Scientists Use Abnormal DNA Repair to Selectively Target Cancer Cells

UNM Cancer Center researcher publishes two papers that describe the novel technique

FOR IMMEDIATE RELEASE:

April 8, 2013 — Albuquerque, NM (UNM Cancer Center) — Developing cancer therapies that have minimal side-effects depends upon finding and killing only the cancer cells, leaving the healthy cells alone. To selectively kill cancer cells, a cross-institution team of researchers has developed a technique that targets cancer cells’ abnormal DNA repair machinery. One member of that team is Alan Tomkinson, PhD, University of New Mexico Professor of Internal Medicine and Associate Director of Basic Research at the UNM Cancer Center. Dr. Tomkinson is an expert in DNA ligases, one of the proteins a cell uses to repair its DNA. He and the team recently published a pair of papers describing their work with chronic myeloid leukemia cells and with breast cancer cells.

In one of the papers, the scientists chose to work with chronic myeloid leukemia cells because, as Dr. Tomkinson explains, “Chronic myeloid leukemia is driven by an oncogene called BCR-ABL. We wanted a form of cancer where we knew what the initiating event was.” For people with BCR-ABL-driven cancer, a chemotherapy drug called Gleevec targets the protein this oncogene produces. But the cancer can become resistant to Gleevec. The researchers were particularly interested in Gleevec-resistant disease because people with this resistance have limited treatment options.

The researchers worked with breast cancer cells for the work described in the other paper. Many breast cancers are dependent upon the hormone estrogen and can be effectively treated with estrogen-blocking chemotherapy drugs like Tamoxifen. But breast cancer cells, too, can become resistant to these anti-estrogens. Again, women with anti-estrogen resistant breast cancers and women whose initial breast cancer tumor is hormone-insensitive have few treatment options.

To target cancer cells, the researchers took advantage of the differences in DNA repair between normal and cancer cells. While every cell has the ability to repair its own DNA—the cell must repair DNA prior to dividing or making proteins—the researchers found that certain human cancer cells have higher levels of DNA ligase III and lower levels of ligase IV than non-cancerous cells. They concluded that these cancer cells use a “DNA ligase III-dependent repair pathway” rather than a “DNA ligase IV-dependent repair pathway” to repair double-strand breaks in DNA. Double-strand DNA breaks are breaks in which both strands of the DNA molecule are broken, splitting the DNA molecule into two pieces. Says Dr. Tomkinson, “If cancer cells are more dependent upon the ligase III-dependent repair pathway for survival then you should be able to selectively target it. So that’s what we did.”

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In their papers, the researchers first show that therapy-resistant breast cancer and chronic myeloid leukemia cells depend more upon the DNA ligase III-dependent repair pathway to repair double-strand breaks. This pathway uses PARP1, another DNA repair protein. They then combined a DNA ligase inhibitor developed by Dr. Tomkinson with a PARP inhibitor. The DNA ligase inhibitor acts on DNA ligases I and III, blocking their activity in DNA repair; the PARP inhibitor also shuts down the DNA ligase III-dependent repair pathway by blocking PARP1 activity. The researchers showed that the combination of DNA ligase and PARP inhibitors reduced the cell’s ability to repair double strand breaks by the DNA ligase III-dependent repair pathway. They also showed that the combination selectively killed the therapy resistant breast cancer and leukemia cells. Finally, they used samples from patients with chronic myeloid leukemia (with the patients’ permission, of course) to test for response differences. They divided the patient samples into three groups based on the levels of DNA ligase III and PARP1 and showed that the combination of DNA ligase and PARP1 inhibitors killed the leukemia cells with higher levels of both DNA ligase III and PARP1.

Preparing this selective targeting treatment for human use is the next step, but it will take time to go through the required animal studies before beginning human clinical trials. The treatment won’t work for everyone, but it may be a new option for patients with therapy-resistant forms of breast cancer and leukemia. Dr. Tomkinson explains, “We can identify patients whose cancers have this specific DNA repair abnormality based on the altered expression of DNA repair proteins. Those patients would be candidates for treatment with the DNA repair inhibitor combination.” And offering more targeted cancer treatment choices to help those with limited options is a step in the right direction.

Paper references

“Targeting abnormal DNA double-strand break repair in tyrosine kinase inhibitor-resistant chronic myeloid leukemias” was advanced-published in the May 28, 2012 online edition of Oncogene (http://www.nature.com/onc/index.html). Authors are: L.A. Tobin (University of Maryland), C. Robert (University of Maryland), A.P. Rapoport (University of Maryland), I. Gojo (University of Maryland), M.R. Baer (University of Maryland), A.E. Tomkinson (University of New Mexico) and F.V. Rassool (University of Maryland). This paper may be found online:
http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2012203a.html

“Targeting Abnormal DNA Repair in Therapy-Resistant Breast Cancers” was first published online on November 23, 2011 and appeared in the January 2012 print edition of Molecular Cancer Research (http://www.nature.com/onc/index.html). Authors are: Lisa A. Tobin (University of Maryland), Carine Robert (University of Maryland), Pratik Nagaria (University of Maryland), Saranya Chumsri (University of Maryland), William Twaddell (University of Maryland), Olga B. Ioffe (University of Maryland), George E. Greco (Goucher College), Angela H. Brodie (University of Maryland), Alan E. Tomkinson
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(University of New Mexico), and Feyruz V. Rassool (University of Maryland). This paper may be found online: http://mcr.aacrjournals.org/content/10/1/96.

About the UNM Cancer Center
The UNM Cancer Center is the Official Cancer Center of New Mexico and the only National Cancer Institute-designated cancer center in the state. One of just 67 NCI-designated cancer centers nationwide, the UNM Cancer Center is recognized for its scientific excellence, contributions to cancer research and delivery of medical advances to patients and their families. Annual federal and private funding of over $65 million supports the UNM Cancer Center’s research programs. The UNM Cancer Center treats more than 65 percent of the adults and virtually all of the children in New Mexico affected by cancer, from every county in the state. It is home to New Mexico’s largest team of board-certified oncology physicians and research scientists, representing every cancer specialty and hailing from prestigious institutions such as MD Anderson, Johns Hopkins and the Mayo Clinic. Through its partnership with Memorial Medical Center in Las Cruces, the UNM Cancer Center brings world-class cancer care to the southern part of the state; its collaborative clinical programs in Santa Fe and Farmington serve northern New Mexico. The UNM Cancer Center also supports several community outreach programs to make cancer screening, diagnosis and treatment available to every New Mexican. Learn more at www.cancer.unm.edu.

UNM Cancer Center contact information
Dorothy Hornbeck, JKPR, (505) 340-5929, dhornbeck@jameskorenchen.com
Michele Sequeira, UNM Cancer Center, (505) 925-0486, msequeira@salud.unm.edu

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