



# Critical connections: How collaboration, cross-training can translate to medical breakthroughs

**In medicine, major victories sometimes lead to puzzling new challenges. For example, intensive care units (ICUs) today are making tremendous strides in helping patients overcome life-threatening illnesses, but many survivors experience debilitating weakness for months or even years afterward.**

Mark Rich M.D., Ph.D., associate professor of neuroscience, cell biology, and physiology, worked with ICU patients during a fellowship on neuromuscular disease 10 years ago. Many had survived bouts with sepsis, a full-body inflammatory state often caused by serious infection, and a common complication among severely ill ICU patients.

Sepsis can lead to multi-system organ failure, coma, or death. Weakness among patients recovering from sepsis stems from issues of the muscles (myopathy) and nerves (neuropathy), which conventional medical thinking attributes to atrophied muscle fibers and dead nerve cells.

Rich wasn't so sure. A hunch led him to look beyond the standard explanation and consider other possible causes of clinical illness myopathy (CIM), as the muscle condition is known.

"Muscle is electrically active," Rich explained, "and in these patients, we found that the electrical signaling is really absent or severely affected."

Even in tissue that appears healthy, as in many patients with CIM, a problem with the electrical signals that trigger muscle contraction could explain the loss of strength and function. Rich's initial investigation led to further studies to determine, with increasing precision, the nature of the muscles' electrical problem. He eventually traced the issue to sodium channels, proteins that regulate the electrical activity of cells. His hunch had paid off.

## **From bedside to bench— and back again**

Timothy Cope, Ph.D., professor and chair of neuroscience, cell biology, and physiology and director of the Comprehensive Neuroscience Center (CNC), has known and worked with

Rich throughout his decade of research related to sepsis. He attributes Rich's success not to a single inspired insight, but to his training as an M.D./Ph.D.

"Because of his knowledge as a neurologist and his abilities as a scientist, he's able to do this kind of work," Cope said. "It's translational science in one of its finest examples."

Rich agrees that having one foot in the hospital and the other in a laboratory worked out well for him.

"First I saw the patients," Rich said, "and I was in a muscle sodium channel lab unrelated to this, doing basic science. That's what the real luck was."

**"This is why the creation of an environment where everybody brings something unique to the table, but all with the same kind of general theme, is critical."**

After establishing sodium channels as the source of CIM, Rich began to wonder if the related loss of nerve function, known as clinical illness polyneuropathy (CIP), might be similarly misunderstood. The question led him from the lab back to a clinical setting.

Encouraged by studies showing that nerve cells removed from CIP patients, much like the muscle tissue in CIM patients, looked healthy but exhibited compromised electrical activity, Rich formulated a new prediction. If the nerves were not actually dying, but were afflicted by an electrical problem like the one he'd documented in muscle, function should return more rapidly.

"In studying patients, we noticed there was a subset who did recover very quickly," Rich said, "and again, that just didn't fit well with dying nerves."

He theorized that rather than slowly regrowing dead nerve cells over the course of several months, some patients were able to restore sodium channel function by replacing faulty or depleted proteins, a process that sometimes took mere weeks.

The next step would be to study an animal model of the condition.

"It's the only way to do the study, because this electrical regulation is so complex," Rich said. "We don't know yet which factor is crucial, so you have to study it in its real situation with the disease."

His initial work based on nerve conductions through the skin seemed promising, but the results just weren't precise enough.

"To do a detailed study of the mechanism," Rich said, would require "intercellular recording, where you poke into individual nerve fibers."

An investigation of this type could provide the very specific information he needed, Rich knew, but the process is so specialized that only a few labs in the world are capable of it. Fortunately, his colleague, Cope, oversees one of them.

### **A true team effort**

Rich and Cope came to Wright State together from Emory University in January 2005, along with colleague Kathrin Engisch, Ph.D. Cope had accepted a position as department chair, attracted by the opportunity to assemble a world-class team and build the university's strength in neuroscience.

One early mark of their success was the award of a \$4.8 million program project grant (PPG) by the National Institute of Neurological Disorders and Stroke in 2007. The award, which is the first PPG in university history, funds an array of

collaborative projects focusing on the recovery of nervous system function following injury.

"These are the kinds of things that can happen when you have a group," Cope said. "This is why the creation of an environment where everybody brings something unique to the table, but all with the same kind of general theme, is critical."

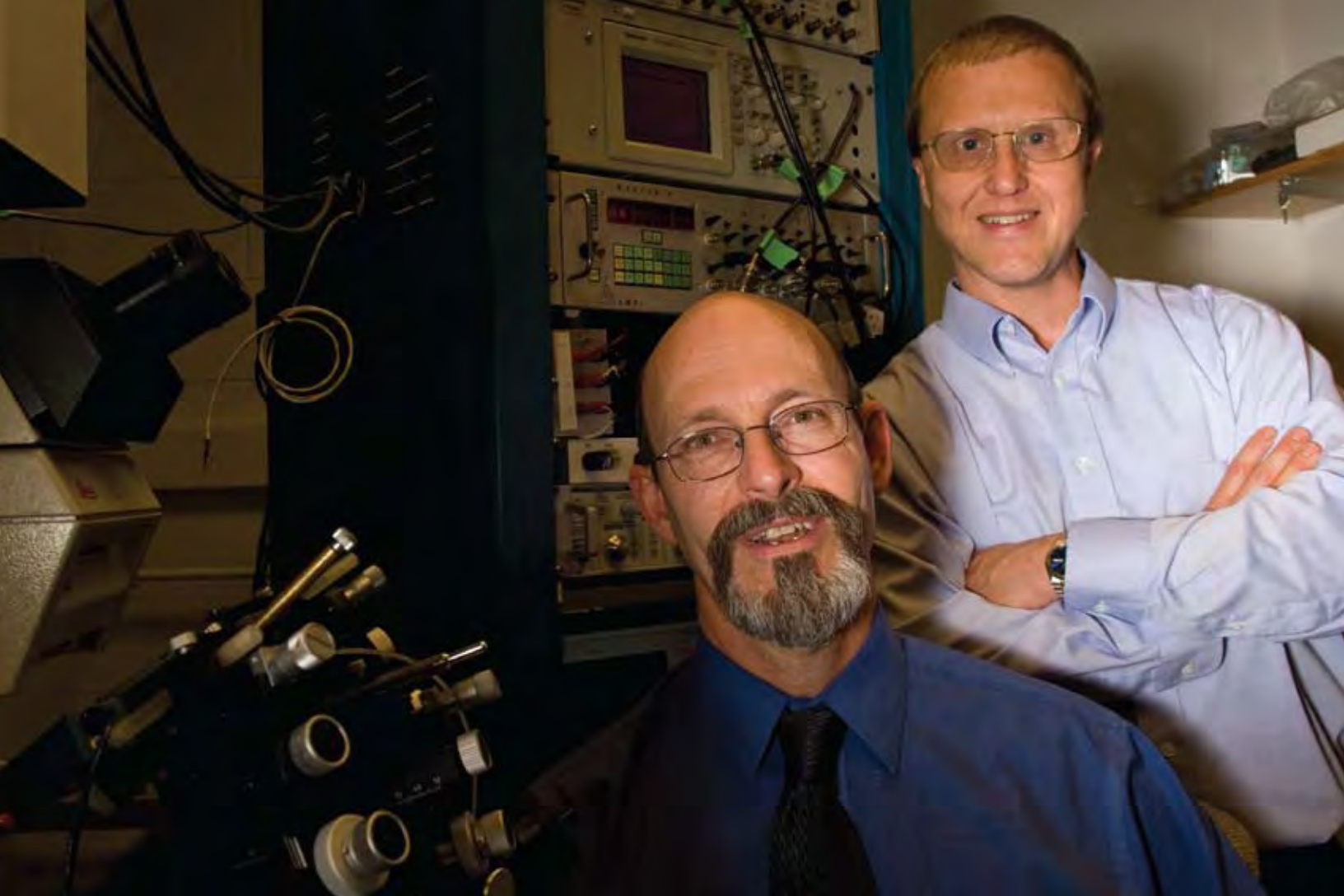
For Rich's research on CIP, collaborating with Cope proved to be essential.

"Through a number of studies, their lab was actually able to determine that [CIP] appeared to be the same kind of problem as in the muscle," Rich said. "The hint was that it's the sodium channel protein again... that instead of having two different illnesses, one where muscle's shrinking and a separate one where axons are dying, we may have a single problem that's due to a single protein."

Based on these findings, Rich speculates that the impact of sepsis on other excitable tissue, such as the heart and brain, might also be linked to a failure of sodium channels. Some clinical evidence supports this idea with heart tissue, although it's far from proven, and the brain tissue connection is purely speculative. If the theory holds true, however, its implications could be profound.

"In that case we would have many of the different complications of sepsis—failure of muscle, nerve, heart, and brain—that might all be tied together by a single problem," Rich said. "That's not proven yet, but it's exciting."

"There's real encouragement from these findings," Cope added, "to think that there is a broadly based problem that comes back down to this single molecule he was first studying."



Rich (standing) and Cope have advanced their research by working closely with one another and other colleagues in the Comprehensive Neuroscience Center, which actively seeks to foster collaboration.

### The benefits of getting back to basics

Rich's research is gaining notice for several reasons. First, sepsis and its complications are becoming more widely recognized as a serious problem. A *New York Times* cover story in January explored the plight of ICU patients and efforts to prevent or reduce long-term complications. Second, his recent investigations of peripheral (sensory) nerves represent something of a breakthrough.

"This is first time we now show another tissue, other than muscle, has the same problem," Rich said. "That's why it's such a big deal."

In one sign of the rising profile of their work, the results of Rich and Cope's

nerve study were featured in the May issue of the *Journal of Clinical Investigation*.

Rich has also been invited to present their findings at a conference in Germany and to join a clinical group in California establishing guidelines for studying patients with CIP and CIM.

Rich is cautious when discussing the potential impact of his research, but it is easy to see why the possibilities are generating so much interest. While most common among ICU patients, sepsis can also affect anyone whose immune system is compromised, including chemotherapy, organ transplant, or HIV/AIDS patients. More broadly, a better understanding of one of the body's primary electrical regulators could affect treatment of cardiac arrhythmia, seizures, chronic

pain, and other disorders related to excitable tissue.

Cope is excited by these possible outcomes, and he understands and supports the drive "to accelerate the process of turning basic science discoveries into clinical treatments." Even so, he is concerned about the temptation to overemphasize translational research.

"The value of basic science has got to be recognized," he said, "even if there's not an immediate connection with one disease or another."

"If there hadn't been years of sodium channel research that was not directly, obviously clinically relevant," Rich agreed, "we would be at a big disadvantage in approaching this problem." **VS**