MS pipeline flowing, but niche remains for neuroprotection

For decades, people with multiple sclerosis have injected themselves daily with immunosuppressant drugs for lack of a better option, in hopes of mitigating the disease's neurodegenerative effects. But newly designed oral therapies for the disorder have proliferated over the past few years, foretelling a future with fewer pricks.

"People are very excited about having a pill instead of an injection," says Todd Eagar, an immunologist at the University of Texas Southwestern Medical Center in Dallas. "Those daily injections are just really taxing on patients."

The first immunomodulating pill to treat multiple sclerosis, Gilenya (fingolimod), manufactured by Swiss drug giant Novartis, gained approval from the US Food and Drug Administration (FDA) last year. And results announced last month hint that there's more on the way.

France's Sanofi published phase 3 trial results from its lymphocyte inhibitor Aubagio (teriflunomide) on 6 October showing similar efficacy as established injectable treatments (*N. Engl. J. Med.* **365**, 1293–1303, 2011). The day before, US-based Biogen Idec announced phase 3 trial data for its twice-daily pill BG-12 (dimethyl fumarate). "It has shown unexpectedly promising data," says Jon Searles, a senior analyst at the research and consulting firm Decision Resources in Burlington, Massachusetts. "Clinicians are impressed with the drug's efficacy on clinical endpoints of relapses and disability."

Amidst the advances come some notable stumbles, though. In June, Germany's Merck KGaA dropped its pill Movectro (cladribine) after the FDA demanded additional trials. Meanwhile, laquinimod, under development by Israel-based Teva and Sweden's Active Biotech, has hit a snag: trial results released in August showed no difference in relapse rate compared to placebo. Despite the drug's poor showing, however, laquinimod's developers have not followed Merck's suit, because the pill promises more than standard immunosuppression: mouse studies suggest it may also protect the brain from further degeneration through other mechanisms, as well.

Biogen Idec and Novartis have also released data from rodent studies suggesting neuroprotective qualities of BG-12 and Gilenya, respectively. "A big unmet need is going to be strategies to repair damage, and it's one thing that might distinguish one drug from another," says Jeffrey Cohen, a neurologist at the Cleveland Clinic in Ohio who was involved with the development of Gilenya.

Ultimately, doctors may suggest mixing and matching oral drugs for multiple sclerosis to combine various mechanisms of action. But comparative and combination studies won't begin until—and if—the drugs are approved. And, because the mechanisms aren't well understood, clinicians are anxious about experimentation. Nonetheless, they wait with bated breath for the pipeline's outflow.

"If they all get through the regulatory approval process, then, if nothing else—even if we don't have comparative data—then we'll have a lot of choices," says Fred Lublin, a neurologist at Mount Sinai Medical Center in New York.

Hannah Waters

Easy to swallow: Oral MS options.

officials there about how they might launch their own patent revitalization program. And Laura Simon, who directs the office of biopharma alliances at the University of Colorado–Denver, is planning something similar. "Lots of discovery-based research is sponsored by government funding, and turning these projects into treatments or diagnostics is a way of better serving the public good," says Simon.

Into the clinic

Moving a concept from the lab to the clinic rarely proves easy. Michael Gollin, a patent attorney at Venable, a law firm in Washington, DC, says that the best universities "achieve superb success," but that other schools "fail to deliver effective products, for lack of focus, internal conflicts or other reasons." He adds that "funding for preclinical and clinical research is increasingly hard to find, and it is not getting any easier to gain regulatory approval."

Nonetheless, the SPARK program boasts many successes in this difficult arena. One of its earliest success stories began in 2007, when the program decided to help Stanford University School of Medicine neuroscientist Craig Garner, who earlier that year co-authored a paper showing that pentylenetetrazole—a $GABA_A$ antagonist—improved cognitive behavior in a mouse model of Down's syndrome (*Nat. Neurosci.* **10**, 411–413, 2007). For one thing, SPARK advisers encouraged Garner to collect data on the lowest effective dose of pentylenetetrazole.

At a SPARK meeting, Garner met molecular-geneticist-turned-venture-capitalist Lyndon Lien, who would become the chief executive of Balance Therapeutics, a company that the two of them founded along with Dan Wetmore, a neurosciences fellow at Stanford. "SPARK taught us that having a really strong team helps you solve each of your problems as you build your company," Garner says. With venture-capital funding obtained late in 2011 and two small-business innovation research grants from the US National Institutes of Health in September 2011, Balance Therapeutics expects to begin clinical trials in the beginning of 2012.

It remains to be seen how, or if, the National Taiwan University will model its own program. But, as the SPARK program gains popularity, Mochly-Rosen reflects that it's not just about the technology. "The best predictor for success," she says, "is the personality of the inventor. It takes someone with that extra zeal."

Mike May