology Department is studying a family of molecular switches, called E2F, that control cell growth and division. These switches are normally regulated by the RB tumor suppressor gene. (The RB gene owes its name to retinoblastoma, a malignant tumor of the retina in which it was originally found to be defective; however, RB has since been found to be mutated in a variety of other cancers.) When RB is working properly, the growth switch is turned on only as needed. But when RB is missing or when it malfunctions, the E2F remains permanently turned on, promoting unchecked cellular growth. ●

When the RB tumor suppressor gene is missing, the result is unchecked cellular growth



Dr. Doron Ginsberg holds the Recanati Career Development Chair of Cancer Research

Experimental leukemia

Pioneering steps

Prof. Nechama Haran-Ghera

Reaserch may improve the treatment of multiple myeloma

Prof. Emeritus Nechama Haran-Ghera of the Immunology Department, a former student and then collaborator of Prof. Berenblum, has continued and extended his studies in a career spanning five decades. She produced several types of leukemia in mice and provided insights into the multiple phases of blood cancer development. It emerged that the development of the disease includes an initial stage in which bone marrow cells are transformed into preleukemic clones; they may remain dormant throughout an animal's life. Haran-Ghera defined immunological and other factors that keep preleukemia in check or, conversely, terminate the dormant state and lead to a burst of overt leukemia. In related research she showed, in a mouse model of radiation-induced acute myeloid leukemia, that certain growth factors used in the clinic to boost the production and/or maturation of blood cells can be hazardous because they augment the proliferation of preleukemic cells and may therefore trigger overt leukemia.

More recently, Haran-Ghera collaborated with Israeli physicians on a study that may improve the treatment of multiple myeloma. She showed that the hormone erythropoietin, widely used to treat anemia in cancer patients, may be helpful in treating the cancer itself. She revealed that erythropoietin affects the cancer indirectly, through the immune system; it was found to prolong survival, cause tumor regression and reduce mortality in mice injected with malignant myeloma cells. These findings have provided the scientific basis for clinical trials of erythropoietin in multiple myeloma and for testing the effects of this hormone on other types of cancer. ●