

# REPORT

Spring 2005

## SWCRF Investigators Lead Research in Epigenetic Therapy



SWCRF-funded investigators are making important contributions to the development of epigenetic therapy - a newly emerging field of cancer research that is providing major insights into the origin, progression and potentially, the reversal of cancer. In January 2005, ten SWCRF-funded investigators participated in the conference "Clinical Translation of Epigenetics in Cancer" organized by Dr. Steven Gore, Associate Professor of Oncology at the Johns Hopkins School of Medicine. During the two-day meeting in Baltimore, MD, scientists were intensively engaged at the translational and clinical level.

"I applaud the SWCRF's role in sponsoring the conference and Dr. Waxman's dedication to making this a rigorous and productive meeting," said Dr. Gore. "Several scientists have said this was the best meeting they have ever attended."

Epigenetics is the study of changes in gene expression by mechanisms that occur without any effect on DNA sequence. It is well known that genes play an important role in diseases. With the completion of the human genome map, scientists can now trace hereditary diseases and cancers to specific mutations in our DNA. These genetic defects explain why healthy cells

can malfunction, leading to disease. But genes only tell part of the story. While the genetic code provides the blueprint for the manufacture of all the proteins in our body, another important code - epigenetics - provides the additional information on how, where and when the genetic information should be used.

A central issue in epigenetics involves how changes in certain genes are "switched" on or off. "Genes that are switched off, or 'silenced' can have a profound effect on the onset and development of cancer," says Dr. Samuel Waxman. "The switch can be targeted to 'turn on' by different drugs so that the gene functions normally, causing the cancer cell to be differentiated and directed to die."

The participating SWCRF-funded investigators were: Dr. Arthur Zelent, Institute of Cancer Research, London; Dr. Reuben Lotan, MD Anderson Cancer Center; Dr. Beverly Emerson, Salk Institute; Dr. James Herman, Johns Hopkins University; Dr. Michael Grever and Dr. John Byrd, Ohio State University; Dr. Ari Melnick, Albert Einstein College of Medicine; Dr. Wilson Miller, McGill University, Montreal; Dr. Jonathan Licht and Dr. Samuel Waxman, Mount Sinai School of Medicine.

### Inside

- 2 From Our Chairman
- 2 Scientific Director's Message
- 3 Meet Our Investigators
- 5 Fundraising Events
- 6 News Briefs



Michael Nierenberg



Samuel Waxman, M.D.



SAMUEL WAXMAN  
CANCER RESEARCH  
FOUNDATION

## From the Chairman

Dear Friends,

This past year has been one of tremendous growth, vision and accomplishment. I am proud to report that our Fall/Winter "Collaborating for a Cure" Benefit was a great success, raising over \$2.5 million for cancer research. More than one-third of the funds raised were targeted specifically for establishing cancer research programs in melanoma, breast and lung cancer. The evening was a powerful display of your energy and commitment as collaborative partners in the search for cancer cures.

This Spring will bring a new round of grant applications from eminent scientific institutions around the world that similarly share the vision of innovative cures for cancer. Many of our important achievements, past and present, are the result of joint efforts with other scientific institutions, within the US and abroad. For this reason, I am reminded constantly that the work of cancer research has neither boundaries nor politics. It is our hope that, together, our efforts may lead us closer to the discovery of new cancer and cancer prevention therapies.

We are enormously grateful for your partnership with us as we expand our network of scientists conducting groundbreaking basic, translational and clinical research. As we move forward, we will continue to share the highlights and successes of our collaborations with you.

## Scientific Director's Message

**B**alancing the "goods" and the "bads" when it comes to evaluating progress in cancer research continues to be a challenge. Consider the following: People are living longer but the rate of cancer increases with age. The number of cancer survivors – nine million - is increasing, but requires enormous resources. The present administration has decreased the National Cancer Institute budget, but now emphasizes collaborative research and development of cancer cell selective therapies. In fact, most new clinical trials supported by government and industry are testing targeted cancer cell selective therapies as opposed to conventional non-specific therapies such as chemotherapy. Keeping with this, in the past year the FDA approved seven cancer cell specific therapies and one non-specific chemotherapy. So on balance, we are making progress.

The SWCRF can be considered a model for the recently described NIH Roadmap for Research. We have emphasized collaborations between basic, translational and clinical research scientists. We have utilized scientific breakthroughs to develop two cancer cell-specific therapies that are used worldwide. We have established international conferences to rapidly disseminate breaking developments. Just review a few of the articles in this issue of the SWCRF Report. Professor Zhu Chen, an international renowned scientist and leader, describes the role of the SWCRF collaboration in the development of the Shanghai Institute of Hematology. This collaboration continues to be robust providing multiple scientific contributions each year.

*(continued on page 7)*

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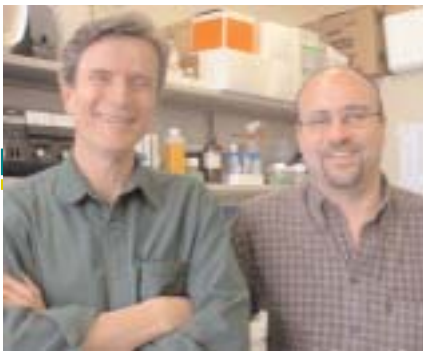
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Dr. Raphael Mira-y-Lopez and Dr. Eduardo Farias

# Vitamin A May Help Prevent Breast Cancer

**D**r. Rafael Mira-y-Lopez, Associate Professor of Medicine and Dr. Eduardo Farias, Post-Doctoral Fellow in Medical Oncology, have discovered how a defect in the way the body processes vitamin A may contribute to breast cancer. The scientists' research shows that when breast cells are missing a specific protein that binds to vitamin A, due to a silenced gene, they are more likely to become cancerous. The study was published in the January 5 issue of the Journal of the National Cancer Institute.

Vitamin A belongs to a family of compounds called retinoids. Individuals who are better able to utilize vitamin A possess the vitamin A binding protein, CRBP-1. This protein regulates retinol metabolism and is involved in retinol storage. "We found that in the early stages of tumor formation, if you don't have CRBP or LRAT (another protein) to store the retinol, it's likely that the receptors will not work normally," said Dr. Mira-y-Lopez. The team of scientists would like to further advance their study by conducting clinical studies, which may eventually translate into a new target for vitamin A-based drugs to prevent breast cancer and other malignancies.

## News Briefs

### Appointment

Dr. Samuel Waxman was named the Albert A. and Vera G. List Professor of Medicine at The Mount Sinai Medical Center. The late Albert and Vera List supported medical research, education and the arts in New York and beyond.

### Research and Collaboration Highlights

**Dr. Julio Aguirre-Ghiso**, SUNY-Albany Gen\*NY\*Sis Center for Excellence in Cancer Genomics, reports on laboratory results suggesting that cancer patients in remission with dormant tumor cells that are nonresponsive to chemotherapy regimes may benefit from treatment with specific inhibitors of a novel survival pathway that can sensitize dormant tumor cells to standard chemotherapy and eradicate them. Dr. Julio Aguirre-Ghiso's laboratory has previously shown that dormancy requires a strong activation of the p38 kinase growth suppressive pathway, in vivo. These results led to the laboratory's recent identification of a novel p38-dependent survival mechanism in dormant tumor cells.<sup>1, 2</sup>

**Dr. Beverly Emerson**, The Salk Institute, reports collaborative work with Dr. Ari Melnick, also an SWCRF-supported investigator, on how genes are aberrantly silenced in human cancers. A silenced gene is characterized by mul-

tle "epigenetic" changes in histone and DNA modifications that result in transcriptional reprogramming. Emerson's laboratory is focused on an in vitro model of how these potentially reversible epigenetic changes are established. They are currently trying to identify which specific DNA binding proteins that interact with silenced promoters actually recruit or target the enzymes responsible for histone and DNA methylation.

**Dr. Reuben Lotan**, University of Texas M.D. Anderson Cancer Center, reports that treatment of non-small cell lung cancer cells (NSCLC) with the non-steroidal anti-inflammatory agent, Celecoxib (Celebrex TM) in combination with the synthetic retinoid Fenretinide (4HPR) results in a marked suppression of cancer cell growth and colony formation by induction of apoptosis or programmed cell death. Dr. Lotan's study indicates that this combination is more effective than treatment with either agent alone in inhibition of growth and induction of apoptosis in NSCLC, and suggests that further study of the combination for lung cancer prevention or treatment is warranted.<sup>3</sup>

**Dr. Neal Rosen**, Memorial Sloan-Kettering Cancer Center, reports on research concerning the development of inhibitors of the signaling pathway activated by mutated B-Raf in melanoma and several other malignancies. Dr. Rosen's laboratory has found that Hsp90 inhibitors degrade Raf and inhibit MAPK activation in melanomas in cell culture and animal models. These data have been used to initiate a phase 2 clinical trial of the Hsp90 inhibitor 17-AAG in patients, and have demonstrated in tumor biopsies that 17-AAG causes Raf degradation and MAPK inhibition, as well as anti-tumor activity. Dr. Rosen is also studying a potent and specific inhibitor of the MEK1 and MEK2 kinase, which selectively suppresses the growth of melanomas and other tumors with B-Raf mutation.<sup>4, 5</sup>

*(continued on page 6)*

# Seventh Annual “Collaborating for a Cure”

**A** record \$2.5 million was raised at the 7th Annual “Collaborating for a Cure” Benefit held on December 2nd at the Metropolitan Pavilion. More than 600 people attended the event, which was generously supported by the Foundation’s Board of Directors. Highlights of the evening included a silent auction, live auction, a commemorative Benefit Journal and a concert by Lyle Lovett with his 14-person band and 12-person choir. A special musical performance was given at dinner by the up-and-coming young band, The Lost Trailers, who composed a song about cancer written expressly for the event.

The live auction, conducted by renowned Sotheby’s auctioneer C. Hugh Hildesley, was an enormous success, raising over \$1.5 million with more than \$775,000 targeted specifically to establish three new cancer research programs in melanoma, breast and lung cancer. Among the exclusive live auction packages were a one-of-a-kind getaway to Harbor Island, two cocker spaniel puppies and dinner catered in one’s own home by Restaurant Daniel. Enthusiastic bidders also vied to sponsor sophisticated research equipment that will enable the Foundation’s laboratory to analyze gene changes in liver cancer.



Lyle Lovett



From left: Mike Walmark, Craig Sedmak, Susan Deitchman and Jennifer Giordano



Michael and Elin Nierenberg



From left: Wes Edens and Warren Spector



From left: Jodi Kaplan, Elin Nierenberg, Alyssa Greenberg and Debbie Shlafmitz



From left: Costas Kondylis, Gary Jacob, Dennis Herman  
Bottom: Sarah Ziegelbaum, Linda Jacob, Linda Herman



Nanci Gelb and her brother Baron Silverstein



From left: Bettina and Spencer Waxman, Ellen and Rick Miller and Mildred Levine



From left: Eric Goldstein, Dr. Samuel Waxman, Jill and J. Jay Mautner

# Benefit Dinner Raises Record \$2.5 Million



C. Hugh Hildesley, auctioneer

**T**he enthusiasm shown by all of SWCRF's supporters makes it possible to expand our network of talented scientists. In the last few years, the number of funded researchers in the US and abroad has grown more than six-fold. This year will see the funding of ten additional scientists, bringing the total number of scientists up to nearly 40 investigators. It is anticipated that the number of laboratory sites will increase to 50 within the next few years. This growth will further the Foundation's efforts to advance basic science into translational research and design clinical trials to test promising cancer treatments.



From left: Adrienne, Robert and Mary Kantor



The Lost Trailers (From left): Stokes and Ryder, with Stacey Williams, center

## Our many thanks to the companies and individuals who made this evening possible through their generous donations:

- |  |  |  |
|--|--|--|
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| Laura Geller Make-up Studios           | New York Yoga                            | Zitomer                                      |
| Judi Gladstein                         | Nickelodeon                              | Zöe Restaurant                               |
| Barry Goodman                          | Elin & Michael Nierenberg                |  |

The Foundation would like to thank our Benefit Committee: Lauren and Brad Egna, Carol Feldman, Alyssa and Clifford Greenberg, Jodi Kaplan, Marci and Glenn Pere, and Debbie and Howard Shlafmitz and extend a special thank you to Elin and Michael Nierenberg, who once again hosted the event.



## An Interview with Dr. Zhu Chen

**D**r. Zhu Chen and the Shanghai Institute of Hematology (SIH) are long-established collaborators with SWCRF. Dr. Chen is Co-Principal Investigator and Director of the SWCRF in China. Presently, he is the Director of the SIH at the Rui-Jin Hospital in Shanghai, China. He also serves as Vice President of the Chinese Academy of Sciences and Director of the Human Genome Center.

Recently, Dr. Chen gave us an overview of his collaborative work with SWCRF and the important role the Foundation has played in the growth and development of China's biomedical research programs at SIH.

### What is the significance of SWCRF's role in developing the Shanghai Institute of Hematology?

The SIH has been in close collaboration with SWCRF for 15 years. In the past few years, SWCRF has been playing a significant role in promoting the development of SIH. With its support and other resources, SIH achieved many important breakthroughs in the molecular biological study of leukemia, such as the cloning of PLZF-RAR $\alpha$  fusion gene, the discovery of structure and functions of the PLZF gene and the establishment of PML-RAR $\alpha$  as a quantitative molecular marker in most APL patients.

Collaborating with SWCRF, SIH also made major achievements in the treatment of APL. Under my direction, we have elucidated the cellular and molecular mechanisms of arsenic trioxide's therapeutic effects in the treatment of APL and other hematological malignancies. We further found that the combined use of all-

trans retinoic acid (ATRA) and arsenic can reach a high quality, disease-free survival (DFS) in most APL cases, making APL the first curable human acute myeloid leukemia.

SWCRF also gave impetus to the internationalization of SIH. Promoted by SWCRF and the International Conferences on Differentiation Therapy, many scientific achievements of SIH, especially the concept of selective induction of differentiation/apoptosis therapy of human leukemia, were soon known by the international research community, benefiting thousands of patients worldwide.

### Can you describe your experience working with and collaborating with SWCRF?

The collaboration between my team and SWCRF has a 15-year history. I can still remember the words of Prof. Samuel Waxman when he invited me to give a talk at a Mount Sinai Grand Rounds Lecture in New York. He said,

"You have done a first-class job, so you should be confident. You should face the audience and speak to them with passion." Though 15 years has passed, the encouragement from Prof. Waxman has become a spiritual force compelling me to work hard.

It is true that the advancement of biomedical science should face the call of society and constantly make new contributions to the foundation of medical knowledge. We should be confident to turn knowledge into a tool to save patients. Medical science belongs to the whole world, going beyond national and geographical boundaries, and also beyond the limitations caused by language, culture, religion and history. The cooperation between SIH and SWCRF is a good paradigm for Sino-US scientific collaboration in the cancer research field specifically, and in medicine generally.

Read the full interview of Dr. Zhu Chen at [www.waxmancancer.org](http://www.waxmancancer.org)

## News Briefs *(continued from page 3)*

### PUBLICATIONS

- 1 Julio A. Aguirre-Ghiso, Liliana Ossowski and Sarah K. Rosenbaum. GFP tagging of ERK and p38 pathways reveals novel dynamics of pathway activation during primary and metastatic growth. *Cancer Res* (2004); 64(20): 7336-45.
- 2 Aparna C Ranganathan, Alejandro P Adam, Lin Zhang, Sharon J. Sequeira and Julio A. Aguirre-Ghiso. Functional coupling of endoplasmic reticulum signaling to drug resistance of dormant carcinoma cells. Manuscript in revision.
- 3 Shi-Yong Sun, Claudia P. Schroeder, Ping Yue, Dafna Lotan, Waun K. Hong, and Reuben Lotan. Enhanced Growth Inhibition and Apoptosis Induction in NSCLC Cell Lines by Combination of Celecoxib and 4HPR at Clinically Relevant Concentrations. *Cancer Biology and Therapy*. In press, 2005.
- 4 Grbovic O, Solit D, Basso A, Friedlander P, Osman I and Rosen N. Mutationally activated, but not wild type B-Raf requires the Hsp90 chaperone for stability and is degraded in response to Hsp90 inhibitors. Submitted.
- 5 Solit D, Basso A, Sawai A, Pratilas C, Leopold J, Sellers W, Rosen N. B-Raf mutation in tumors confers selective sensitivity to the antiproliferative effects of MEK inhibitors. Submitted.

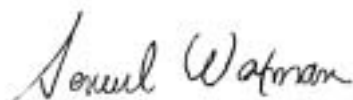
(continued from page 2)

## Scientific Director's Message

**D**r. Raphael Mira-y-Lopez, a SWCRF investigator at The Mount Sinai School of Medicine, recently reported a significant scientific breakthrough that has led to a better understanding of how abnormal Vitamin A metabolism may play a role in the development of breast cancer. Similarly, Professor Michael Grever, a recent recipient of the David Workman Memorial Award, and his colleagues are reporting on remarkable effects of targeted treatments in lymphoma and chronic lymphocytic leukemia. Collaborative breakthroughs further demonstrating the active programs of the SWCRF are described in the News Brief Section.

The private sector is an important partner in the collaboration for cancer cures, particularly in this setting of diminishing government support. There is no easy way to describe the "giving back" generosity of so many people throughout 2004. This strong support has initiated the formation of new breast, lung and melanoma programs. It will also allow the SWCRF to award more individual grants and, for the first time, program grants to support three or more scientists already in collaboration.

Each day I am reminded that there is much more to be done for people suffering from cancer. All of us have shared this sadness, and together, we can say we are making a difference.



## Generosity Abounds Among Children and Parents of Nursery School & Kindergarten

**T**he children and parents of Congregation Sons of Israel in Manalapan, NJ hosted a special Mitzvah Day to raise money to help find a cure for cancer and to celebrate the spirit of giving. "We do a mitzvah, or a good deed, a month," said Renée Narson, director of the school. "Every month is a designated charity. The children learn that giving of tzedakah is a part of them." Tzedakah, the Hebrew word for charity, not only refers to benevolence and generosity, but also includes the idea of justice and the performance of a duty. The funds raised were donated to the Foundation and matched by Mindy and Allen Grafstein, parents of Casey.



From Left: Delaney Engel, Casey Grafstein and Samantha Aronson

**Mitzvah days are so much fun  
Doing good deeds for everyone!  
Raising money to find a cure  
Our goals are simple, kind and pure.  
We wanted to help The Waxman Foundation  
And so we did it with a celebration!**

—The children and parents of Congregation Sons of Israel

(continued from back cover)

## Workman Memorial Award

**C**LL, one of the most common forms of leukemia among adults in the Western Hemisphere, is characterized by an accumulation of abnormal white blood cells in the blood and bone marrow. The disease results in progressive bone marrow failure and impaired immunity. There is currently no cure for CLL, but promising research like that of Drs. Grever and Byrd has led to new approaches to manage the disease.

The Workman Memorial Award will enable Dr. Grever to continue the development of novel therapies for patients with CLL. Already, Dr. Grever and his colleague Dr. John Byrd are pursuing the development of Flavopiridol, a

highly effective agent for the treatment of CLL. Drs. Grever and Byrd intend to further focus their research to identify how this agent results in rapid tumor reduction, and to predict which patients are likely to benefit. In addition, they are searching for combinations of novel therapies to further enhance the number of patients who safely achieve a complete response to therapy.

"The support of the Samuel Waxman Cancer Research Foundation will be extremely important in our efforts to improve therapy for patients with CLL, currently an incurable malignancy," Dr. Grever said. "It is a great honor to receive the David Workman Memorial Award."

# Second David T. Workman Memorial Award Presented to Dr. Michael Grever

**F**riends and family of David Workman gathered at the New York Academy of Sciences on November 8th for the second David T. Workman Memorial Endowment Lecture and presentation of the Workman Memorial Endowment Award to Dr. Michael R. Grever, Chairman of the Department of Internal Medicine at the Ohio State University School of Medicine.

The evening was a tribute to David Workman's 20 years of dedication to the Foundation. Mr. Workman was one of the initial leaders of the Foundation and served as Board Chairman for a number of years. He survived his first bout of cancer; however, twenty years later in 1997, he succumbed to a second cancer for which no life-saving drugs were – and still are not – available.

The Workman Award was formally established in 2003 as a two-year, \$50,000 grant to enable the clinical develop-



From Left: Dr. Jonathan Licht, Dr. Michael Grever and Dr. Samuel Waxman

ment of novel selective therapies for poorly treatable forms of cancer. This year's Workman Award will support the research of Dr. Grever and his colleague, Dr. John Byrd, on chronic lymphocytic leukemia (CLL). *(continued on page 7)*

The Foundation's Newsletter is available by email. If you would prefer to receive our Report electronically, and to help us keep costs down, please send your email address to report@waxmancancer.org

**HOLD THESE DATES**

**23rd Annual Golf Tournament**  
**Monday, June 27th, 2005**  
 Rockrimmon Country Club

and

**2nd Annual**  
**A Hamptons Happening**  
**Saturday, July 23rd, 2005**  
 At The Mill, a historic residence  
 and home of  
 Dena K. Weiner and  
 David Rozenholc

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