# iuscc research news

May 2009

## IU Simon Cancer Center researchers target telomeres to attack tumors

Hoping to develop more effective long-term attacks on cancer, researchers at the IU Simon


Miller

Cancer Center are conducting the first human tests of a breast cancer drug regimen that includes a compound meant to force cancer cells to grow old and die.

The early stage clinical tests are an attempt to block a mechanism cancer cells use to avoid the aging process that affects most normal cells. If successful, the new therapy could enhance the effects of other cancer treatments.

"This is really a completely different way of trying to tackle the problem that hasn't been tested in the clinic before," Kathy Miller, MD, said.

The new approach is based on research into telomeres, the caps that protect the ends of the 46 chromosomes in each cell that contain our genetic information. The telomeres help prevent genomic instability. Each time a cell divides, the telomeres shorten. When they become too short, losing their protective ability, it's a signal to the cell to die, or to go into a state of permanently arrested growth called senescence.

Telomeres in cancer cells generally are shorter than those in normal cells. That offers a tempting target, except that cancer cells know a trick. Cancer cells produce an enzyme called telomerase, which provides maintenance services on the telomeres, preventing them from reaching the critically short stage that would set off the cell death signal.

So, researchers have figured, if they could block cancer cells from producing telomerase, they could make them easier

to kill. But how to do that? Several approaches seemed possible, including one that Brittney-Shea Herbert, PhD, then a post-doctoral researcher, was working on 10 years ago at the University of Texas Southwest in Dallas. Her approach: Find a special type of chemical compound, called an oligonucleotide, that


Herbert

would block access to telomerase and prevent it from doing its job. She began working with a new compound, with the chemical name GRN163L, that had been developed by Geron Corp. of Menlo Park, Calif.

Dr. Herbert has continued to work with GRN163L -- now called imetelstat sodium -- in the laboratory since coming in 2003 to the IU School of Medicine. She has published work showing that imetelstat disrupts telomere maintenance, in the process suppressing both tumor growth and metastasis (the appearance of tumors in other tissues). Another study found that telomere damage in breast cancer cells treated with the compound caused the cells to be more susceptible to radiation treatment. Furthermore, she has shown that imetelstat can restore the sensitivity of Herceptin-resistant breast cancer cell lines in the laboratory.

"What's interesting about GRN163L is that it can get into almost any cancer cell type, including drug resistant cancer cells. That's been a problem: A lot of agents cannot be taken up into drug resistant cells. This telomerase inhibitor can be taken up in any cell type; you can target those cells. So that's why we hope this will be great for reducing recurrence and metastasis," Dr. Herbert said.

Such results have made imetelstat an attractive compound to test in conjunction with other anti-cancer drugs, which is what brought Drs. Miller and Herbert together. They are testing imetelstat with the drugs Taxol and Avastin, initially to determine the appropriate dose of imetelstat, test whether the three drugs are safe to give in combination, and to determine whether there are side effects that must be dealt with.

Assuming the first phase goes well, a second phase of testing will begin more formal evaluation of how well the combination therapy works.

Dr. Miller's research has shown that Taxol and Avastin are more effective in combination than Taxol alone, shrinking tumors in about twice as many women and providing such benefits more than twice as long. The therapy doesn't cure metastatic disease, though. Eventually the tumors become resistant to the drugs and other treatments are necessary.

If, as expected, imetelstat doesn't raise side effects issues, and "if it makes the cells more sensitive to the effects of the Taxol and Avastin, and allows the benefits of that therapy to continue for a much longer period of time, that would be a big benefit for those women with metastatic disease. It would also then give us the support for looking at this agent even earlier in the course of disease," Dr. Miller said.

Dr. Herbert's research indicated that imetelstat can reduce metastatic spread of cancer, though it's not yet clear what the mechanism is. But, as Dr. Miller points out, for patients that will be a distinction with little difference.

"Whether it actually prevents the cells from spreading or they spread but can't grow to make clinically apparent tumors we don't know, but I can tell you my patients don't care," she said.

*--Eric Schoch*

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## Komen awards $1 million grant to tissue bank at IUSCC

Researchers with the Susan G. Komen for the Cure Tissue Bank at the IU Simon Cancer Center will continue their unique work thanks to a second $1 million grant from the Komen organization.

Susan G. Komen for the Cure awarded the grant, enabling researchers to continue to collect and share healthy breast tissue samples with researchers worldwide to help understand how breast cells turn cancerous.

The tissue bank -- the nation's first and only healthy breast tissue bank -- currently has tissue from more than 450 women and blood samples from more than 4,500.

"We are the only collection of this much normal tissue in the world," Anna Maria Storniolo, MD, co-principal investigator of the Susan G. Komen for the Cure Tissue Bank at the IU Simon Cancer Center, said. "There's no question that it is a unique and incredibly precious resource."

Komen provided a $1 million research grant to help start the tissue bank just over a year ago.

Researchers from the Dana-Farber Cancer Institute and Walter Reed Medical Army Institute already are using specimens from the bank.

"In breast cancer, in order to figure out what is abnormal, you have to be able to compare it to normal. Because of that, the normal controls from the Komen Tissue Bank are incredibly important," Storniolo said.

"Research studies help us do more than develop new treatments. They also advance our understanding of how breast cancer develops in the first place, which can lead to new ways to detect or prevent the disease. This tissue bank is a unique opportunity for women to participate in and contribute to the research process," Diana Rowden, vice president of Health Sciences for Komen, said.

By collecting blood and tissue from women with and without breast cancer, researchers will be able to determine the differences between these populations, which could lead to a better understanding of the disease. Blood and tissue

samples taken from women without the disease are especially helpful because there are few collections of so-called "normal" specimens.

In order to identify the changes cells undergo as they transition from normal to malignant, and to detect the earliest indication of malignant transformation, it's vital to obtain and study "true normal" breast cells.

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## News Briefs

### Cancer Research Day winners announced; keynote address is online

The keynote address from the May 6 Cancer Research Day is now online. Kornelia Polyak, MD, PhD, of Dana-Farber Cancer Institute, presented "Breast Tumor Evolution." Overall, Cancer Research Day drew 101 scientific posters from students, fellows, and faculty conducting cancer research at IUPUI, Indiana University-Bloomington, and Purdue University. Cash awards were presented for best posters by graduate students and post-doctoral/medical fellows. See the list of winners and finalists.

### BioCrossroads seeks nominations for Life Sciences Champion of the Year

For the second year, BioCrossroads will be recognizing the individual who has made the most positive impact on the growth of the state's life sciences sector. The Life Sciences Champion of the Year award will be given to an entrepreneurial, research, corporate, medical, academic, or philanthropic individual who has made particularly significant achievements in the development and promotion of Indiana's life sciences sector. Criteria includes:

- Must be a resident of Indiana
- Must be an individual supporting Indiana's life sciences growth via entrepreneurial, research, corporate, medical, academic, or philanthropic work
- Judging will be based on assessments of cumulative contribution, not specific achievements over the course of a year

In honor of the award recipient, BioCrossroads will give grants to two teachers in the science, technology, engineering, or mathematics disciplines to pursue professional development through the Indiana Science Technology Engineering and Mathematics (I-STEM) Resource Network. The I-STEM Resource Network will select the teaching recipients.

The deadline for submissions is Wednesday, July 15. Finalists will be selected in mid-September and the award will be presented at the Indiana Life Sciences Forum on Oct. 20.

Leonard J. Betley, chairman and president of the Richard M. Fairbanks Foundation Inc. and the Regenstrief Foundation and chairman of the Walther Cancer Foundation, was the inaugural recipient of the award for his multiple roles within the life sciences community and his commitment to improve healthcare.

**Cancer center members in the news**

- The discovery by **Sunil Badve**, MBBS, MD, FRCPath, **Harikrishna Nakshatri**, BVSc, PhD**,** and colleagues that FOXA1 is a prognostic marker in breast cancer (*Clinical Cancer Research*) recently led to the commercialization of that biomarker. The Indiana Research and Technology Corporation (IURTC) has granted Clarient -- an anatomic pathology and molecular testing services resource for pathologists, oncologists, and the pharmaceutical industry -- the exclusive license to commercialize the FOXA1 biomarker. The biomarker predicts the likelihood of recurrence and long-term, disease-free breast cancer survival. The FOXA1 marker, also known as forkhead box A1, is a gene known to be associated with a specific subtype of breast cancer. Recent data presented at the 2009 USCAP (United States and Canadian Academy of Pathology) meeting demonstrated that the expression of FOXA1, now known to be an estrogen receptor associated transcription factor, correlated with Oncotype Dx(R) when performed in patient samples from IU. In this clinical study of 79 ER-positive, node-negative breast cancer patients, researchers found that FOXA1 expression identified the same low risk, ER-positive, node-negative patients who can be spared toxic chemotherapy. Researchers concluded Oncotype Dx and the FOXA1 marker can potentially be used interchangeably if further validation studies confirm the findings.


Badve

- After surgery to remove the head of the pancreas, invagination of the pancreas into the small intestine resulted in a lower rate of pancreatic fistula, according to researchers at the IU Simon Cancer Center and the Jefferson Pancreas, Biliary and Related Cancer Center in Philadelphia. The research was published in the May 2009 *Journal of the American College of Surgeons*. The IU Simon Cancer Center members involved in the study were **Thomas Howard**, MD, FACS; **C. Max Schmidt**, MD, PhD, FACS; **Atilla Nakeeb**, MD, FACS; **Henry Pitt**, MD, FACS; and **Keith Lillemoe**, MD, FACS. Read more.

- **George Sledge Jr.**, MD, takes office as president-elect during ASCO's 45th Annual Meeting in Orlando in June. The following IU Simon Cancer Center

members are presenting abstracts at the annual meeting: **Gabriela Chiorean**, MD; **Larry Cripe**, MD; **Richard Foster**, MD; **Noah Hahn**, MD; **Nasser Hanna**, MD; **Paul Helft**, MD; **Kathy Miller**, MD; **Kevin Rand**, PhD; **Kent Robertson**, MD, PhD; and **Michael Robertson**, MD.

- **Gabriela Chiorean**, MD, and Peter O'Dwyer of the Abramson Cancer Center of the University of Pennsylvania are leading a phase I clinical trial of GGTI-2418. GGTI-2418 is a synthetic peptidomimetic inhibitor of geranylgeranyltransferase I (GGTase I) that induces apoptosis by downregulating several pivotal oncogenic and tumor survival pathways. "We are excited to participate in the first study of this novel agent," Dr. Chiorean said. "The development of a molecule to inhibit the geranylgeranyltransferase pathway would be a significant advancement in cancer treatment." The primary objective of the phase I trial is to determine its safety, tolerability, and recommended Phase 2 dose. Patients with metastatic solid tumors for which standard treatments have failed or for whom standard therapies are not available will be evaluated.

- While attending spring training in Cincinnati earlier this year, **Keith Lillemoe**, MD, spotted Eric Davis, the former Baltimore Orioles outfielder. Davis is known for a dramatic ninth-inning home run in Game 5 of the 1997 American League Championship Series while undergoing chemotherapy. Lillemoe waved to Davis, now a special assistant to the general manager of the Reds, and said, "Hi, Eric. Remember me?" Even though it had been 12 years, Davis indeed did remember. Lillemoe was the Johns Hopkins surgeon who had removed a tumor from his colon. Davis told the *Baltimore Sun*, "You don't forget people like that." Read the full story.


Lillemoe