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Alex Kentsis (left) and Thomas Look discovered an escape mechanism enabling acute myeloid leukemia cells to grow after drug treatment.

Scientists discover backup growth system in leukemia cells

Like a wrestler with one arm pinned to the mat, a cancer cell whose growth is halted by a drug molecule is not necessarily ready to concede defeat.

So, when Dana-Farber scientists found that acute myeloid leukemia (AML) cells stopped dividing when a key protein was blocked, they weren't shocked when the cells eventually began growing again. What surprised them was the speed of the rebound: Within days of being treated, the cells were proliferating as if nothing happened.

When cancer cells recover the ability to grow and divide after drug treatment, it is often the result of a mutation – a change in a gene or group of genes that allows the cells to shake off the drug's effects. In

this case, the escape was too rapid to have involved mutation. Somehow, the cells were engineering their own revival.

In a new study in the journal *Nature Medicine*, researchers led by Thomas Look, MD, and Alex Kentsis, MD, PhD, identify not only the protein they first targeted – an ignition switch for cancer cell growth in nearly half of all AML patients – but also the cells' strategy for circumventing front-line drug treatment. Their findings suggest that therapies directed at both the initial growth trigger and the backup system may have the best chance for success.

“Despite years of research effort, the treatment of AML, particularly for people who aren't helped by standard therapy

and for the elderly, is very difficult,” Look says. “There is a major need for therapies that target the specific genetic defects of AML cells. The challenge has been that, in many cases, the genes driving the disease have been impossible or hard to block with drugs.”

In their research, Look's team used RNA interference – a technique for silencing individual genes – to systematically eliminate one protein after another in AML cells to see which were necessary for the cells' survival.

The leading candidate was HGF, a growth-provoking protein that switches on a receptor called MET, a kind of portal for incoming cell signals. When investigators muzzled the gene for HGF or genes

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Better care is Maine conference objective

When home is three hours away from the clinic where one gets cancer treatment, patients and their caregivers can feel the strain. Even in an age of instant communication, the coordination of care between community medical centers and distant cancer hospitals isn't always smooth.

With that issue in mind, Dana-Farber recently sponsored a one-day conference with care teams from Maine Medical Center (MMC) and other health care facilities in the state, focusing on the needs of Maine patients who come to DFCI's Longwood campus for stem cell transplants. Held in Portland, Maine, the

conference gave Maine-based and Dana-Farber clinicians a chance to view cancer care from each other's perspective and to discuss how to reduce the “bumps” in transferring patients between the two systems.

“An average of 50-60 patients from Maine complete their stem cell transplants at Dana-Farber every year, the largest group from any state except Massachusetts,” says Amy Emmert, administrative director of the hematopoietic stem cell transplant program at the Institute.

“For more than a year, we've been talking with people at Maine

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Dana-Farber honors exemplary college grad

Although Taylor Wensley joined Dana-Farber as a volunteer in February 2011, those who know her say that her contributions are inversely proportional to her time here. Wensley, a 2012 Emmanuel College graduate, was awarded the Sidney Farber Volunteer Award for her commitment at a June 7 recognition event.

At the ceremony, Institute President Edward J. Benz Jr., MD, thanked Dana-Farber volunteers for their dedication to patients, families, and staff, and for choosing to spend their free time fulfilling essential roles throughout the Institute.

“All of our volunteers are incredibly giving and empathetic people who are the quintessential embodiment of compassionate care,” said Patricia Stahl, MEd, program manager of Volunteer Services. “They are the front lines of the social and emotional impact that's so important here.”



Taylor Wensley

In addition to managing a full course load and interning at a homeless shelter, Wensley volunteered at the Institute three days a week. “Cancer is something that hits close to home for me,” said Wensley. “Once I started volunteering, I wanted to interact, learn, and do more.”

Wensley took on many volunteer roles, serving as an ambassador, working the food cart, preparing care bags, covering the front desk, and training incoming volunteers. Perceptive and tenacious, she created new initiatives, including

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Spiegelman honored for diabetes research



Bruce Spiegelman, PhD, has been awarded the Banting Medal by the American Diabetes Association (ADA). Spiegelman received the award and presented the Banting Lecture at the ADA's 72nd Scientific Sessions June 8-12.

The medal, named in honor of Frederick Banting, the co-discoverer of insulin, recognizes significant contributions to the understanding, prevention, and treatment of diabetes.

Spiegelman, of Cancer Biology, is the Stanley J. Korsmeyer Professor of Cell Biology and Medicine at Harvard Medical School.

“Spiegelman has been at the forefront of the revolution in molecular metabolism for a quarter of a century,” read a statement from the ADA announcing the award. “He was the first to suggest that inflammation lies at the heart of insulin resistance.”

Also cited was his research that identified a molecule, PPARγ, as the master regulator of fat cell development; described a co-activator molecule, PGC-1, in energy homeostasis and heat generation; and identified the transcription factor PRDM16 as the regulator of brown fat development.

“The insights provided by Dr. Spiegelman have led to numerous drug discovery efforts that will improve diabetes prevention and treatment for years to come,” said the ADA’s statement. “His discoveries have also generated powerful tools and concepts that allow many others in related fields to advance their studies.”

“I am very grateful to receive this award on behalf of the students and fellows who have dedicated themselves to our work on energy metabolism,” says Spiegelman. “Our work is very basic and touches upon many areas of therapeutics, such as diabetes, cancer, and neuromuscular degeneration. It is great to know that our colleagues in the metabolic disease area recognize our contributions.”

Social workers shine at Boston conference

More than a dozen members of the Dana-Farber/Brigham and Women’s Cancer Center (DF/BWCC) Social Work Practice helped lead sessions and presented posters at the 28th annual Association of Oncology Social Work conference at the Westin Boston Waterfront.

The DF/BWCC Social Work Practice includes social workers from Dana-Farber, Brigham and Women’s Hospital, and DFCI’s four satellite facilities. At the conference, practice leaders led a session titled *Toward a Transformation of Care in Oncology Social Work: Building a New Paradigm for Care Across Systems*, in which they shared insights from a 2009 redesign of their practice model. The redesign enhanced

the way social work services are delivered to oncology patients. Other DF/BWCC-led sessions at the May 30-June 1 event included: *The Unique Contributions of Oncology Social Workers to the Health Care Team, Innovations for Palliative Care Social Work in the Oncology Setting, Innovative Group Programming for Young Adults*, and *Model for Interdisciplinary Geriatric Oncology Practice*.

Staff from DF/BWCC have been involved with the development of oncology social work since its beginnings more than 30 years ago. “Talking with oncology social workers from across the country allows us to see the tremendous work being done by our colleagues, and be inspired by clinical approaches and innovations,” says Philip Higgins, MSW, LICSW, who helped lead a palliative care session.

“We shared best practices and learned a great deal from each other through the synergy of being with social workers from many different settings,” adds Jane Bausch, MSW, LICSW, who presented on the historical roots of hospital social work.

Oxnard awarded grants to study familial lung cancer in never-smokers



Geoffrey Oxnard, MD, has received a two-year award from the Bonnie J. Addario Lung Cancer Foundation and a three-year Career Development Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology to study patients with inherited EGFR gene mutations. These mutations are a potential risk factor for lung cancer in non-smokers, which is the seventh most common cancer worldwide.

Central to Oxnard’s research is T790M, an EGFR mutation rarely found in lung cancer at diagnosis, and which may indicate an underlying inherited mutation. Because inherited T790M mutations are very rare, “we’ve not previously had a system that allows us to find families who carry them,” says Oxnard.

The new study focuses on first finding patients with T790M in their lung cancer. Oxnard has teamed up with the Addario Lung Cancer Medical Institute, a network of leading research institutions sharing a centralized infrastructure. Several commercial laboratories also agreed to refer patients identified to have T790M in their lung cancer. If blood testing identifies an underlying inherited mutation, patients are invited to refer their relatives for testing. “By leveraging the routine EGFR genotyping of lung cancers being done worldwide, we can now cooperatively study a phenomenon previously thought too rare to study,” says Oxnard.

William Kaelin receives grand prize of Institut de France

In a prime example of how basic research in one field can lead to unexpected discoveries in another, William Kaelin, MD, was awarded a prestigious French prize for advances in the field of cardiovascular disease.

Kaelin and two other scientists shared the Grand Prix of the Lefoulon-Delalande Foundation in a June 6 ceremony in Paris at the Institut de France, a learned society founded in 1795.

Receiving the award with Kaelin were Peter Ratcliffe of Oxford University in England and Gregg Semenza of Johns Hopkins University School of Medicine. Previously, the three shared the 2010 Canada International Gairdner Award, which in some instances has preceded a Nobel Prize.

“What I like about this prize is that it underscores the value of unfettered research curiosity,” says Kaelin, who is funded in part by the Howard Hughes Medical Institute (HHMI). HHMI provides long-term funding to scientists at their own institutions to explore high-risk projects with the potential for big payoffs.

The award recognizes discoveries that addressed a question unanswered for many decades: How do the body’s cells and tissues sense and respond to changes in oxygen availability? “It has been a medical detective story, with scientists coming at it from different angles,” says Kaelin.

Kaelin says he came across the answer to the oxygen-sensing question while studying von Hippel-Lindau (VHL) disease. People born with a mutation affecting the VHL gene tend to develop cancers of the kidney, adrenal glands, and pancreas, as well as nervous system tumors that look like tangles of small blood vessels. Kaelin suspected that the growth of extra blood vessels might be the result of an abnormal response to normal levels of oxygen in the tissues.

Following up this lead, Kaelin discovered that the VHL protein helps regulate cellular responses to changes in oxygen availability. It does this by adjusting the levels of another protein, HIF, or hypoxia-inducible factor, which activates red blood cell production and blood vessel formation when oxygen levels are low. In VHL disease, HIF mistakenly increases red cell production and spurs the growth of extra blood vessel networks, even when there’s plenty of oxygen in cells and tissues.

But still there was the missing link: How does VHL protein sense the amount of oxygen in its environment? Kaelin found that evolution provided a mechanism for oxygen-sensing.

When oxygen is plentiful, oxygen and hydrogen atoms form “hydroxyl groups” that are attached to HIF; the VHL protein “sees” this and destroys the hydroxylated HIF. When oxygen is low, too few oxygen atoms are



William Kaelin works in his lab.

available for HIF to be hydroxylated; as a result, VHL protein then allows HIF activity to rise. In VHL disease, cancer cells hijack HIF to supply themselves with the nutrients and oxygen they need to grow and spread.

When these findings were first published in 2001, they opened new avenues for treating kidney cancer and for designing new therapies for other diseases.

“Uncovering this mechanism for the first time was its own gratification,” says Kaelin. “It accelerated the successful clinical testing of angiogenesis inhibitors for kidney cancer and set in motion clinical trials of new drugs for treating anemia and cardiovascular diseases.”

Buying organic: What does it mean?

In this new series of articles in Inside the Institute, Dana-Farber nutrition experts share tips on balanced and healthy eating. To learn more, visit www.dana-farber.org/nutrition.

Recent trends advocate “organic” fruits and vegetables, but what does the word actually mean? Organic refers to the way farmers grow and process their products. Instead of chemicals, herbicides, insecticides, and antibiotics, they use natural fertilizers, beneficial insects, and crop rotation cycles. Organic farmers use preventive measures to deter disease by allowing cattle to roam outdoors and feed off of soil that is free of chemicals.

The United States Department of Agriculture (USDA) established an organic certificate program that grants a stamp of approval for meeting strict government standards. This certifies that the product is 95 percent or more organic. Although many farmers follow these practices, it is a lengthy process to attain the USDA approval. “Buying local” supports farmers who have not yet achieved this official certification but are following organic procedures. It is important to visit your farmers market, get to know your producer, and understand the practices behind your food purchases.

Why buy organic?

Some prefer the taste of organic products, while others are concerned about pesticides and food additives or want to support local farming by reducing pollution and conserving water and soil quality.

So, is there a significant nutritional difference between conventional and organic produce? The answer is still controversial. The benefits of a diet rich in fruits and vegetables outweigh the risks of pesticide exposure.

Food tips:

- Buy local produce in season.
- Read food labels carefully (organic does not always mean healthy; beware of sugar, fat, and sodium in packaged foods).
- Wash fresh produce thoroughly to remove dirt, bacteria, and pesticides.

Buying organic isn’t cheap. The Environmental Working Group compiled a list it calls the “Dirty Dozen,” or the top-ranking products for pesticide residue. Your grocery cart doesn’t need to be all or nothing, but try to stick to organic for your Dirty Dozen picks:

Dirty Dozen (Most pesticide residue)	Clean 15 (Least pesticide residue)
1. Apples	1. Onion
2. Celery	2. Sweet corn
3. Strawberries	3. Pineapples
4. Peaches	4. Avocados
5. Spinach	5. Asparagus
6. Imported nectarines	6. Sweet peas
7. Imported grapes	7. Mangoes
8. Sweet bell peppers	8. Eggplant
9. Potatoes	9. Domestic cantaloupe
10. Domestic blueberries	10. Kiwi
11. Lettuce	11. Cabbage
12. Kale/collard greens	12. Watermelon
	13. Sweet potatoes
	14. Grapefruit
	15. Mushrooms

activated by MET, the cells in nearly half the AML samples either slowed their growth or died.

The reprieve was brief, however. In less than two weeks, the surviving cells were back to their breakneck growth. The reason, researchers found, was that the shutdown of the MET-associated genes prompted the cells to crank up their production of HGF – in effect, signaling themselves to grow.

The surge in HGF to 30 times its previous level overpowered the growth-slowing effect of the MET inhibitor.

“A built-in feedback loop enables the cells to sense when the MET receptor has been shut down and to adapt by increasing their supply of HGF,” Kentsis explains. “This kind of self-induced growth has been known to occur in solid tumors; this is the first time it has been found

in AML.” When investigators added a second inhibitor to block the feedback loop, it produced a sustained die-off of AML cells that lasted many weeks. While the study involved a very rare, lethal form of AML, researchers expect other forms have similar backup mechanisms that can be defeated by drugs.

“Our study demonstrates that in developing personalized cancer medicines, we will also need to block the intrinsic escape mechanisms that are launched by the cancer cells if patients are to realize a sustained benefit,” Look remarks.

Contributing to the study were Dana-Farber’s Casie Reed; Takaomi Sanda, MD, PhD; Amanda Christie; Suzanne Dahlberg, PhD; Lisa Moreau, PhD; and Andrew Kung, MD, PhD.

STAFF ID



Anna Norcross
Hematology Services
New patient coordinator
At Dana-Farber since: February 2011

Describe your role here.

Our patients are primarily referred for non-cancerous hematologic diagnoses. I interact with prospective patients and their referring physicians’ offices. I initiate a Dana-Farber account for each patient, gather relevant records, and schedule the first appointment. An important part of my position is reducing the anxiety felt by patients as they encounter

the complexity of our institution for the first time. I do this by providing written and verbal communication with each new patient, which explains who we are and what we do. Easing the transition is a challenging and satisfying part of my work.

What is your educational background?

I have a bachelor’s degree in theater and history from UMass Amherst.

What brought you to Dana-Farber?

Dana-Farber was a chance encounter. I was looking for something new (after several years stage managing theater productions), and Kathleen McDermott, a friend and longtime Partners nurse, pointed me in this direction.

What is most rewarding about your work here?

I love working with passionate, dedicated staff. I enjoy forming relationships while learning about hematology and the behind-the-scenes of health care. And it is rewarding to provide a supportive, guiding hand to new patients.

What is the biggest challenge in your role?

It is important to patients that the person answering the phone recognizes and knows something about their diagnoses. I take advantage of Tuesday hematology conferences and medical terminology courses and I pester my co-workers. I learn a little more every day. Understanding the clinical aspects helps me to communicate more effectively.

How does your role contribute to the mission of Dana-Farber?

I strive to provide the compassionate piece of Dana-Farber’s mission, and am part of the bridge connecting patients to expert care here.

What do you do for fun in your spare time?

I love plants and earth. I mess around in my garden and with City Growers, a local urban gardening organization, and theMOVE, a group that coordinates farm volunteer trips. I also battle on behalf of native plants, pulling out invasive varieties everywhere I go, to my family’s embarrassment.

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Story ideas are welcome and may be sent to Naomi Funkhouser at 450 Brookline Ave., OS301, Boston, MA 02215. You may also call 617-632-5560, fax to 617-632-5520, or email Naomi_Funkhouser@dfci.harvard.edu. The Dana-Farber website is at www.dana-farber.org; the intranet is at www.dfcionline.org.

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How sweet it is: Scooper Bowl a success

30,000 visitors. 10,000 gallons of ice cream. \$335,000 raised. One cause: the 30th annual Jimmy Fund Scooper Bowl® presented by FedEx.

Held June 5–7 at Boston’s City Hall Plaza, the Scooper Bowl is synonymous with the start of summer. While the sun shone reluctantly during the three-day event, attendees arrived en masse to taste ice cream, gelato, frozen yogurt, and sorbet from 10 of the nation’s leading ice cream companies. This year, SoCo Creamery’s Salted Caramel and Byrne Dairy’s Holy Cow were among the favorite flavors.

The nation’s largest all-you-can-eat ice cream festival relies on volunteer scoopers like Clayton Shih, a Dana-Farber employee who helped dish out frozen treats for his second year. “Volunteering for the Jimmy Fund is personally meaningful for me, as I recently lost a close relative to lung cancer,” says Shih, training analyst in Patient Accounting. “This is my way

of stepping up to make a difference. I’m proud to offer my time to have a positive effect.”

“I really like helping out at the Scooper Bowl, which I do every year along with my colleagues in the Information Systems-Project Management Office,” adds Michael Madden, project specialist in Information Systems. “To see the smiles on all the kids’ faces really makes it all worthwhile. My daughter, Charlotte, has been talking about the event for the past two weeks. Everyone is in a jovial mood, and serving ice cream along with volunteering for Dana-Farber is very rewarding.”

All proceeds from the Scooper Bowl benefit the Jimmy Fund, which supports pediatric and adult cancer research and care at Dana-Farber Cancer Institute.

Since its inception in 1983, the Jimmy Fund Scooper Bowl has raised more than \$3 million. NF



Volunteer Award *continued from page 1*



Taylor Wensley (far left), who received the Sidney Farber Volunteer Award, is pictured here with Volunteer Services staff Pat Stahl, Matt Kiggins, and Deb Toffler (left to right).

working with staff to cut waste and finding ways to donate uneaten food to those in need.

“Taylor truly demonstrated her commitment to helping others, dedicating herself fully in a short period of time,” said Deborah Toffler, MSW, LCSW, director of Volunteer Services and the Shapiro Center for Patients and Families. “She is the kind of volunteer who brings a new perspective and an energetic spirit to volunteering.”

The award is made possible by Rowena and Charles Simberg and includes a \$2,500 prize. Wensley will allocate these funds to the Friends’ Place CARE Bag Program, which provides complimentary support bags for patients starting treatment and for caregivers.

Last year’s award recipients, Anne and Dick Tonachel, were delighted by Wensley’s honor. “Taylor has really brought joy to patients. They’d look for her and she made sure she found them every week,” said Anne. “She very much

deserves this award and is an example to each of us for how to be caring and helpful without being intrusive.”

Wensley also has a way of “turning sadness into hope,” added Stahl.

According to Toffler, there are more than 400 volunteers whose roles are integral to the organization, offering supportive One-to-One program phone conversations, snacks and a warm smile, patient wayfinding, financial or legal assistance, or reading material to distract from a long infusion session.

“We all talk about the ‘special sauce’ – a term often used by Dr. Benz – of what makes Dana-Farber unique,” said Toffler. “It’s not only the excellent clinical care that patients receive, but that extra support and kindness of volunteers that makes people feel good and a part of a community.”

To view a full list of volunteers and years of service, visit the “Awards and Recognition” section of the Volunteer Services page on *DFCI Online*. AD

Maine conference *continued from page 1*

Medical Center, our main collaborator in the state, on ways to improve the patient pathway between Dana-Farber and MMC,” adds Emmert. “The goal is to better prepare the patient, and prepare us for the patient.”

Improved coordination of care can do more than simply reduce inefficiencies or inconveniences. Studies show that survival rates have risen more slowly for cancer patients treated far from home than for those treated locally. (Some Maine patients come from more than 400 miles away, roughly the same distance as between Boston and Washington, D.C.)

The benefits of coordination are especially evident in cases of bone marrow or stem cell transplant – the complexities of which can be magnified when patients travel long distances for treatment. In Maine, transplant patients may have their initial tests and work-up at a community hospital like MMC, travel to Dana-Farber for the transplant itself, and then return to Maine for follow-up care. “This is a clear area where Dana-Farber and Maine caregivers need to be in sync,” Emmert comments.

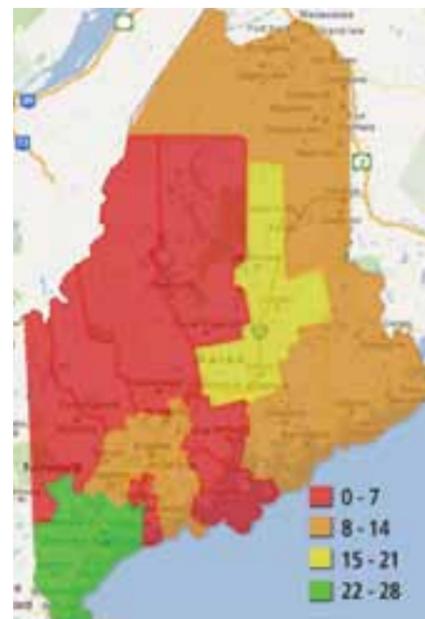
Basic questions

The conference attracted 30 clinicians from seven Maine health centers – physicians, social workers, patient navigators, nurses, physician assistants, and dietitians – one of whom made a nearly 300-mile round-trip to attend. “Many of them had very basic questions about the elements of care at Dana-Farber, the details of the services we provide,” says Bethany King, quality improvement analyst. By the same token, Dana-Farber representatives at the conference said they weren’t as familiar as they’d like to be with the services patients receive in Maine.

“We learned that patients’ medical records aren’t moving between Maine care providers and Dana-Farber as smoothly as they could be,” Emmert remarks. “Key milestones in the care process aren’t being communicated well.”

Attendees formed teams to discuss ways of improving communication between Dana-Farber and its care partners in Maine, and easing the burden of travel on patients and their families. Among their suggestions was to arrange for a van to shuttle patients from a mall in southern Maine to Dana-Farber, and then back in the evening. Another was to hold an open house at the Institute for Maine caregivers who wish to observe the patient treatment process in action. These ideas and others will be explored in the coming months. RL

Completed transplants by patient’s county of residence



The Maine stem cell transplant data was collected from January 2007–December 2011.