The most vulnerable brains

An increase in premature births means that more babies are at risk of neurological damage. **Erika Check Hayden** talks with researchers who are developing ways to help these children.

Julia lies with her eyes closed in an incubator, twitching her tiny limbs in a quiet, sedated sleep. Like the other babies in this intensive-care unit, she is surrounded by a phalanx of machinery. But unlike her nursery mates, this baby isn't wrapped in a warm blanket. Her doctors at the Children's Hospital of the University of California, San Francisco (UCSF) have left most of her days-old body bare and placed her on a blue mat that is cooling her to a hypothermic 33.5°C. Gauze wrapping holds a network of electrodes against her skull. The electrodes are sending a stream of signals to a nearby monitor, which is being watched carefully by David Rowitch.

Like a growing number of babies in the United States, Julia (not her real name) is at risk of permanent brain damage. The trend is driven by increasing rates of preterm births coupled with medical advances that allow the survival of very premature babies — and also full-term babies such as Julia, whose births were not straightforward. Although these advances have focused on babies' hearts and lungs, they have largely ignored the newborn brain.

Rowitch, a neonatologist, is one of a handful of doctors around the world who hope to reverse this trend by using advances in basic

neuroscience to develop treatments for injured newborn brains. He and Donna Ferriero, chief of paediatric neurology at the hospital, founded the university's Newborn Brain Research Institute in 2006. Two years later they created one of the nation's first neurointensive-care nurseries, where Julia is now sleeping. They and other scientists are pushing to get treatments into clinics as soon as possible to make up for what they call years of inadequate funding for research into brain damage in babies.

"It is frustrating to see the lack of progress that has been made over the course of the past 20 years," Rowitch says. "There has really been very little in the way of any meaningful therapy."

A potential first step is the experimental cooling treatment that Julia is undergoing. Doctors throughout the San Francisco Bay area, and some even further away, identify possible candidates for this intervention as they check newborns for seizures or other signs of lack of oxygen around the time of birth. Within hours, the child is transferred to UCSF's neurological nursery and nestled on a refrigerated mat. For the next three days, nurses and

doctors monitor the patient's brain activity on an electroencephalogram, watching for signs of seizures. A video camera records the baby's fitful sleep. Then, the newborn is slowly warmed up and wheeled to a magnetic resonance imaging machine in a specially designed incubator, where a technician will conduct brain scans. After being released, the child must return periodically to UCSF for many years for check-ups.

Cool care

If all goes well, the hypothermic treatment will avert further brain damage beyond the initial injury. A study of 325 babies published last October¹ found that the cooling intervention cuts the risk of brain damage. Of the children that received the hypothermic treatment, 44% survived without a neurological abnormality compared with 28% in the control group who received regular intensive care. The treatment may work by lowering the demand for oxygen among stressed neurons, allowing them to recover from damage.

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UCSF began offering the hypothermic treatment in July 2008 and has now treated more than 80 newborn babies. It is one of a growing number of hospitals in North America and around the world that offer such hypothermic treatment to newborns at risk of brain damage. A 2007 study, for instance, found that 28% of the neonatal units in the United Kingdom offer this kind of treatment², and it is spreading across other European countries as well as less wealthy nations such as South Africa. But cooling a baby's entire body to spare its brain is a blunt instrument. Rowitch envisions a future of more precise treatments targeted at specific molecules that orchestrate neural development.

Recent advances provide some optimism on this front: in his own research, Rowitch has discovered hints that the injured brains of babies might be more capable of recovering than doctors previously thought. With collaborators at UCSF, Rowitch is building a translational-research programme aimed at understanding more about the healthy and injured developing human brain, and converting those findings into therapies. "That would really be the vindication of this programme," he says.

Formative years

Rowitch took an interest in brain injuries in newborns during his medical training and later, when he set up his first lab at the Dana-Farber Cancer Institute in Boston, Massachusetts, in the 1990s. He began a research programme that would soon lead to high-profile discoveries in the molecular basis of brain cancer. His collaborator, Charles Stiles of Dana-Farber, says that Rowitch was often happiest spending his time with sick babies at the neonatal intensive-care unit at Children's Hospital Boston.

"Most of the physician-scientists I know would dread that one month of the year when they had to fulfil their clinical obligation, but David really looked forward to it," says Stiles. "He loved putting on the scrubs and spending all night in the premature critical-care ward. He loves the machines and he loves little babies."

There, Rowitch witnessed the sweeping changes in medical care that are allowing increasingly premature neonates to survive, even those born as early as 24 weeks. At the same time, assisted-reproduction techniques, which often lead to multiple births, have helped to drive up the rates of prematurity by 36% in the United States since the early 1980s. As the number of extremely premature births climbs, more children face the risk of brain injury because their developing organs can not deliver enough oxygen to the brain; 20% of babies born before six and a half months of pregnancy are at risk of stroke and neurological complications such as cerebral palsy, a

movement disorder caused by brain damage. About half will have learning deficits and other cognitive problems. The financial burden is enormous: it costs nearly US\$1 million to treat and care for each patient with cerebral palsy in the United States over that person's lifetime.

But the understanding of the neural complications of prematurity has not kept pace with this surge in very young babies. Scientists know little about early brain development, in part because parents who lose children are reluctant to allow research on them. That makes it difficult for scientists to conduct structural studies of human brain development using the kinds of detailed molecular analyses that are now common in research on non-human brains.

Rowitch is trying to move the field forwards by setting up a paediatric neuropathology lab to

The brains of premature babies are vulnerable to damage that can cause lifelong complications.

collect and study donated brains from deceased babies and children. He is also collaborating with Arturo Alvarez-Buylla, a neuroscientist at UCSF, to perform the first detailed molecular analyses of autopsied brains of children who died from various causes between birth and the age of 18.

By staining molecules to identify cells at different stages of development, Rowitch and Alvarez-Buylla have succeeded in tracing some neural growth patterns. Preliminary data from 45 brains, for example, suggest that one area of neural growth — the subventricular zone — generates fewer new brain cells by 18 months of age or may completely stop by that point.

Rowitch says this type of data is crucial for understanding exactly what goes wrong when the brains of newborns are damaged. For instance, it is important to know whether stroke wipes out sources of new cells in the still-developing brain, or whether it prevents repairs to damaged cells, or causes damage through both mechanisms.

Rowitch is also approaching this question from a different direction, by studying the brains of newborns who have died after suffering brain injuries. This work builds on his earlier discovery of genes that direct developing brain cells to grow into oligodendrocytes, a type of glial cell³. Such cells protect neurons by wrapping their long signalling projections, called axons, in a protective myelin sheath.

Rowitch's gene discovery led him to study diseases involving malfunctioning oligodendrocytes, such as periventricular leukomalacia (PVL), a form of brain injury in fetuses and newborns that can result from stroke, and which can progress into cerebral palsy. The conventional wisdom is that PVL occurs when a stroke kills off oligodendrocytes in a certain region of the brain, leading to the death of neurons.

When Rowitch and his collaborators studied the brains of 18 children who had died after being diagnosed with PVL, however, they found plenty of oligodendrocytes in the injured regions. It looked as if new oligodendrocyte precursors were migrating to the site of the injury to replace cells that had been destroyed by the stroke⁴. But something was stopping the precursors from developing into oligodendrocytes that produce myelin.

The finding has important implications, Rowitch says, because repairing damage is a much more practical treatment strategy than trying to prevent damage. It may be difficult to predict which babies are at risk of injury, and even harder to access the baby *in utero*. "This profoundly shifts the kind of questions you can ask about PVL," Rowitch says. His lab is now trying to better understand the signals that block repair, so that they may be reversed — a strategy that might also work for patients with multiple sclerosis, which is also caused by a loss of myelination.

Forced separation

Such basic-science studies will take years, but in the meantime, the UCSF team is working to improve current treatments. For instance, a team of doctors and nurses monitors Julia around the clock. No one, including her parents, can move her from her cooling bed, which means that she won't be picked up or cuddled for the first few days of her life. She seems quiet and comfortable, with the help of a low dose of sedatives, and doesn't cry. Still, Rowitch says his team knows it is difficult for parents to be separated from their babies so soon after birth. So the researchers are trying to determine whether some babies might benefit from shorter doses of cooling.

And the clinic has begun testing new candidate therapies to prevent brain damage. Ferriero has performed extensive tests of the

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David Rowitch monitors a baby undergoing cooling treatment at the University of California, San Francisco's Children's Hospital.

hormone erythropoietin in rats, and has found that this red-blood-cell boosting compound prevents long-term cognitive damage in rat models of neonatal stroke⁵. Erythropoietin is already used to treat premature babies with immature circulatory systems, and UCSF will begin a clinical trial to test it on newborns at risk of brain damage this month.

Other candidates for clinical trials include magnesium, which is already used in adult stroke patients. The intervention seems to decrease the rate of cerebral palsy in children surviving very premature births⁶ and lowers the rate of neurological problems, at least in the short term, of full-term newborns who suffer from oxygen deprivation⁷.

Even now, Ferriero says, doctors can make a big difference by adjusting the way they treat vulnerable babies. For example, studies have revealed that over the past decade, the pattern of brain injury seen most often in premature babies is shifting away from PVL to a slightly less severe form of damage, apparently because of changes in hospital procedures⁸. To Ferriero, this underscores

the importance of monitoring the brains of vulnerable babies, which is not currently done in most intensive-care nurseries.

"They monitor pulse, they monitor temperature, they monitor heart rate. But the brain, which runs it all, is being totally ignored, until something really bad happens, and then it's too late," Ferriero says. She points out that many infant seizures go undetected, because there are no outward signs of a problem. But these seizures can be detected by an electroencephalogram. If doctors can catch the seizures early enough, they can intervene to stave off further damage.

So for now, the most important result of UCSF's programme may be convincing other doctors to start paying attention to the neonatal brain. Ferriero and Rowitch have invited doctors from around the country to visit the Neurointensive Care Nursery, and some, such as the Phoenix Children's Hospital in Arizona, have started setting up similar nurseries. "That's the wave of the future," says Cristina Carballo, medical director of Phoenix's Neuro-Neonatal Intensive Care Unit. "It means we can diagnose and treat neurological

issues faster to improve neurodevelopmental outcomes."

But the movement to pay more attention to brain injuries in babies, and to use neuroscience to treat them, is still young; even its proponents counsel caution. "We're really still taking baby steps," says Huda Zoghbi, the director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital in Houston.

For now, even those small steps are helping patients such as Julia. As she sleeps through her hypothermic treatment, her anxious father can only watch from the bedside. It's hardly the welcome to the world he had hoped for his daughter, but it will give her a good shot at thriving when he finally takes her home. ■

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— Donna Ferriero

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