National Multiple Sclerosis Society

Research Highlights

Recent research progress in MS Summer/Fall 2007

2007 Marks Great Progress in Drug Development for Multiple Sclerosis

By Sara Bernstein

There are now 132 ongoing, planned, or recently completed clinical trials in multiple sclerosis, according to "Clinical Trials in Multiple Sclerosis 2007" – a list compiled by the National MS Society.* This vibrant scene is bringing new hope for oral drugs, for better options for progressive disease, and for novel approaches to alleviating symptoms. More than 30,000 people with virtually all types of MS have participated in these studies; without their help and that of thousands in the future, developing better treatments for this disease would be impossible.

Oral Therapies

Oral therapies are a hot topic in MS drug development. Currently approved MS treatments require ongoing injections or infusions that can cause significant reactions and discomfort.

"Developing oral therapies that are safe and effective is crucial," says John Richert, MD, Executive Vice President for Research & Clinical Programs for the Society. "More and more studies are showing how important early treatment is for improving the course of MS down the road, and having approved oral therapies would greatly increase the proportion of people who are willing to get on therapy early and to remain on therapy."

Oral **laquinimod** (Teva Pharmaceuticals), an immune-modulating drug, is under study in 1,000 people with relapsing-remitting MS (RR MS, a course of MS characterized by clearly defined flare-ups followed by complete or partial remissions). Results of an earlier study in 306 people showed that 0.6 mg of laquinimod reduced the number of active lesions by 38% when compared with placebo, but not 0.3 mg. The new study is comparing the higher dose against placebo.

Oral **cladribine** (EMD Serono) is being tested in 1,290 people with RR MS worldwide. Cladribine is a medication that has been used to treat hairy cell leukemia. Pilot

*Clinical Trials in MS 2007 is available online at http://www.nationalmssociety.org/ClinicalTrials.

Inside…

Bold New Initiative: Fast Forward™

The National MS Society is about to launch Fast Forward,™ a bold new initiative to speed the delivery of new treatments to people with MS. The core focus is to:

- Increase the number of drugs in the development pipeline by connecting basic research to drug development and by funding research performed by small pharmaceutical and small biotech companies.
- Increase the MS focus and the speed with which these drugs are brought to clinical trial.
- Fund clinical trials of potential MS drugs.
- Expedite the re-purposing of existing drugs to treat MS.

Stay tuned for the launch of this exciting new venture!

studies have suggested a benefit in both RR and progressive MS, and while a trial in progressive forms of MS showed no clinica- benefit, it did show a significant reduction in MRI-detected disease activity. The drug already has been designated by the FDA as a "fast-track product," which should expedite its review when the trial is completed.

Fingolimod (FTY720, Novartis Pharmaceuticals) – an oral drug that binds to a docking site on immune cells, preventing them from attacking the brain and spinal cord – is under study in 2,000 people with RR MS in Europe and North America. This study is based on results of a smaller earlier study reported in 2006, which showed that up to 77% of people taking fingolimod in a cohort of 255 people with active, relapsing MS remained relapse-free over two years.

Teriflunomide (Sanofi-Aventis), an oral agent that may modulate T cells, is being tested in 1,050 people with RR MS in Europe and North America. Earlier results showed that teriflunomide significantly reduced MRI-detected disease activity in 179 people with relapsing MS.

A controlled clinical trial of oral **estriol**, a sex hormone, added to Copaxone® (glatiramer acetate, Teva Pharmaceutical Industries Ltd.) is starting in 130 women with RR MS. This study is being funded by the National MS Society in partnership with the Society's Southern California chapter and the National Institute of Neurological Disorders and Stroke. Rhonda Voskuhl, MD – lead investigator of this trial – had conducted an early-phase trial of estriol in 12 women with MS, and found decreases in disease activity during estriol treatment in women with RR MS.

Oral fumarate (**BG00012**, Biogen Idec) is being tested in 1,011 people with RR MS. This drug inhibits immune cells and molecules, shifting the immune response from inflammatory to anti-inflammatory. In an earlier study in 257 people with RR MS, treatment with high dose BG00012 led to a 69% reduction in active inflammation on MRI scans.

Progressive MS

Therapies under study in 2007 also tackle the treatment of progressive forms of MS — including secondary-progressive MS (SP MS, characterized by an initial period of RR MS,

followed by a steadily worsening disease course with or without occasional flare-ups), and primary-progressive MS (PP MS, a slow but nearly continuous worsening of disease from the onset, with no distinct relapses or remissions).

"There are too few treatment options for people with the progressive forms of MS, and especially primary-progressive disease," says Richert. "We're investing heavily in finding ways to rebuild the nervous system to restore function to those whose disease has led to progressive disability. In the meantime, researchers are also uncovering new clues to what causes progression, and seeking new approaches to defend against the chronic immune assault."

A clinical trial of **rituximab** (Rituxan®, Genentech and Biogen Idec) is ongoing in 435 people with PP MS. Rituximab is a drug delivered by intravenous infusion that depletes immune B cells, which may play a role in the immune attack on brain and spinal cord tissues in MS. In two studies of rituximab in people with RR MS reported earlier this year, the drug significantly reduced relapses and MRI-detected disease activity. Rituxan has been associated with severe adverse effects including fatal infusion reactions and progressive multifocal leukoencephalopathy (a brain infection), but these have not occurred in the MS studies.

Enrollment has begun for a study testing the safety and effectiveness of the experimental drug **MBP8298** (BioMS Medical Corp.) in 510 people with SP MS in the U.S. MBP8298, a synthetic fragment of a protein in myelin (the substance that insulates nerve fibers and is damaged in MS), reduces the production of spinal fluid antibodies that react against that protein. This drug is administered intravenously every 6 months. In an earlier study, investigators administered 500 mg of either MBP8298 or inactive placebo to 32 people with SP MS or PP MS. In that study, the subgroup of patients with the immune system-related genes HLA DR2 and/or DR4 experienced a delay in worsening of disease, occurring at an average of 78 months compared to 18 months in those taking placebo. Based on these results, the current study is enrolling people with SP MS who are positive for HLA DR2 and/or DR4.

Cyclophosphamide is a potent immunosuppressive drug that is usually given to treat cancer, and has been used for treating MS for many years, mostly in uncontrolled studies. The side effects of short-term treatment with high doses are hair loss, nausea, occasional bladder injury, and risk of infection. Now Bruno Brochet, MD, and researchers in France are evaluating the effectiveness of intravenous cyclophosphamide compared with intravenous methylprednisolone for delaying disability in 360 people with SP MS.

Research indicates that the loss of nerve cells and fibers is the main contributing factor to long-term disability in MS, so finding treatments that can prevent this damage is crucial. **Lamotrigine** (Lamictal®, GlaxoSmithKline) is an oral drug currently used to prevent seizures in people with epilepsy. Raju Kapoor, MD, PhD, and colleagues at National Hospital for Neurology and Neurosurgery, London are testing if it can prevent or slow progressive loss of brain tissue (atrophy) in 120 people with SP MS.

Symptom Relief

A key strategy of the MS treatment regimen is to alleviate symptoms, such as fatigue and pain, and improve gait and other functions. "Until we find a cure, drugs and techniques that can improve MS symptoms are crucial to the treatment plan of people with MS," says Richert.

Fatigue is the most common symptom of MS, affecting up to 90% of people with the disease. Dean M. Wingerchuk, MD, and colleagues recently found that people taking the equivalent of four regular **aspirin** tablets daily had reduced MS-related fatigue compared with those taking inactive placebo. Now they are attempting to confirm the benefit of aspirin in 135 people with MS-related fatigue at three sites in the U.S., with funding from the National MS Society.

Spasticity, or increased muscle tone, an often painful symptom that can interfere with walking and other controlled movements of the limbs, is experienced by as many as 70% of people with MS. Proponents of the use of marijuana (cannabis) or its derivatives in MS have suggested that it may help reduce spasticity, although it has been difficult for researchers to obtain objective data of its effectiveness. With Society funding, Mark Agius, MD, and colleagues are conducting a placebo-controlled study to test the safety and effectiveness of inhaled **cannabis** and of oral tetrahydrocannabinol, a cannabis derivative, for the treatment of spasticity in 60 persons who have MS and spasticity.

The cannabis-derived drug **Sativex**® (GW Pharmaceuticals) is being tested for its ability to treat MS-related pain in 174 people in Canada and Europe. Sativex, which is administered as a spray into the mouth, has been approved in Canada to treat pain.

Many people who have MS experience problems walking. Society grantee Barbara Giesser, MD, and colleagues at UCLA are testing a new rehabilitation approach called **"locomotor training"** to improve ambulation in 40 persons with progressive MS. Locomotor training involves a robotic device that moves the legs while the person is suspended over a treadmill. In an earlier pilot study funded by the Society, four people with MS who received this training showed improvement in muscle strength, spasticity, endurance, balance, walking speed, and quality of life.

A clinical trial is testing the safety and effectiveness of **Fampridine-SR** (an oral, sustained-release formula of 4-aminopyridine being developed by Acorda Therapeutics) compared with inactive placebo to improve walking ability in 200 people with all types of MS. Fampridine-SR may improve the conduction of nerve signals. In a previous study of Fampridine-SR in 301 people with MS, 35% of those on active therapy experienced an average of 20% improvement in walking speed. Two serious adverse events were anxiety in one participant and a seizure during a serious infection in another.

Looking Forward

We've come a long way. In the Society's 2002 listing, only three studies included more than 1000 patients. In just five years, that number has jumped to 10.

"This increase in larger, later-phase studies is an important sign that more experimental treatment options are making their way through the drug development pipe-

Tracking MS Trials

Significant progress has not only been made in clinical research in MS, but in the availability of information about that research. This is partly due to the International Committee of Medical Journal Editors who, in 2004, began to require investigators and pharmaceutical companies to list clinical trials in public registries – even before patients are enrolled – if they wished to eventually publish the results. At the time, ClinicalTrials.gov (the National Institutes of Health's database of information on clinical trials, and the largest registry at the time) contained 13,153 studies in various diseases. Now, ClinicalTrials.gov lists more than 40,000 trials. Here are key sites for getting information about MS studies in particular:

- The National MS Society – Find "Clinical Trials in MS 2007" and a list of Trials Recruiting Patients that is indexed by state, with a page for international studies. www.nationalmssociety.org/ClinicalTrials
- ClinicalTrials.gov – At this writing, this database lists 284 MS studies, with 151 recruiting. http://www.clinicaltrials.gov/
- NARCOMS – This registry of people willing to participate in MS research was initiated in 1993 by the Consortium of MS Centers to facilitate multicenter studies. As of May 2007, the number of participants surpassed 32,000. http://www.mscare.org/cmsc/CMSC-NARCOMS-Information.html
- CenterWatch.com – This service currently has 75 MS study listings nationwide. Includes information about clinical trial participation, both in English and Spanish. "Drug Directories" section contains information on study results. http://www.centerwatch.com/
- MS International Federation – Resources on all aspects of clinical trials, including participation, ethical issues, and links to further resources. http://www.msif.org/en/research/clinical_trials/index.html

line, despite the new complexities of current clinical trial design," says Richert. "We're working hard to find new ways – such as our new Fast Forward™ initiative [see p. 2] – to feed that pipeline to bring better treatments to people with all forms of MS." ❑

Preclinical Research: The Driving Force Behind MS Drug Development

Behind every clinical trial are years of preclinical research. During preclinical drug development, investigators identify a therapeutic target and subsequently evaluate the safety and effectiveness of a drug in cell cultures in the laboratory (called in vitro studies) and in animal models (in vivo). Preclinical drug testing is required by the U.S. FDA to show how a drug works and its potential toxicity before studies in people can proceed. The payoff from preclinical studies can be considerable; the National MS Society funded preclinical work that led to the development of all six approved disease-modifying MS treatments.

A recent scan of "Pharmaprojects," a proprietary database tracking global pharmaceutical development, identified 104 agents in preclinical studies in the commercial sector that could ultimately have application to multiple sclerosis [see Table 1]. Society-funded grantees are also actively investigating compounds in vitro and in vivo in hopes of finding the next drug to be approved for treatment of MS. Here is just a small sample of their promising work:

Society grantees Arthur Vandenbark, PhD, and Halina Offner, PhD (Oregon Health & Science University, Portland) conducted the preclinical research on **recombinant TCR ligands** (RTLs), molecules that inhibit the function of inflammatory T cells. T cells are the major players in the immune attack that damages nerve fiber-insulating myelin in MS, and T cell receptors (TCRs) are the proteins that T cells use to recognize their targets, such as components of myelin. Most recently, the team showed that RTL therapy administered well after onset of EAE (an MS-like disease) in mice partially reversed the clinical deficit and promoted myelin repair and nerve fiber regeneration (Journal of Neurochemistry 2006;98 [6]:1817-27).

In 2007, Artielle Immunotherapeutics began an early phase clinical trial to determine the safety of RTL1000 in 36 people with RR and SP MS.

Preclinical research also is necessary to show that a drug used for other diseases could be safe and effective for people with MS. Stephen Waxman, MD, PhD (Yale University, New Haven, CT) has focused his laboratory efforts on sodium channels, tiny pores on the surface of nerve fibers that are essential for nerve signaling. Waxman's team found that **phenytoin**, a sodium channel-blocker used for epilepsy, can protect nerve fibers from damage in mice with EAE.

Waxman is continuing these studies as part of a National MS Society Collaborative MS Research Center Award to Yale colleague Jeffery Kocsis, PhD. Their most recent findings suggest that phenytoin provides long-term protection of nerve fibers, preventing degeneration and improving clinical symptoms in mice with EAE (Brain, December 2006;129:3196-3208). Based on this research, the Center team is now designing an early phase study of phenytoin in a small number of people with MS.

Another drug in preclinical research for MS is **PPAR-alpha,** a medicine already used

Target	Possible Role in MS	Suppress/block↓ or Stimulate↑
CD4	Protein on the surface of attacking T cells	↓
Interleukin-17	Immune messenger protein that spurs on attack	↓
Apoptosis	Process by which attacking T cells die	↑
B-cell activating factor	Regulates both B and T immune cells	↓
Cannabinoid receptors	Docking sites in the brain that may control inflammation	↑
Adenosine receptors	Docking sites that may modulate both immune response and nerve cell survival	↑

Table 1. MS is a complex disease, presenting academic investigators and pharmaceutical/biotech companies with many opportunities for interrupting the immune attack launched on the brain and spinal cord. Here are some molecules/processes being targeted by these companies in preclinical research, what role they may play in MS development, and whether therapeutic strategies are being developed to suppress or stimulate them. (Pharmaprojects)

to treat cholesterol disorders. PPARs are naturally occurring molecules called "peroxisome proliferator-activated receptors" that appear to play a role in modulating inflammation. With funding from the Society, Michael Racke, MD (Ohio State University, Columbus) and colleagues demonstrated that a molecule mimicking PPAR-alpha can inhibit EAE in mice (The Journal of Immunology 2004 May 1;172[9]:5790-8). Now the team is examining these capabilities further in immune cells taken from people with MS, to determine whether changes to the human immune system can be induced. These studies represent the next step toward clinical trials of PPAR-alpha or related compounds in people with multiple sclerosis.

An exciting area of preclinical MS research focuses on **cell transplantation** to replenish myelin-making or nerve cells lost in MS. Transplantation strategies in particular require strenuous preclinical testing, because introducing foreign cells carries potential risks for the recipient. Gianvito Martino, MD (San Raffaele Hospital, Milan, Italy) and colleagues showed in 2003 that immature nerve cells (adult mouse neural stem cells) injected into the blood or brain cavities of mice with EAE can move throughout the brain and spinal cord to sites of tissue damage, promote repair, and

reverse symptoms.

Martino was subsequently funded by the Society and is also now a member of an international team focusing on nervous system repair and protection funded through the Society's Promise:2010 campaign and led by Charles ffrench-Constant, PhD, FRCP (University of Cambridge, UK). Recently they reported that neural stem cells injected into mice with EAE could be tracked using the same magnetic resonance imaging that clinicians use to track disease in people with MS. The researchers spotted the cells as early as 24 hours after transplant and as late as 20 days afterward. These findings are important, as the eventual use of such therapies in people would demand noninvasive methods of tracking treatment success (Stem Cells 2007 Jun 28; [published online ahead of print]).

These and other preclinical efforts are the driving force behind clinical trials, providing the necessary background to move experimental treatments through the pipeline and into the lives of people with MS.❑

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PLEASE NOTE: This is the final issue of "Research Highlights." Look for us in the newly designed national magazine in November.

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