



BY  
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# A Compound of Interest

Protein kinase inhibitors show promise as cancer drugs

**P**rotein kinases are enzymes that catalyze important chemical reactions, called phosphorylation, in cells. While some phosphorylation reactions are not required in normal cells that have completed their development, they are critical for the survival of cancer cells. As a result, researchers at pharmaceutical companies worldwide are working to develop anti-cancer drugs that inhibit the ability of various protein kinases to catalyze the phosphorylation of their protein substrates. One of the promising protein kinases being targeted with this new class of drugs is called Src. A drug that inhibits the ability of Src to catalyze the phosphorylation of its protein substrates can block the growth of cancer cells, while not being toxic to normal cells.

Although a number of such companies are pursuing inhibitors of the Src enzyme, no approach they have taken to date has proven to have advantages comparable to the one developed by a medicinal chemist at the University at Buffalo. In fact, the methodology for designing and synthesizing protein-kinase inhibitors developed by David Hangauer, PhD, is so promising it has resulted in the formation of a UB faculty start-up company that is attracting the interest of major players in the pharmaceutical industry worldwide. The new company, Kinex Pharmaceuticals, LLC, has an exclusive option to license Hangauer's technology from the university, and UB has filed two international patents on the new approach. As currently projected, the company expects to have compounds in human trials within two years.

"We are focusing our strategy on developing drugs that shrink tumors and prevent metastases with minimal or no side effects," says Hangauer, associate professor of medicinal chemistry in the Department of Chemistry in UB's College of Arts and Sciences. "For the broad range of cancers we are targeting, there are no good therapies out there with minimal side effects."

A key advantage of the protein kinase inhibitors being developed by Kinex Pharmaceuticals is that they target a unique binding site, which greatly reduces the chance that patients will develop resistance to the drugs—a problem that already has rendered ineffective some of the protein kinase inhibitors first marketed.

"For a drug that patients will take for the rest of their lives, resistance is a huge issue, particularly because the cancer

genome is unstable and it mutates very quickly," says Hangauer, who also is Kinex Pharmaceuticals' vice president for research and development.

Another key advantage to the drugs being developed using Kinex Pharmaceuticals' method is that they will be more selective than the protein kinase inhibitors currently on the market due to the fact that Hangauer pursued a binding site designed by nature to accept as substrates only proteins specific to this enzyme. Other companies are pursuing a site that binds ATP, a substrate that is ubiquitous for all 1,000 protein kinases in the body.

"Even if the enzyme mutates our binding site, thereby preventing the drug from binding there, its natural substrates also will not be able to bind at the site," explains Hangauer. "The result still will be cancer cells that cannot grow and spread to other parts of the body."

**T**he prospect of being able to avoid the development of resistance is powerful testimony to the potential of Hangauer's method for exploiting protein kinase inhibitors as cancer drugs, according to Allen Barnett, PhD '65, chief executive officer of Kinex Pharmaceuticals and research professor of pharmacology and toxicology, in the UB School of Medicine and Biomedical Sciences. Barnett formerly was vice president of technology acquisition and external collaborations of the Schering-Plough Research Institute, where he was responsible for evaluating and developing several multi-billion dollar drugs, including Claritin.

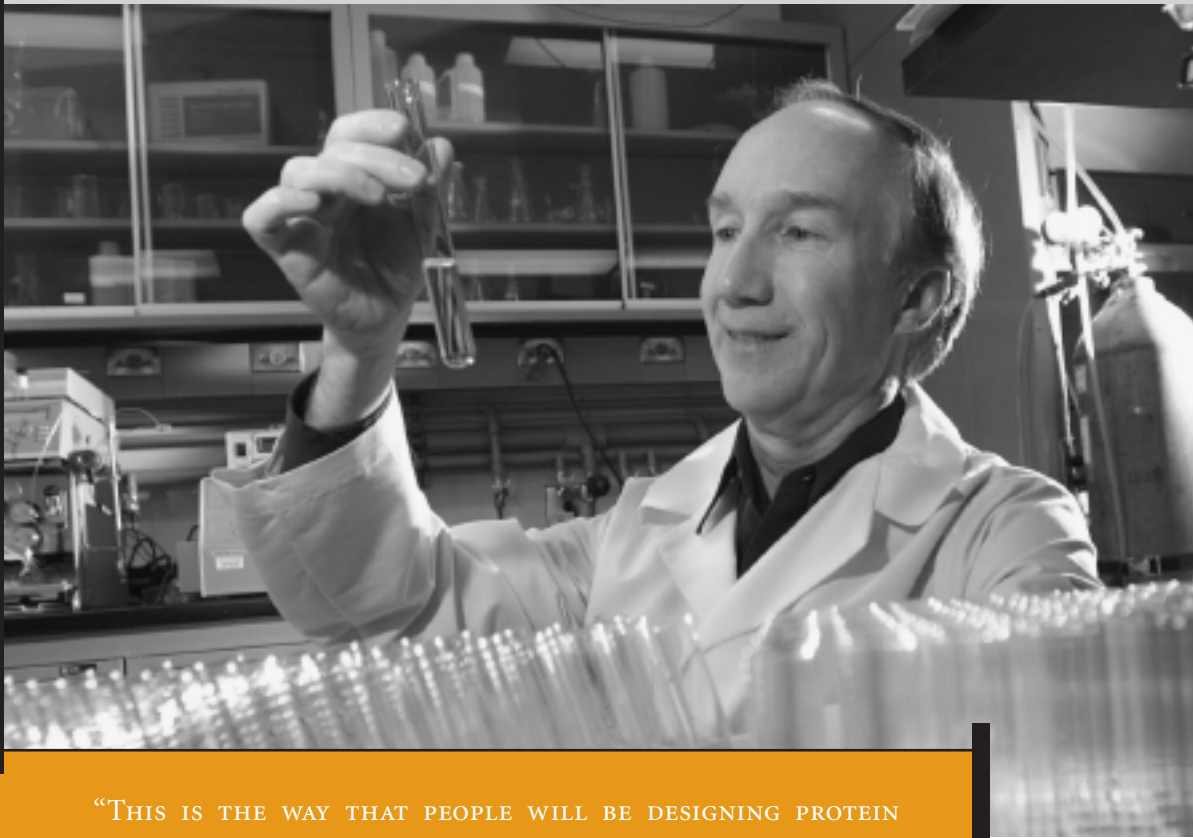


Photo by Bill Wipperfurth

David Hangauer, PhD

“THIS IS THE WAY THAT PEOPLE WILL BE DESIGNING PROTEIN KINASE INHIBITORS IN THE FUTURE, IF WE ARE SUCCESSFUL,” OBSERVES BARNETT, REFERRING TO HANGAUER’S EXPLOITATION OF COMBINATORIAL CHEMISTRY—A CHEMICAL SYNTHESIS TECHNIQUE WHERE HUNDREDS OR EVEN THOUSANDS OF NEW CHEMICAL COMPOUNDS ARE SYNTHESIZED AT ONCE.

While the resistance issue is probably Kinex Pharmaceuticals’ most powerful advantage over other protein kinase inhibitors for treating cancer, the high selectivity of its compounds, also greatly reduces the severity of potential side effects, notes Hangauer. In some cases, the effective dose could be as much as one hundred times less drug than the protein kinase inhibitors now on the market.

“This is the way that people will be designing protein kinase inhibitors in the future, if we are successful,” observes Barnett, referring to Hangauer’s exploitation of combinatorial chemistry—a chemical-synthesis technique where hundreds or

even thousands of new chemical compounds are synthesized at once. Compared to traditional methods, the technique allows medicinal chemists to discover new drugs at what seems like warp speed.

“David’s work has reached the stage where the basic technology is in place and no new discoveries are needed,” Barnett explains. “He has the target, he has the lead compounds, they work selectively, they don’t hit other targets. The next step is to convert it into a real drug.”

This involves improving potency, performing animal and pharmacokinetic studies and developing more compounds around the initial leads, activities that are

not covered by research grants, which is why the company now is approaching the investor community, both locally and nationally. “Right now, I view this as a scale-up project,” says Barnett.

“We used our proprietary process to target our drugs to a different binding site on this particular enzyme,” adds Hangauer. “We decided early on that going after this particular binding site would put us ahead of the game.”

**S**o far, that strategy has proven successful. Screening tests in tumor cells at the National Cancer Institute, as well as at Roswell Park Cancer Institute in the laboratories of Ralph J. Bernacki, PhD, Department of Pharmacology and Therapeutics, and Thomas Nicotera, PhD, Department of Molecular and Cellular Biophysics, have shown that Hangauer’s compounds have activity against all of the major cancers, including those for which current drugs



are not very effective, such as lung cancer, highly metastatic prostate cancer, colon cancer and ovarian cancer.

In addition, Hangauer's protein kinase inhibitors also are showing significant promise in preventing noise-induced hearing loss in collaborative research with Donald Henderson, PhD, professor in the UB Department of Communicative Disorders and Sciences and director of UB's Center for Hearing and Deafness, and Nicotera, who is adjunct associate professor in the same department.

Barnett posits that the same basic approach Hangauer has used to develop the anti-cancer compounds also could be used to attack other enzymes in the same class and to target other diseases. Notably, the new class of compounds has shown activity against enzymes involved in a broad range

of other diseases and conditions, including Type II diabetes, autoimmune diseases, osteoporosis, stroke and psoriasis.

"To me, the decision about establishing a company is based on whether or not there is something lasting," says Barnett. "If there's just one idea or one product, then you don't need to develop a company; but if you're talking about something that potentially is useful for other types of drugs and classes of drugs and can lead to a pipeline of products, then that's the basis of a business, and that's what I see in Kinex."

In applying for the broadest possible patent protection on Kinex Pharmaceuticals' technology and compounds, UB also has made a significant commitment to the company.

"Kinex has an excellent platform for development of a new class of drugs with

great potential in cancer therapy and for other diseases," says Robert Genco, DDS, UB vice provost for the Office of Science, Technology and Economic Outreach and SUNY Distinguished Professor in the UB Department of Oral Biology. "The company has an excellent management team. Dr. Barnett is experienced in drug development and Dr. Hangauer is a committed and very talented scientist."

In addition to Barnett, Johnson Y. N. Lau, MD, former chair and chief executive officer of Ribapharm, Inc., who took that company public in one of the largest biotech initial public offerings ever, is executive chairman of Kinex Pharmaceuticals. Lyn Dyster, PhD '91, who successfully founded the biotech firm GenCyte, is Kinex Pharmaceuticals' vice president for operations and business development. **BP**

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