

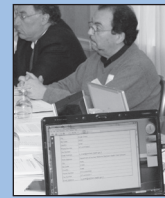
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Will Stem Cell Treatment of Cancer Be Possible?

Howard Cedar, Ph.D., and Yehudit Bergman, Ph.D., professors at Hebrew University – Hadassah Medical School and recipients of 2008-09 ICRF Professorship Awards, have taken a major step toward **treating diseases through stem-cell therapy** by unraveling the mechanism of differentiation, in which flexible embryonic cells turn into fixed, mature cells.

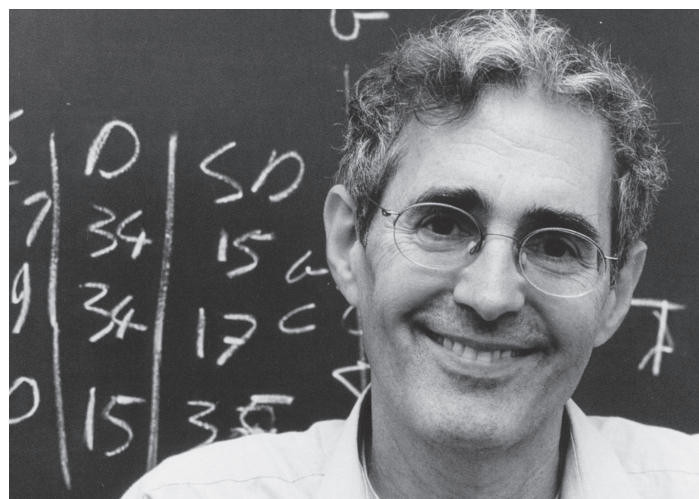
“This is another brick in the wall of discovery” that may someday allow embryonic cells to be used to repair diseased tissue and organs, Dr. Cedar said. **This could revolutionize the treatment of chronic disorders**, especially those of middle and old age.

All embryonic cells have the flexibility to do anything; but, once they begin the differentiation process, they attain their adult form and function. This happens about the time the embryo settles into the uterus and begins to change and grow. “The way the programming is done, it’s very unidirectional. Coming back is very difficult,” Dr. Cedar said, explaining that the human body instinctively tries to remain stable. “If you can take any cell in the body and go backward, then you can use that cell to make a different kind of tissue.”

Dr. Cedar’s and Dr. Bergman’s team may have found a way to do that by identifying a master regulatory enzyme called G9a, which is responsible for shutting down the ability of cells to develop into more than one kind of mature cell when the embryonic cells are ready to begin differentiation. “If you can get rid of G9a, that will help you go backward,” Dr. Cedar said.

The researchers have so far accomplished this goal only in lab mice because of the illegality associated with human genetic testing. Eventually, they hope to be able to take an individual’s own blood cells, place them in a culture to perform the reversion process, then reprogram the cells as needed.

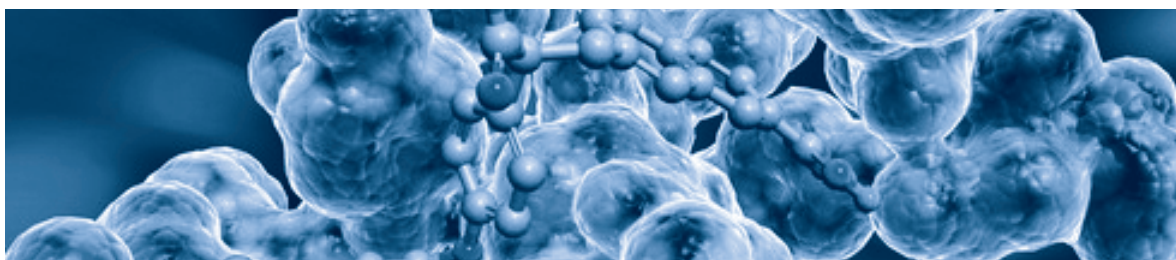
Dr. Cedar points out the efficiency of using a patient’s own cells, rather than those of another person or embryo. “When you put cells into the body from another person, the body responds. You have an immune



response and that prevents any of this from working,” he said. “Every cell in the body has the same exact genetic material, but in every cell it’s programmed differently.”

By removing G9a from a patient’s own developed cells, doctors would be able to begin with a clean slate that is completely compatible with the patient’s own immune system.

“We can’t say if our discovery will turn into something very practical, but it is a novel finding that produced much amazement when Yehudit presented it at scientific meetings at Harvard and in Australia. Our article in *Nature Structural & Molecular Biology* offers genetic proof of the power of G9a,” Dr. Cedar said.



RNA: A Powerful Partner to DNA

Everyone knows about the famous double helix of DNA, the substance in every cell of our bodies that carries our genetic code. Not so familiar is RNA, which scientists – including many funded by ICRF – are realizing plays a crucial role in determining which genes are active and which proteins are produced. They can **contribute to the formation, or the blockage, of many diseases, including cancer.**

First, a little background: Both RNA and DNA are strands made up of the chemical units that represent the “letters” of the genetic code. Each letter pairs with only one other letter, so two strands can bind to each other only if their sequences are complementary.

Genes contain the blueprints for creating proteins and are made of DNA. When a protein needs to be made, its genetic code is copied from the DNA

onto a single strand of “messenger” RNA, which carries the blueprints to the cell’s protein-making machinery. Proteins then perform most of a cell’s functions, including activating other genes. **Scientists are now finding that RNA itself seems to be playing a role in determining which genes are active and which proteins are produced.**

Why is this important to cancer researchers? They are looking at micro-RNAs, which are snippets of RNA that interfere with messenger RNA. Micro-RNAs affect many bodily processes and diseases, and some even contribute to the formation of cancer, while other micro-RNAs help block it.

The biggest research effort is on a process called RNA interference, which occurs when a short snippet of double-stranded RNA, called small interfering RNA, enters a cell, which treats it like

a micro-RNA it might make on its own. That results in the silencing of a gene that corresponds to the inserted RNA.

Small interfering RNA could be synthesized into a drug, but it hasn’t been conclusively shown that it would work in people. It could silence genes beyond its intended target, causing unwanted side effects. The biggest challenge, though, is delivering the RNA into cells where it is needed.

While RNA interference is known to turn genes off, sometimes it is desirable to turn genes on or increase their activity levels to fight some diseases. Recently, researchers have found that RNA can do this, too. As a result, **they are now hard at work in order to determine whether RNA therapy can be used to treat diseases, including cancer.**

Dr. Margalit New Insights Through Bioinformatics

Hanah Margalit, Ph.D., is a professor of Medicine at the Hebrew University of Jerusalem, Department of Molecular Genetics and Biotechnology, and the recipient of a 2008-09 ICRF Project Grant. She works in the field of bioinformatics, which is the collection, classification, storage, and analysis of biochemical and biological information using computers. Bioinformatics is used to gain new biological and medical insight into the genes and proteins that play a role in tumor transformation and for the design of new treatments.

Margalit’s team uses bioinformatics to look for a possible relationship between a new group of genes and cancer. These genes do not produce proteins, as is typical of most genes; but, rather, micro-RNAs (see story above), which are now believed to play an important role in the regulation of cellular processes. Evidence suggests that these genes are involved in development and in malignant transformation.

“By finding target genes known to be involved in cancer, we aim to understand how impairment of the micro-RNAs affect tumor growth,” Margalit says. “We

developed a way to predict micro-RNA targets that **has already led to an important discovery:** a new mechanism, mediated by micro-RNAs, by which viruses fight against immune system genes. This finding may have important implications in cancer research, as cancer-causing viruses also express micro-RNAs.”



Dr. Canaani

Targeting a Hard-to-Treat Breast Cancer

Breast Cancer

Dan Canaani, Ph.D., is chairman of the Biochemistry Department at Tel Aviv University and recipient of a 2008-09 ICRF Project Grant. After years spent investigating the mechanisms of cancer, he refocused his research on actually curing the disease. Inspired by a genetic screening method in yeast that he taught his advanced genetics students, he decided to try to establish a similar method for human cells that would be able to screen for anticancer drugs and target genes that will be highly selective for cancer cells.



Now, after developing the appropriate technologies, **Dr. Canaani and his team have begun the application stage of the project by searching for new targets and lead compounds for breast cancer patients for whom there are few treatment options.** Their type of breast cancer lacks the three “receptors” known to fuel most breast cancers, and which are targeted by most successful treatments for breast cancer.

Because none of these receptors are found in women with this “triple negative” breast cancer, their tumors generally do not respond to receptor-targeted treatments and, depending on the stage of its diagnosis, it can be particularly aggressive and more likely to recur than other subtypes of breast cancer.

“If successful, it may pave the way to selective drugs linked to pre-defined molecular aberrations, and therefore have fewer side effects,” Dr. Canaani said.

Dr. Sperling

The Finer Points of RNA Splicing

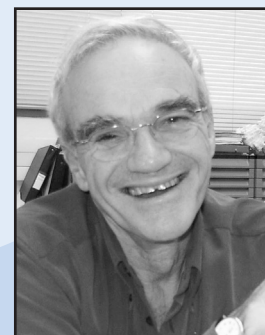
Joseph Sperling, Ph.D., is The Hilda Pomeranic Professor of Organic Chemistry at the Weizmann Institute of Science and the recipient of a 2008-09 ICRF Project Grant. He and his team are addressing a question related to the regulation of gene expression, a process whereby DNA is transcribed into messenger RNA and the latter is translated into functional proteins, which sustain all living systems.

Because the information encoded in the RNA chain is split, this molecular

chain must be cut at a number of points and only the pieces important to the production of a functional protein are joined together. This process, called RNA splicing, must be extremely accurate because even minor mistakes lead to mutated, non-functional proteins that may underlie a broad range of diseases, including the development of certain cancers.

This research is based on a discovery made in Sperling’s lab that a particular aspect in RNA splicing is sensitive to stress conditions and to treatment with

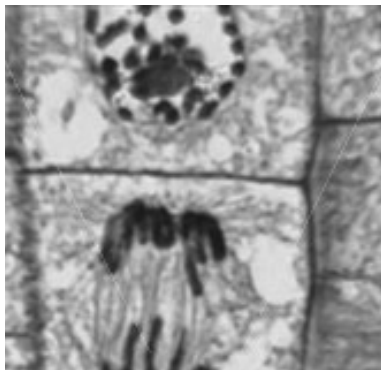
certain drugs. “We have therefore proposed to gain insight into this mechanism and to develop diagnostic tools to identify its malfunction,” Sperling said. **“We expect that this undertaking should allow, in the future, the development of new drugs to control and repair defects in the RNA splicing mechanism in malignant cells.”**



Dr. Shav-Tal

Studying Cells in Real Time

Yaron Shav-Tal, Ph.D., is a member of the Mina & Everard Goodman Faculty of Life Sciences at Bar-Ilan University and recipient of a 2008-09 ICRF Research Career Development Award. While working on his doctorate, he became interested in how the structure of the cell nucleus, where all genetic information (DNA) is stored, relates to the different functions of the nucleus. He now studies the gene expression pathway in normal and cancerous cells – that is, how a gene “turns on” and subsequently leads to a biological function.



His team’s specialty is the use of high-resolution fluorescent microscopy on living cells, which enables them to peer into cells and follow biological processes as they occur in real time within the natural landscape of the cell, in contrast to biochemical experiments

conducted on dead cells in the lab. The molecules that deliver genetic information from the cell nucleus to the cell body are the focus of their studies.

Dr. Shav-Tal’s team uses these techniques to understand how different genes function under normal conditions and during aberrant conditions such as cancer. Such insights allow scientists to devise new ways of approaching cancer and, ultimately, to develop new treatments for the disease.



2009 Sees a Bumper Crop of Grant Applications

ICRF's 2009 Scientific Review Process took place in New York in March as this issue of *ICRF Insights* went to press. **This year, we received 170 grant applications – the most ever** – divided into the following categories: four Professorships, four Clinical Research Career Development Awards, 20 Research Career Development Awards, 137 Project Grants, and five Postdoctoral Fellowships.

Panel A, chaired by Dr. Peter Stambrook of the University of Cincinnati, reviewed 94 applications in the areas of molecular and cellular biology, genetics, and tumor viruses. Panel B, chaired by Dr. Louis Weiner of the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center, reviewed 71 more

clinically oriented applications related to immune mechanisms, hormonal activity, diagnosis and therapy. Look for updates in the next issue of *ICRF Insights*.

The large number of applications received indicates that ICRF funds are

needed now more than ever. **Please help us to ensure that the potentially life-saving cancer research work of ICRF-funded scientists can continue and flourish by making a donation today.**



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Take Advantage of New Gift Options!

We realize that these are challenging financial times for all of us – and no less for these scientists. As you look at your ability to support ICRF, please consider taking advantage of a tax-free IRA gift.

Tax-free rollover gifts from traditional or Roth IRAs to charities like ICRF were extended into 2008 and 2009 by the newly signed Emergency Economic Stabilization Act of 2008, thereby allowing:

- donors age 70 or older to contribute,
- contributions in 2008 or 2009 that are less than \$100,000, and/or
- transfers from an IRA directly to ICRF.

As was the case in 2006 and 2007, this legislation does not permit an IRA charitable rollover to fund life income gifts such as charitable gift annuities. However, a donor can use these funds to pay a pledge. To properly complete the gift, your IRA administrator must make the check payable directly to the Israel Cancer Research Fund.

Please consider joining us in supporting some of Israel's best and brightest researchers. For more information, please call one of our offices listed on the back of this newsletter.

HAPPY PASSOVER! Wishing you and your family an enjoyable Holiday.