PRESS RELEASE

UNM Cancer Center Scientists Discover Novel Chemical that Controls Cell Behavior

First-in-class chemical compound might control metastases

FOR IMMEDIATE RELEASE:

March 12, 2013 — Albuquerque, NM (UNM Cancer Center) — It's the spread of the original cancer tumor that kills most people. That's why cancer researchers vigorously search for drugs that can prevent metastases, the spread of cancer. The research team co-led by Angela Wandinger-Ness, PhD, and Larry Sklar, PhD, at the University of New Mexico Cancer Center has found a chemical compound that appears to control cell migration and adhesion, two important characteristics of metastatic cancer cells. The team recently published a paper describing how the first-in-class compound acts on various cells.

Dr. Wandinger-Ness, a UNM Professor of Pathology and Director of the Fluorescence Microscopy and Cell Imaging Shared Resource, studies proteins called GTPases. GTPases act like chemical switches to control how cells behave: how much a cell grows, what shape it assumes, when it enters the next growth stage, and how tightly it sticks to its surroundings, among several hundred other things. Dr. Wandinger-Ness was interested in a particular GTPase called Cdc42; it controls cell migration and cell adhesion. "It's an important target in many diseases," says Dr. Wandinger-Ness. "Cancer is just one. But there were no compounds that target this GTPase." So she collaborated with Dr. Sklar and Tudor Oprea, MD, PhD, to find a compound that did. And they were successful.

Dr. Sklar is a UNM Professor of Pathology and co-Leader of the Cancer Biology and Biotechnology Research Group at the UNM Cancer Center. He created and now oversees the UNM Center for Molecular Discovery. Dr. Oprea is a UNM Professor of Medicine and co-Director of the Flow Cytometry & High Throughput Screening Shared Resource at the UNM Cancer Center. He analyzed Cdc42 using three-dimensional molecular rendering software. The team used Dr. Oprea's analysis of Cdc42 to visualize how a compound might interact with the Cdc42 GTPase to stifle its activity. Then they searched for such a compound in the UNM Molecular Discovery library.

The search process was akin to finding a needle in a haystack, but the latest high throughput flow cytometry equipment and molecular rendering software available at the UNM Cancer Center speeded their analysis significantly. The team analyzed thousands of compound candidates by first narrowing their search to the few hundred likely candidates and then testing those against several kinds of GPTases at a time. "From a purely discovery perspective, that's a high impact, novel way to look for small molecules," says Dr. Sklar. The compound they found is called CID2950007.

Structurally similar to NSAIDs — non-steroidal anti-inflammatory drugs — CID2950007 restrains the Cdc42 GTPase from changing a cell's cytoskeleton. Much like a skeleton gives a human body shape, a cell's cytoskeleton keeps the cell from collapsing on itself. The cytoskeleton enables a cell to move by growing amoeba-like legs called filopodia. Cdc42 also helps to keep cells where they need to be by enabling them to adhere more tightly to their surroundings. So, while uncontrolled growth and movement are hallmarks of metastatic cancer cells, growth and adherence are important traits for healthy cells. Tightly controlling just how Cdc42 causes a cell to behave is crucial.

In the paper published February 4, 2013, the team of scientists report that CID2950007 was the only compound they found that affected the Cdc42 GTPase without affecting any other GTPases. This selectivity is important to control the compound's effects on a cell. They also found that the compound works by changing the physical structure of Cdc42, so it doesn't destroy Cdc42 but it does control how Cdc42 interacts with other proteins in the cell. Their studies showed that CID2950007 decreased filopodia growth and cell adhesion in ovarian cancer cells and prevented cell adhesion in white blood cells. And their studies demonstrated that CID2950007 blocked Hantavirus infection in monkey kidney cells. By affecting the Cdc42 GTPase, and thus the cytoskeleton, CID2950007 has the potential to fight not only cancer but also infectious diseases.

Human use of CID2950007 as a cancer drug is a long way off. Before the Food and Drug Administration approves any drug for human use, it first requires the successful results of several toxicity and dose escalation studies on several types of animals. Then, the clinical trials process, which can take over 10 years, may begin.

"There are going to be a lot of side effects because these adhesion proteins have many other functions," says Dr. Sklar. So refining CID2950007 into a drug will take further collaboration and studies before toxicity studies and dose escalation studies can begin. To refine the compound, the UNM Cancer Center researchers will continue to collaborate with Jeffrey Aubé, PhD, Kansas University Distinguished Professor of Medicinal Chemistry, and Jennifer Golden, PhD, Assistant Director of the Specialized Chemistry Center at Kansas University. Still, control of GTPase Cdc42 offers promise as a way to control cancer metastasis. Says Dr. Wandinger-Ness, "there's a lot of enthusiasm for a compound like this — because there weren't any. This is a first-in-class."

Paper reference

"Characterization of a Cdc42 Inhibitor and its Use as a Molecular Probe" was published online in the *Journal of Biological Chemistry* on February 4, 2013 (http://www.jbc.org/) . Authors are: Lin Hong (University of New Mexico); S. Ray Kenney (Univerisity of New Mexico); Genevieve K. Phillips (UNM Cancer Center); Denise Simpson (Univerisity of Kansas); Chad E. Schroeder (Univerisity of Kansas); Julica Nöth (Univerisity of Kansas); Elsa Romero (University of New Mexico); Scarlett Swanson (University of New Mexico); Anna Waller (University of New Mexico); J. Jacob Strouse (University of

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The paper is available to the public at:
http://www.jbc.org/content/early/2013/02/04/jbc.M112.435941.full.pdf+html

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.

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