

Research Now is a quarterly feature of **Momentum**, produced by the Society's Research and Clinical Programs Department.

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PHOTO BY JOE SHYMANSKI

Fingolimod (Gilenya): How far will it go to treat MS?

Fingolimod has made it—the first oral disease-modifying drug approved by the U.S. Food and Drug Administration to treat relapsing multiple sclerosis. This is a tremendous milestone in MS, and opens up more treatment options for people with MS. However, the possibility of serious side effects necessitates the need for pre-testing and ongoing monitoring to reduce risks. Research continues on fingolimod, to truly understand its effects, and to explore suggestions that fingolimod may have potential for other benefits

beyond inhibiting MS immune attacks.

The fungus of eternal youth

In the early 1970s, scientists isolated the drug cyclosporine A from a fungus, and in later years revealed that this drug was a potent suppressor of the immune system. Researchers began looking at other fungi, and in 1992, Tetsuro Fujita, PhD and colleagues (Kyoto University, Japan) hit the jackpot when they isolated an immunosuppressive from *Isaria sinclairii*—a fungus

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known in Chinese herbal medicine as a potion for “eternal youth.” **Journal of Antibiotics** 1994;47:208–15 Their early studies of this agent, called ISP-1, showed that it was 10 to 100 times more potent than cyclosporine, but was also rather toxic. The team then created a synthetic version that came to be known as FTY720 (later called “fingolimod”), which also displayed potent immunosuppressive capabilities, but in a less widespread fashion—thus avoiding major toxicity. **Bioorganic & Medicinal Chemistry Letters** 1995;5:853–856

The development of FTY720 continued through laboratory studies and then clinical trials for indications including MS, kidney transplantation and asthma. The company that developed it in pre-clinical stages, now known as Mitsubishi-Tanabe Pharmaceuticals, sold worldwide development rights—excluding Japan—to Novartis Pharmaceuticals.

But how does it work?

Although it was long recognized that FTY720 was sequestering T cells in the lymph nodes, it was 2002 before scientists discovered exactly how the drug was exerting its immune-suppressing attributes. Volker Brinkmann, PhD, and scientists at Novartis reported that FTY720 specifically binds to sphingosine 1-phosphate (S1P) receptors—docking sites on

T cells—to home in on them and keep them in the lymph nodes. When the team administered FTY720 to rats, the drug completely prevented the development of EAE, an MS-like disease. **The Journal of Biological Chemistry** 2002;277:21453–21457

Learning from clinical trials

Fingolimod (now going by the brand name Gilenya) made its way through the MS pipeline. In a two-year phase III trial known as FREEDOMS involving 1,272 people with relapsing-remitting MS, fingolimod at either of two doses significantly reduced relapse rates (the primary endpoint of the study). Disease progression was measured by two standard MS clinical assessment tools known as the EDSS and MSFC, and after 24 months people on either dose showed slower progression than people taking the inactive placebo. Secondary measures also favored both fingolimod doses, including MRI to detect tissue injury and brain atrophy. **The New England Journal of Medicine** 2010;362:387–401

Positive results also were reported from a one-year clinical trial called the TRANSFORMS study, comparing two different doses of fingolimod with an active treatment, Avonex (interferon beta-1a, Biogen Idec) in 1,292 individuals with relapsing-remitting MS. Both doses of fingolimod reduced relapse rates

over one year (the primary endpoint), and also reduced disease activity on MRI. Not surprising after only one year’s time, measures of progression were no different in the fingolimod and Avonex groups. **The New England Journal of Medicine** 2010;362:402–415

Potential risks

A small number of serious herpes infections occurred, and two deaths from herpes infections occurred in the TRANSFORMS trial in people taking the higher dose of fingolimod. A few cases of skin cancer have also occurred.

In both studies, the lower dose of fingolimod was better tolerated.

Elevations in liver enzymes, without accompanying symptoms, were common in those receiving fingolimod. Other side effects included a transient reduction in heart rate and blockage of heart conduction which generally normalized after the first dose; a mild elevation of blood pressure starting during the second month of therapy; and macular edema (swelling of the retina), which occurred more frequently in those taking the higher dose.

In the course of evaluating this agent, FDA staff identified another potential area of concern: the possibility for a gradual decline in lung function. The agency’s recommendations related to this and the other

potential side effects are discussed in the drug's approval label.

What else does it do?

At the same time that Gilenya still undergoes clinical trials including one in people with primary-progressive MS, research on its mechanisms of action continues. Dr. Brinkmann's team joined with Ludwig Kappos, MD (University of Basel) to examine immunological data from clinical trial participants. The team found that fingolimod specifically reduced "central memory T cells"—T cells that have already responded to a foreign trigger and are now acting out in a stronger and quicker fashion. One type of these cells, Th17 cells, may play a particularly significant role in the development of the MS immune attack. **Neurology** 2010;74:403–410

In an accompanying editorial in **Neurology**, Anthony Slavin, PhD (Boehringer Ingelheim) and Scott Zamvil, MD, PhD (University of California, San Francisco) noted that studies clarifying the exact cell populations affected by fingolimod are crucial, given the safety concerns that appeared in the clinical trials. "One obvious concern [about fingolimod] is that the selective trapping of TN [naïve T cells] and TCM [central memory T cells] within lymph nodes may impair development of both new and memory immune responses to infectious

pathogens, as well as reduce surveillance of malignancies," they wrote. "The potential relationship between redistribution of lymphocyte [T cell] subsets and safety profile of [Gilenya] in MS should be clarified by further immunologic investigations." **Neurology** 2010;74:388–389

The possibility of promoting myelin repair?

Even now that Gilenya is approved to treat relapsing MS, and risk mitigation and post-marketing safety monitoring programs are in place, scientists are still exploring the full potential of this drug.

A team funded by the National MS Society and others is conducting experiments designed to see if this drug may actually act on oligodendrocytes and their ability to repair myelin, the substance that insulates nerve fibers and is a main target of the MS immune attack. Grantee Betty Soliven, MD (University of Chicago) teamed up with Jack Antel, MD (McGill University, Montreal) to examine the effects of fingolimod on oligodendrocytes (myelin-making cells), since S1P is involved in signaling



Isaria sinclairii, the fungus that inspired the development of Gilenya.

by molecules in oligodendrocyte progenitors (immature oligodendrocytes).

This collaboration has already yielded several important findings. They showed in lab dishes that fingolimod could regulate many aspects of oligodendrocyte function or behavior, such as cell survival, differ-

entiation, and extension toward nerve fibers. **Glia** 2007 55: 1656–1667; **Annals of Neurology** 2008;63:61–71 Dr. Soliven is continuing this research with a new grant from the Society.

On the horizon

The approval of fingolimod culminates years of drug development and heralds an exciting era in MS treatment. Waiting in the wings is oral cladribine, for which an FDA approval decision is expected in December.

Oral therapies are only one class of many exciting treatments moving through the MS pipeline. Others include the sex hormone estriol, adult stem cell transplantation, and infused drugs that require infrequent dosing. These developments mean people with MS will have more treatment options, and also more complex choices to make that will require thoughtful conversations with their health-care professionals.

Researchers vet vaccines for MS in the lab and early trials

Our image of vaccines is a powerful one—after all, vaccines eradicated polio. Conventional vaccines are usually killed or altered infectious agents that boost the ability of the body’s immune system to fight the infection. “Vaccines” under research for MS, however, focus on disarming or neutralizing the misdirected immune attack on the brain and spinal cord. It’s a tricky business, considering that the trigger for this attack is still not known, but researchers funded by the National MS Society and others are bringing this strategy into early clinical studies.

Developing DNA vaccines

Lawrence Steinman, MD (Stanford University, CA), former winner of the Society and American Academy of Neurology’s John Dystel Prize for outstanding contributions to MS research, has played a key role in bringing one vaccination strategy to clinical trials in people with MS. His team designed customized DNA vaccines containing the genetic material that instructs several myelin proteins, in order to induce maximal immune system tolerance. Myelin is the substance that insulates nerve fibers, and is a target of the immune attack in MS. The vaccines suc-

ceeded in reducing relapse rates in mice. **Nature Biotechnology** 2003;21:1033–1039

Dr. Steinman co-founded Bayhill Therapeutics, Inc., a company that then licensed the compounds from the Stanford team. Bayhill funded a phase II study of BHT-3009 vs. inactive placebo in 289 people with relapsing-remitting MS. The study did not show statistically significant differences in the primary endpoint for the rate of new, active lesions, but showed a significant effect on a number of secondary endpoints including a reduction in the rate of active MRI lesions between those on therapy and those on placebo from weeks 8 to 48 of the study. Immunological data in a pre-selected subgroup of patients showed that immune tolerance was achieved, with a reduction in antibodies to components of myelin. **Annals of Neurology** 2008;63:611–20 Plans for a phase III trial are underway.

Taking on T cells

Several groups worldwide are developing vaccines using pieces of myelin proteins, or peptides—which are targets for immune T cells—to induce immunity to the MS attack by these cells.

One of these teams is a true

success story for the National MS Society’s research programs. David Wraith, PhD, began his career in MS research with a postdoctoral fellowship from the Society. He then developed a novel vaccination strategy and founded **Apitope International NV** to develop this strategy further. Apitope has developed synthetic peptides that might be able to train immune cells to ignore target tissues and thus suppress an attack. The lead product is ATX-MS-1467, an equal parts mixture of four peptides, which increases the activity of regulatory T cells.

Apitope recently announced that the drug was safe and well tolerated with promising early evidence of potential efficacy in a pilot clinical trial in 6 people with secondary-progressive MS. Now, Apitope has received \$1 million in funding for a clinical trial from Fast Forward, LLC, a nonprofit organization established by the Society to accelerate the development of MS treatments. In partnership with Merck-Serono, Apitope is conducting a larger study to determine safety and effectiveness in 40 people with relapsing forms of MS (relapsing-remitting, and secondary-progressive with relapses).

Opexa Therapeutics sponsored a one-year, multi-center

trial of Tovaxin, a T cell vaccine, in 2008. The placebo-controlled study involved 140 patients with relapsing-remitting MS and 10 patients who had experienced a neurological episode that put them at possible risk for MS. Those on treatment received five monthly subcutaneous injections of their own deactivated immune T cells and were followed for one year. The treatment was found to be safe, but did not achieve statistical significance in the primary endpoint, which was the reduction of disease activity on MRI in those on active therapy versus those on placebo. **World Congress of MS 2008**, Abstract #56

Additional data reported this year, however, show significant clinical benefit, and the vaccine succeeded in increasing the levels of regulatory T cells, which may help to suppress the immune response. **American Academy of Neurology 2010**, Abstract #P04.211 In a June 7 letter to shareholders, Opexa says it plans to meet with the FDA to discuss future studies.

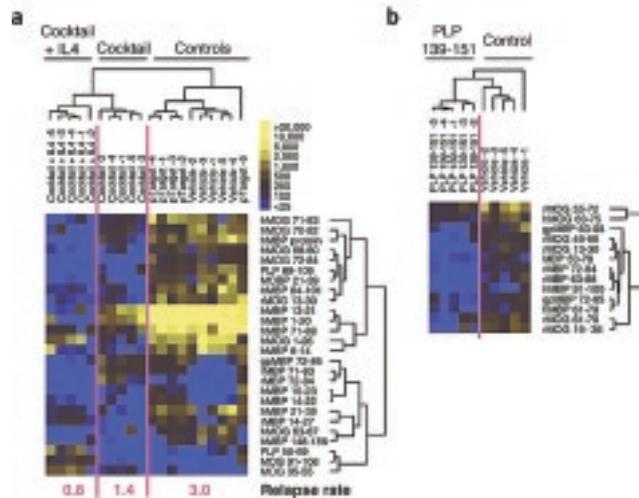
According to a research progress report from the University of Hamburg, Germany, Roland Martin, MD, and colleagues recently began a study called “ETIMS”, or Establish Toler-

ance in MS. The team selected seven peptides of myelin proteins to which T cells have shown high reactivity in MS. They coupled these peptides to antigen-presenting cells (APCs). Although T cells are main players in the attack that destroys myelin, they get clues about what to attack from APCs. The team is currently testing safety in a phase I study in 6 patients, and will soon begin a phase IIa trial in 12 people with early relapsing-remitting MS to determine whether treatment reduces brain inflammation on MRI. The work is based on preclinical work by Stephen D. Miller, PhD (Northwestern University), a longtime grantee of the Society.

With funding from the Society and others, Arthur Vandenberg, PhD, Halina Offner, Dr. Med., and colleagues at Oregon Health & Science University developed molecules called

recombinant TCR ligands (RTLs), which are designed to inhibit the ability of specific T cells to initiate damage to myelin. Artielle ImmunoTherapeutics, Inc., is developing one of these molecules, RTL1000, as a potential treatment for MS. In a small safety study in 34 people with relapsing-remitting or secondary-progressive MS, doses of 2 mg to 60 mg were safe and well tolerated, with higher doses producing moderate side effects (hypotension and diarrhea). The clinical efficacy of RTL1000 will be evaluated in larger Phase II studies. **American Academy of Neurology**, Abstract #S21.003

Vaccinations for MS are making real progress through the MS pipeline. Although more studies are underway to bring this therapeutic strategy to the clinic, the progress to date indicates some new avenues for stopping MS in its tracks.



This microarray from Dr. Steinman’s early work in MS-like disease in mice shows the variety of myelin proteins responding to BHT-3009.



ART WOLFE/GETTY IMAGES

Propelling MS research through tough times

by Patricia O'Looney, PhD

The economy may have slowed down, but MS hasn't. So even in these challenging times, the Society's research programs are building capacity aimed at stopping disease progression, restoring function, and ending MS forever.

Research funding moves forward in 2010/2011

The Society continues to fund and even expand funding for MS research efforts. In the spring of 2010, the Society's scientific peer review committees and the Research Programs and Advisory Committee reviewed a record number of grant requests. The ensuing projects launched this fall span a broad range of novel approaches and strategies.

The Society will continue funding Pilot Research Grants in 2011. This program provides seed money for short-term projects to investigate new, untested ideas and attract new researchers to the MS field. These small grants (\$44,000 for one year) allow researchers to quickly determine whether a novel idea is worth pursuing, and to gather data needed for full grant applications. With a rolling deadline, researchers generally know within two months whether they will receive funding. This program has an outstanding track record in fostering essential innovation, leveraging follow-up funding, and attracting new researchers to our mission.

The Society has also issued a special Request for Applications for an early-stage study of fac-

tors that influence MS disease progression. Accordingly, we are funding two feasibility studies—one based at Harvard with international partners, and one based in Buffalo with a consortium of MS centers across New York State. The two groups are taking different approaches to establishing longitudinal studies to determine why some people with MS have mild courses while others experience serious worsening of symptoms over time. The results may not only offer avenues for predicting who is likely to experience progression, but also suggest ways to prevent or stop progression.

The upswing continues

In 2011 our research funding will propel our mission of connecting people, ideas, and vital resources to accelerate the development of new treatments for people with MS.

Earlier in 2010, Fast Forward announced four funding agreements with Centrion Therapeutics; Cognosci, Inc; Innate Therapeutics, Ltd; and Oregon Health and Science University. These agreements focus on drug development for nerve protection and repair in MS and were funded in conjunction with EMD Serono. A special contribution by long-time supporters Eric and Sharon Hovde helped complete the funding package.

Fast Forward also announced a funding agreement with Canbex Therapeutics to develop a treat-

ment for MS-related spasticity, and a \$1 million funding agreement with Five Prime Therapeutics to advance a biologic molecule that targets the MS immune attack in novel fashion.

Leveraging funding from other sources also increases research capabilities. The Network of Pediatric MS Centers of Excellence, established through the Society's Promise 2010 initiative, was recently awarded a five-year grant from the National Institutes of Health to study the genetic and environmental risk factors, and their interactions, in pediatric MS. This federal grant will provide \$3,212,658 to help this talented team understand more about how MS begins in children, knowledge that can eventually be applied to more common, adult forms of MS.

In August of this year, author J. K. Rowling—whose mother, Anne, had MS—donated \$15.5 million to create a regenerative neurology center at the University of Edinburgh. This generous gift leverages the earlier work and collaborations developed by an Edinburgh team led by

Charles French-Constant, PhD, and funded from the National MS Society's Promise: 2010 initiative and other sources. The funding will help this team to take the crucial next steps to develop ways to repair MS damage and restore function to people with MS.

Responding to the fast pace

The National MS Society is keeping pace with the ever-accelerating nature of research in MS. The recent emergence of chronic cerebrospinal venous insufficiency (CCSVI) as an important lead to follow is a case in point. Last March, after a joint peer review in collaboration with the MS Society of Canada, the Society announced funding of seven new research projects aimed at understanding how CCSVI may relate to the MS disease process. The studies began in July, and information about the projects can be found on our Website at www.nationalMSSociety.org/ccsvi.

To make it possible to support emerging research opportunities like CCSVI, the Society established the Rapid Response Research Fund. This fund expands our collective ability to drive more and better treatments to people with MS.

Beyond funding

To help build research capacity, the Society must go beyond funding research projects, to increasing the

availability of shared resources. These include MS tissue and DNA banks, and networking opportunities to help cement young investigators' commitment to the field of MS. The 2nd Tykeson Fellows Conference on MS convened in June 2010, brought 57 young research and clinical fellows together to learn about each other's latest research efforts and to forge new collaborations. This conference was launched by a generous contribution from Mr. Donald Tykeson, active volunteer and Honorary Life Director of the Society's National Board of Directors.

To enable broad dissemination of some milestone research data, in June a collection of pivotal MS papers—featuring guidelines on stem cell transplantation research, pediatric MS, and other current topics—was posted online in a “Web Focus” feature from Nature Publishing Group. The Society and Fast Forward sponsored this to ensure three months of free access to these papers, a move that increases awareness of the significant progress made in these areas and may spark new collaborations and new ideas.

Tough financial times aren't yet behind us, but the National MS Society continues to move research forward toward a world free of MS. ■

Dr. O'Looney is the Vice President of Biomedical Research Programs at the National MS Society.

Dr. Patricia O'Looney comments on the FDA advisory committee's recommendation of fingolimod (Gilenya).



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