A Drug and its Champion: Persistence Matters

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Research

Give it up for Lisa McKerracher. She has certainly earned her merit badge for persistence. A compound she discovered 20 years ago, Cethrin, is now entering a Phase II/III clinical trial for acute spinal cord injury. It could be a game-changing drug, based on earlier trial results. McKerracher, who never lost faith in Cethrin despite setbacks and many months looking for cash, thinks the drug has a real chance to make a real difference.

McKerracher trained with Albert Aguayo, the modern father of SCI regeneration, at McGill University. Aguayo had previously figured out that nerves in the central nervous system (CNS) will grow if their environment is made more hospitable. McKerracher helped figure out what made the SCI environment so hostile. In 1994, her lab, and that of Marie Filbin at Hunter College, simultaneously discovered a molecule called MAG that actively prevents regeneration after CNS injury.

Several other inhibitory proteins were identified in the 1990s. McKerracher and others set out to find ways to neutralize the inhibitors, and thus promote regeneration. She found that when the spinal cord is injured, a signaling molecule called Rho is abnormally activated. Calming the Rho response helped nerves to grow.

McKerracher published a very cool 1999 paper using an optic nerve model showing that blocking Rho promotes CNS regeneration. In 2002, she published a paper that put her on the SCI science map, "Rho Signaling Pathway Targeted to Promote Spinal Cord Repair." Paralyzed mice got better. Cethrin stimulated axon regeneration and recovery of hindlimb function.

McKerracher figured out how to block Rho, a pathway by which several types of myelin-related inhibitory proteins converge against spinal cord nerve cells. She called it Cethrin; it's a recombinant (engineered) version of C3 transferase, derived from Clostridium botulinum. That makes Cethrin a sort of cousin to Botox.

McKerracher got a patent for Cethrin, and soon thereafter made an alliance with a company called Boston Life Science to take the drug to trial. BLS soon changed its name to Alceres, which did take the drug through an early trial, with a very promising results. In 2006 it was reported that of 37 patients who got Cethrin within days of their injury, 31 percent improved from complete to incomplete (AIS A to AIS B). That's quite a bit better than the conversion rate for historic controls patients (basic standard of care, which converts closer to 10 percent). The trial also noted that 18 percent of subjects overall and 38 percent of those with cervical injuries improved to ASIA C or better. Striking results, indeed, published in the literature in 2011 (covered by me here).

To make a long story short, Alceres intended to move Cethrin forward but failed to do so. McKerracher got the intellectual property rights back. Her company, BioAxone, assembled a team, and eventually arranged financial backing ($10 million initial payment) from the biotech company Vertex Pharmaceuticals.

(Vertex has two drug products on the market, both targeting cystic fibrosis: Kalydeco, which costs over $300,000 a year, and Orkambi, at $259,000 a year. The company posted net product revenues of $1.7 billion in 2016.)

Vertex calls the multicenter trial SPRING, which is derived from SPinal Cord Injury in Rho Inhibition InvestiGation Trial. They are now recruiting patients with C4, C5 or C6 AIS A or B injuries, in patients that undergo decompression/stabilization surgery starting **within 72 hours of injury**. The trial is placebo controlled; that is, some patients will get Cethrin, or VX-210 as the company calls it, and some will get a dummy drug.

According to its listing at ClinicalTrials.gov, the SPRING study will "determine the efficacy and safety of VX-210 in subjects .... Secondary objectives include the specific evaluation of the effects of VX-210 on neurological recovery and daily function after spinal cord injury."

I asked McKerracher about the trial, and about hanging in there to see the trial happen.

"When I first started a company I thought that handing a drug off to a larger partner would guarantee the best shot at success," she continued. "What I have learned along the way is, you can't just 'set it and forget it.' If you want to see a promising treatment approved and available to all patients, you must remain constantly involved, you must remain an advocate and champion."

Persistence matters, said McKerracher.

"For all the extraordinary advances that have been made with biotechnology, there needs to be a commitment and persistence to ensure forward progress. Passion and persistence will carry you far, but working with extraordinary people, who have the scientific expertise and the commitment to shared values, is critical.

I asked McKerracher why she thinks Cethrin could be so important to the field.

"The first approved drug will change the field of SCI forever," she said. "It is difficult to be a trailblazer in any field. First movers have an advantage, but fast followers get to ride the wake."

"This is a new indication with no predefined pathway to success. That said, we are very excited to be the trailblazer and to be setting the standard for future therapies. With one success, follow-on drugs will be developed, pharmaceutical companies will realize the commercial potential, and competition and new drug approval will quickly follow."

"This will mean more choices for patients, more potential to achieve the maximum recovery possible."

What makes this acute trial different than others?

"The current clinical trial with Cethrin has the potential to be transformative for several reasons: it is the first Phase 2/3 clinical trial being run by a pharma company with significant resources and the clinical trial has all the newest bells and whistles: it is a large placebo-controlled study, it has new outcome measures developed to measure functionally important hand and arm functions (Cue-t and Grassp), it has sample collection for later biomarker studies, and it is being run by an internal team experienced in running successful clinical trials."

"Despite funding for many, many preclinical studies on axon regeneration, there has been little translation of novel first-in-man molecules that have potential to stimulate repair by promoting axon regeneration and plasticity. Cethrin is first drug to enter late-stage clinical trial that has a regenerative mechanism of action. To be clear, regeneration has been a very futuristic ideal. I am thrilled to see this ideal progress into a Phase IIb/III clinical trial."

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