**Folding Proteins – Curing Cancer**

Brian Blagg, PhD, Associate Professor of Medicinal Chemistry at the University of Kansas has spent the past five years pursuing the goal of curing cancer. His research involves studying ways to inhibit a specific protein that allows cancer cells to grow. That protein, Hsp90, is gaining attention among cancer researchers as a target to help stem progression of the disease.

Anticancer drug development research has focused on molecularly targeted therapies for several years. The idea has been highly successful in a few cases such as Gleevec® (Novartis). However, most of current cancer drug development is aimed at narrow classes of cancers. But Hsp90 inhibitors have multiple antitumor-specific effects, meaning that they might be active in a broader range of cancers.

Hsp90 is what’s known as a “chaperone,” a protein that assists in the folding or unfolding of molecular structures. When Hsp90 encounters a damaged protein, it can send it down one of two pathways, either refolding the protein, or targeting it for degradation by the proteasome. Small molecules that block the Hsp90 ATPase activity, and thus its folding capacity, proved to enhance the degradation of oncoproteins, and show selective toxicity for tumor cells. In other words, Hsp90 folds proteins required for cancerous growth. Prof. Blagg’s research focuses on designing and synthesizing inhibitors of this folding process.

Research at other institutions involving Hsp90 inhibitors have not yet lived up to the promise of their target, in large part due to

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**Center of Innovation Planning Grant Awarded**

It was announced in January that the University of Kansas was the recipient of a Kansas Bioscience Authority Centers of Innovation planning grant to develop a business plan for an Innovation Center in Drug Delivery. The planning grant proposal was developed through the combined efforts of the Biotechnology Innovation and Optimization Center (BIO Center), The Office of Therapeutics, Discovery and Development (OTDD), and business consultants.

The Center of Innovation in Drug Delivery would transform outstanding drug–delivery capabilities at KU into an integrated, high-performance drug–delivery organization. Drug–delivery technology allows the right dose of a pharmaceutical to achieve its desired effect at the right time, in the right place, and without undesired consequences.

Roger Rajewski, BIO Center Director worked closely with Ken Lynn, a biotechnology industry consultant, Scott Weir, OTTD Director, and Michael Hughes, OTTD Project Manager, to produce the planning grant. The team will prepare a final proposal for the collaborative research Center of Innovation for submission this summer.

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**KU and Mayo Clinic Cancer Center Team Up**

The University of Kansas Cancer Center and the Mayo Clinic Cancer Center are working together on a National Cancer Institute (NCI) funded investigational agent that is designed to prevent cancer. The project represents an opportunity to leverage the strengths of two research entities to fast track a new cancer prevention therapy to patients.

The two institutions are developing and executing an exploratory clinical trial. Several investigational formulations of the drug will be developed at KU under the direction of Roger Rajewski, PhD, Director of the Biotechnology Innovation and Optimization Center (BIO Center). The investigational formulations will then be tested in clinical trials at the Mayo Clinic in Rochester, Minn.

This joint research grant focuses on a drug designed from a naturally-occurring anti-cancer agent found in vegetables such as broccoli, cauliflower and cabbage. The agent, SR13668, is a synthetic version of a compound that naturally inhibits Akt, a protein that can stop a cell from destroying itself, thus keeping a malignant cell alive. This protein is abnormally active in many human malignancies such as breast, prostate, lung, pancreatic, liver, ovarian and colorectal cancers, and in cell and animal experiments, SR13668 has exhibited the ability to inhibit tumor growth, and potentially tumor invasion. However, in early animal studies at the NCI, SR13668 was shown to be very poorly absorbed following oral administration.

Research at the BIO Center is focusing on the use of novel formulation approaches to increase the amount of SR13668 that is absorbed by the body following oral administration. These novel formulations will be used at the Mayo Clinic to conduct studies on a small number of healthy volunteers to determine how the formulations

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KU and Mayo Clinic Cancer Center Team Up

of SR13668 are absorbed, distributed, and metabolized within the body. These short-term Phase "0" studies are not meant to treat cancer or to demonstrate that these agents can prevent cancer — larger clinical trials may be held to determine the drug’s effectiveness against cancer.

It is natural for the two institutions to work together to advance this particular investigational anti-cancer agent from development to clinical trials, according to Scott Weir, PharmD, PhD, director of the KU Office of Therapeutics, Discovery and Development.

Paul Limburg, MD, MPH, Mayo Clinic gastroenterologist and co-investigator of the study, said this potentially novel drug might provide a new way to think about preventing cancer.

"While searching for treatment is important, even more so is finding effective ways to prevent cancer, and we hope to do so by working together in this effort," said Limburg, who also serves as the director of the Cancer Prevention Network, a nationwide consortium funded by the NCI to organize, promote, and conduct cancer prevention research.

Weir said he hopes this initial project will set the stage for expanded collaborations with Mayo Clinic to jointly discover and develop anti-cancer agents.

KU Cancer Center Director Roy Jensen, MD, said this joint effort illustrates the university’s outstanding research strengths and capabilities in its effort to improve cancer care. ▼

Center of Innovation Planning Grant Awarded

KBA announced the Centers of Innovation process last summer. Funding can be used for a number of purposes, with the expectation that the resulting research can be readily applied to commercial products and processes. A unique feature of the program is the close collaboration required between Kansas companies and Kansas research universities. The dominant factor in awarding the grants was expected economic return, according to the KBA. The KBA has said that it would award up to $1 million in grants to organizations to develop the research centers.

“We’re going to bring scientists, eminent scholars, engineers and business entrepreneurs together, let them all do what they do best, and then help them keep that success going on their own,” said KBA President Tom Thornton. “When we do that, everyone benefits, and our state further develops as an international leader in research and bioscience business,” Thornton said.

Through the Centers of Innovation program, Kansas can address its dual needs to build world-class bioscience research centers in its research institutions and to assist existing and emerging bioscience industries in capturing new knowledge and research findings for their product and production functions. The Centers of Innovation will focus on research and development in core technology areas that establish national and international research excellence and lead to high commercial payoff in new products and processes. KBA funds will leverage significant private and federal funds and enable Kansas to have several large-scale national and international centers within 10 years.

The Kansas Bioscience Authority provided funding for three planning grants for collaborative research Centers of Innovation. Both the Lawrence and KU Medical Center campuses will participate in launching the proposed centers. KU is the lead institution on the Drug Delivery Center of Innovation. An individual with a proven track record in private sector, nascent technology development will be recruited to direct the Center. This individual will be aided by a Board of Directors chaired by an industry biotechnology leader with a majority of Board members from industry.

When the awards were announced Steve Warren, Vice Provost for Research and Graduate Studies said “KU is pleased to be working with the authority ... on projects that are extremely important to the future of our state. KU brings a lot of resources — great researchers and research facilities — to these teams. Each funded center will be a major investment in productive research, and will have a significant economic impact in Kansas.”

According to the KBA the planning grants will lead to increased public-private partnerships. The Kansas Bioscience Authority is a $581-million initiative created by the Kansas Economic Growth Act of 2004 to expand the state’s world-class research capacity and bioscience clusters; support the growth of bioscience startups; and stimulate bioscience business expansion and attraction. ▼ - contributions from Kevin Boatright, Research and Graduate Studies

Mehmet Tanol, Ph.D., Research Associate at the BIO Center along with is wife Oznur celebrate their newly acquired U.S. citizenship with apple pie. Oznur also works as a Research Aide in the BIO Center labs.
BIO Center Posters Presented

Scientists from the Biotechnology Innovation and Optimization Center (BIO Center) attended the 2007 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition in San Diego. More than 9,000 pharmaceutical scientists from around the world attended the meeting to discuss the latest research and discoveries impacting the pharmaceutical industry. The four-day meeting kicked off with coordinated keynote and plenary lectures about combining biomedical research in the fields of academia and industry, and features a wide variety of educational programming, and more than 2,000 poster presentations.

Roger Rajewski, Director of the BIO Center attended the meeting, along with three Center scientists, John L. Haslam, Michelle Kennedy, and Mehmet Tanoğlu; along with Scott Weir, Director of the Office of Therapeutics, Discovery and Development.

John Haslam discusses a BIO Center poster with another scientist at the 2007 AAPS Annual Meeting and Exposition in San Diego.

BIO Center scientists presented two posters on potential drug product technologies developed at the Center:

- Pulmonary Delivery of Sodium (2,6-diisopropylphenoxy) methyl phosphate: A Water Soluble Prodrug of Propofol. Michelle P. McIntosh and Roger A Rajewski.


Founded in 1986, the AAPS is an individual membership society of 13,000 pharmaceutical scientists who have joined together to serve the public and their own common professional interests. “The AAPS meeting provides a venue for exposure of our scientists to the latest technologies and equipment in the industry,” said Rajewski. “At the same time, it provides an opportunity to share their work with colleagues.”

Folding Proteins – Curing Cancer

problems with bioavailability, solubility and toxicity. Hsp90 inhibitors are
problems with bioavailability, solubility and toxicity. Hsp90 inhibitors are primarily
natural products or natural product derivatives. The structural complexity of the
natural products makes the search for related compounds that are more drug-like
challenging, and so researchers have been looking for new families of Hsp90 inhibitors
without these limitations.

This is where the Biotechnology Innovation & Optimization Center (BIO Center) comes
into the picture. The BIO Center is working closely with Prof. Blagg and 25 research
collaborators at KU and 40 research partners worldwide to unlock this complex
problem. The Hsp90 project team is currently in the process of selecting the best
candidates for preclinical development. The BIO Center is aiding in this effort by
synthesize sufficient compound for efficacy testing in animals, formulation of
the compounds for delivery in testing, and evaluating technologies to increase the
solubility of the compounds in aqueous media.

Roger Rajewski, BIO Center Director said,
“The Center has made a major commitment
over the last two years to the development of
these agents. It is an exciting time as the
lead compounds progress through preclinical proof-of-concept and toxicity
testing.”

As the preclinical development effort
progresses, Prof. Blagg says he hopes to
move into clinical trials with some of the
compounds his group has developed. It is
likely that some of these compounds will be
used to spin-off a new pharmaceutical
company or will be licensed to an
established company in the near future. ▼

- with contributions from Lauren Beatty and Kansas IDeAs magazine; Kirkpatrick, P. Nature Rev. Drug Discov. 3, 646 (2004); Pat McCaffrey. Therapeutic Takedown: Hsp 90