Babies born prematurely—as much as three months too soon—have a better chance of surviving than they did just a decade ago. But they face serious neurological problems that HHMI investigator David Rowitch sees too often in his clinical rounds at the University of California, San Francisco (UCSF). Using tissue from a new neonatal brain bank, he is gathering clues to devise treatments for brain-injured babies and perhaps also for adults with multiple sclerosis.

“We routinely take care of babies in the United States that are born at about six months of gestation, weighing about a pound,” says Rowitch, a neonatologist. “About 10–20 percent will develop cerebral palsy—an inability to move and talk normally—and as many as 50 percent will develop learning, cognitive, or behavioral problems.” At least some of those problems, Rowitch says, stem from damage to the protective myelin coating that insulates nerve cell axons in the “white matter” of the baby’s brain.

“Therapies to limit the damage or enhance repair don’t exist,” Rowitch says. Answering even basic questions about the developing human brain has been tough because of the lack of autopsied tissue from young children available for study.

Last summer, however, Rowitch and colleagues published two studies, conducted using tissue from the neonatal and pediatric brain bank that he helped establish at UCSF in 2009 with HHMI support, that offer clues to nerve cell repair as well as human brain development.

In earlier work, Rowitch and postdoc Stephen Fancy had noticed that white matter injuries in some premature babies look similar to the damaged patches of myelin in multiple sclerosis. Closer study of brain bank specimens revealed why: In both cases, myelin-making cells known as oligodendrocytes and the progenitor cells that give rise to them (known as OPCs) rush in to repair the initial injury. Mysteriously, they don’t complete their task.

“The obvious question is, why aren’t these cells—which are all showing up at the right time in the right place—finishing the job they are almost hardwired to do?” Rowitch says. “We figured there had to be some inhibitor present, right there in the area of the lesion.”

Reporting in Nature Neuroscience in June 2011, the team suggests one plausible reason for the blocked repair: overactivation of the Wnt pathway, as measured by expression of the gene AXIN2. Wnt is well known as an important, complex signaling pathway involved in the development of most organ systems throughout the body. When the scientists injected an experimental drug that slows degradation of the Axin2 protein directly into patches of damaged myelin in mice, it inhibited Wnt, and the OPCs lining the wound rapidly differentiated into healthy, myelin-making oligodendrocytes. The myelin injuries healed 30 percent faster than similar injuries in untreated mice.

Many questions remain. “We still don’t know enough about this particular drug’s toxicity—especially in young children,” Rowitch says. “And, I think it would be simplistic to think this pathway is the only thing going on in the inhibition of myelin repair.” Still, he says, the results suggest it might be possible to speed mending of tattered myelin with a drug soon after injury, before the underlying axon is permanently harmed.

Where and When Development Occurs

“Every baby’s brain contains a variety of immature precursor cells that could, in theory, be enlisted to help mend injuries,” says Rowitch. But first scientists need to
David Rowitch’s team improved remyelination repair in mouse models of demyelination using a small molecule Wnt inhibitor. An injection of lysolecithin removed oligodendrocytes and myelin, while sparing the axons. In the mice that received the Wnt inhibitor along with the injection, remyelination was more rapid than in mice that received no inhibitor with the injection. Note the thicker black myelin around the axons on the electron microscopy image on the right.

know more about how and what these cells do. To that end, he has been collaborating with UCSF neural stem cell biologist Arturo Alvarez-Buylla and neurosurgeon and postdoctoral fellow Nader Sanai, now at Barrow Neurological Institute in Phoenix, to map the trajectory of human stem cell activity emanating from a rich pocket of neurogenesis in the brain known as the subventricular zone (SVZ).

The SVZ has been well characterized in mice, in nonhuman primates, and, to a lesser extent, in human fetuses and older adults. But no one knew if or how activity in that region changed over the course of brain development in newborns and young children.

Now, by carefully comparing the cellular architecture of brain tissue from 54 infants, young children, and teens, Rowitch, Sanai, and Alvarez-Buylla have begun filling that information gap—and turning up surprises. For one thing, at least some of the stem cells arising from the SVZ travel to a different region in the human brain than in the mouse brain.

“In humans we’re seeing streams of cells from the SVZ moving not just into the olfactory bulb but also toward the frontal cortex,” says Sanai, who was an HHMI fellow during his medical school training at UCSF. “That newly discovered pathway raises questions about the mechanics of how the brain developed and evolved.”

Another dramatic twist: after a period of robust neurogenesis in the first year of life, the human SVZ apparently slows down, sharply tapering production of brain cells by the time a child is 18 months old, and then slowing to almost zero by age two. The finding should help settle conflicting earlier reports, say Sanai and Rowitch, that suggested the SVZ might churn out new cells well into adulthood. The results were reported October 20, 2011, in Nature.

The first year of life is a window of particular vulnerability and opportunity for the brain, says Rowitch. It’s a period of tremendous growth, organization, and flexibility, as fresh neural connections are created, broken, and remade. A better understanding of how things can go wrong in that critical period, he says, could ultimately improve the chances that things will go right. —DEBORAH FRANKLIN