The story of Lemtrada: improving the lives of those living with Multiple Sclerosis (MS)

Lemtrada (alemtuzumab), previously known as CAMPATH, is a humanised monoclonal antibody whose target is CD52, a protein found on mature lymphocytes (a type of immune system cell). It was originally developed for use with bone marrow and solid organ transplantation and in leukaemia and is still used, under the CAMPATH name, for these conditions. However, it has a new role under the name Lemtrada, as a treatment for multiple sclerosis (MS), which was approved in May 2014 by the National Institute for Health and Care Excellence (NICE). Clinical trials, published in The Lancet in 2012, revealed that Lemtrada is making a real impact in the treatment of this difficult and disabling condition.

These publications, and ongoing research, are the culmination of many years of effort by scientists in the UK and elsewhere. Indeed, according to the co-discoverer of the CAMPATH family of antibodies, Geoff Hale, over 2,000 people (from researchers and clinicians to patent lawyers) have been involved in the development of this important treatment. He also acknowledges the invaluable contribution of the patients who took part in early clinical trials of what was, at the time, a very experimental drug.

FROM THE LAB TO THE CLINIC

The origins of CAMPATH-1 lay in the need for a treatment for graft-versus-host disease (GvHD), a complication of bone marrow transplantation. In 1979, Herman Waldman and Geoff Hale at the Department of Pathology at Cambridge University, funded by the MRC, isolated monoclonal antibodies from rats, which could eliminate donor T lymphocyte ("T") cells from bone marrow prior to transplantation. It is the attack of these donor T cells on the recipient that causes GvHD. One of these antibodies, CAMPATH-1M, gave virtually complete elimination of the T cells and was selected for further development.

The first bone marrow transplant using CAMPATH-1M for T cell depletion was carried out at Hammersmith Hospital in 1982 on a patient with severe aplastic anaemia (inability to produce mature blood cells). Soon after, it was trialled on a small group of patients with leukaemia and findings were published in The Lancet in 1984. This study was confirmed by other trials in Europe, leading to the establishment of the international CAMPATH users group, which sparked many clinical collaborations over the following 15 years.

The Cambridge lab then came up with another antibody, called CAMPATH-1G. This gave good results in two leukaemia patients and pointed the way to a new direction in this research – the need for a humanised version of the CAMPATH antibody.

As it happened, (see p. 3-4) Michael Neuberger and Greg Winter at the MRC Laboratory of Molecular Biology (just over the road from the pathology labs in Cambridge) were working on producing fully humanised monoclonal antibodies as an important step up from the rat or mouse versions. The two teams worked together to develop humanised CAMPATH (CAMPATH-1H).

The first patient to be treated with CAMPATH-1H was a woman suffering from non-Hodgkins lymphoma. The treatment shrank her tumour-affected spleen from 4.5kg to 0.6kg. Moreover, there were no tumour cells detectable in her blood or bone marrow. This patient still had tumour cells in her spleen, however, and required further treatment with CAMPATH-1H. She did, unfortunately, relapse again and died shortly afterwards. But much had been learned about CAMPATH-1H and how it works. The second patient to be treated fared better, with complete remission of his lymphoma and, over the years, he and his family were very active in fund-raising to support the research.

It was difficult to produce enough of the CAMPATH antibodies to meet growing demand from the research community. Therefore, in 1990, the Therapeutic Antibody Centre (TAC) was set up to take care of large scale antibody production.

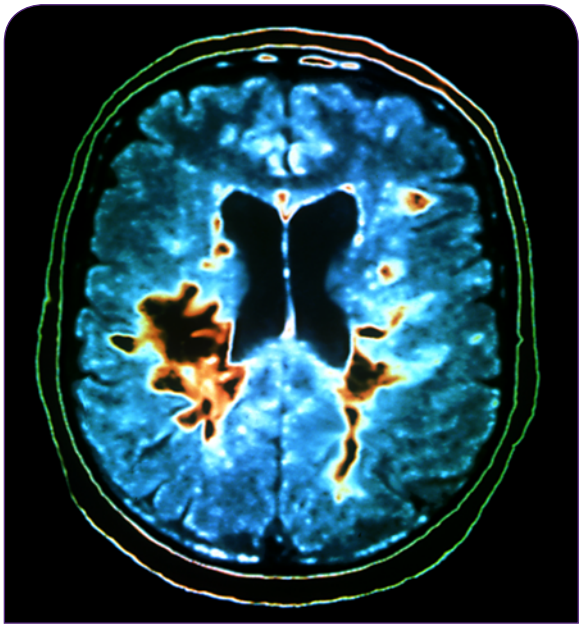
Shortly after the TAC opened, Waldman and Hale were approached about a young woman with a rare autoimmune disease, with a view to trying CAMPATH-1H, as no other treatment had worked for her. After just a short course of the antibody, the patient responded with complete remission. She also produced a very strong immune response to CAMPATH-1H which meant that her blood samples proved very valuable in the further study of the antibody. This **patient, Nicola Cole, has contributed a great deal over the years to the development of CAMPATH, so it was highly appropriate that she was the one to open the new TAC in Oxford in 1995**. This was the start of the development of CAMPATH-1H for other autoimmune diseases, including rheumatoid arthritis and, later, multiple sclerosis.

Commercial development of the CAMPATH family

- In 1985, the British Technology Group (BTG, which handled tech transfer for the MRC) licensed CAMPATH-1M to Wellcome Biotech for application in bone marrow transplant.
- CAMPATH-1G and CAMPATH-1H were also licensed to Wellcome Biotech as these looked more promising for clinical applications – including organ transplantation and autoimmune disease.
- Eventually Wellcome (the parent company, into which Wellcome Biotech was absorbed) dropped CAMPATH-1H and BTG licensed it in 1997 to LeukoSite, a small US biotech company, which was later purchased by Millennium, who continued the development of CAMPATH-1H with ILEX Oncology.
- In 2001, the antibody was first licensed for the treatment of chronic lymphocytic leukaemia. Genzyme acquired ILEX from Millennium and began to develop CAMPATH-1H for multiple sclerosis.
- In 2011, Sanofi acquired Genzyme and clinical development of Lemtrada continues.

LEMTRADA IN MULTIPLE SCLEROSIS

In 1991, Alastair Compston's group at the Department of Neurology in Cambridge, was contacted about CAMPATH-1H by a middle-aged patient with MS. She went, within a few months, from being confined to a wheelchair to being able to ski. Magnetic resonance imaging (MRI) scans showed a reduction in the inflammation that is one of the hallmarks of MS. The researchers began a pilot trial and, by 1998, 29 patients had been treated with CAMPATH-1H.



A coloured MRI scan of the brain of a patient suffering from MS. The black/orange lesions highlight the destruction of the myelin sheaths around the axon nerve fibres of the brain and spinal cord which cause MS. Lemtrada has been shown to slow down this damage to the brain tissue.

Further research followed, culminating in two Phase III trials. In the CARE-MS 1 trial, Lemtrada was compared with Rebif (interferon beta-1a, a signalling protein) in people with relapsing remitting MS not previously on treatment. Those on Lemtrada were around 55% less likely to experience a relapse over the next two years. The CARE-MS 2 trial compared Lemtrada with Rebif in people with relapsing remitting MS who had experienced at least one relapse when on Rebif or Copaxone (glatiramer – a protein which mimics the nerve cell coating myelin that is lost in MS). Those on Lemtrada were around 50% less likely to have a relapse and 42% less likely to experience disability over the next two years.

In 2014, NICE recommended Lemtrada as treatment for relapsing-remitting MS. The antibody is given by infusion once a year, for five days in the first year and three days in the second. For the patient, this compares favourably with other treatments, which involve oral tablets or weekly injections. Recently, Genzyme announced magnetic resonance imaging data that show that Lemtrada is associated with a slowing of brain atrophy (loss of neurons and connections) in MS.

30 years on from its beginnings in the lab, Lemtrada's benefits for patients continue to grow.