

## LOCKING ON: TARGETING CANCER CELLS ONE AT A TIME

After more than a decade of research into a unique gene present in more than 30 forms of cancer, Professor Avraham Hochberg is contributing a powerful weapon in the fight against some of the most lethal forms of the disease. Working in partnership BioCancell Therapeutics, Professor Hochberg and his Hebrew University team are developing promising new diagnostic and treatment methods which have been recently approved for clinical trials in Israel and the United States.

A biochemist at Hebrew University's Silberman Institute of Life Sciences, Professor Hochberg has spent the past 15 years investigating a gene in humans called H19. "I discovered a gene that expresses itself in the



*Prof. Avraham Hochberg and his research team.*

embryo and vanishes in the mature adult—but reappears in 33 types of cancerous growth," the scientist told *Scopus Magazine* (Spring 2006).

Armed with the knowledge that H19 is present only in cancer cells,

Professor Hochberg was able to use it like a homing device for a new cancer drug that he compares to a guided missile locking on to its target.

BioCancell is harnessing a potent diphtheria toxin to pinpoint and

*Continues on page 6*

## BLOOD VESSEL FORMATION AND DISEASE

Professor Eli Keshet, the Woll Sisters and Brothers Professor of Cardiovascular Diseases at Hebrew University's Faculty of Medicine, is a leading authority on angiogenesis, the process by which blood vessels are formed. Since cancerous tumors depend on a vascular supply in order to grow, the ability of scientists to control blood vessel formation would enable them to "starve tumors" as a method of cancer treatment.

Professor Keshet's research has led him to VEG, a growth factor that

can inhibit or promote the activity of tumor angiogenesis. This pioneering work has been fostered through the use of animal models that simulate human behavior, and Hebrew University laboratory research has resulted in an FDA-approved anti-angiogenic drug for treating colorectal cancer.

Biovascular research is also contributing to a better understanding of blindness. At The Hebrew University, work is being done to develop new treatments for diabetic retinopathy

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## BOOSTING THE EFFECTIVENESS OF STEROID-BASED CANCER THERAPY

by Professor Eitan Yefenof  
Chairman  
Lautenberg Research Center

While steroid hormones such as Gluco-corticoids (GC) are widely used in the treatment of leukemia and lymphoma, their effectiveness has been only recently understood. Lymphoid cells express a GC receptor (GR) that binds the GC molecule and initiates a process of programmed cell death known as apoptosis. The most dramatic intracellular event that occurs following GC binding is an instant migration of GR to the nucleus, where it triggers the expression of certain genes.

A major medical concern with GC therapy is that as treatment progresses, the cancerous cells develop a resistance to GC-induced death, which causes tumors to relapse. Surprisingly, the resistant cells continue to express GR, which migrates to the nucleus upon GC



binding. As a result, scientists have been seeking to identify the defect that confers resistance to cells. In a recent study published in the *Journal of Experimental Medicine*, Lautenberg Center scientists, working with HU's Department of Pharmacology, provided an answer to this enigma.

We discovered a new variant of GR, that upon GC binding, migrates to the mitochondria rather than to the nucleus. While the nucleus is the brain center for genes, the mitochondria is

a functional organelle that generates energy through chemical reactions. Within the mitochondria, the GR-GC complex provokes the release of enzymes that catalyze a reaction needed to induce programmed cell death. This particular GR is lost in cells that are chronically exposed to GC, making them resistant to further treatment. It is the mitochondrial and not the nuclear GR that is vital to maintaining GC sensitivity in malignant cells.

Even more importantly, we discovered that certain drugs, known as PKC inhibitors, can restore the expression of the mitochondrial GR, thus conferring GC sensitivity to otherwise resistant cells. Our Lautenberg Center research indicates that doctors can boost the effectiveness of glucocorticoid-based therapy if additional drugs are administered along with GC to prevent the emergence of GC resistant cells. ■



The Lautenberg Center for General and Tumor Immunology held its annual retreat April 2-4, 2006, at Ein Bokek on the Dead Sea. Designed to allow students and junior fellows to present their research projects in an informal setting, the retreat included staff discussions about future Lautenberg Center projects. Guest speaker Dr. Klaus Rajewsky of Harvard Medical School addressed the latest developments in his own research.

## LAUTENBERG CENTER RESEARCH HIGHLIGHTS

- Liver cancer is being tackled by Professor Yinon Ben-Neriah, whose research group has discovered a molecular link between chronic inflammation in the liver and the development of liver cancer. Prof. Ben-Neriah is working to prolong the pre-malignant state of liver cancer by playing a “genetic trick” that can switch off the transcription factor which leads to full-blown cancer. Study findings were published in *Nature*.
- Professor Ofer Mandelboim and his team identified a viral protein that paralyzes the cyto-toxic activity of Natural Killer (NK) cells. This protein plays an essential role in Cytomagalo Virus, (CMV) infection and its spread. The neutralization



*Left: Professor Yinon Ben-Neriah*

*Right: Professor Ofer Mandelboim and graduate student researchers*

of this protein is likely to slow down or even prevent infection by CMV and other related viruses. Study findings were published in *Nature Immunology*.

- Lautenberg Center scientists are spearheading drug therapies that treat diseases in targeted ways – so as to avoid destroying normal

cells in the process of killing cancerous ones. They are improving the screening procedures for bone marrow cleansing and transplantation, and identifying the proteins in organ tissue in order to facilitate more accurate matching for potential organ recipients. ■

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## RABBI SHAI SHACKNAI MEMORIAL PRIZE 2006

### *Dr. Hans Clevers*

The Hebrew University Faculty of Medicine and the Lautenberg Center for General and Tumor Immunology awarded the Rabbi Shai Shacknai Memorial Prize for 2006 to Dr. Hans Clevers for his outstanding contributions in the field of cancer biology.

Dr. Hans Clevers directs the Hubrecht Laboratory/Netherlands Institute of Development Biology. He received his MD and Ph.D. from the University of Utrecht, and conducted his postdoctoral training at the Dana-Farber Cancer Institute. In 1991, Dr. Clevers became chairman



of the Department of Immunology at the Faculty of Medicine, Utrecht University. Since 2002 he has directed the Hubrecht Laboratory,

Netherlands Institute for Developmental Biology of the Royal Dutch Academy of Sciences.

Dr. Clevers is a member of the European Molecular Biology Organization, the Royal Dutch Academy of Science and was honored with the Catharijne Prize for Medical Science and the Spinoza award.

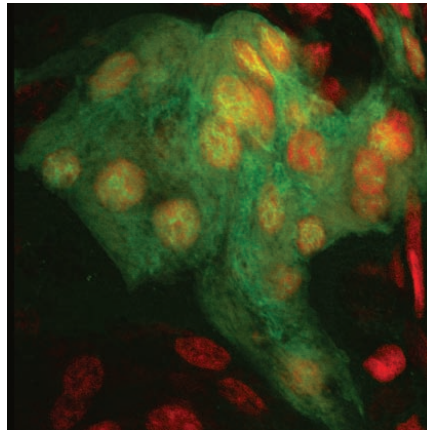
Visiting Hebrew University on February 2006 to accept the Shacknai Prize, Dr. Clevers presented lectures on “Sculpting the Gut by Developmental Signaling Pathways.” ■

## DR. YUVAL DOR: STEM CELLS IN PANCREATIC CANCER AND TYPE I DIABETES RESEARCH

When the Israel Cancer Research Fund (ICRF) selected its first recipient of the Barbara S. Goodman Endowed Research Career Development Award for Pancreatic Cancer, Dr. Yuval Dor of Hebrew University was honored. A faculty member in the Department of Cellular Biochemistry and Human Genetics, Yuval Dor is a Hebrew University alumnus who conducted his post-doctoral work at Harvard University, mentored by Douglas Melton, a leading developmental biologist. Their approach aims to cure diseases through regenerative medicine—harnessing the body’s own resources to combat life-threatening illnesses.

While earning his Ph.D. at The Hebrew University Faculty of Medicine, Yuval Dor was mentored by Professor Eli Keshet, the Woll Sisters and Brothers Professor of Cardiovascular Diseases. Their laboratory used transgenic mouse models to study angiogenesis—the process by which blood vessels are formed. When Dr. Dor returned to Israel to join HU’s faculty in 2002, he and Prof. Keshet resumed their collaboration. They are currently studying the role of blood vessels in pancreas development, beta cell regeneration and the development of diabetes complications.

The two main human diseases associated with the pancreas are Type I diabetes, also known as juvenile diabetes, and pancreatic cancer, which has a nearly 100% mortality rate. Dr. Dor’s laboratory



*A structure in the pancreas called an acinus, which produces digestive enzymes. Acini may contain cells that give rise to pancreatic cancer.*

team is working to understand which molecular pathways play essential roles in initiating pancreatic cancer and which cell type gives rise to the disease. His study, published in *Cancer Cell* (September 2005), suggests that a rare cell type in the adult pancreas termed the centroacinar cell might represent the elusive cell of origin for pancreatic cancer. This finding has important implications for the diagnosis and cure of this fatal disease.

Several outstanding HU post-doctoral researchers are participating in this research. Their backgrounds are diverse: Dr. Judith Magenheim came to Israel from Argentina, Dr. Miri Stolovitch came from Russia, and Drs. Zvika Granot and Sharon Yagur are sabras. Three team members are pursuing graduate degrees: Seth Salpeter, a New Yorker who made aliyah, Israeli-born Noa Weinberg from kibbutz Ramat-Magshimim and Tomer Nir, an M.D.-Ph.D. candidate.

Type I diabetes is a childhood disease where the body destroys its own insulin-producing beta cells. Dr. Dor’s laboratory has been striving to establish whether beta cells have the capacity for regeneration. Responsible for producing insulin, beta cells are found in the pancreas. Once their cellular origins are known, it may become possible for scientists to apply this knowledge to expanding beta cell mass, either in the body or in the culture dish, for transplantation purposes.

In a study published in *Nature* (May 2004), Yuval Dor and colleagues Juliana Brown, Olga Martinez and Douglas Melton introduced their discovery that most beta cells are generated by self-duplication and do not originate from adult stem cells, as previously believed by many scientists. This finding has spurred efforts to generate beta cells in laboratories. Explains Dr. Dor:

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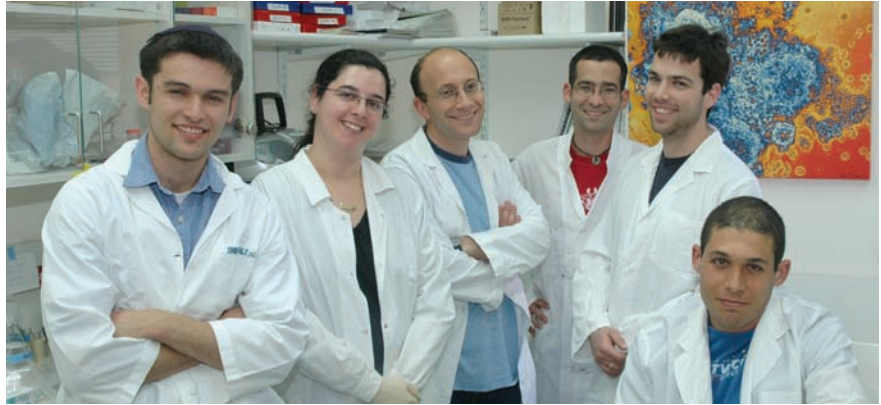
“OUR STUDY CASTS DOUBT ON THE POTENTIAL OF ADULT STEM CELLS FOR DIABETES THERAPY, AND SUGGESTS THAT PRE-EXISTING BETA CELLS OR HUMAN EMBRYONIC STEM CELLS OFFER A BETTER CHANCE FOR A CURE.”

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Pioneering work demands cutting-edge resources. Dr. Dor shares a sophisticated confocal microscope

with famed cancer researcher, Dr. Howard Cedar, the Harry and Helen L. Brenner Professor of Molecular Biology. The Israel Prize winner is known for his research in DNA Methylation, a molecular process that activates and deactivates genes. The confocal microscope enables HU scientists to “visualize” the cells and tissue being investigated with unprecedented precision.

State-of-the-art equipment expands basic knowledge, accelerates the development of effective new treatments, and contributes to cures. Another much-needed tool that the laboratory hopes to acquire is a fluorescence activated cell sorter, or FACS. The FACS enables scientists to run a heterogenous mixture of cells, such as dissociated pancreatic cells



Dr. Dor and his research team.

or partly differentiated embryonic stem cells, and rapidly isolate a subset of desired cells. This powerful technology permits the investigation of rare populations of cells, facilitating their analysis and further cell growth.

American Friends interested in supporting vital medical research at

The Hebrew University have opportunities to provide resources for outstanding new faculty; student scholarships; and state-of-the-art laboratories. Please contact AFHU’s national office, or a regional office for further information. ■

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## PROGRESS IN THE FIGHT AGAINST CANCER

*Professor Hillel Bercovier*

*Vice President of Research and Development*



The Hebrew University of Jerusalem is on the frontlines of the war against cancer. Recognizing the global urgency of this work, vast scientific resources are being brought to bear.

Leading the way is HU's Faculty of Medicine, including the Lautenberg Center for General and Tumor Immunology and the School of Pharmacy. Innovative research projects are in progress at the Silberman Institute of Life Sciences. Utilizing the tools of nanotechnology through the Krueger Family Center for Nanoscience and Nanotechnology, scientists are developing bionano-capsules to expedite drug delivery. Embryonic stem cell research is also underway. These varied efforts, while crucial to cancer treatment, are also applicable to many devastating diseases from AIDS to diabetes.

The Spring 2006 Cancer News Update highlights some of these new developments. Professor Avraham Hochberg has developed a new therapy for bladder cancer.

Professor Eitan Yefenof, chairman of the Lautenberg Center, recently published a study describing his discovery of a new variant of GR (a Gluco-corticoid receptor) that can help to induce "programmed cell death" in cancer cells.

Professors Amos Panet and Zichria Zakay-Rones, have discovered that a virus which usually affects birds, Newcastle Disease Virus (NDV), exists in a weakened variant (NDV-HUJ) with the potential to kill cancer cells. This work has led to clinical trials of the oncolytic virus on patients suffering from highly aggressive brain tumors.

Much as HU can boast of eminent cancer researchers, we are also recruiting outstanding new faculty. One such individual is Yuval Dor, who is studying ways to regenerate human beta cells. Dr. Dor conducted his doctoral research under the supervision of HU Professor Eli Keshet, an expert on vascular biology, and is again collaborating with Eli Keshet—this time as a colleague.

Hebrew University scientists are making major research inroads. We deeply appreciate the support of American Friends, and hope that you will continue to stand with us as partners in medical progress. ■

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destroy H19-carrying cancer cells, without inflicting damage on healthy surrounding tissues. "Because the cancer cell is an anarchist and does not accept the laws of the body, we had to find something that could beat it using its own weapon," Professor Hochberg said. "In the case of H19, it is on 'on' in the embryo, 'off' in the mature adult, and 'on' again in cancer...[the treatment] kills only those cells in the 'on' position—the cancer cells."

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**"THE TUMORS VANISHED... THE PATIENT HAS BEEN FREE OF CANCER FOR THREE YEARS."**

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The technology has already been credited with the dramatic improvement of two Israeli bladder cancer patients—and induces none of the dangerous side effects common to conventional chemotherapies. Illustrating the drug's effectiveness in one patient, Professor Hochberg explained that after six weeks of treatment "the tumors vanished... the patient has been free of cancer for three years."

As BioCancell works to bring the new therapy through final trials and into the marketplace, Professor Hochberg is using this same precise approach to explore new ways of treating cancers of the liver, pancreas and the ovaries. ■

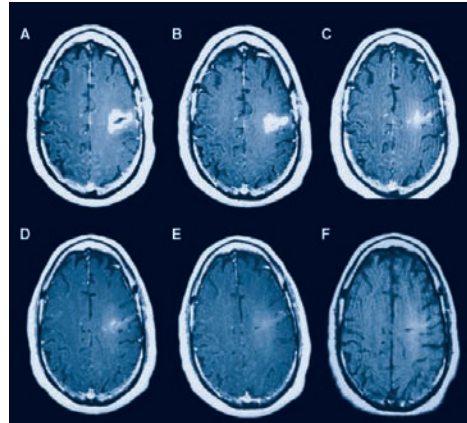
## A VIRUS TO MAKE YOU WELL?

Two leading cancer researchers at Hebrew University's Department of Virology have found an unlikely ally in their search for an effective cancer therapy: a virus.

In a five-year investigation of the Newcastle Disease Virus (NDV), a pathogen found primarily in birds, Professors Amos Panet and Zichria Zakay-Rones discovered a unique variant of NDV with the potential to target and eradicate tumor cells. While most viruses infiltrate living cells indiscriminately, the NDV-HUJ virus, a weaker variant discovered by Hebrew University researchers, seeks out cancer cells whose compromised defenses leave them vulnerable to attack. This discovery may lead to the development of an effective new cancer-fighting weapon. Unlike chemotherapy, which harms healthy tissue in the process of attacking cancer cells, the NDV-HUJ oncolytic virus allows for treating cancer cells in a more selective manner.



Prof. Panet and Zakay-Rones



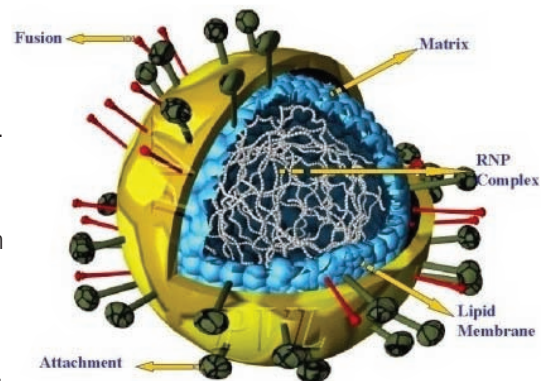
Brain scan shows diminishing Glioblastoma tumor following viral therapy.

First-stage research mapped the NDV-HUJ genome, enabling Prof. Panet and Zakay-Rones to compare it to other strains of the virus. The research team then analyzed NDV-HUJ's role in prompting a poptosis, or "programmed cell death". Encouraging cancer cells to self-destruct is basic to cancer treatment.

This research was put to the test in a phase I clinical trial carried out in 2002 and 2003 in collaboration with the Hadassah Medical Center. The experimental NDV-based therapy was administered to 14 patients suffering from Glioblastoma Muliforme (GBM), an aggressive type of brain tumor with a survival rate of less than three percent. After receiving the NDV-HUJ virus treatment, one of the patients exhibited a regression

of the tumor, a highly encouraging result. No adverse side effects were reported.

Another positive sign for oncolytic viral therapy is its easy acceptance by the human body. A bird virus, the NDV variant does not provoke a strong immune response in humans, thereby ensuring it reaches targeted cells and retains its therapeutic potency. The NDV-HUJ virus also holds promise for treating other forms of cancer. Professor Panet and his team are investigating viral therapy in relation to lymphoma and lung cancer.



Computer rendering of the NDV-HUJ virus

TheraVir, a new start-up company, has been established to pursue commercial development of the viral-based treatment. ■

## MDC1, A KEY PLAYER IN THE CELLULAR RESPONSE TO DNA DAMAGE

Dr. Michal Goldberg of Hebrew University's Department of Genetics is investigating how the DNA molecules that encode genetic information in our cells keep their integrity.



Dr. Michal Goldberg

Cancer involves mutations in the DNA of normal cells. Since the cells in our body are constantly exposed to internal and external agents that can damage DNA and cause mutations, it is vital that cellular DNA damage response mechanisms detect and repair the damaged DNA. In particular, the DNA damage response is needed to protect cells from a genomic crisis, which may trigger the uncontrolled growth of cells, resulting in cancer. Understanding how the DNA damage response is regulated helps scientists to understand how cancer evolves and will lead to the development of new therapies.

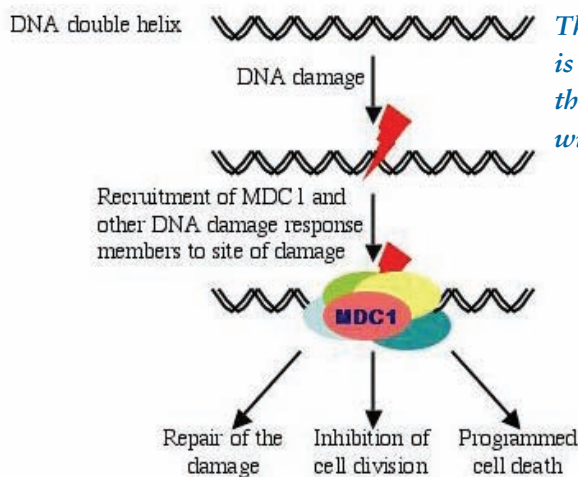
Dr. Goldberg's laboratory is currently focused on MDC1, an adaptor protein that plays a major role in the cellular response to DNA damage. Once DNA is

damaged, MDC1 rapidly activates, recruiting different members of the DNA damage response mechanism, and relocating this repair group to the site of the damage.

MDC1 is crucial to halting the division of damaged cells and for repairing DNA

double-strand breaks--the most lethal type of DNA damage.

Studying how MDC1 is regulated during the cellular response to DNA damage, and discovering which proteins interact with MDC1, occupies Dr. Goldberg and her six-person laboratory team, which includes doctoral and undergraduate students. Human cell cultures form the basis of their studies. The cells are grown, treated with different agents that damage the DNA, and are harvested, after which proteins are extracted and analyzed for MDC1 function. Study findings have been published in *Nature* (2003) and *The EMBO Journal* (2004). ■



*The MDC1 protein is crucial to halting the growth of cells with damaged DNA.*

## A NEW WAY TO TREAT BRAIN TUMORS

*Professor Alexander Levitzki*

Working with researchers from Ludwig-Maximilians University in Munich, Alexander Levitzki, the Wolfson Family Professor of Biochemistry at Hebrew University, has pioneered a way to combat brain tumors by selectively targeting only malignant cells. Their preclinical study published in *PLoS Medicine*, details a new approach to treating Glioblastoma Multiforme (GBM) brain cancer. By building upon previous research that showed GBM tumors could be distinguished from normal tissue through their overproduction of a molecule called EGFR, the researchers were successful in binding a nucleic acid to cancer cells. Influenced by this nucleic acid trigger, the cells undergo programmed death. The treatment does not damage normal brain tissue and may be similarly helpful in treating breast and lung cancer.



Professor Alexander Levitzki

Professor Levitzki received the 2005 Wolf Prize in Medicine, one of the world's most prestigious honors, and recently won a 2005 Competitive Award from the Prostate Cancer Foundation, a U.S. nonprofit organization that funds "high impact research projects." ■

## PROFESSOR JACOB HOCHMAN: ADDRESSING THE THREAT OF MALIGNANT LYMPHOMA

Lymphoma, particularly involving the eyes and the central nervous system, is a deadly form of cancer. Until recently, no adequate experimental model existed whereby scientists could study the metastasis of this disease. Consequently, Professor Jacob Hochman, an expert in cellular biology at the Silberman Institute of Life Sciences, has been spearheading new ways to investigate how this cancer spreads through the human body. Professor Hochman and his laboratory team developed a unique, patented model which applies to non-Hodgkin's lymphoma (NHL). NHL is the sixth most common cancer in men and the fifth most common in women.

Professor Hochman's laboratory first developed a means of inoculating a lymphoma cell line in mice, providing scientists with a model for studying lymphoma metastasis to the brain and eyes. These Rev-2-T-6 cells, it has been discovered, can also serve as a model system for studying childhood leukemia and its effect on the central nervous system (CNS).

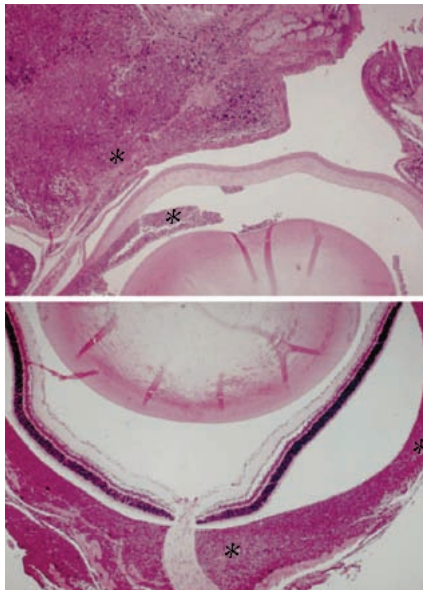
Once inside the brain, the Rev-2-T-6 lymphoma cells migrate along the optic nerve sheath, infiltrating various compartments of the eye. The Hebrew University laboratory team, comprised of Professor Hochman, Nirit Assaf, a former M.Sc. student, and Professor Jacob Pe'er, an ocular oncologist and head of the Department of Ophthalmology at Hadassah Medical Center, collaborated with Professor Otmar Wiestler, a neuron-oncologist and



*Professor Jacob Hochman*

head of the German Center for Cancer Research in Heidelberg. Using histopathology and immunohistochemical analysis, they were able to trace the presence of the Rev-2-T-6 cells within the eye and brain as well.

This innovative research is important for many reasons. Once having



identified the major routes of lymphoma metastasis, Professor Hochman's team will be able to characterize the molecular mechanisms and genes used by lymphoma cells as they multiply and travel throughout the brain and into the eyes. This knowledge will facilitate early diagnosis of the cancer, plus the development of new therapeutic methods for combating CNS and ocular lymphoma. The research may be applicable to other types of brain-seeking tumors as well, given that Rev-2-T-6 cells use infiltration routes common to other CNS tumors. "At present this is the only experimental model available whereby the metastasis of lymphoma to the brain and eyes can be studied in immune competent mice," stated Professor Hochman.

Professor Hochman's research promotes a deeper understanding of the immune responsiveness of the eye and brain towards malignant lymphoma, information that may lead to new ways to impair tumor development.

Another aspect of the research involves the use of laboratory subjects in order to introduce the human multi-drug resistance (MDR1) gene into eye and brain-infiltrating lymphoma cells. A goal is to discover how to reverse multi-drug resistance in tumors that "hide" within the brain. ■

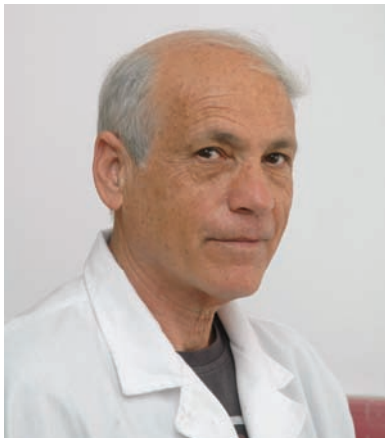
*Lymphoma cells (asterisks) infiltrating various compartments of the eye.*

## BLOOD VESSEL FORMATION AND CANCER

*Continued from page 1*

and macular degeneration, two age-related conditions. Macular degeneration, a leading cause of blindness, represents a group of diseases that cause sight-sensing cells in the macular zone of the retina to lose function. Diabetic retinopathy occurs when blood vessels in the eye are damaged as a complication of diabetes.

Heart disease is another major medical challenge, with ischaemic heart disease occurring when normal blood vessels are occluded. Currently, bypass surgery is used to repair damaged hearts by improving blood flow to the damaged organ. By developing the ability to “grow” new blood vessels, medical science could create new means to effectively address heart disease.



*Professor Eli Keshet*

Eli Keshet describes his research as disease oriented, with the Ein Kerem campus, home to the Faculty of Medicine and the Hebrew University-Hadassah Hospital, creating “important links between basic

and translational research in the form of clinical trials.” He finds intellectual excitement in exploring the basic mechanisms of biology and explains that productive clinical trials result from the “basic principles we uncover in our laboratory.”

Professor Keshet’s oft-cited work on angiogenesis and VEGF has been published in many scientific journals. In 2004, the European Vascular Genomic Network (EVGN) was launched to address cardiovascular disease by integrating post-genomic research with more traditional biomedical approaches. The Hebrew University of Jerusalem, represented by Eli Keshet, is one of only 27 institutions worldwide to participate in the EVGN.■

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## JILL WASSERMAN

*National Executive Director of Planned Giving*

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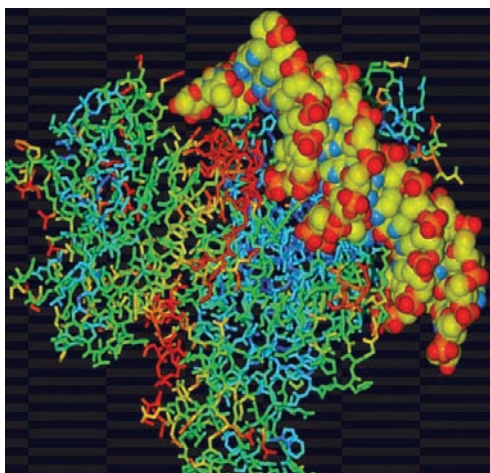
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## HOW TUMOR CELLS DIE: CANCER-FIGHTING LESSONS FROM THE HUMAN BODY

**D**r. Assaf Friedler of Hebrew University's Institute of Chemistry is investigating the human body's natural defenses against cancer for clues about how malignant tumors can be eliminated—perhaps even before they begin.

A recipient of undergraduate, master's and doctoral degrees from The Hebrew University, Dr. Friedler completed his post-doctoral research at Cambridge University, where he worked in the lab of Professor Sir Alan Fersht at the Cambridge Center for Protein Engineering. In addition to co-heading Hebrew University's new undergraduate integrated chemistry-biology program, he is conducting advanced research into how specialized proteins in the human body react in the face of disease, including cancer.

Human cells have a number of mechanisms that help to keep them from becoming cancerous. When a cell recognizes that it is undergoing



*Tumor Suppressor P53 complexed with DNA*

a malignant transformation—the process by which tumor cells are created—it immediately halts its own replication until damaged DNA can be repaired. If repair proves impossible, the cell promptly begins apoptosis, a programmed “suicide” sequence designed to eliminate the potential cancer from the body. When this cellular fail-safe breaks down, tumors can gain a dangerous foothold.

The focus of Dr. Friedler's research is the sophisticated chemical chain of command that governs how cancer cells are identified and destroyed. Scientists currently know that a tumor-suppressing protein known as p53 is responsible for instructing suspected cancer cells to stop

dividing, and if necessary, to die. Dr. Friedler and his team are zeroing in on another important protein, ASPP2, which is responsible for coordinating the timing and approach of p53's assault on tumor cells.

By gaining information about the complex ways ASPP2 facilitates human response to the presence of cancer cells, the researchers are developing the foundation of a vital new therapy.

“We are currently studying the molecular details of these highly important protein-protein interactions,” said Dr. Friedler. “We will use the information as a basis for the design of anti-cancer drugs that stimulate apoptosis of cancer cells.” ■



*Dr. Assaf Friedler and a colleague at the Institute of Chemistry.*

### CANCER RESEARCH *update*

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