When the Connections No Longer Work:

After Nerves Regenerate

Our wired communication system sends and receives electrical impulses from the central nervous system (CNS) through a highly specialized peripheral nervous system (PNS). Damage or disease of the PNS, peripheral neuropathy, includes more than 100 classifications, each unique in its presenting symptoms, based upon the type of nerves damaged—motor, sensory, or autonomic, or combinations of these. The most common cause of peripheral neuropathy is trauma, as in carpal tunnel syndrome. But, chemotherapy and a wide range of systemic diseases, including diabetes mellitus, vascular disease, and kidney disorders, also damage nerve cells. Unlike the CNS, the damaged PNS can regenerate both neurons and nerve circuitry.

“We know that damaged peripheral nerves regenerate, but regeneration is not synonymous with recovery,” says Timothy Cope, Ph.D., professor and chair of the Department of Neuroscience, Cell Biology, and Physiology and director of the Comprehensive Neuroscience Center. “Neither sensation nor movement return to pre-injury levels after nerve regeneration. Although regeneration of the PNS is necessary to restore voluntary movement, injury initiates changes in the spinal cord that do not reverse with regeneration. Problems remain in timing and strength of muscle contraction, problems that prevent normal movement.”

Why this is so is the focus of the school’s most recent grant from the National Institute of Neurological Disorders and Stroke (NINDS). A team of researchers received a prestigious Program Project Grant—the first Program Project Grant Wright State has received. These grants are extremely competitive, and the five-year, $4.8 million grant award underscores the high caliber of neuroscience research being conducted at Wright State.

“Getting this grant places us in an elite category in neuroscience research,” says Howard M. Part, M.D., dean for the Boonshoft School of Medicine. “Our team’s impressive accomplishment reflects the hard work and dedication of our outstanding scientists, as well as the continued support of our community, espe-
cially from The Kettering Fund and from the Oscar Boonshoft family.”

Program Project Grants are designed to “encourage multidisciplinary research approaches to a diverse array of nervous system disorders,” according to NINDS, and the guidelines require at least three interrelated projects that contribute to the program objective. Five collaborative projects, each led by a Wright State National Institutes of Health-funded investigator, will work through a shared instrumentation core to better understand the recovery—or lack of it—from neurotrauma.

The team of Wright State investigators—Drs. Francisco Alvarez, Timothy Cope, Kathrin Engisch, Robert Fyffe, and Mark Rich—are accomplished researchers in fields covering developmental biology, synaptic function, and sensorimotor behavior of the spinal cord and PNS. “The wide array of approaches and expertise that we have as a team is likely to accelerate our understanding because we can attack the problem of limits on regeneration with greater insight and technical expertise than any one of us could achieve alone,” says Dr. Cope.

Cutting-edge methodologies will be shared across the five projects. Studies will examine neurons and synapses using electrophysiological tools to evaluate their function. Microscopy and associated imaging techniques will assess structure and changes in protein expression. “Collaboration with the other team members is critical to placing our findings in the context of functional and structural changes that are occurring in the CNS and PNS after nerves regenerate,” adds Dr. Fyffe.

“Essential details about the mechanisms underlying changes following PNS injury are largely unknown and must be obtained in order to develop clinical applications to many common human conditions, including spinal cord injury,” adds Dr. Cope. “How can we get the nervous system to regain normal function? Our studies should help answer this question.” —Judith Engle

Project One: Circuit Plasticity
Timothy Cope, Ph.D.
Professor and Chair of Neuroscience, Cell Biology, and Physiology
Director, Comprehensive Neuroscience Center

“After nerve damage and regeneration, we lose the stretch reflex in affected muscles, adversely affecting our ability to control movement. We suggest that damage to the PNS creates problems in spinal/neural circuits which do not reverse after nerve regeneration.”

Project Two: Excitatory/Inhibitory Balance
Francisco J. Alvarez, Ph.D.
Associate Professor of Neuroscience, Cell Biology, and Physiology
Director of Imaging Core Facilities

“Motoneurons control the activity in our muscles, but their function is in turn modulated by a fine balance between excitatory and inhibitory influences. We suspect that deficits in reacquiring this balance following nerve injury and regeneration are partly responsible for the incomplete restoration of motor function.”

Project Three: Synaptic Plasticity
Mark Rich, M.D., Ph.D.
Associate Professor of Neuroscience, Cell Biology, and Physiology

“Injury changes how the synapses transmit at the neuromuscular junction and we theorize that reduced cellular activity at the time of injury adversely impacts signaling strength.”

Project Four: Molecular Regulation of Release
Kathrin Engisch, Ph.D.
Associate Professor of Neuroscience, Cell Biology, and Physiology

“We are examining the underlying molecular mechanism caused by the change of cellular activity. The process at the molecular level indicates that the protein Rab3A plays a major regulatory role.”

Project Five: Postsynaptic Excitability
Robert E. W. Fyffe, Ph.D.
Associate Dean for Research Affairs

“Our laboratory will use new imaging techniques to help determine how the excitability and electrical properties of motoneurons are regulated after nerve injury.”