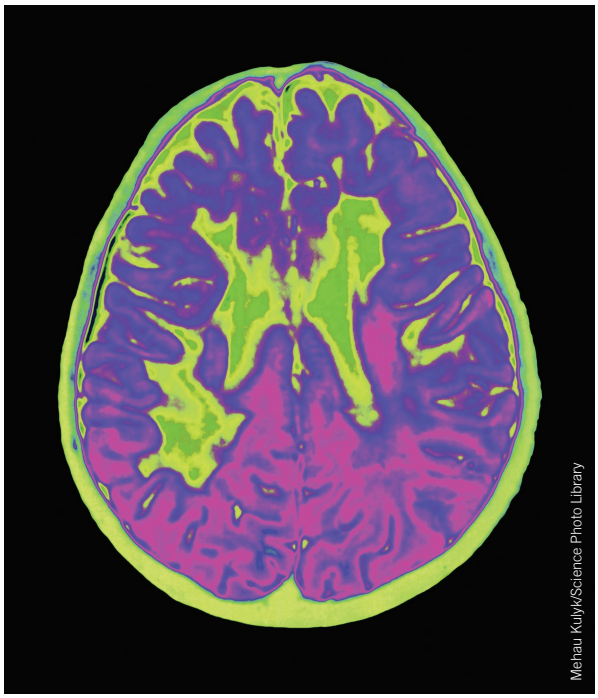
Buzz around Campath proof-of-concept trial in MS

When news broke in October that an approved cancer therapy had, for the first time, halted the progress of multiple sclerosis (MS), excitement was tangible among clinicians and patient groups. The phase 2 study's results are certainly unprecedented in MS. But whether Campath (alemtuzumab), a monoclonal antibody (mAb) already approved to treat leukemia, actually 'reverses' MS, as some news stories in the mainstream media trumpeted, and how it works remain unresolved. The next two years are expected to reveal much about not only Campath in MS, but also the competitive landscape for this indication where the tradeoff between efficacy and safety remains a tough hurdle for drug developers.

Campath was the first humanized mAb to be developed as a therapy. It has a long, illustrious history, dating back over two decades to anti-lymphocyte rat antibodies first raised by Herman Waldman and Geoffrey Hale (*Mol. Biol. Med.* **3**, 305–319, 1983). The name Campath derives from the pathology department at Cambridge University, UK, where the academics worked.

The monoclonal was raised to target B and T cells and was initially pursued as treatment for graft-versus-host disease. However, Campath took off as a therapeutic only when Greg Winter and colleagues, also at Cambridge University, humanized the recombinant DNA-derived antibody, which became known as alemtuzumab.

Campath targets the cell surface glycoprotein CD52 present on all mature lymphocytes and has been used to treat B-cell chronic lymphocytic leukemia since 2001 when it was approved. The notion that Campath might also work as a treatment for MS was pioneered in 1991 by Alistair Compston, at Cambridge University, UK, also the lead investigator in the recent *New England Journal of Medicine* study (*N. Engl. J. Med.* **359**, 1786, 2008). He speculated that the antibody might work by destroying the mature T and B lymphocytes that drive the autoimmune attack against nerves and brain tissue in MS patients. After treatment, the immune system would be replenished, but this time, without the auto-reactive lymphocytes.



An MRI brain scan shows lesions attributable to multiple sclerosis, which were reduced in people taking the experimental drug Campath.

The strategy is indeed promising. Results from the latest study, funded by Cambridge, Massachusetts–based Genzyme and partner Bayer Schering, of Leverkusen, Germany, look "extremely attractive," says Jerry Wolinsky, who directs the Multiple Sclerosis Research Group at the University of Texas Health Science Center in Houston.

In the phase 2 trial, known as CAMMS223, Campath was administered once yearly to 334 previously untreated individuals with early relapsing-remitting MS. This regime cut patients' risk of relapse by 74% and reduced the rate of sustained accumulation of disability by 71%, compared with patients treated with the standard treatment Rebif, a high-dose interferon β-1a from

SELECTED research collaboration

Partner 1	Partner 2	$ (millions)
ImmuPharma (London)	Cephalon (Frazer, Pennsylvania)	500
Shenzhen Neptunus Interlong Bio-Technique (China)	GlaxoSmithKline (GSK, London)	78
Dyadic International (Jupiter, Florida)	Codexis (Redwood, California)	10
Galapagos (Mechelen, Belgium)	MorphoSys (Planegg, Germany)	*

Table 1 Selected MS therapies in late-stage development

Developer (location)	Drug	Status
Merck (Darmstadt, Germany)	Rebif (interferon β-1a), new formulation	BLA
Accentia Biopharmaceuticals (Tampa, Florida)	Revimmune (cyclophosphamide)	Phase 3
Acorda Therapeutics (Hawthorne, New York)	Fampridine SR (4-aminopyridine), targets potassium channels	Phase 3
Biogen Idec	Panaclar (dimethylfumarate), targets NF-κB	Phase 3
	Rituxan (rituximab), targets CD20	Phase 3
BioMS Medical (Edmonton, Alberta, Canada)	MBP8298 (dirucotide), synthetic peptide version of a portion of human myelin basic protein	Phase 3
Genzyme (Cambridge, Massachusetts)	Campath (alemtuzumab), targets CD52	Phase 3
Merck (Whitehouse Station, New Jersey)	Cladribine (oral), purine analog, anti-neoplastic	Phase 3
Novartis (Basel, Switzerland)	Fingolimod, targets sphigosine 1-phosphate receptor	Phase 3
Teva Pharmaceutical (Jerusalem)	Laquinimod, targets T lymphocytes	Phase 3
Sanofi-Aventis (Paris)	Teriflunomide, targets DNA synthesis	Phase 3

BLA, biologics license application.

Merck Serono. Patients were followed for three years; those on Campath scored higher on a standard disability scale than before starting the treatment, whereas patients on Rebif deteriorated. The benefits were long lived, lasting at least three years.

Even more striking, perhaps, are the magnetic resonance imaging scans that suggest the drug may be reversing the symptoms of the disease. Imaging data revealed that people in the Campath arm increased brain volume after a year, whereas the brain volume in the group receiving standard interferon experienced a decline.

"We're not saying people are cured," cautions neurologist David Margolin, Genzyme's lead medical monitor in the phase 2 and ongoing phase 3 program. But Campath patients' disability scores improved dramatically "within a few months, and this is not driven by just a few individuals," adds Margolin, who has an MS specialty practice at Massachusetts General Hospital and the Brigham and Women's Hospital in Boston. "Clearly, there is some recovery occurring, only in the [Campath] population as a group. Thirty percent of Rebif patients improved, but more of them worsened," whereas Campath achieved "remarkable stabilization" of disease. The other benefit of Campath is its once-yearly administration.

"It's not reversing MS," says Lauren Krupp, neurologist at Stony Brook University Hospital in New York and director of the

Details
Cephalon will pay a $15 million upfront payment to obtain an exclusive, worldwide license to ImmuPharma's Lupuzor now in a phase 2b study for systemic lupus erythematosus. As part of the agreement, ImmuPharma will receive a one-off license fee, milestone payments and royalties that may total $500 million. Cephalon will assume all expenses for phase 3 studies and subsequent commercialization for Lupuzor, an immunomodulating spliceosomal peptide recognized by lupus $CD4^+$ T cells.
The two companies have inked a formal cooperation agreement leading to a joint venture (JV) company worth $78 million in assets. The JV will seek to co-develop seasonal and pre-pandemic influenza vaccines, initially targeting viral strains specific to China, Hong Kong and Macau. GSK expects to contribute $31 million in return for a 40% stake in the JV, whereas Neptunus will contribute $47 million in assets.
Codexis, a company developing improved biocatalysts, obtained a license to use Dyadic's C1 expression system for large-scale production of enzymes utilized in biofuels and pharmaceutical intermediate production. The agreement includes an upfront payment by Codexis of $10 million subject to certain performance criteria.
MorphoSys and Galapagos will co-develop novel antibody therapies to treat bone and joint diseases, including osteoporosis, osteoarthritis and rheumatoid arthritis. Galapagos will provide antibody targets using its adenoviral target discovery platform. MorphoSys will contribute its HuCal antibody technologies to generate fully human antibodies directed against these targets. Under the terms of the agreement, the companies will share R&D costs and future revenues equally.

IN brief

Myriad wins *BRCA1* row

After seven years of dispute, the European Patent Office (EPO) has decided to uphold Myriad Genetics' patent on the *BRCA1* 'breast cancer gene' but in a limited form. In 2001 patents were granted to Salt Lake City, Utah–based Myriad for using the genes *BRCA1* and *BRCA2* to diagnose women's predisposition to breast and ovarian cancers. But international research institutes and genetics societies filed an opposition to the patents. "It became clear that the patent owners did not intend to offer licenses [to other institutions], or at least not at a reasonable price," says Gert Matthijs from the Center for Human Genetics, University of Leuven, Belgium. "This [pricing issue] has angered the genetic community, even more than the idea that genes and diagnostic tests could be patented." As a result, EPO revoked the patent for *BRCA1*. Myriad then filed an appeal requesting that the patent be maintained in a revised form. The November 19 ruling gives the patent owners the right to collect royalties on tests carried out across Europe, although the patent's original scope has been reduced to cover only frameshift mutations, not *BRAC1* itself. EPO says the patent cannot be contested at the European level; however, it is still possible for opponents to go to national courts to further reduce the scope of the patent. Myriad's William Hockett says the company is pleased with EPO's decision.

—Nayanah Siva

Value-driven price deal

Small companies and patients stand to benefit from the recently renegotiated Pharmaceutical Price Regulation Scheme (PPRS). Rather than the 5% across-the-board price cut to medicines proposed in June, the finalized deal recommends a pricing scheme that staggers and delays price cuts. PPRS is a voluntary agreement between government and industry on pricing of branded drugs supplied to the National Health Service (NHS). The finalized PPRS recommends a 3.9% price cut in February, followed by a 1.9% cut in January 2010, and for small companies with sales up to £25 ($37.5) million in 2007, the first £5 ($7.5) million sales will be exempt from the price cut. For the first time, the UK's Bioindustry Association (BIA) has been involved in PPRS negotiations, working closely with the Association of British Pharmaceutical Industry on aspects affecting small companies. As part of the agreement, companies that supply the NHS will be allowed to introduce drugs at lower initial prices with the option of negotiating higher prices at later stages if the clinical value of a product is proved. This flexible pricing scheme agreed upon in November will ensure patients have faster access to novel medicines, and encourage industry innovation. "This is a definite plus," says Nick Scott-Ram, the BIA's strategy consultant on this issue. "The PPRS is now taking a more value-based approach to everything. We have come out of 18 months of negotiation in a reasonable position."

Susan Aldridge

Pediatric Multiple Sclerosis Comprehensive Care Center, who is nonetheless guardedly optimistic. "You have patients with relapses and remissions. If you get rid of the relapses, then over time, it's going to look like there is less [of a] persistent neurologic deficit. It's just a function of the drug's effects on the relapses, rather than turning the disease around."

The claims of disease reversal regarding Campath are still "a big stretch," says Wolinksy, who points out that the extrapolations are made by hopeful onlookers and boosters and not by the drug makers Genzyme and Bayer Schering. "The absolute good news is, if we treat early and aggressively, we can expect remarkable outcomes, but at a cost for a fair percentage of patients."

"None of these drugs are going to fix neurons that are dead and gone, but some probably will help to slow the neurodegenerative processes," Margolin says.

Clinicians and regulators worry over side effects, particularly the risk of developing a rare neurological condition progressive multifocal leukoencephalopathy (PML), the brain infection that bedevils the α-4 integrin antagonist Tysabri (natalizumab), comarketed by Biogen Idec, of Cambridge, Massachusetts, and Dublin-based Elan. Thus far, no cases of PML have shown up in MS patients exposed to Campath. Years of experience using Campath for chronic lymphocytic leukemia treatment may not be informative as patients with this form of leukemia can develop PML, independently of Campath.

Despite the troubles associated with Tysabri, people with MS may still retain "an overall positive view" toward the treatment, says David Williams, head of business development for PatientsLikeMe, an online health community for patients with life-changing conditions including MS. "Campath will be the same way, if it's approved," Williams predicts, though the risks as known so far are hardly identical.

With Campath, safety issues could arise over a potentially fatal autoimmune disorder. In the phase 2 trials, 20% of Campath-treated patients developed thyroid disorders compared to 3% on Rebif. Krupp notes, however, that thyroid trouble seems to occur with MS anyway, for reasons that are not well understood. More serious is the development of immune thrombocytopenic purpura (ITP). Three patients in the Campath group developed this complication and one of them died. "Some people would suggest management of ITP is easy, but if it were straightforward and easy, they wouldn't have had the first one die," Wolinsky says. Margolin notes that the fatal case of ITP—the first to arise —"took everyone by surprise," whereas the others fully recovered with treatment, and one did so spontaneously. Krupp, for her patients, "would consider [Campath] in patients where all of those things, as bad as they sound, are 'not as bad' as what's happening with their MS."

Other promising mAbs in late-stage development for MS include Rituxan (rituximab), an approved therapy for rheumatoid arthritis and non-Hodgkin's lymphoma from Biogen and S. San Francisco, California–based Genentech, in phase 3 trials (**Table 1**). Another drug currently in phase 2 studies is Zenapax (daclizumab), an immunosuppressant mAb for organ transplants from Biogen and PDL Biopharma of Fremont, California. Leerink Swann analyst William Tanner wrote in a September research report that consultants were "not overly impressed" with Zenapax, holding out hopes for other compounds, though the safety profile of Campath may be of concern. Still in the game, but just barely, is Basel–based Novartis' S1P1 modulator FTY720 (fingolimod), which has run into serious safety issues in pivotal testing.

For Campath, efficacy could win over safety concerns. One phase 3 trial aims to enroll 525 patients like those in phase 2 with early, relapsing, remitting disease; the other will test relapsing MS patients and intends to enroll 1,200. Campath could be filed for approval with the FDA as early as 2011, probably as a monotherapy. "With the findings to date, I don't see any reason to add another drug," Margolin says, though some neurologists speculate that Campath might be used as induction therapy, to be followed by interferon or Copaxone (glatiramer).

An ongoing debate in MS therapy is how the disease's inflammatory and neurodegenerative aspects overlap and what this means for drug developers. "None of these drugs are going to fix neurons that are dead and gone, but some probably will help to slow the neurodegenerative processes," Margolin says. "We hope our trials will establish Campath as the treatment of choice, if patients are relapsing."

Randy Osborne, Mill Valley, California