STEM CELLS as a PATHWAY to NEURO REGENERATION

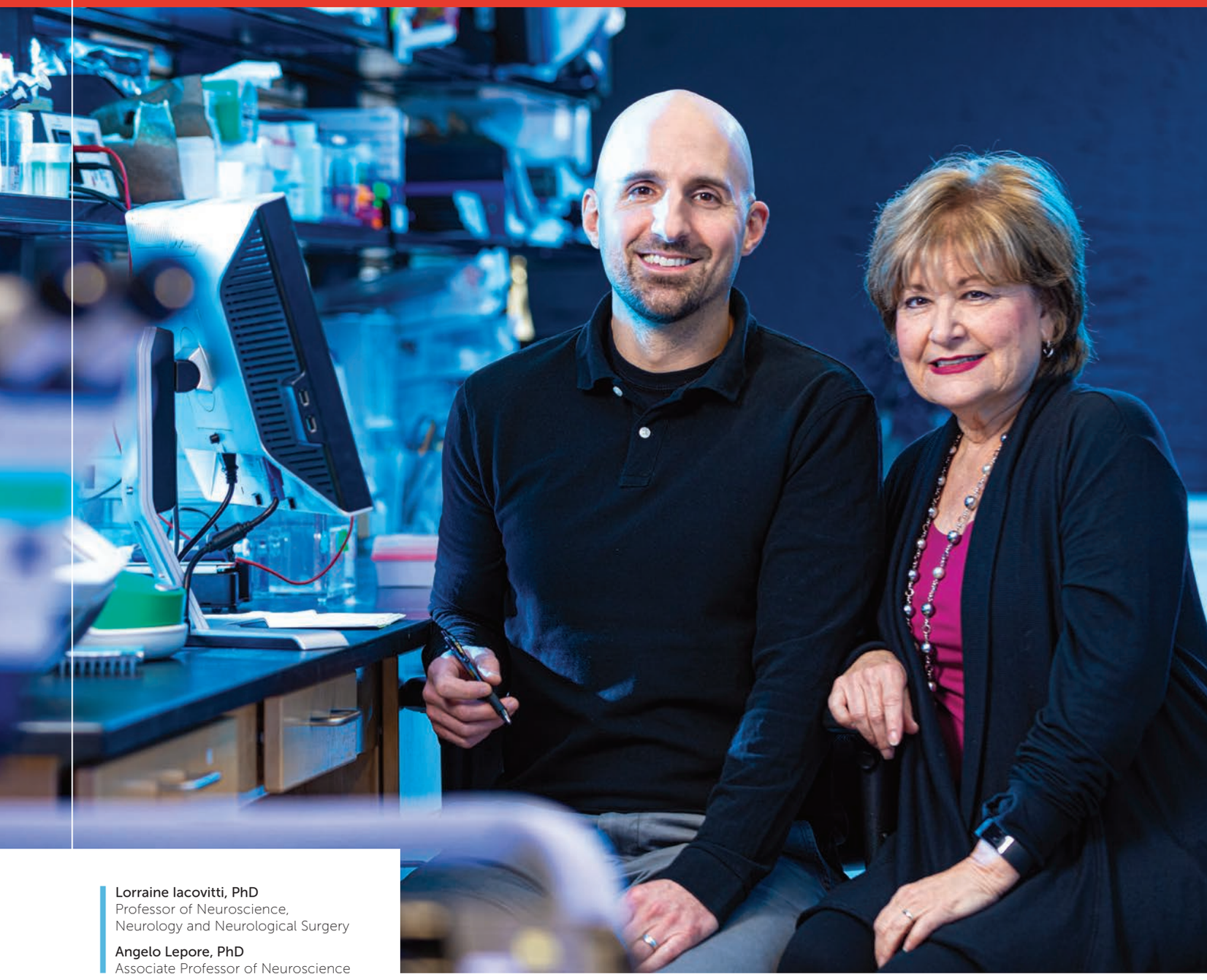
BIOSCIENTISTS' ABILITY TO CREATE INDUCED PLURIPOTENT stem cells—which can be differentiated into many kinds of cells has opened new pathways for research and treatment of many medical conditions. One of the most notable areas of advancement by stem cell researchers at Jefferson is in treatment for conditions affecting the central nervous system.

For more than 20 years, **Lorraine Iacovitti, PhD**, professor of neuroscience, neurology and neurological surgery, has been making major research contributions in stem cell biology and the use of induced pluripotent stem cells (iPSCs) to pursue therapies for stroke and neurodegenerative disease. Her breakthrough discovery for prompting stem cells to differentiate into dopamine neurons has overcome a major obstacle to using iPSCs therapeutically. More recently, in studying an animal model of stroke, she discovered the existence of stem cell niches in the brain, which means that new cells can be created throughout the adult brain. That work also showed a dramatic surge in stem cell proliferation and differentiation due to molecular and cellular changes in the blood-brain-barrier after stroke. Her lab is now pursuing opportunities to leverage these changes to deliver stem cell therapeutics.

Recently, Dr. Iacovitti has also identified distinct roles in Parkinson's disease played by nervous system cells called astrocytes. Parkinson's is characterized by degeneration of dopamine neurons in the substantia nigra region of the brain, while those of the neighboring ventral tegmental area (VTA) are relatively spared. In comparing the two regions, Dr. Iacovitti found that astrocytes in the VTA produce growth factor GDF-15, which can protect dopamine neurons from the disease. The findings suggest that microenvironments in the brain may play a significant role in neurons' susceptibility to neurodegenerative disease—and they raise the tantalizing possibility of a new Parkinson's therapy using patient-specific iPSC-derived VTA astrocytes.

Iacovitti's colleague, **Angelo Lepore, PhD**, associate professor of neuroscience, is also using iPSC-derived astrocytes, but for a different purpose: to study cellular mechanisms underlying traumatic spinal cord injury (SCI). He is particularly interested in understanding SCI-related respiratory dysfunction and chronic neuropathic pain; and he hopes to develop stem cell-based therapies that both address the primary injury and protect neurons during the period of secondary damage that patients experience. Toward that end, Dr. Lepore is working on several research paths involving astrocytes: identifying molecules that inhibit or promote regeneration of the axons that extend from nerve cells; uncover astrocytes' role in maintaining normal nervous system function; and to pinpoint how alterations in synapse signaling contribute to SCI disease processes.

It is known that, after SCI, astrocytes often lose the capacity to properly regulate glutamate in neuronal synapses, which contributes to further neurological damage. Dr. Lepore's lab has demonstrated that



Lorraine Iacovitti, PhD
Professor of Neuroscience,
Neurology and Neurological Surgery

Angelo Lepore, PhD
Associate Professor of Neuroscience

transplanting iPSC-derived astrocyte progenitor cells can help protect respiratory function in animal models of SCI. Now they are doing the fundamental work necessary to demonstrate the potential of using patient-specific iPSC-derived astrocyte progenitor cells therapeutically.

Astrocytes also naturally promote growth of axons, which are long fibers that extend from neurons to convey electrical signals to other neurons and muscles—a significant fact, given that axons do not regenerate after central nervous system injury. Dr. Lepore and his colleagues are engaged in a long-term NIH-funded study of the role astrocytes might play in promoting of axon regeneration and sprouting to recovery of respiratory function following SCI. Thus far, using a rat model of SCI, the researchers have demonstrated that astrocyte stem cells transplanted at spinal injury sites promote robust axon growth and significant restoration of diaphragm function—by prompting regenerating axons to reconnect the neural circuit between brain, spine and diaphragm that regulates breathing. They have also found that astrocytes significantly dampen the pro-inflammatory response that promotes secondary damage. In their continuing work, they are selectively silencing defined neuronal populations involved in respiratory control, in order to understand which kinds of axon growth actually promote recovery of diaphragm function—information that will be essential to develop new therapies. ■