

New system involves an agent that acts as its own carrier

A Well-Delivered Drug

BY ELLEN GOLDBAUM

THE PROBLEM of efficiently delivering drugs, especially those that are hydrophobic or water-repellant, to tumors or other disease sites has long challenged scientists to develop delivery systems that keep these drugs intact until reaching their targets.

IN AN INNOVATIVE RESPONSE to this challenge, scientists in UB's Institute for Lasers, Photonics and Biophotonics and Roswell Park Cancer Institute (RPCI) have developed a solution in which the delivery system is the drug itself.

Their work relates to photodynamic therapy, a form of treatment developed at RPCI that involves injecting patients with a non-toxic photosensitizing drug that migrates to fast-growing cells. When the photosensitizer is exposed to red light, a highly reactive molecule called a singlet oxygen is produced, which kills the cells while, for the most part, sparing surrounding healthy tissue.

The new drug-delivery system—which is described in the February 1, 2007, issue of *Molecular Pharmaceutics*—involves the use of nanocrystals of pure HPPH, a photosensitizer currently in Phase I/II human clinical trials at RPCI for treating various types of cancer. The UB researchers found that the nanocrystals of HPPH (2-devinyl-2-(1'-hexyloxyethyl) pyropheophorbide), were taken up by tumors in vivo, with efficacy comparable to conventional, surfactant-based delivery systems.

"In this case, the drug itself acts as its own carrier," says Haridas Pudavar, PhD UB research assistant professor of chemistry and a coauthor.

The nanocrystals present a major advantage over methods of delivery

involving other carriers, according to Paras Prasad, PhD, SUNY Distinguished Professor in the Department of Chemistry in the College of Arts and Sciences, executive director of the institute and a coauthor. Because other delivery systems, especially those containing surfactants, commonly used with HPPH and many other drugs may add to the toxicity in the body, they have been considered imperfect solutions.

"Unlike formulations that require separate delivery systems, once this drug is approved, no additional approvals will be needed," says Prasad, who adds that a patent has been filed on the work.

"Our published data in animal models demonstrate no difference in drug activity with the nanocrystal formulation," notes Ravindra Pandey, PhD, Distinguished Professor of biophysical sciences at RPCI and a coauthor on the paper.

"This is a case where the easiest formulation works the best," adds Indrajit Roy, PhD, UB research assistant professor of chemistry and another coauthor.

The researchers found that because HPPH is amphiphilic, i.e., partially soluble in water and oil, nanocrystals of it will self-assemble; that is, in solution the molecules aggregate, but not into such big clusters that they settle to the bottom.

"It's a controlled formation of a colloidally stable suspension of nanosized crystals," explains Tymish Ohulchansky, PhD,

UB senior research scientist and a coauthor. The researchers originally were investigating nanocrystals as a delivery method for hydrophobic dyes in bioimaging applications, another

promising use for nanocrystals that they continue to pursue.

Further in vivo studies with HPPH nanocrystals are being conducted by scientists at UB and RPCI, including Pandey and Allan R. Oseroff, MD, chair of the Department of Dermatology at RPCI and in UB's School of Medicine and Biomedical Sciences.

The UB-RPCI team is exploring the use of the same technique for delivering other hydrophobic drugs, including those used in chemotherapy.

Additional coauthors on the paper are Koichi Baba, PhD, former postdoctoral research associate in the UB Department of Chemistry, and

Yihui Chen, PhD, postdoctoral research associate at RPCI.

The nanocrystal research was supported by the National Institutes of Health, the John R. Oishei Foundation and UB's New York State Center of Excellence in Bioinformatics and Life Sciences, with additional support from RPCI.

In related work, the UB researchers have achieved improved depth penetration of HPPH using two-photon photodynamic therapy, research that was published in the February 9, 2007 issue of the *Journal of the American Chemical Society*. **BP**

For more information on photodynamic therapy and the history of its development at Roswell Park Cancer Institute, go to Buffalo Physician's web site at www.smbs.buffalo.edu/bp/, click on Past Issues, and scroll down to the Fall 2002 issue, which features a Special Report on this subject.



Action Elucidated

BY LOIS BAKER

Formerly unknown action of receptor channel described

A FORMERLY UNKNOWN action of the acetylcholine receptor channel, a protein that regulates the electrical activity of nerve and muscle cells, is described by UB biophysicists in the April 19, 2007 issue of *Nature*.

Acetylcholine is a neurotransmitter that carries chemical messages across certain brain synapses and across all human nerve-muscle synapses. Acetylcholine receptors bind the neurotransmitter and set in motion a cascade of molecular activity that ultimately results in thought or motion.

"The acetylcholine receptor chan-

nel is a molecule-sized valve that opens and closes to regulate the flow of electricity in nerve and muscle cells," explains Anthony L. Auerbach, PhD, professor of physiology and biophysics in the School of Medicine and Biomedical Sciences and senior author on the study.

"Before our work, most scientists thought that this protein had a small number of moving parts, perhaps even just one. Also, they thought that these parts moved, between closed and open, smoothly and nearly instantaneously. Our work has shown that the recep-

tor is made up of a much larger number of moving parts, maybe 20 or so, and that these parts jiggle about when they move."

Prasad G. Purohit, PhD, postdoctoral associate working with Auerbach, is first author on the paper. Ananya Mitra, a doctoral student in the laboratory, also contributed to the study.

The researchers use a technique called single-molecule kinetic analysis to probe the transition state of the receptor's "gating mechanism" and to estimate the timing of motions within the protein's opening process.

"Perhaps this newfound understanding of how a protein machine works, how

it changes shape in order to carry out its appointed task, will someday lead to better protein engineering and drug design," says Auerbach. "If you want to build a better protein, or to modify its function, an important first step is to understand the ones nature has given us."

Auerbach has conducted research for 18 years into the molecular processes involved in protein activity in the nervous system and how synaptic receptors are activated by their transmitters. He and

scientists working in his laboratory now are studying how the subunits that form the receptor work together, and how the protein limits its receptiveness to signaling mechanisms.

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The research is funded by a National Institutes of Health Jacob Javits Award in the Neurosciences to Auerbach. **BP**

A Fusion of Expertise

Faculty joining forces to study pathogenic microbes

BY
LAUREN
MAYNARD

PATHOGENIC MICROBES, such as bacteria, viruses or fungi, are more than just natural health threats. They can also be weapons of bioterrorism that have the potential to threaten human beings and their environments worldwide. Because of this, demand has sharply increased in recent years for pathogen research.

GIVEN THE URGENCY of this demand, and the fact that University at Buffalo has well-established strengths in molecular science and infectious disease research, it's not surprising that one of the first core research groups to form at the New York State Center of Excellence in Bioinformatics and Life Sciences was the Infectious Disease and Genomics Group.

The group—which includes Anthony A. Campagnari, PhD; Thomas A. Russo, MD; and Steven R. Gill, PhD—is in the

early stages of translational research that fuses expertise in immunology, molecular biology, bacteriology, genomics and bioinformatics in order to develop novel methods aimed at identifying vaccine, diagnostic and treatment targets for microbial diseases.

In addition to their joining forces on the third floor of the Center of Excellence, each investigator continues to maintain his own lab on UB's South Campus.

Funding to house and equip the group's shared lab comes from various

sources, including a \$1 million grant from the center's state-supported start-up fund; a \$2 million systems biology grant from the Department of Defense, whose principal investigator is center director Bruce Holm, PhD; and several other grants to individual investigators from the National Institutes of Health (NIH).

In addition to sharing a staff of research scientists, space and time, Campagnari, Russo and Gill have ready access to the center's growing inventory of cutting-edge equipment, including biostatistical software, a Roche Genome Sequencer FLX System and an Affymetrix DNA microarray machine for gene analysis. With this advanced technology, the investigators can analyze microbes at the DNA level, a capacity that is enhanced by database support they receive from staff in the Center for Computational Research, which is also housed in the Center of Excellence.

Using whole-genomic sequencing and microarray technology, says Campagnari, the team can apply genomic data to several defense research applications.

An example is a joint study in which members of the group are working to unravel the genomes of three strains of the *Acinetobacter baumannii* pathogen, which is often found in U.S. hospitals and now is also infecting wounded soldiers in the Middle East. The study, which is funded as a subcontract under Holm's DOD grant, is focusing on a highly drug-resistant strain isolated from an infected soldier in Iraq and another that was responsible for hospital-acquired infections in Buffalo.

Many of these strains are highly resistant to antimicrobials, Gill says, which

has increased national interest—and, consequently, funding support—for studies that identify new antimicrobial drug targets or potential vaccine candidates. To continue their research on *A. baumannii*, the group is applying for an NIH grant.

Pathogenic targets found at the lab could one day be used in commercial diagnostics. Since 2002, Campagnari's lab has been involved in collaborative studies with CUBRC, an industrial partner that also has a lab at the center, to identify specific bacterial targets

that will eventually help scientists develop hand-held detectors that would be used for rapid diagnostic testing.

The group also is collaborating with UB Distinguished Professor Timothy

USING WHOLE-GENOMIC SEQUENCING AND MICROARRAY TECHNOLOGY, SAYS CAMPAGNARI, THE TEAM CAN APPLY GENOMIC DATA TO SEVERAL DEFENSE RESEARCH APPLICATIONS.

Murphy, MD, to analyze bacteria that cause infections in the middle ear and lower-respiratory tract.

In the long term, the group's goal is to be self-sufficient through its scientific collaborations and to remain open to innovation rather than become a core group that acts as a testing services provider.

"We're confident we'll be there in a year's time," Gill says. **BP**



Pictured LEFT TO RIGHT: Campagnari, Russo, Gill

PHOTO BY NANCY PARISI

The Campagnari Lab

ANTHONY A. CAMPAGNARI, PHD, professor of microbiology and immunology at UB, is an internationally recognized expert in bacterial pathogenesis. His research targets microbial virulence mechanisms and putative vaccine targets. His laboratory is currently studying *Moraxella catarrhalis*, a human respiratory pathogen that is a major cause of otitis media in young children; *Haemophilus ducreyi*, a bacterium that causes the sexually transmitted disease chancroid, implicated in HIV transmission; and *Acinetobacter baumannii*, an emerging pathogen that is a significant cause of morbidity in wounded military personnel currently serving in Iraq and Afghanistan.

The Russo Lab

THOMAS A. RUSSO, MD, is a professor in the Department of Medicine and Division of Infectious Diseases in the UB School of Medicine and Biomedical Sciences. His lab studies strains of *Escherichia coli* that cause infections outside the intestinal tract, including urinary tract, abdominal, pulmonary, soft-tissue and surgical wound infections, meningitis, and bacteremia. He also collaborates with Campagnari to study the *A. baumannii* pathogen.

The Gill Lab

STEVEN R. GILL, PHD, a molecular biologist, joined UB in 2005 as an associate professor of oral biology in the School of Dental Medicine. His main areas of study are oral and gastrointestinal bacteria. Previously, at the Institute for Genomics Research in Rockville, Maryland, Gill's team published the world's first collective genome of the trillions of microbes in the human gut. Through collaborations at UB and Roswell Park Cancer Institute, Gill has initiated new efforts to examine microbial populations involved in oral infections and oral cancers.