At the age of thirty-six, a friend we’ll call Sandra needed a lumpectomy and radiation for breast cancer. Her recovery was uneventful; she called her cancer “a thing of the past.” That was twenty-three years ago. Recently, a recurrence necessitated a mastectomy. This time Sandra’s recovery has been difficult, and now her doctors are “discouraged.” Unfortunately, her story is familiar.

Researchers whose goal is to eradicate breast cancer the first time around are looking for the reasons Sandra and so many other women have breast cancer recurrences after a long period of health.

Building on work done by John Dick with leukemias in the late 1990s, Dr. Ben Neel, the Director of the Cancer Biology Program at Beth Israel Deaconess Medical Center in Boston, is investigating the idea that a small population of cells is responsible for tumor formation. In the past, before the molecular age in cancer biology, many scientists believed all tumor cells were more or less the same. Now more researchers think that the vast majority of cells help cancer grow and spread but just a few chemotherapy-resistant stem cells can produce a whole new tumor.

“In many tissues a small number of stem cells give rise to a larger number of proliferating cells and then the proliferating cells generate cells that differentiate and form the final tissue,” says Dr. Neel, who is also Professor of Medicine at Harvard Medical School. “To give you an idea, in a mouse, total bone marrow has about 20 million cells. Only about ten thousand of those are stem cells. Yet one of those cells, if purified, could give rise to the entire bone marrow.

“Since the tumor stem cell has infinite self-renewal capability, it can just grow back,” says Dr. Neel. “And it can grow back with more mutations which make it more difficult to kill.”

Dr. Neel and his colleagues are trying to demonstrate that what has been learned about tumor hierarchy in research on leukemias also applies to breast cancer. Both mouse and human models are helping him and his coworkers toward that goal, and to develop ideas about how to target tumor stem cells selectively, with drugs. “The ultimate goal is to use biopsy to identify tumor stem cells and determine their self-renewal and survival characteristics,” Dr. Neel

(continued on page 7)
From the Chairman & Scientific Director

Dear Friends,

2006 is off to an incredible start! Our “Collaborating for a Cure” Benefit raised a record breaking $2.8 million. Because of your generosity we continue to fund vital research programs all over the world so that one day our children can live in a world without cancer.

As you will read in News Briefs and Milestones, we’ve made significant progress in treating leukemia and other forms of blood malignancies. We also report on two breakthroughs in science: new and specific treatments of melanoma and lung cancer and basic research in breast cancer stem cells which will result in saving more lives in the not-so-distant future.

This year, we will continue to expand our research in the fields of Breast, Lung, Prostate, Liver and Pancreatic Cancer, Leukemia and Lymphoma, Melanoma, Aberrant Gene Expression and Preventing Metastasis. We are just now receiving applications for our 2006 granting cycle. Not only has this impressive pool grown in size but it also contains applicants from top research institutions, one of which includes a Nobel Laureate. Most importantly, 85% of all funds raised will go directly into cancer research.

To sustain this level of activity and dedication to our mission, Dr. Ethan Dmitrovsky has joined Dr. Jonathan Licht as Associate Scientific Director. Dr. Dmitrovsky is the Andrew G. Wallace professor at Dartmouth Medical School, and the Chairman of the Department of Pharmacology and Toxicology. He also serves as a member of the Lance Armstrong Foundation Scientific Advisory Board. By this time next year, our researchers will be able to log on to a secure site and share their latest findings. What makes our Foundation unique is its insistence that our researchers collaborate. As grants are awarded only upon proof of this collaboration, this site will bring us to a new level of greatly enhanced communication.

To add to this year’s excitement, we have just hired a new Director of Development, Mark Silverstein. He joins us with 15 years of solid fundraising experience. To add to this, we are winning in the battle to defeat breast cancer. Although more women will get breast cancer, better education leading to earlier diagnosis and coordinated treatment by surgeons, medical and radiation oncologists and genetic advisors is leading to a higher cure rate and a decrease in mortality. This achievement has required billions of dollars, worldwide innovative research, government commitment and women’s advocacy pressure.

How then does a small foundation such as SWCRF contribute to this massive commitment to beat breast cancer?

As you will read in this newsletter, the SWCRF is focusing on the tragedy of late recurrence of breast cancer due to dormant and cancer stem cells. Dormant cancer cells are difficult to detect, treat and can revert to aggressive growing tumor-forming cells. SWCRF scientists have found a specific signal to block this reversion, and inhibitors have been developed which may become drugs that can be used to kill the dormant cancer cells.

A close cousin to the dormant cancer cell may be the breast cancer stem cell, the mother lode that gives birth to each tumor. The SWCRF is funding outstanding work to solve the riddle of the breast cancer stem cell and expose its Achilles heel, so that a specific treatment can be developed.

The SWCRF breast cancer program is expanding. It includes research projects to identify nonfunctioning genes that cause cancer (continued on page 7).

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Max Wicha, Committed Cancer Sleuth

D r. Max Wicha, a founding member of the SWCRF Advisory Committee and distinguished cancer researcher, recently defended his cancer stem cell hypothesis in an article published in the journal of the American Association for Cancer Research. He is committed to this idea, as he believes in fact he developed this concept over 20 years ago at the University of Michigan Cancer Center in Ann Arbor.

The stem cells are really the root of the plant, and what we’ve been doing is essentially using some herbicide that just kills the leaves.

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More than 800 people attended our 8th annual gala raising a record $2.8 million. Our evening began with entertainment by the up-and-coming band Sam Winch, followed by a sumptuous dinner and a live and silent auction. The gala was a powerful display of the energy and commitment of our supporters as collaborative partners in the search for a cure.

Our many thanks to the companies and individuals who have made the “Collaborating for a Cure” Benefit Auction and Dinner such a special event.

The foundation would like to thank our Event Chairs Elin & Michael Nierenberg and the Benefit Committee: Penny & Steven Beberman, Dale & Peter Claman, Lauren & Brad Egna, Carol & Mark Feldman, Judi & Gary Gladstein, Alyssa & Clifford Greenberg, Linda & Dennis Herman, Linda & Gary Jacob, Mary Kantor, Jodi & Marc Kaplan, Costas Konidylis, Marcia & David Lavigne, Mildred & Abner Levin, Amy & Thomas Marano, Jill & J.J. Maymuth, Marcia & Glenn Pere, Laurie & Charles Schafman, Deborah & Howard Shafritz, Juliette & Larry Silver, Kristin & Clifford Sterling, Bettina & Spencer Waxman, Dana K. Weiner & David Rozenholc.

Event Photos by © Rebecca Weiss Photography
Breast Cancer

Dr. Liliana Ossowski, Mount Sinai School of Medicine, reports progress on the goal of forcing cancer cells that have spread from the primary tumor into distant organs into dormancy, preventing them from dividing to form metastases. In 2005, studying two proteins — integrin and urokinase — that interact with one another starting a cascade of events that leads to cancer cell growth, Dr. Ossowski pinpointed the site on the urokinase receptor to which the integrin binds, initiating the cascade. Now, using unbiased screening and the collaboration of a computer biologist, 100,000 compounds are being searched for those that can break the bond of these two proteins.

Lung Cancer Clinical Trial for EGFR Resistant Cells

Dr. Jeffrey Settleman, Harvard University, has shown that approximately 10% of non-small cell lung cancers harbor specific activating mutations within the epidermal growth factor receptor (EGFR) gene. Lung cancer patients with EGFR mutations respond rapidly and dramatically to specific EGFR inhibitors Gefitinib (Iressa) and Erlotinib (Tarceva). This has resulted in significant extension of life. However, relapse can occur due to drug resistance. In Dr. Settleman’s lab, a distinct class of EGFR inhibitors has been demonstrated to overcome some secondary drug resistance mechanisms in tumors. Clinical trials will soon be conducted with lung cancer patients who relapsed on Iressa or Tarcea.

Understanding Drug Interaction and Tumor Suppression

Yosef Shaul, Weizmann Institute of Science, reports that his lab has discovered a protein degradation pathway that is amenable to pharmacological manipulation. In this pathway, certain proteins are degraded “by default” by cellular degradation complexes called the 20S proteasomes. Some proteins degraded by this pathway are directly relevant to cancer, such as tumor suppressor protein p53. Another protein, NQO1, associates with 20S proteasomes, binds to and protects proteins from degradation. Degradation of a protein can be induced with drugs that inhibit NQO1; protein levels can also be raised with drugs that increase expression of NQO1. The lab is currently working toward deeper understanding of this system.

Research Progress on Cancer Dormancy

Dr. Albert Baldwin, University of North Carolina School of Medicine, reports that cellular factor NF-kappaB, when activated in many cancers, provides signals for cell survival and tumor cell migration and metastasis. His studies indicate that standard cancer therapies further activate this factor, blunting their effectiveness. During the past year Dr. Baldwin has shown that one regulatory protein in the NF-kappaB pathway (IKKappa) controls growth and survival mechanisms found in many cancers. He is working to obtain an inhibitor of this pathway to test in models. In clinical trials new compounds are being tested to determine if they work synergistically with chemotherapy or radiation in blocking NF-kappaB activation.

New Studies on Cell Survival and Metastasis

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## HOLD THE DATES: Special Events Calendar 2006

<table>
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<th>Date</th>
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| Monday, May 22nd, 2006 | 24th Annual Golf Tournament  
Brae Burn Country Club  
Come win the $1 Million prize for a “hole in one” |
| Monday, October 23rd, 2006 | David T. Workman  
Memorial Award Ceremony  
New York Yacht Club |
| Saturday, July 8th, 2006 | 3rd Annual Hamptons Happening  
Gourmet Tasting Stations  
and Silent Art Auction  
On Georgica Pond, Wainscott |
| Thursday, November 30th, 2006 | “Collaborating for a Cure”  
Benefit Dinner  
Silent and Live Auction |

Help us keep costs down, please send your email address to report@waxmancancer.org