A Part of Phase 1 Testing
mandated by the Food and Drug Administration (FDA), KX2-391 is being administered to a group of patients with advanced cancer who have not responded to other therapies. In non-human testing, the drug has been shown to be active against all cancers, according to Kinex Pharmaceuticals chief executive officer Allen Barnett, PhD ’63. KX2-391 may be the first small-molecule drug discovered and developed in Buffalo that has progressed to the human trial stage. The phase 1 trial is a first step toward FDA approval of the drug and is intended to test the safety and dosage tolerability of the drug.

“We’re very excited about the drug’s potential,” Barnett says. “As we go further in the drug’s development and do broader testing, we get better and better data. If the drug works half or a third as well as it’s worked in preclinical trials, it will have blockbuster potential.”

During non-human testing by Kinex over the past two years, KX2-391 has reduced tumors in several types of cancer. The drug was created from the work of David Hangauer, PhD, UB associate professor of chemistry, who developed a compound that targets Src (“sark”) kinase, a protein that is linked to the survival of cancer cells. Hangauer’s drug compounds, known as protein kinase inhibitors, are designed to shrink tumors and prevent metastases.

“Kinas are considered one of the most lucrative classes of drug targets in the pharmaceutical industry, and Hangauer is the first to develop a kinase drug that targets a unique site on the kinase target. KX2-391 is the first in this class of drugs to progress to the clinical trial stage. “We have the first success to come from this approach,” explains Hangauer, who also serves as Kinex senior vice president of research and development. “Our drug compound has been shown to be active against all cancers.”

“Cancer is a very tough disease to treat with drugs,” he adds, “but we think this will be better than any kinase inhibitor currently available.”

Hanguer also sees great potential for using related drug compounds, under development at Kinex, to treat autoimmune diseases like lupus, ulcerative colitis and rheumatoid arthritis. Roswell Park Cancer Institute and M.D. Anderson Cancer Center in Houston are performing the phase 1 trials, which are expected to enroll a total of 50 patients and last about a year. Alex Adjei, PhD, MD, senior vice president of clinical research at Roswell, is principal investigator for the phase 1 study at Roswell. Adjei is a national leader in translational research, drug development and thoracic oncology. The drug was synthesized by Albany Molecular Research Institute, a contract research organization, and the final dosage form for human trials was prepared in UB’s New York State Center of Excellence in Bioinformatics and Life Sciences, where Kinex Pharmaceuticals is headquartered. Kinex’s progress has been bolstered by significant cost savings from their use of Center of Excellence facilities and its funding programs, including funding from the UB Center for Advanced Biomedical and Bioengineering Technology.

Kinex originally licensed three patent filings from UB that describe the drug’s makeup, as well as a methodology for the design and synthesis of this and other kinase inhibitors. Kinex now has four issued patents and six other filings under review. Marnie L’Avigne, PhD, director of business development at UB’s Center of Excellence, says the drug’s progression to human trials “is a critical milestone” in the development of a local life-sciences economy.

“We’re banking on our ability to create private-sector jobs in drug discovery and development, rather than licensing university-developed technologies to out-of-state firms, which has been the more common path for moving locally grown inventions from the lab to the marketplace.”

Success for KX2-391 and Kinex would be a huge win for Buffalo’s emerging biotechnology industry, agrees Lyn Dyster, PhD ’91, Kinex vice president for operations, who, like Barnett and Hangauer, earned a doctoral degree at UB.

“Big pharma is thriving by licensing innovations from small-drug discovery and development companies like ours,” Dyster says. “If the success of Kinex and other Buffalo companies like Smart Pill will put Buffalo on the biotech map and help other local companies grow.”

Collaboration between scientists at UB’s Center of Excellence, Roswell and Hauptman Woodward Medical Research Institute—as well as the attraction of new companies like Clovis’ “Bridges to Buffalo”—should continue to fuel groundbreaking life-sciences research in Buffalo, according to Barnett.

“You’re starting to see the right kinds of scientific and entrepreneurial activity and partnerships you need to build a biotech industry in Buffalo,” Barnett says. “If Kinex is successful, you’ll start to see more local investment in local companies and also more investors from the outside starting to take a closer look at Buffalo opportunities.”
Molecular Signature for ALS Discovered

Peptide ‘fingerprint’ identified in both forms of the disease

A NANOTECHNOLOGY developed at UB has enabled researchers to identify a molecular signature common to both familial and sporadic cases of amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease.

It is the first time that a common molecular signature of ALS has been found in patients with both familial and sporadic cases, where no other family members have the disease.

The finding, published in the July 2007 Proceedings of the National Academy of Sciences (PNAS), reveals that a peptide found in a gene in spinal cord fluid is common to patients with the disease.

The work was done through a collaboration of UB chemists with scientists studying ALS at California Pacific Medical Center Research Institute, The Johns Hopkins University, University of California at San Diego and University of Pittsburgh.

Troy Wood, PhD, associate professor of chemistry in UB’s College of Arts and Sciences and a coauthor on the PNAS paper, began working with the ALS researchers following a talk given in 2005 at UB’s New York State Center of Excellence in Bioinformatics and Life Sciences by Vishwanath R. Lingappa, PhD, a research institute scientist from California Pacific.

At the suggestion of Bruce A. Holm, PhD, senior vice provost and executive director of the Center of Excellence, Wood began working with Lingappa to identify an unknown protein species he and his team had found in nanogram quantities (billionth of a gram) in spinal cord fluid samples from ALS patients.

“Only nanotechnology is capable of identifying a species in these amounts,” he says. “Because of the minute amounts of analyte that are present in some samples, nanospray technologies, in particular—which reveal what we call a peptide’s mass ‘fingerprint’—have emerged as one of the most important tools in the field of proteomics.”

In the ALS research, the UB researchers used trypsin, an enzyme, to digest or break down the unknown analyte into small peptide pieces that constitute the “fingerprint,” which, in turn, allows researchers to identify the species through mass spectrometry.

“The nanospray emitter allows you to handle very low fluid volumes so you need just a few microliters of sample,” explains Wood. “Without this technology, you would need milliliters—from a hundred to a thousand times more sample.”

Once the trypsin digestion process is complete, the fluid is then injected by syringe into the nanoelectrospray emitter.

The nanospray emitter that Wood developed and patented, called the “NiagaraFlow,” then atomizes the fluid, turning it into a very fine mist. Those ions can then be identified by mass spectrometry, an analytical chemistry technique that identifies analytes by their mass.

When an electrical potential is applied, the peptide is emitted as a fine mist of extremely small droplets, each of which is smaller than a micron, a millionth of a meter.

“Because the spray is emitted at such a low rate, 10 nanoliters per minute, we had around a hundred minutes during which the mass spectrometer could collect data before the sample was exhausted,” says Wood.

The UB researchers identified that this unique, cross-linked species contains superoxide dismutase, a protein that had been previously linked to the familial form of ALS.

“These results say that the mechanism in ALS involving superoxide dismutase is even more general,” says Wood. “But without the nanospray technology, we couldn’t have identified it.”

The peptide provides researchers with an important piece of information as to where to focus future research.

The work was supported by UB’s Center of Excellence, the National Institutes of Health, the California Pacific Medical Research Institute, the Forbes Norris MDA/ALS Research Center and the ALS Association.

Nanogenexys, a company formed by Troy Wood and located in the UB Technology Incubator, funded the development of a commercial version of the nanospray emitters based on the initial invention developed at UB.

Antimicrobial agents disrupt cell wall of bacterium

Staph-Killing Clay Studied

What makes some clays such powerful antimicrobial agents capable of killing MRSA and other virulent bacteria? It’s a question that UB geologists have been studying for several years.

WITH FUNDING FROM the National Institutes of Health’s National Center for Complementary and Alternative Medicine, the UB scientists are studying the surface characteristics of naturally occurring antimicrobial clays, including some clays from France, to determine why they are such effective killers of bacteria.

Researchers from Arizona State University’s School of Earth and Space Exploration, to whom the UB researchers are under subcontract on that grant, have recently shown that French clays can destroy methicillin-resistant Staphylococcus aureus, also called MRSA.

The UB researchers also have modified and patented Bioclay, a different type of clay that is highly successful in destroying a range of bacterial agents and which will soon be tested against MRSA.

Some of the UB researchers’ results on the surface characteristics of the French clays were presented at the annual meeting of the Geological Society of America in Denver in early November.

Rossman Giese, PhD, professor of geology in UB’s College of Arts and Sciences, and Tracy Bank, PhD, assistant professor of geology at UB, are using several techniques to study the French clays, including atomic force microscopy. In particular, they study the weak interactions that are responsible for the stickiness of clay particles.

“We look at the attraction or repulsion between natural and modified clays and bacteria,” says Giese.

The UB researchers found very little interaction between the French clays and one kind of bacterium.

For Bioclay, on the other hand, the killing mechanism may be quite different. Unlike antibiotics, which are essentially a chemical weapon against bacteria, Giese says he and his colleagues have reason to believe that Bioclay kills through purely physical means.

“The bacterium has to come into physical contact with Bioclay in order for something to happen,” Giese explains. That contact turns deadly.

“Unlike antibiotics, the antimicrobial agents in the Bioclay disrupt the cell wall of the bacterium causing the bacterium to leak to death,” he adds. “The nice thing about that is that it is unlikely that the bacterium can evolve to avoid it, so resistance to this antimicrobial clay is unlikely to become a problem.”

Bioclay has been very effective in lab testing, says Giese.

“Our studies show that when we mix a bit of our modified clay at very low levels into sewage sludge that contains all kinds of bacteria, the modified clay kills everything,” says Giese. “Nothing in the sewage sludge will grow in it.”

The formulation developed by Giese and colleagues in the Department of Geology and in the UB School of Medicine and Biomedical Sciences was recently licensed to a Buffalo startup company, also called Bioclay Inc.

The first application for that product is to treat HEPA filters in hospitals with the clay, in order to trap and kill potentially lethal bacteria.

In addition to Giese, other UB researchers who developed Bioclay are Pat Costanzo, formerly a faculty member in the UB Department of Geology; Paul J. Kostyniak, PhD, professor of pharmacology and toxicology and director of the Toxicology Research Center; and Joseph A. Syracuse, research scientist with the same center.
I N RECENT YEARS, scientists have proved that severely restricting calories leads to a longer life.

Now, a new study conducted by scientists at UB has shown for the first time that such a diet also can maintain physical fitness into advanced age, slowing the seemingly inevitable progression to physical disability and loss of independence.

THE STUDY—published in the October 2007 issue of Journals of Gerontology Series A: Biological Sciences and Medical Sciences—was supported with grants from the National Institutes of Health.

Using a rat model of lifetime caloric restriction, it showed that the diet reduces the amount of visceral fat, which expresses inflammatory factors that in humans cause chronic disease and a decline in physical performance and vitality across the lifespan. Have we finally discovered the Fountain of Youth? No. But we may be getting a little closer.

This is the first study to report that caloric restriction reduced production in visceral fat of the inflammatory cytokine IL-6 and enhanced performance on overall physical function assessments,” says Tongjian You, PhD, assistant professor of exercise and nutrition sciences in the UB School of Public Health and Health Professions and principal investigator.

“In addition, rats that ate a normal diet lost a significant amount of lean muscle mass and acquired more fat, while calorie-restricted rats maintained lean muscle mass as they aged.”

The study was conducted with male rats in three age groups—18, 24 and 29 months, comparable to ages 50-70 years in humans—that had been fed either a normal or 40-percent calorie-restricted diet from birth. The animals were put through tests to determine grip strength, muscle tone, stamina and swimming speed.

Results showed that animals on the restricted-calorie diet had significantly higher physical performance scores than animals fed a normal diet. They also had less fat, a lower fat-to-lean body mass, amount of visceral fat and the amount of pro-inflammatory cytokines and C-reactive protein, a marker of chronic inflammation.

Results showed that animals on the restricted-calorie diet had significantly higher physical performance scores than animals fed a normal diet. They also had less fat, a lower fat-to-lean body mass, amount of visceral fat and the amount of pro-inflammatory cytokines and C-reactive protein, a marker of chronic inflammation.

The stumbling block on this path to remaining forever young is that humans could not adhere to such a severe diet.

“Based on an average of 2,000 calories per day for adult women and 2,500 for men, cutting by 40 percent would mean surviving on 1,200 and 1,500 calories per day, respectively,” explains You.

“It’s very difficult for people to maintain that type of diet for short periods of time, and it would be nearly impossible over a lifetime while staying healthy. Starting on a diet like that in the senior years would be harmful.”

You says that a more moderate form of caloric restriction, 8 percent, is achievable in humans, based on recent findings, and may have positive effects on specific oxidative stress and inflammatory biomarkers.

“Preclinical testing of this 8-percent regimen could be informative and beneficial in translating to humans,” he notes.

Researchers on the study, in addition to You, were William E. Sonntag, PhD, and Xiaoyan Leng, MD, PhD, from Wake Forest University School of Medicine, and Christy S. Carter, PhD, from the University of Florida and the Malcolm Randall VA Medical Center in Gainesville.

Data also were collected on whole body mass, lean body mass, fat mass, percent body fat, the ratio of fat-to-lean body mass, amount of visceral fat and the amount of pro-inflammatory cytokines and C-reactive protein, a marker of chronic inflammation.

In the related theme of “Balancing Priorities,” nurses commented on the need to interrupt their job trajectory to care for family, described returning to school in their middle years and their wish for a better work schedule, less shift work on holidays and weekends, increased opportunity for promotion and for salary increases.

Some nurses described switching positions to lessen stress and lower the pace, and taking part-time positions for more personal time and to avoid work-place politics. As one nurse commented: “I have found as I age…my time off is more important than most all other aspects.”

A major theme under “Practice Deterrents” was pay inequity. Commented one participant: “Money is a major issue with many nurses. Although people say money is not a motivator, almost every nurse I know would be much more motivated if we were paid well enough so that we are not forced to work two jobs and if our advanced degrees were compensated.”

Another common deterrent was lack of respect, which is the reason one respondent is leaving the profession: “We have demanding, stressful roles. Yet our employers see us as expendable, replaceable and interchangeable with a variety of lesser-trained support staff.”

Other comments echoed this concern: “The voice of experience is not respected; the older nurse is not valued,” noted one respondent.
A NEW STUDY conducted by scientists at UB’s Research Institute on Addictions (RIA) suggests that most parents are aware of and accurately evaluate the extent of their teenager’s cigarette smoking, marijuana use, drinking and overall substance use.

HE SCIENTISTS also found that parents were less likely to be aware of their children’s use (especially younger teens’ use) if they themselves had personal problems or were using alcohol more frequently. Also, in cases where parents provided lower estimates of substance use, they were nearly twice as likely to underestimate frequency of marijuana use and quantity of alcohol use.

The study was funded by the National Institute on Drug Abuse and published in the July 2007 issue of the Journal of Child and Adolescent Substance Abuse.

What novel about its findings is that, for the first time, it provides detailed statistics about parental knowledge of teen substance use for families in which the teen’s substance use is causing the parent stress, but the teen is not necessarily in treatment. Previous studies have been restricted to families with a teen in substance abuse treatment or families with no current substance use issues.

For a six-month reporting period, 82 percent of parents accurately evaluated the presence of teen cigarette smoking; that is, the parents’ reports corresponded with their teen’s reports of their own smoking. Eighty-six percent of parents accurately evaluated the presence of teen marijuana use. However, only 72 percent of the parents in the RIA study accurately reported the presence of illicit drug use (other than marijuana) by teens.

“This study begins to dispel the notion that parents don’t know the extent to which their teens are using cigarettes, alcohol and illicit drugs,” says lead researcher Neil B. McGillicuddy, PhD. “It seems that, despite a few exceptions, many parents do know the extent of their teenager’s substance use. Parents can use this knowledge to help themselves cope with teenage substance use and the resulting stress on the family, as well as to begin conversations with their teen about making changes.”

“What we would hope people come away with from this study,” he continues, “is that parents can be more aware of their teen’s substance use by reducing their own alcohol use, giving more attention to what their teen is doing, particularly if the teen is younger, and taking steps to reduce their own psychological distress. Participation in parenting programs, especially those geared toward coping with an adolescent’s substance use, can give the parent important skills to deal with teen behavior and have been found to reduce the parent’s distress.”

McGillicuddy’s colleagues on the study were Robert G. Rychtarik, PhD, RIA senior research scientist and research associate professor in the Department of Psychiatry in the UB School of Medicine and Biomedical Sciences, Elizabeth T. Morshheimer, EdM, senior academic advisor with UB’s Student Advising Services, and Michelle R. Burke-Storer, MS, of the Urban Institute in Washington, DC.

To learn more about this study, its methodology and results, visit the UB NewsCenter website at www.buffalo.edu/news and search “McGillicuddy.”

I

wish you a happy (and healthy) new year on behalf of the Medical Alumni Association! As we enter 2008, the governing board is working hard to develop new programs that will serve the mission of the medical school as well as foster collaboration between alumni, students, faculty, residents and other university groups.

We are in the process of developing a Research Mentoring Program to provide greater research opportunities for current medical students. Many medical students have increased interest in research opportunities and the need for research experience that will enable them to compete for top residency programs. It is our hope that the mentoring program will lead to enhanced opportunity, exposure and interest in research for our medical students, thus strengthening their skills and expertise when applying for residency.

Additionally, to assist students as they start the process of identifying a residency program, we are working on an alumni HOST program. We have begun recruiting alumni throughout the country to “host” a medical student while they are interviewing for their residency program or in town to learn more about postgraduate work or employment opportunities. Host alumni may support a student in a variety of ways that includes providing housing for a night or transportation to or from the airport, to an interview, or to a tour of the city. As many of you know, finding a residency program can be a costly endeavor and we are excited about being able to offer support to our students during this time.

Finally, in an effort to help recruit UB students into our residency programs and retain physician here in Western New York, we have changed the format of Community Physician Lunches. We have teamed up with UB department chairs and current residents of those departments to talk to medical students about the residency programs at UB medical school and life as a resident in Western New York. Special thanks to the Departments of Surgery and Family Medicine for their participation. We hope our students find this format helpful and once they learn about the great residency programs available here, they make UB their number one choice come Match Day.

If you are a faculty member who would welcome the opportunity to mentor a medical student in research, or if you are an alumni/alumna interested in becoming a HOST member, we welcome you and your ideas. Please call Jennifer Lobaugh, director of special events and constituent relations at the medical school at 1-877-826-3246 or (716) 829-2773, or e-mail jlobaugh@buffalo.edu.

Lastly, for alumni who are celebrating a reunion in 2008, Reunion Weekend and Spring Clinical Day is May 2–3 in Buffalo. In response to popular demand, it is my pleasure to announce that Dr. Michael Roizen, author of Befit Fix, will return as the lecturer for Spring Clinical Day. He will discuss his bestselling book, You: Staying Young. As a preview to his talk, I encourage you to discover your “real age” by visiting www.realage.com. Please see page 47 for all reunion weekend event details.

As always, we welcome your feedback, so please feel free to e-mail me.

Sincerely,

HELEN M. CAPPACINNO, MD ’88
President, Medical Alumni Association
Helenca@wd.com