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Years-Old Mayo Research Bearing Fruit?

MS Groundwork Laid, Acorda Taking Program 'On The Road'

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National Editor

The science of tissue regeneration took a jump forward almost exactly four years ago, when Mayo Clinic scientists Arthur Warrington and Moses Rodriguez published a paper in the *Proceedings of the National Academy of Sciences* about getting myelin to grow by using human monoclonal antibodies reactive to the cells that produce myelin around the axons, called oligodendrocytes.

"All their work before that had been with mouse antibodies," said Andrew Blight, chief scientific officer of Acorda Therapeutics Inc., whereas Mayo pulled theirs directly from human patients.

It looked like a potential magic bullet for multiple sclerosis. It still does, at least to some – albeit a bullet that has yet to be loaded into a gun, much less fired. Hawthorne, N.Y.-based Acorda has built a re-myelinating antibody program based on an exclusive license to patents derived from 15 years of Mayo research.

"We've only looked at two," Blight said. "There are others we've spent very little time with." Of the two, Acorda has settled on an antibody nicknamed, for the moment, Lym 22, as holding the most promise.

Recent news from Acorda came in April, when the firm said its Fampridine-SR missed the endpoints of two pivotal Phase III trials in spinal cord injury, but showed positive trends in a Phase II MS trial. (See *BioWorld Today*, April 15, 2004.)

The company said it would pursue the MS indication with another Phase II or Phase III trial, depending on the FDA's preference. Meanwhile, though, there's the monoclonal antibody program licensed from Mayo.

Whereas Fampridine-SR is believed to restore function by pharmacologically compensating for myelin loss in some axons, the Mayo monoclonals might actually replace the lost myelin – helping MS patients do even better.

Rodriguez, the main author of that long-ago *PNAS* paper (a seminal publication that has been followed by

plenty more research in journals) was the same investigator who, in the 1980s, came up with the idea of sending immune-system monoclonal antibodies after autoimmune cells that had gone haywire and wrecked the myelin.

Mayo ran with the ball. The clinic took samples from 102 blood donors with abnormal antibodies cranked out in large numbers by the misdirected B cells. Patients had various blood dyscrasias, including lymphomas, myelomas and something called "macroglobulinemia of uncertain significance," but it didn't really matter which they had, since all led to the same disorder: an abundance of IgM, the heaviest hitter of the body's 10 immunoglobulins. Those abnormal antibodies are the ones Acorda has managed to make recombinantly.

Whereas previous MS efforts had used as their model experimental allergic encephalitis, Mayo's scientists infected mice with a toxic virus – Theiler's murine encephalomyelitis – that demyelinated the animals' axons, leading to the paralysis common in MS, thereby providing a more precise mimic of that disease.

Then they cut loose the monoclonals. Result: Mice rebuilt myelin in their spinal cords, but showed no change in MS scores and they remained paralyzed. Researchers gave treatment late in the disease, figuring results might be easier to notice. Had the virus not reached chronic stage when the drug was given, they surmised, outcomes might have been better.

They were right. Since the first Mayo work, investigators have shown "you can get even more re-myelination if you treat [the mice] early," Blight told *BioWorld Today*. And the results seem more real than those gained in the past, he said.

"A lot of MS work is done in models that are really more inflammatory [than aimed at myelin]," he noted, pointing to the standard model: experimental allergic encephalitis, a condition in animals that "somewhat resembles" MS, but not as much as Theiler's virus.

Building on the Theiler's findings, Acorda has been "moving from very interesting academic research to getting something that's ready for preclinical development in a serious way," Blight said. "We're about to take this on the road."

Partners are being sought to develop the antibodies and to help push along the preclinical work with a related program focused on glial growth factor 2 (GGF2), which is the most advanced in a class called neoregulins, licensed by Acorda in 2002 from CeNeS plc, of Cambridge, UK. The overseas firm had gained GGF2 in its \$44 million buyout of Cambridge, Mass.-based Cambridge Neuroscience Inc. in 2000.

"We've brought these two [programs] together because they seem to offer two different approaches to the same end," Blight said. GGF2 works in animal models of MS and "we didn't want to just stay with the antibodies. It gives us some flexibility going forward."

Whether myelination drugs might work in spinal cord injury – an area of particular interest to Acorda – is "still being worked out in practice," Blight said, adding that "MS is clearly where you would start" testing them.

GGF2 might have wider use, if animal models are valid clues. "There's interest around cardiovascular potential as well as neuroprotection in Parkinson's disease," Blight said.

For now, "the two programs are sort of neck and neck, in terms of where they are in development," he said. "GGF2 was more advanced, but we've really caught up." The growth factor was "one animal, and we knew what it was like and how it had to be developed," whereas the monoclonal antibody set was more diverse and mysterious, Blight said.

Acorda has fixed that. "It needs a lot of development effort to really move it into the clinic, but we've done the basic groundwork," he said. "We've also done a lot of work on things like dose response, and the potential for isotype switching, technical things to make it clear we have the right path" – and to let Acorda supply answers to questions put by would-be partners.

Some of the questions, at least. "It's a new area," Blight said. "There's nothing out there that has taken this approach." ■