migration of autoreactive T lymphocytes into the brain. Natalizumab is more effective than either interferon-β or glatiramer acetate, and is usually well tolerated. A downside to this drug, however, is that, of some 66,000 patients treated with it, more than 30 patients have developed an often fatal brain infection called progressive multifocal leukoencephalitis (Biogen Idec drug information, March 2010, personal communication).

Finally, another drug approved for treating both RR-MS and the early phase of the secondary progressive form of multiple sclerosis, which usually follows RR-MS, is mitoxantrone. Although this drug efficiently blocks the progress of multiple sclerosis, its use is severely restricted because it can be toxic to the heart and has caused cancers known as secondary leukaemias in up to 2.8% of patients[7]. All the approved treatments require frequent injections or periodic intravenous infusions. So an effective oral treatment would be highly desirable.

The two large-scale, phase III clinical trials on RR-MS patients[1,2] tested the efficacy of an immunomodulatory agent called fingolimod (FTY720), which can be taken orally. In the FREEDOMS trial[1], some 1,300 patients were randomly selected for treatment over a two-year period with either FTY720 or a placebo drug. The TRANSFORMS trial[2] also involved almost 1,300 patients, who were given either FTY720 or interferon-β for one year. In the two trials, and for the two tested doses of the drug (0.5 and 1.25 milligrams daily), FTY720 reduced relapse rates by more than 50% compared with the placebo and by 38–52% compared with interferon-β. Moreover, this drug was superior to both placebo and interferon-β in its long-term effects based on brain imaging data and the time it took for patients to develop further disability.

How does this promising drug influence the autoimmune response in multiple sclerosis? Studies in both animal models and human patients[3,8,9] have indicated that autoreactive T lymphocytes are essential for initiating the disease process, and their passage from the blood to the brain is crucial for sustaining it. Like natalizumab, FTY720 interferes with T-lymphocyte migration, albeit in an entirely different way. This synthetic derivative of the antibiotic myriocin is structurally similar to a natural lipid called sphingosine-1-phosphate (S1P). An essential function of S1P is to promote both lymphocyte homing in immune organs such as the thymus and lymph nodes and lymphocyte egress to the peripheral blood[10,11].

Like S1P, the active (phosphorylated) form of FTY720, FTY720-P — which is generated through the action of the enzyme sphingosine kinase 2 — interacts with subtypes 1, 3, 4 and 5 of the transmembrane S1P receptor ($S1P_{1,3–5}$) to trigger several downstream signalling pathways in the cell[12]. S1P affects many biological processes, including blood-vessel formation, cell differentiation, proliferation and immune-cell migration. Not surprisingly, different activities have also been reported for its analogue FTY720-P.

In the context of multiple sclerosis, by far the most relevant effect of FTY720-P relates to its interaction with the $S1P_1$ receptor. On binding of FTY720-P, this cell-surface receptor is internalized for several days. With reduced numbers of $S1P_1$ receptors around, T lymphocytes cannot respond to S1P signals, which would otherwise mediate their migration from the thymus and lymph nodes to the peripheral blood and from there to the brain. Consequently, T lymphocytes remain trapped in lymph nodes, and their numbers and availability in the bloodstream are greatly reduced. FTY720-P also affects the number of specific-antibody-secreting B-lymphocyte subtypes in the different immune compartments, as well as their location within these sites[13]. Other immune cell types, such as natural killer cells, monocytes and polymorphonuclear cells, remain unaffected, at least in number.

As for the activity of FTY720 in the central nervous system, this drug can cross the blood–brain barrier, which normally shields the brain. Once in the brain, it potentially exerts positive effects by interacting with $S1P_1$, SIP_3 and $S1P_5$ receptors on astrocytes and oligodendrocytes — cells that wrap around nerve fibres as a myelin sheath[14].

FTY720 is therefore a highly promising immunomodulatory drug not just for multiple sclerosis but also for other autoimmune diseases and for preventing organ-transplant rejection. Moreover, because of its novel mechanism of action, it might be suitable for combination therapy. Its use, however, will not be without problems. During both trials[1,2], cases of moderately serious herpesvirus infections were noted. This observation contrasts with data from animal studies[15,16], which reported that FTY720 does not compromise protective immune responses during viral infections and may even enhance them. Why herpes infections occurred or have been reactivated in the human trials remains a mystery.

Several more-serious adverse events have also been reported in the two FTY720 human trials[1,2]. These could be due to FTY720 interacting with more than one S1P-receptor subtype, and include cardiovascular complications, an eye condition known as macular oedema, infections, benign and cancerous tumours, and a type of brain inflammation called haemorrhagic encephalitis that has been reported previously[17]. Whether these side effects were caused by FTY720 acting on the endothelial cells lining blood vessels or on other cells of the central nervous system remains unknown. Without doubt — just as investigations of FTY720 have provided seminal insights into the functioning of the immune system, beyond its potential as a drug — much more will be learned from further

50 YEARS AGO

The first hovercraft has begun the hard task of practical development ... The experimental version now flying, the 'SR-NI', is an oval dish on top of which are mounted the propulsion and control systems, and the air compressor ... A reasonably flat operational surface is required and early applications may well be over surfaces which existing vehicles find difficult, for example, marsh, snow, sand, ice and shallow rivers. Serious consideration has been given to a 400-ton car ferry capable of carrying eight hundred passengers and eighty cars across the channel at a speed of 90 knots ... If the hovercraft can prove its worth with modest payloads over short distances, then serious thought could be given to developing a trans-ocean hovercraft capable of crossing the Atlantic in 24 hr.

From *Nature* 19 March 1960.

100 YEARS AGO

'The International Aëro And Motor Boat Exhibition' — Monoplanes comprise by far the larger number of machines in this exhibition. Apart from any inherent advantages of this design ... there is no doubt that its popularity, both with makers and buyers, is owing to Blériot's flight across the Channel last summer. There are twenty monoplanes, nine biplanes, and one triplane, all of these being full-size machines ... Of machines shown by members of the Royal Aëro Club, one of the most interesting is a Short Wright biplane, the first of its kind built in England, and belonging to the Hon. C. S. Rolls ... In general design it closely resembles the machines used by the Wright brothers ... Another Short biplane is shown ... fitted with Short's patent front elevators ... The speed is about 48 miles per hour, and the machine has made a large number of flights, that of March 1, 1910, being of 32 minutes' duration in covering a distance of about 25 miles.

From *Nature* 17 March 1910.

50 & 100 YEARS AGO