

Health Talk & You

EUISIK YOON (LEFT) HOLDS HIS "MICROFLUIDIC CHIP," WHICH HE AND COLLEAGUES JOHN OHLFEST (CENTER) AND WALTER LOW (RIGHT) HOPE TO USE IN SCREENING DRUGS AGAINST TUMOR STEM CELLS.

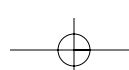
Connections

From inspiration to application, diverse disciplines work together to open new windows into the world of the brain.

Euisik Yoon has a plan to separate individual cells into microscopic chambers, so that each cell can be exposed to a different condition. Walter Low has a whole lot of cells he wants to expose to a whole lot of different conditions.

A match made in heaven? No—at the University of Minnesota.

Last year Yoon, a professor of electrical and computer engineering, described his ideas for his device, which he calls a "microfluidic chip," at a seminar Low happened to attend. Low, a professor of neurosurgery, knew he'd stumbled onto something good. Low had been working with colleague John Ohlfest, director of the gene therapy program in the department of neurosurgery, on strategies for quelling the growth of cancerous stem cells in brain tumors. Low and Ohlfest faced two big challenges: the veritable explosion of cancer chemotherapies in recent years, and the fact that each tumor is unique, with a unique response to treatment.





LIVER SPECIALIST CLIFFORD STEER SAYS URSODEOXYCHOLIC ACID, FOUND IN BILE, IS A "REMARKABLE MOLECULE" — AND SHOWS GREAT POTENTIAL FOR TREATING NEURODEGENERATIVE DISORDERS.

ing and medicine," Ohlfest says. "We've got a very good team."

This collaboration against cancer is only one of hundreds of interdisciplinary research projects at the University of Minnesota that focus on the nervous system. Just as the brain integrates input from many sources to create functions far beyond a simple sum of the parts, these projects synergistically enhance researchers' ability to address big issues. From reversing the devastation of neurodegenerative disease, to loosening the stranglehold of mental illness, to dealing with damage from accident or stroke, they stand to revolutionize neuroscience in the years ahead.

"We have seen that where disciplines meet, breakthroughs happen," says Deborah E. Powell, dean of the medical school. "That's why it is so exciting to encourage these collaborations among our neuroscientists, along with our University colleagues, in such disciplines as engineering and psychology. In the short term, our understanding of everything from the mind to neurodegenerative disorders will grow greatly; in the long term, this new knowledge will improve care for patients and benefit our families and communities."

Saving Cells

A specialist in liver disorders might seem an unlikely person to make inroads into neuroscience. But in the late 1990s, an accidental observation led Clifford Steer, professor of medicine, to discover amazing properties of one component of bile—a substance livers make to help with digestion—that appears to hold great promise for treating neurodegenerative disorders.

It all started when former student Cecilia Rodrigues visited Steer's lab and decided to take a look at liver tissue they had exposed earlier to various bile acids. She saw that one compound they used destroyed cells, whereas another, called ursodeoxycholic acid, or "urso," seemed to save them. Intrigued, Steer and Rodrigues started exploring why. They discovered that urso inhibits apoptosis—programmed cell death.

"I thought, wow, this may have some potential," Steer says.

The researchers began looking at the effect of urso on other kinds of cells. They discovered *in vitro*, and in laboratory animals, that it showed promise as a therapy for a spectrum of nervous system disorders, including Parkinson's disease, Huntington's disease, and stroke.

"There is a whole armamentarium of drugs. How do we screen them to identify which one might be effective?" Low asks.

The answer, he realized, could very well be Yoon's chip device. Yoon, Low, and Ohlfest are now working together to develop a high-throughput system for screening drugs against tumor stem cells.

Says Low: "We're combining technologies—the latest developments in brain tumor stem cells with the latest developments in microfluidics." If all goes as hoped, the outcome will be a way to tailor treatment to individual brain cancers.

"This is very sci-fi, but my ultimate dream is to take a tumor, drop it in a chip, and two days later it tells you [what treatment to use]," Ohlfest says.

There are a few—well, many—details to work out before that dream comes true. But the researchers are pretty confident they can make it happen.

"It's the quintessential interface between engineer-

"...My ultimate dream is to take a tumor, drop it in a chip, and two days later it tells you [what treatment to use]."

— JOHN OHLFEST

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"It's just a remarkable molecule," Steer says.

Neurologist Gareth Parry is currently conducting a Phase 1 clinical trial to determine whether urso is effective against ALS (Lou Gehrig's disease). Steer hopes to obtain funding to begin testing in patients with other brain or eye diseases who might benefit from urso's anti-apoptotic action.

Imaging Alzheimer's

When you look to your future, what do you fear? For many Americans 55 and older, their number one health dread is Alzheimer's disease.

In 1995, efforts to understand Alzheimer's took a giant leap forward when neuroscientist Karen Hsiao Ashe, developed a strain of mice with a human gene predisposing them to Alzheimer's disease. Over the dozen years since, Ashe's transgenic mice have been used in a variety of venues to advance understanding of the disease.

Several years ago, Michael Garwood, professor of radiology and associate director of the University of Minnesota's Center for Magnetic Resonance Research (CMRR), and Mayo Clinic colleagues Clifford Jack and Joseph Poduslo, began using a variation of Ashe's mice to develop a technique for detecting amyloid plaques—accumulations of protein that herald the presence of the disease—in a living brain.

With seed money from the Minnesota Partnership for Biotechnology and Medical Genomics (the U-Mayo Partnership), the researchers used the CMRR's powerful 9.4 Tesla magnetic resonance imaging (MRI) machine to look inside the brains of living mice with Alzheimer's. As they had hoped, they were able to see the plaques in enough detail to count and quantify them.

That's exciting for a number of reasons, Garwood says. The ability to study plaque development in mice allows researchers to test the efficacy

of anti-Alzheimer's drugs. And the MRI also opens the door to better understand Alzheimer's in humans. Garwood hopes to eventually use the machine to see the progression of Alzheimer's disease in patients, using it as both a diagnostic tool and a way to assess therapies. "We ultimately would like to do this in humans," Garwood says.

The researchers are now developing a dye to improve the sensitivity and specificity with which they can view plaque material.

"We wouldn't be doing anything we're doing without [Dr. Ashe's] mice," Garwood says. "Her development was absolutely critical."

"We have seen that where disciplines meet, breakthroughs happen."

DEBORAH E. POWELL

A Moving Experience

One of the brain's big jobs is to tell muscles when, where, and how to move. But what if the muscles don't get the message—what if the critical connections have been disrupted by a paralyzing injury or nerve-destroying disease? Is that the end of a person's being able to interact with the rest of the world?

Not if Bin He can help it. A professor of biomedical engineering, He is exploring ways to use computers to interpret and follow through on electroencephalogram (EEG) signals emanating from the brain.

He uses an electrode-studded hood, worn by a human volunteer, which records neural activity from the scalp. The human volunteer performs a task—say, moving a virtual object using a computer mouse. By applying complex mathematical processing that has

MICHAEL GARWOOD, PROFESSOR OF RADIOLOGY AT THE U, TEAMS UP WITH MAYO CLINIC COLLEAGUES CLIFFORD JACK (SEATED) AND JOSEPH PODUSLO (LEFT) TO ADVANCE THE STUDY OF AND TREATMENT FOR ALZHEIMER'S DISEASE. ALSO PICTURED: GRADUATE STUDENT ANGELA SNYDER.



SF-3



BIOMEDICAL ENGINEERING PROFESSOR BIN HE HOPES TO USE COMPUTERS TO RESTORE MOVEMENT TO PEOPLE WHO SUFFER FROM A PARALYZING INJURY OR DISEASE. GRADUATE STUDENT HAN YUAN IS SEEN FITTING AN ELECTRODE-STUDED HOOD ON A VOLUNTEER PATIENT.

scientists in order to move this work from research lab to real world," He says.

Continued Discovery

To encourage even more interdisciplinary collaboration—key, many believe, to transforming the University of Minnesota into one of the top three public research universities in the world—the University recently established an Institute for Translational Neuroscience.

Directed by Harry Orr, professor of laboratory medicine and pathology, the institute will bring researchers from diverse disciplines together to advance understanding of the brain and move that understanding into clinical application. The focus is on neuroengineering, memory research and care, neurodegenerative and neuromuscular diseases, and neurodevelopment and mental health—"areas in which we're strong in many ways, and areas that have a high potential for having an impact on medicine," Orr says.

The idea, Orr says, is to bring together collaborators in the Institute of Technology, the College of Liberal Arts, the Academic Health Center and other parts of the University to bring inspiration to application.

"The Institute of Translational Neuroscience will further enhance our research in the neurosciences defined very broadly across the university," he says. "The translational aspect of what we're doing is to move things from the basic research arena to impacting human health."

With a commitment of startup money, the institute aims to attract top scientists in the spectrum of disciplines shaping the discoveries that will lead to tomorrow's cures.

"What drives research is faculty," Orr says. "This is a vehicle for recruiting world-renowned faculty."

■ MARY HOFF

taken years to develop, He plucks from the noisy recording the subtle signals of the brain telling the hand how to move. He then programs a computer to interpret those signals to perform the task using only brain waves to guide it.

"I never believed [it would be possible] until I started doing the research," He says. "Now I believe it."

He is collaborating with colleagues in the CMRR to learn how the EEG signals correspond to neural activity inside. He records EEGs of an individual performing a simple motor task. Then the functional magnetic resonance imaging (fMRI) is used to observe activity within the brain as the subject performs the same task. By combining the spatial resolution afforded by fMRI with the temporal precision EEG offers, the approach provides an exceptional picture of brain activity over space and time.

He hopes his research will one day help people with paralysis or movement disorders perform basic tasks with the help of a computer that translates thought into action.

"We would partner with neuroscientists, neurologists, electrical engineers, mechanical engineers, and industrial

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For health information from the University of Minnesota, see the *Health Talk & You* Web page, www.healthtalkandyou.com.

For more information on health sciences research at the University, go to the AHC research Web page, www.ahc.umn.edu/research.

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