MULTIPLE SCLEROSIS

Fast Forward And Myelin Repair Foundation: Two Routes To New MS Drugs

Despite the availability of new oral medicines, broader advances in multiple sclerosis remain farther away, especially for patients with advanced MS. Two nonprofit groups are thinking creatively — and spending millions of dollars — to make those breakthroughs come sooner.

BY ALEX LASH

- MS remains a mysterious disease with relatively few validated targets. Whether it's collaborations among academics, shared translational research resources, or side-by-side project funding with Big Pharma, two foundations are building connections to speed up the science.
- The National MS Society launched its venture philanthropy group Fast Forward five years ago to fund industry biotech projects. It has been spare so far with its disbursements, but it promises to spend \$60 million in the next five years.
- The Myelin Repair Foundation is focused on an aspect of MS that has only been considered a viable therapeutic target for a few years. It is building a translational medicine lab to validate new compounds and repurpose old ones.

Researchers and drug developers have made plenty of headway fighting multiple sclerosis since the first interferon drugs became available in the 1990s. The field hit a new milestone recently with oral drugs reaching the market – the first is *Gilenya* (fingolimod) from Novartis AG, and others are in Phase III. They aren't front-line therapies yet, but the hope of drugs that don't require regular injections or visits to the infusion clinic is shaking up the field, and in some ways re-routing attention to more pressing needs, such as more specific immune treatments that could be safer and more efficacious than current immunosuppressants, and new strategies to combat the advanced form of MS that so far has defied attempts to treat it.

But in this age of shrinking venture commitments to new research, penny-pinching Big Pharma research budgets, and uncertain government support, new advances in multiple sclerosis are going to be hard-fought victories. As in other disease areas with smaller patient populations, MS patients are looking to nonprofit

foundations to help push new treatments forward. Those groups are finding that potential successes may come in unusual ways.

The National Multiple Sclerosis Society, or NMSS, is the MS area's leading charity. Five years ago the organization launched a venture philanthropy arm, Fast Forward LLC, specifically to fund work at for-profit companies. A smaller group, the Myelin Repair Foundation, has been funding a network of academic researchers for eight years, and its contributions have helped move two therapies into the clinic. But the MRF is pushing into new territory by starting a translational R&D lab to assess treatments, whether discovered by their academic network or offered as re-purposing material by companies. It's an ambitious move and it parallels the attempts of some academic centers, such as the University of California, San Francisco, to move their research up the pipeline into areas that require greater scale, more resources and industry experience. (See "Back To School: Big Pharmas Test New Models For Tapping Academia " — IN VIVO, February 2011.) (Other MS nonprofit groups, including the Multiple Sclerosis Association of America and the Multiple Sclerosis Foundation, are more concerned with public education and patient assistance programs.)

The cost of MS drugs has risen sharply of late, up 21% in 2010 and accounting for 21% of health plans' specialty costs, according to Medco Health Solutions Inc.'s Drug Trend Report 2011. (See"MS Boon: Many Drugs On The Way, But Will Payors Swallow The Cost?" — IN VIVO, April 2012.) The new orally available drugs, though more convenient, aren't necessarily enough to elicit coverage from payors, who are increasingly pushing back against high MS drug costs. They'll need to see better efficacy from the oral drugs than from long-standing offerings that often have 15 years or more of safety data.

A CONFOUNDING DISEASE

Multiple sclerosis is actually a series of conditions that require different methods of treatment, and they can be divided into two main categories: relapsing-remitting MS (RRMS) and progres-

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sive MS. Most patients start with the relapsing-remitting form, in which their symptoms flare up then go into remission with partial or complete - but temporary - recovery. The progressive version steadily worsens, with or without relapses. Symptoms vary based on the areas of the nervous system incurring damage, as the immune system attacks the body's own nerve sheaths, made from myelin. RRMS usually tips over into progressive MS, but a small percentage of MS patients don't have any transition; their disease starts right in with the progressive form.

Why the immune system mis-recognizes myelin as a pathogen is still unknown, and the murky biology is a main reason for the challenges in target validation. But it's possible that these two modes of disease are from distinct phases: the inflammation from the autoimmune response, and the acute damage to the myelin and underlying nerve fibers. Many drugs beat back the immune system in rather broad fashion to treat RRMS, and their efficacy shrinking lesions in patients' myelin can be measured with MRI. There are also a few drugs approved to treat secondary symptoms that the disease causes, such as nerve pain, incontinence, and spasticity. But nothing so far has worked against progressive MS, in which the nervous system continues to degenerate even though the lesions are no longer apparent.

One problem facing researchers who are looking for agents that restore function or protect the brain from damage is carving out new clinical measurements. "In RRMS and the agents used to treat it, there's a well-defined pathway," such as measuring the number of relapses a year, says Tim Coetzee, PhD, the president of NMSS' Fast Forward. "But when you're thinking about restorative therapy, we're not sure of the measures the regulators will accept as clinically meaningful. We're in early stages of having to think about that. It's unlikely that simply putting patients in an MRI will be satisfactory. So far, regulators haven't accepted imaging as surrogate markers for clinical meaningfulness."

Clinical trial design is one of the areas in which Fast Forward is investing. Even though it's working with early-stage companies and MS programs, Coetzee says that "cost containment is a concern. The assets we're working on are so early stage no one's tried to monetize them yet. It nags at us, though, that we need to be vigilant about the cost implications of agents being developed."

One strategy for reducing overall MS costs is to develop alternative trial designs beyond the widely used Expanded Disability Status Scale (EDSS), developed 60 years ago and updated in the 1980s, according to the NMSS. "MS trials are among the most expensive out there, which speaks to the variability of the disease and the need for more biomarkers," says Coetzee. "EDSS doesn't have subtle sensitivity. It needs a larger number of patients to see an effect. If one could develop alternative designs and measures, you could, after the acceptance of regulatory authorities, potentially see a reduction in the costs of trials."

THE FAST FORWARD MODEL

Financially speaking, Fast Forward has gotten off to a slow start, having distributed in five years just under \$5 million of its own cash. Its original goal was to deploy \$60 million by the end of 2012; Coetzee says the recession slowed its progress. The new goal is to distribute the rest of the \$60 million in the next five years.

Fast Forward has also reconsidered its financial demands. At first the group was open to taking warrants of its grantees' equity, but it has stopped because holding warrants on its balance sheet required annual estimation of the warrants' fair market value. For private companies, it was too much time and effort and Fast Forward didn't want to pay outside valuation consultants, says Coetzee. Instead, they ask for royalties based on milestones and cap them at a modest return of three to five times cash back in a typical deal, which is structured as a sponsored research agreement..

A small slice of Fast Forward's funding is coupled with much larger sums from EMD Serono, a US division of Merck Serono SA, which markets Rebif (interferon-beta 1a). In two rounds of joint funding, the partners have committed \$2.4 million, most of it from EMD Serono, to seven projects – four at for-profit companies. They have just released a request for proposals for a third round, which will have a translational focus. In this round, projects must have potential to lead to drug candidates that either target certain B-cell lineages or "orphaned" G-protein coupled receptors (orphaned, because, so far, they don't have ligands identified to help elucidate them as drug targets). (See "A More Integrated Approach To Looking At GPCR Signaling" — START-UP, October 2011.) Funding per project is relatively small, up to \$500,000. EMD Serono has the right to first negotiation of a license if the program hits certain milestones. As with previous rounds, one-fifth to one-tenth of the cash would come from Fast Forward, and it would expect a 4x return.

To succeed, Fast Forward needs to fund projects that ultimately land with a big drug firm with resources to carry them through late-stage trials. So far, one Fast Forward-funded company has subsequently struck a licensing deal: Belgian firm Apitope International NV's Apitope Technology (Bristol) Ltd. subsidiary, which is developing a synthetic peptide that aims to promote immune system tolerance of myelin. Merck Serono is the licensee and in early 2009 agreed to pay up to \$204 million total when the program was preclinical. Specifics weren't disclosed. It has since completed a small Phase I trial in patients with secondary progressive MS. (Apitope was not funded through the FF-EMD program.)

The other eight firms that have received money through the general fund so far are Amplimmune Inc., Athersys Inc., Axxam SRL, CanBex Therapeutics Ltd., Concert Pharmaceuticals Inc., FivePrime Therapeutics Inc., LineaGen Inc., and Provid Pharmaceuticals Inc. It has funded for for-profits through the collaborative fund with EMD. (See Exhibit 1.)

For San Francisco-based FivePrime, an antibody discovery and development firm, FF pledged \$1 million to help test a promising immunology-focused candidate against MS. The compound FPA-008 neutralizes the effects of the cytokines interleukin-34 (IL-34), which FivePrime discovered, and colony stimulating factor 1 (CSF-1), both of which could be expressed in MS lesions and drive the destructiveness of the disease. These cytokines regulate the innate immune system, which many researchers feel is responsible for the progressive form of MS. To test the theory using human samples, FivePrime plans to identify and stratify MS patient populations who express various levels of the targets. Fast Forward has been helpful not just with cash but with outreach to academic labs and clinical researchers. "This is a new area, and selecting the right patient populations has been challenging," says FivePrime Vice President, biology, Brian Wong MD, PhD. "We need a lot of pioneering work just to find validated patient tissue."

The same holds true for mouse models in progressive MS; to augment its own efforts, FivePrime found models in their backyard at UCSF. FF's award covers preclinical work, so if FivePrime

Exhibit 1

Fighting MS One Biotech At A Time: The Fast Forward Portfolio

COMPANY NAME	PROJECT DESCRIPTION	AMOUNT GRANTED	FUND SOURCE
Amplimmune	Preclinical development of recombinant fusion protein to target the inflammatory response in MS	\$500,000	General Fund
Apitope	Design and conduct of Phase IIb trial of lead compound in relapsing and secondary progressive MS	\$1 million	General Fund
Athersys	Preclinical animal studies of MultiStem adult stem cell therapy for progressive MS	\$640,000	General Fund
Axxam	Preclinical validation of a small molecule immune therapy Development of small molecules to prevent axonal injury	1) \$470,000 (joint funding with the Juvenile Diabetes Research Foundation) 2) \$431,000	General Fund EMD Serono Collaborative Fund
CanBex Therapeutics	Accelerate testing of anti-spasticity small molecule	£242,500 (\$386,000)	General Fund
Centrion	Preclinical studies of compounds related to lamotrigine, an approved epilepsy therapy, as neuroprotective agents	\$275,000	EMD Serono Collaborative Fund
CognoSci	Preclinical efficacy testing of COG112 to promote myelin repair	\$330,000	EMD Serono Collaborative Fund
Concert Pharmaceuticals	Preclinical work on a modified version of benzodiazepine for treating spasticity and neuropathic pain	\$750,000	General fund
FivePrime Therapeutics	Preclinical testing of a biologic to target specific cells of the innate immune system	\$1 million	General fund
Innate Therapeutics	Phase lla trial in patients with progressive MS using MIS416, an agent derived from bacteria	\$550,000	EMD Serono Collaborative Fund
LineaGen	MS biomarker studies	\$622,000	General fund
Provid Pharmaceuticals	Development of animal model and preclinical work on lead compound	\$310,000	General fund

SOURCE: National Multiple Sclerosis Society

decides to take the compound into the clinic for MS, it will have to find more funding.

Coetzee says FF won't hamstring a company if the money earmarked for its return is better plowed back into operations at a crucial juncture of the company's life: "If a program stops because we've recouped an investment, it's suboptimal."

Much of the \$60 million it aims to spend in the next five years will likely go to biotechs with limited budgets that would otherwise set their sights on larger autoimmune indications. "Without Fast Forward we'd be going into lupus, rheumatoid arthritis, or something else," says Amplimmune CEO Michael Richman. "They have become important conduits in the translational process."

MYELIN REPAIR IN TRANSLATION

As Fast Forward pushes for translational programs, its smaller cousin is gearing up its own. After nearly a decade funding academics to understand the underlying biology of myelin repair, The Myelin Repair Foundation is opening a laboratory near its Saratoga, CA headquarters in Silicon Valley that it hopes will serve as a hub for myelin repair research: taking in compounds from academics,

biotechs and Big Pharma, running them through a battery of assays, some of which MRF has helped develop, and moving the promising candidates out into the clinic – or back to the clinic, as the case may be. (*See Exhibit 2.*) "The emphasis is on already-marketed drugs," says VP of drug discovery Jay Tung, PhD, a 20-year industry veteran who was most recently with **Elan Corp. PLC**. "We can maybe play leapfrog if we can reposition a target or, even better, a compound."

It will require cash. MRF founder and President Scott Johnson, himself diagnosed with MS in 1976, likes to think of his foundation as a scrappy biotech. He wants to raise \$80 million over the next six or seven years, roughly double what they've raised in their first seven years (of which they have spent \$35 million). "Just like any other biotech start-up, we expect our run rate to increase," says Johnson.

Two programs have reached the clinic helped by MRF funds. One is an adult stem cell therapy developed by one of its key academic collaborators at Case Western Reserve University in Cleveland. The Phase I trial at the Cleveland Clinic is sponsored by the National Institutes of Health and the US Department of Defense. MRF is not funding it.

The second program doesn't quite fit the definition of myelin repair. It uses a patient's own peripheral blood leukocytes, which are

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covalently bound to a "cocktail" of seven myelin peptide antigens, according to Stephen Miller, PhD, whose lab at Northwestern University's Feinberg School of Medicine developed the platform and the MS-specific therapy. After intravenous administration, the antigencoupled leukocytes die and induce immune tolerance for the specific antigen - in this case, myelin. It's the same goal as the Apitope technology: retrain the immune system without a broad suppressive effect.

Because it has not shown ability to repopulate damaged myelin, however, MRF will not continue to fund the drug. (The program currently needs funding to progress to a Phase IIa trial.) Instead, the MRF wants to spin out the technology into a for-profit biotech and advance it, so that the antigens are covalently linked to biodegradable nanoparticles, not the patient's leukocytes, which is too costly and complex for widespread application, says Miller. Miller, who says a launch is likely in the next several months, will head the scientific advisory board and have an ownership stake. The unnamed company will also explore the technology in other autoimmune diseases. The idea is that, if the technology works to tolerize the immune system to myelin, perhaps it could do the same with other normal tissues that the immune system recognizes as antigens in other diseases. MRF owns 100% of the intellectual property.

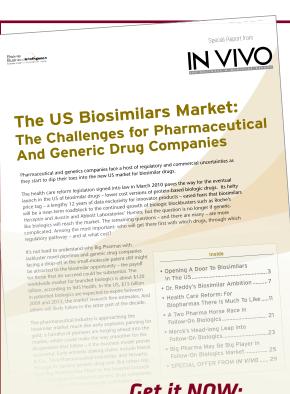
The nascent start-up is an outlet for MRF-funded research that the foundation might otherwise walk away from because of its narrow mandate. But it also underlines the organization's establishment of the translational lab as a way to leapfrog the slow, uncertain years of basic science it has funded the past eight years. The discovery core of what MRF calls its Accelerated Research Collaboration (ARC) consists of four principal investigators (PIs) spread across the country. Northwestern's Miller is one; the others Exhibit 2

Eight Years Of Myelin Repair Foundation Funding: A List Of Projects

A List of Frojects			
PROJECT	DESCRIPTION		
DTA (Diptheria Toxin subunit A) mouse	A mouse model that rapidly demy- elinates then gradually replenishes its myelin in a 70-day cycle.		
In-Vitro CNS Myelination Assay	An assay that uses myelinating cells of the mammalian CNS and myelination targets to screen compounds for potential to promote remyelination.		
Autologous Mesenchymal Stem Cell Transplantation in MS	Research at Case Western Reserve University that has led to a current Phase I trial at The Cleveland Clinic.		
Antigen-specific therapy using peripheral blood leukocytes bonded to myelin peptide antigens	Completed Phase I at University of Hamburg. Phase IIa at University Hospital Zurich awaiting funding.		

SOURCE: Myelin Repair Foundation

are Robert Miller, PhD, (no relation) at Case Western, Ben Barres, MD, PhD, of Stanford University, and Brian Popko, PhD, of the University of Chicago. Instead of working independently and applying for grants, as most foundations ask academics to do, each PI proposes experiments three times a year. They jointly write and adjust a research plan on a similar schedule, with feedback from the MRF staff and scientific advisory board. The four main inves-



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tigators openly share all research, and revenues that might eventually flow from their work are also shared equally.

The radical departure from typical foundation-funded work made Bob Miller skeptical at first, but he signed up for two main reasons: "First, there was a certain air of novelty about it that was interesting," Miller says. "It was clear even then that if you could have an open collaboration you could move forward more rapidly. And the people at MRF as well as the other principal investigators were people I'd known and respected a long time."

One example of the collaborative effect is a molecule Bob Miller's team discovered in Cleveland that seems to regulate both myelin repair and the immune system. Steve Miller is testing the effects of the molecule in "a more sophisticated way" in the immune system, and Popko is testing it in animal models of demyelination that the other investigators don't have locally. "That would never happen in the outside world," says Bob Miller.

EXPLORING THE DUNGEON

With its new translational lab, MRF would like to find potential myelin repair agents coming from the other direction: candidates owned by drug companies that are ripe for repurposing. MRF might unearth the compounds by focusing on promising targets - it has identified targets in 15 different drug classes so far by cross-checking its own database with one owned by one of its advi-

sory board members - and asking people in industry to search their catalogs. "We might ask, 'Do you have anything in your dungeon that crosses the blood-brain barrier?" says Tung. If MRF finds a promising compound or chemical matter that modulates a relevant target, it might ask the owner to come test it in the translational lab.

Tung says MRF is in talks with an undisclosed pharma company to run a pivotal trial for a generic cardiovascular-pulmonary drug that MRF is currently validating. It's not widely used anymore, says Tung, because it's been eclipsed by newer classes. MRF wouldn't be able to pay for large late-stage trials; if post-validation a pharma won't sponsor the trial, MRF could try for a clinician-sponsored trial, says Tung. If the compound enters the translational program, the goal is to wall off use of the drug in MS, perhaps with a tweak of the formulation that wouldn't affect the dosing profile and trigger the need for new safety studies.

If the lab accepts a compound from an industry source, the molecule's owner will have to pay for the work. But calling the lab a contract research organization is "a little too stark of a statement," says Johnson. "Companies are coming to us not just for assays and platforms but access to our brain trust." (MRF just announced that Biogen Idec Inc. Chief Medical Officer Alfred Sandrock, MD, has joined its board of clinical advisors.)

No matter how much expertise MRF lets outsiders tap into, the group will have to prove to big drug firms its lab can reach the scale, quality control and consistency they require to feel confident taking a compound into a clinical program.

Both Fast Forward and the MRF will ultimately be judged by the compounds they help push into the clinic and, eventually, into the hands of doctors treating MS patients. But it's too soon to make those judgments. Both groups' models are squarely aimed at providing cash and other resources to get drug programs into the clinic, but rarely deep into it. "I don't think it's good use of nonprofit money to pay Pharma to move things forward," says MRF President Johnson. "We don't want to be funding and financing the later stages."

Rare is the disease foundation that can afford to do so. The Cystic Fibrosis Foundation, generally acknowledged as the biggest spender among its peers, says it put \$75 million toward the de-

> velopment and approval of Vertex Pharmaceuticals Inc.'s Kalydeco (ivacaftor), a twice-a-day pill for a subset of cystic fibrosis patients. (See "Vertex Gets Quick FDA Approval Of Kalydeco; Prices New CF Drug At \$294,000 Per Year" — Health News Daily, February 2, 2012.) Both Fast Forward and MRF officials said they were well aware of Kalydeco's steep price tag, \$294,000 a year. With resistance already brewing among payors on MS drug pricing, officials at both MRF and Fast Forward acknowledge that their models must accommodate, and even proactively encourage, lower costs across the board.

> Both groups' models have drawn attention in the disease advocacy world, but it remains to be seen how replicable they are. To disburse millions of dollars a year, as FF wants to do, requires a minimum level not just of cash in the bank but of budgetary stability. "The worst case

scenario is that you commit \$500,000 per project and not be able to fulfill that obligation," says Pat Furlong, president of Parent Project Muscular Dystrophy.

Furlong, whose group distributes between \$4 million and \$6 million a year, roughly split in half between academic and industry researchers, wants to see more foundations who share similar disease pathologies band together to share resources. The MRF's idea to have academics collaborate and potentially expand their work to other autoimmune disease is, at least philosophically, perhaps a step in that direction.

"We've just hit the tip of the iceberg," says Amplimmune's Richman. "We need better therapies for patients not responding to current ones, and new therapies for those whose disease is progressing. These nonprofits help build the networks that facilitate the process. Not any one person has all the pieces in the puzzle." [A#2012900083]

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