Innovations

Rebuilding the spine

Acorda Therapeutics, Inc.

Chemistry & Biology 2000, **7**:24–25

1074-5521/00/$ – see front matter

Hype does not come naturally to Andrew Blight. As Vice President for Research and Development at Acorda Therapeutics, Inc. (Hawthorne, New York), Blight trusts that the media will always portray his company's goal — a cure for spinal cord injury (SCI) — as being closer than it really is. But while Blight is struggling with the realities of complex drug trials, the basic science of central nervous system (CNS) regeneration looks downright exciting. A new generation of neuroscientists, trained in the young field of nerve growth and guidance, is hungry to apply their knowledge to CNS regeneration, even as the pioneers in the field are getting molecular.

"The regeneration field is exploding right now," says Ben Barres of Stanford University, California. Still, Acorda CEO Ron Cohen realizes the immensity of the challenge. "Someone has taken a hatchet to the major power grid cable coming into New York City," says Cohen. "An engineering tour de force is required."

The first signs of hope

Cohen's realism comes from his medical training — he even avoided a neurology residency because, he says, "the definition of neurology practice was diagnose and adios." After six years in another biotech company, however, he "felt that SCI chose me," he says. "I became convinced that this was the right time to work on nerve repair — that it was not a quixotic venture."

The first glimmer of hope for CNS regeneration came in 1981, when Samuel David and Albert Aguayo of McGill University in Montreal showed that lesioned CNS neurons could regrow if they were provided with a bridge made of tissue from the peripheral nervous system (PNS). "I had been taught that when you damage a nerve in the CNS it cannot recover," says Cohen. "That had not changed as dogma since the days when medical information came on papyrus." The 1981 experiments "told us for the first time that neurons in the CNS have the capacity to grow," says David.

The growth of a few nerve cell axons was exciting, but not enough to justify a company. "There are 2 million axons in an average spinal cord," says Cohen. "We had no idea how to grow back and reconnect 1.5 or 2 million axons, so no one even bothered. It was so daunting."

Will Superman walk again? First the exciting science must confront formidable practical challenges.

Blight's results told Cohen he didn't have to reconnect all the axons. When Blight took a careful look at damaged spinal cords, he found that animals that retained less than 10% of their axons intact could still walk. Meanwhile, Wise Young at New York University Medical Center had coordinated a study showing that high doses of methylprednisolone, a corticosteroid thought to act as an anti-oxidant, had beneficial effects if given within 8 hours of injury. The effect was modest, but it proved that SCI was a tractable problem. Young helped Cohen form Acorda in 1995.

A small molecule fix for SCI

Blight's inspection of damaged spinal cords had also uncovered a great number of nerves that were uncut, but lacking their insulating sheath of myelin. This provided the rationale for tests of 4-aminopyridine (4-AP or fampridine), an existing experimental drug that was known to block potassium channels exposed by the missing myelin sheath. Although 4-AP will not heal SCI, and cannot substitute for all the functions of myelin, a continuous dose may improve symptoms.

A slow-release formulation of 4-AP has been supplied by Elan Corporation, plc (Dublin, Ireland) and tested by Acorda in two phase II trials, with a third to follow in 2000. Cohen says multiple trials have been necessary in part because of the difficulty of defining accurate measures of effectiveness. "The beneficial effects depend on what axon groups have been demyelinated, but the FDA forces you to select a primary outcome," says Cohen. Acorda has come up with its own scoring system to evaluate improvements in areas such as bowel, urinary and sexual function, and hopes to enter phase III trials in 2000.

The difficulty with trials confirms that 4-AP is not a wonder cure, but "no one's ever felt that," says Blight. "It's a first step to do something in the chronic stage." Cohen says the company is "disproportionately reliant on the success of our lead product," but he is confident that 4-AP will be the company's first major source of cash.

Grand ambition

The benefits promised by 4-AP may improve life for those with SCI, but Christopher Reeve's campaign to cure SCI is promising more than improved urinary function. "Motor function is the keys under the lamppost — this is where people want to find improvement," says Blight. "If you find other improvements it's not such an obvious sell."

The research community has obliged with a string of 'cures' in animal studies, some of which have yielded little in the way of practical promise for humans. "There is a whole series of what look like flashes in the pan," says Blight. "This is a phenomenon that is more predominant in spinal cord repair than in any other field. That doesn't help the reputation of the field."

"You can't blame people for the waves of excitement, as these are important advances," says Marc Tessier-Lavigne (University of California, San Francisco). "On the other hand, what really amounted to proof-of-principle experiments should have been couched in those terms."

The philosophy at Acorda is to lower both expectations and the threshold for declaring success. "The aim is to chip away at the problem," says Blight. "Most responsible people in the field think the idea of a magic bullet is romantic. It's a matter of moving forward by inches rather than taking one great leap."

"From the get-go we understood it would be a multipart problem," says Cohen. "We can give people usable single functions with monotherapy. But if you are talking about getting people out of wheelchairs, that will take multiple approaches."

Overcoming the barriers

Regeneration requires overcoming the CNS's resistance to growth. "There are probably many barriers," says Blight. "The primary barrier to regeneration is probably understanding what the primary barrier is."

An obvious physical barrier is scar tissue, which Proneuron Biotechnologies, Inc. (Ness-Ziona, Israel) hopes to combat with autotransplanted macrophages, in human trials in 2000. Acorda, meanwhile, is looking at growth signals: both the lack of positive signals and the presence of inhibitory signals.

Their positive signal is L1, a cell adhesion molecule found in the developing but not mature CNS. Cohen says L1 could be used for acute or chronic injuries, with the mechanics of L1 delivery to be determined. One option is to attach L1 to the artificial fibers designed by Acorda collaborator Patrick Tresco (University of Utah, Salt Lake City), in the hope that the fibers will act like pioneering axons that instruct other axons to follow them. Delivery may be restricted to a small area around the site of injury.

Acorda's anti-inhibitory program is focused on the M1 IgM antibodies discovered by Moses Rodriguez (Mayo Clinic, Rochester, Minnesota). Rodriguez stumbled on M1 after immunizing mice with myelin to increase the symptoms of experimental multiple sclerosis (MS), an autoimmune demyelinating disease. But instead his immunization yielded protective M1 auto-antibodies. M1 antibodies bind to oligodendrocytes — the myelinating cells — and probably act both by turning on oligodendrocytes, and by recruiting scavenger immune cells to dispose of damaged oligodendrocytes. If animal studies are successful, Acorda will test M1 initially in MS.

The M1 antibodies may be related to the IN-1 IgM antibody, which Martin Schwab (University of Zurich, Switzerland) used in 1990 to achieve dramatic recoveries from SCI in rats. IN-1 recognizes at least one of several myelin-associated nerve growth inhibitors (papers announcing the cloning of the major IN-1 target are in press), but has not been further developed by its licensee, Regeneron Pharmaceuticals (Tarrytown, New York). Regeneron has switched its emphasis to cancer and the immune system, but has not released the IN-1 technology back to Schwab. "It drives me crazy, and it drives patients even more crazy to think that time passes by," says Schwab.

Schwab has not, however, managed to replace the pentameric IgM antibody with a simpler IgG, and recent evidence from McGill's David suggests that IN-1 may not be the whole story. In the December 1999 issue of *Neuron,* David reports that rats immunized with a myelin preparation show a greater regenerative response than is seen with IN-1 alone. Myelin injections into humans are impractical because of fears of MS, but David's experiment suggests that effective therapy will follow once the important inhibitors are molecularly defined.

The preoccupation thus far has been on neuron growth not wiring. Past experiments have shown "remarkable specificity," says Tessier-Lavigne. "That suggests there is information that can guide the axons." Cohen agrees that "there's a certain amount of black box thinking that as long as you get the axons across they'll figure out a way to connect properly. And even if they don't the brain will be plastic enough to translate it."

Rebuilding the spine

"Every year there is a theme at the Society for Neuroscience meeting," says Cohen. "This year was the year of the stem cell."

Stem cells are perhaps our best chance at reconstructing a damaged spinal cord. Human safety trials have been done with fetal cell transplants, but few of those cells turn into neurons. Acorda's proposed solution involves their patented stem cells that produce only neurons.

To promote growth and re-myelination, others have transplanted Schwann cells (the PNS equivalent of oligodendrocytes). Unfortunately, Schwann cells and oligodendrocytes erect an inhibitory barrier when they encounter each other. Olfactory ensheathing cells may be the answer, as these cells guide regenerating olfactory neurons from the PNS into the brain. Early transplants look promising, although the migration of the transplanted cells encourages some researchers and alarms others.

Cohen describes himself as the company's "biggest skeptic" about cell therapy. "It's very difficult to produce a reproducible therapy out of cells," he says. "I'm wary of it." But in the end it may be the only true answer. "If we were talking about improving on balloon angioplasty then don't bother," he says. "But here we have a true tissue engineering problem. It stands to reason that if we hope to solve this we have to bite the bullet and deal with cells."

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