

momentum

Fall 2004

A newsletter from the DAMON RUNYON CANCER RESEARCH FOUNDATION

a brighter future

[FOCUS ON: CHILDHOOD LEUKEMIA]

As part of our continuing series on specific cancers, this issue of 'momentum' focuses on how the most sophisticated genomic technologies are revealing new information about leukemia—the most common form of cancer striking children.

For the parents of a six-month old child, each day brings the possibility of an exciting new change—a first word, the ability to sit up, the beginnings of a crawl. Imagine the disbelief then of families who learn that their babies have leukemia and must start fighting to retain their place in this world so soon after entering it. Having to break this kind of news to parents has led Damon Runyon-Lilly Clinical Investigator **Scott A. Armstrong, MD, PhD**, into hot pursuit of the causes and cures of childhood leukemia.

ABOUT ALL

The most common type of childhood cancer, acute lymphoblastic leukemia (ALL), strikes about 2,500 children in the United States each year. Thirty years ago, available treatments allowed only 1 in 10 of these children to survive. Since then, great numbers of children have participated in clinical trials to test different treatment regimens, so that today, nearly 80% of children with ALL are cured, mostly using chemotherapy. While applauding past progress, Scott, a physician scientist at the Dana-Farber Cancer Institute/Children's Hospital, is committed to doing better still. He focuses on infants with ALL, who face a bleaker future, with only about 40% living long enough to celebrate their sixth birthday. Armed with a Damon Runyon-Lilly Clinical Investigator Award, Scott has established a laboratory dedicated to research that will not leave any child with ALL behind.

did you know...

60% of children with cancer enroll in clinical trials but only 1% of adult cancer patients do

Progress has been much faster in pediatric cancers than in most adult cancers, and many credit the high participation of children in clinical trials as the major factor. With nearly 400 new cancer drugs currently in clinical trials, the need for participation from people of all ages has never been greater.

For more information about how clinical trials are conducted or to find a trial for a specific disease, go to www.clinicaltrials.gov.

IT'S IN THE GENES

One of the first questions Scott tackled at Dana-Farber is why infants have a poorer outcome than older children with ALL. Instead of using the traditional method of trying different combinations of chemotherapies, he took an innovative approach by turning to a new ally—the recently mapped human genome. Using the most sophisticated genomic technologies, Scott and his colleagues showed that the pattern of gene activity in the infant cancer looks different from other types of leukemia. The genetic “signature” of the infant cancer was distinct enough to give it a new name—“Mixed Lineage Leukemia” or MLL. One feature of the newly identified disease that particularly intrigued Scott was a mutation in a gene called “FLT-3.” The mutation caused the FLT-3 protein to be stuck in the “on” position in MLL. Because FLT-3 is a member of the family of enzymes that the body often uses to promote cell growth, Scott wondered if the mutation might be helping leukemia cells reproduce rapidly.

HITTING THE TARGET

Only a few hundred babies in the United States will be diagnosed with MLL this year, and drug companies do not typically spend time looking for cures that would have such limited use. Explaining this unfortunate fact to the parents of an infant with MLL doesn't sit right with Scott, who is determined to use his discovery about the potential cause of MLL to find better treatment options. “If we can shut down the activity of FLT-3 in patients with MLL, we just might cripple the leukemia cells without damaging any normal cells in the process,” notes Armstrong. This approach, known as “targeted therapy,” is the future of cancer medicine. Fortunately, drugs that inhibit FLT-3 already existed and were being tested at Scott's own institution for a different type of cancer. After some preliminary work in animals, Scott hopes later this year to start trying one of these inhibitors in infants who have relapsed MLL.

A HEALTHY SURVIVAL

Fueling Scott's enthusiasm for this line of investigation is a similar finding in another type of leukemia, chronic myelogenous leukemia (CML), that led to the development of the very successful drug Gleevec. “Developing targeted therapies for childhood cancers is crucial because the side-effects of chemotherapy in children go beyond the unpleasantness experienced during treatment,” says Armstrong. Studies of long-term survivors



Scott A. Armstrong, MD, PhD

of ALL have shown that most go on to have adverse consequences of their years on chemotherapy, including learning disabilities, heart failure, and growth retardation.

SPEEDY DISCOVERY

“The speed with which we can now go from discovering a new disease, to finding the underlying defect, to treating patients with a drug that attacks the real cause makes this a very exciting time to be in cancer research,” remarks Armstrong. Although the road of a physician scientist conducting patient-oriented research is not an easy one, Scott has noticed a subtle shift starting to occur in academic medical centers following the success of Gleevec. “There is heightened interest in using what we've learned in the laboratory about the basic mechanisms of disease to improve patient care,” he says. “The existence of awards like the Damon Runyon-Lilly Clinical Investigator Award may have helped turn the tide, and I am thrilled to have been given the resources to follow my passion.”

The Damon Runyon Cancer Research Foundation has a partnership with Eli Lilly and Company to fund the Clinical Investigator Award.

you're hired!

Annual Breakfast Raises Over \$1 Million

NBC Universal's newest star, **Donald Trump**, capped off this year's Breakfast honoring CEO **Bob Wright** with a \$100,000 gift to support Damon Runyon scientists. The event included a provocative discussion with leading scientists on the future of cancer research, led by CNBC's **Maria Bartiromo**. NBC executive and cancer survivor, **Jeff Zucker**, announced the establishment of the Suzanne and Bob Wright Scholar in recognition of their support of the Foundation.

From left: Donald Trump, Suzanne and Bob Wright, Maria Bartiromo.



young novelist with breast cancer leaves lasting legacy

True heroism is writing your first novel while dying from cancer. **Stephanie Williams** lived to see her gripping and poignant work published this June, dying of breast cancer literally weeks later at the age of 33. We are honored that she selected the Damon Runyon Cancer Research Foundation to receive a portion of the proceeds from *Enter Sandman*.

To learn more about her moving story and find out how to purchase her novel, please go to our website at www.drcrf.org.



Above: *Enter Sandman*
Right: Author, Stephanie Williams



what to say...

At some point we will all know someone facing cancer or another serious illness. We want to "say the right thing," but often struggle to find the right words. Stephanie Williams left some practical advice that we all can use.

DO treat me normally, but maybe a little more kindly and considerately.

DO realize that I actually have a life and care about the little things, the details of daily life, as you do.

DO know that I also care about the little details in your life. Don't be afraid to tell me about your awful boss because I have "bigger things" to worry about. I feel like the same person I ever was—treat me as such.

DON'T assume I remember everything you say to me, especially if I'm on chemo. There is such a thing as "chemo brain" that can make me seem senile.

DON'T EVER try to comfort me by saying, "You could live to be 80 and I could be hit by a truck tomorrow." I've got a truck speeding directly toward me. You don't.

DON'T be afraid to visit me because of the way I might look or you might act. We'll get through it.

DON'T push me to talk, but let me know that if I want to, you'll listen.

GO VERTICAL
THE ABSOLUTELY URBAN CLIMB FOR CANCER

GO VERTICAL moves to Boston!

Capitalizing on the success of the past two fundraising stair-climbs up the Sears Tower in Chicago, the Foundation will host the first stair-climb at Boston's John Hancock Tower – the tallest building in New England – on Sunday, February 6, 2005. The third annual Sears Tower stair-climb will be held this year on Sunday, November 14, 2004.

Log-on to our website, www.drcrf.org, for further information on these events or call Michael Stiver at 212.455.0501.

new awardees

16 New Damon Runyon Fellows Selected



Damon Runyon Fellowship Award

The Damon Runyon Fellowship Award supports the training of the brightest young postdoctoral scientists by established investigators in leading laboratories across the country. In May, the Foundation's Scientific Advisory Committee chose 16 new Fellows for the \$134,000 awards (\$174,000 for physician scientists*) designed to enlist the skills and creativity of the next generation in the fight against cancer.

Jennifer A. Benanti, PhD

"Genome-wide screen for targets of the SCF (Cdc4) ubiquitin-ligase" with David P. Toczyski, PhD, University of California, San Francisco, California

Laura A. Buttitta, PhD

"Control of cell cycle exit upon differentiation" with Bruce A. Edgar, PhD, Fred Hutchinson Cancer Research Center, Seattle, Washington

Sreekanth H. Chalasani, PhD

"Molecular analysis of a specific synapse in the brain of *Caenorhabditis elegans*" with Cori I. Bargmann, PhD, The Rockefeller University, New York, New York

Clark C. Chen, MD, PhD*

"Comparative analysis of DNA repair and damage response after proton and photon irradiation" with Alan D'Andrea, MD, PhD, Dana-Farber Cancer Institute, Boston, Massachusetts

Markus Covert, PhD

"Dynamics of LPS-stimulated activation of NF- κ B" with David Baltimore, PhD, California Institute of Technology, Pasadena, California

Sarah Delaney, PhD

"Mutagenesis by hyperoxidized guanine lesions" with John M. Essigmann, PhD, Massachusetts Institute of Technology, Cambridge, Massachusetts

Thomas E. Edwards, PhD

"Crystallography studies of riboswitches" with Adrian R. Ferre-D'Amare, PhD, Fred Hutchinson Cancer Research Center, Seattle, Washington

Wendy V. Gilbert, PhD

"Mechanisms of translation initiation by a cellular IRES" with Jennifer A. Doudna, PhD, University of California, Berkeley, California

Claudio A. Hetz, PhD

"BCL-2 regulation of the endoplasmic reticulum stress response and apoptosis" with Stanley J. Korsmeyer, MD, Dana-Farber Cancer Institute, Boston, Massachusetts

Karsten Hueffer, PhD

"Studies of the biology of *Salmonella* effector protein SopB" with Jorge E. Galán, DVM, PhD, Yale University, New Haven, Connecticut

Amanda M. Jamieson, PhD

"Role of toll-like receptors in immunosurveillance of tumors" with Ruslan Medzhitov, PhD, Yale University, New Haven, Connecticut

Elizabeth Prescott, PhD

"Probing the role of the transcriptional corepressor RIBEYE at ribbon synapses" with David Zenisek, PhD, Yale University, New Haven, Connecticut

Feng Shao, PhD

"The role of ubiquitin-mediated proteolysis in mouse hematopoietic and embryonic stem cell differentiation" with Marc W. Kirschner, PhD, Harvard Medical School, Boston, Massachusetts

Daniel D. Shaye, PhD

"A screen for targets of Wg/Wnt and Dpp/TGF- β involved in cell migration" with Jordi Casanova, PhD, Institute of Barcelona, Barcelona, Spain

Vincent J. Starai, PhD

"Mechanistic studies of calcium flux during homotypic vacuole fusion" with William T. Wickner, MD, Dartmouth Medical School, Hanover, New Hampshire

Megan T. Valentine, PhD

"Establishing the mechanism of kinesin processivity" with Steven M. Block, PhD, Stanford University, Stanford, California

4 New Damon Runyon-Lilly Clinical Investigators Chosen



Damon Runyon-Lilly Clinical Investigator Award

The Clinical Investigator Award provides support for the development and training of a new breed of patient-oriented researchers capable of bringing the laboratory to the bedside in search of breakthroughs. These \$995,000 awards provide the resources and training structure essential to nurturing independent clinical investigators. In April, the Clinical Investigator Award Committee, chaired by Richard J. O'Reilly, MD, from Memorial Sloan-Kettering Cancer Center, chose four new awardees to receive this honor. The award is generously supported by Eli Lilly and Company.

Charles G. Drake, MD, PhD

"Integrating clinical and laboratory studies to develop immunotherapy for prostate cancer" with Drew M. Pardoll, MD, PhD, Johns Hopkins University, Baltimore, Maryland

Jakob Dupont, MD

"Development and analysis of tumor specific T cells for adoptive immunotherapy of epithelial ovarian cancer" with Richard J. O'Reilly, MD, Memorial Sloan-Kettering Cancer Center, New York, New York

John V. Heymach, MD, PhD

"VEGF receptor inhibitors for non-small cell lung cancer: clinical studies and novel surrogate markers of activity" with Bruce E. Johnson, MD, and M. Judah Folkman, MD, Dana-Farber Cancer Institute, Boston, Massachusetts

Jeremy N. Rich, MD

"Maximizing clinical efficacy of epidermal growth factor receptor tyrosine kinase inhibitors in glioblastoma therapy" with Henry S. Friedman, MD, and Darell Bigner, MD, PhD, Duke University Medical Center, Durham, North Carolina

congratulations to all!

[science NEWS]

Steven F. Dowdy, PhD (DR Fellow '90-'93) has found a way to restore the protective function of the tumor suppressor protein p53 in cancer cells. Since nearly half of all human cancers have p53 mutations, this strategy has great potential therapeutic benefit.

Gregory J. Hannon, PhD (DR Fellow '92-'94) has shown that a protein called Argonaute2 plays a key role in RNA interference (RNAi), the very powerful tool for silencing genes. RNAi technology allows researchers to explore gene function in many basic research, drug discovery, and clinical settings and holds tremendous promise as a therapeutic strategy.

Matthew L. Meyerson, MD, PhD (DR Fellow '95-'98) and **William R. Sellers, MD (DR-Lilly Clinical Investigator '01-'06)** have found a genetic mutation that can predict if lung cancer patients will respond to the new drug Iressa. According to Meyerson, this result "demonstrates how the growing understanding of human biology and the Human Genome Project are converging to produce an immediate effect on cancer care."

Bruce W. Stillman, PhD (DR Fellow '79-'81) has been awarded the 2004 Alfred P. Sloan, Jr. Prize from the General Motors Cancer Research Foundation for "the

most outstanding recent contribution in basic science related to cancer research." Dr. Stillman was lauded for his work on understanding DNA replication, a process that is often abnormal in cancer cells. Dr. Stillman was also recently named President and CEO of Cold Spring Harbor Laboratory, where he served as Director since 1994.

Xiaodong Wang, PhD (DR Fellow '91-'94) has been elected to the National Academy of Sciences, one of the highest honors that can be earned by a U.S. scientist. Dr. Wang is the George L. MacGregor Distinguished Chair in Biomedical Science at the University of Texas Southwestern Medical Center in Dallas, where he works on the biochemical pathways involved in apoptosis (cell death).

Andrew E. Wurmser, PhD (DR Fellow '03-'06) has found that adult stem cells in the brain can change their destiny and become blood vessel cells instead of nerve cells. This finding fuels the possibility that adult stems may hold promise in treating cancer and regenerative diseases.

Jing Yang, PhD (DR Fellow '00-'03) has found that a protein called Twist plays an essential role in tumor metastasis. Interestingly, Twist is usually only active during fetal development, but when tumors reactivate it later in life, they acquire the ability to spread to other tissues.

momentum PHOTO GALLERY



a star is born

Damon Runyon Foundation founder Walter Winchell visits Capuchino High School in San Bruno, California, to take in a performance of "Guys and Dolls", which is based upon the stories of his friend Damon Runyon. Who's the lovely 17-year old playing the lead role of Miss Adelaide? None other than Suzanne Marie Mahoney, better known today as breast cancer survivor Suzanne Somers.

Damon Runyon Cancer Research Foundation

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And it's easy! Simply call our dedicated Broadway Tickets line at 212.455.0550 between 9 am and 5 pm, Monday through Friday. Payment can be made by credit card (Visa, MasterCard or American Express) or by check. Your tickets will be waiting for you at the box office on the night of the show.

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(For more information about our Broadway Tickets service, go to www.drcrf.org)

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There is only one way we will triumph over cancer—by funding brilliant and creative scientists. After providing for your loved ones, consider a bequest to the Damon Runyon Cancer Research Foundation. You will be helping to provide the steady stream of support needed to maintain the fast pace of groundbreaking research that will lead to new treatments and save lives. The following is sample language you can share with your attorney:

I give the sum of \$ _____ to the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation, a charitable corporation located in New York, New York, for its general charitable purposes.

You can also leave a specific asset or a percentage of your estate to the Foundation. For more information, please call 212.455.0500.

Damon Runyon Cancer Research Foundation

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