MILESTONE 11

CAMPATH-1H: a tale of much patience and many patients

The humanized monoclonal antibody CAMPATH-1H (alemtuzumab) was approved in 2014 for the treatment of patients with relapsing–remitting multiple sclerosis, but the CAMPATH story began more than 30 years earlier as a question of basic research. The clinical application of CAMPATH-1H is a tale of extraordinary perseverance involving multiple patient trials by teams at the University of Cambridge and, later, the University of Oxford.

In 1979, Herman Waldmann and colleagues were using the hybridoma technique developed by César Milstein and Georges Köhler (MILESTONE 9) to generate rat monoclonal antibodies specific for human lymphocytes with the aim of using these antibodies as short-term therapy to achieve long-term benefit in transplantation and autoimmune disease and, through such applications, to better understand the mechanisms of immunotolerance. They identified an immunoglobulin M (IgM) clone (CAMPATH-1), later shown to bind the glycoprotein CD52, that could fix human complement and eliminate lymphocytes *in vitro*. The first study of CAMPATH-1 was published in 1983 and described the treatment of peripheral blood mononuclear cells with monoclonal antibody and complement, which killed more than 99% of lymphocytes without affecting hematopoietic progenitor cells. Realizing the clinical potential of their findings, the authors concluded that CAMPATH-1 "could potentially be of use in any situation where depletion of lymphocytes is required."

A follow-up study published in 1984 described 11 patients who received bone-marrow transplants from which T cells had been depleted through the use of CAMPATH-1. Patients were given no additional immunosuppression. No signs of graft-versus-host disease were observed for up to 12 months, but the late graft failure seen in two patients suggested that *in vivo* depletion of recipient T cells as well as of donor T cells would be required for successful engraftment.

Thus, Waldmann and colleagues (notably Geoff Hale, Greg Winter and Mike Clark) set out to improve the *in vivo* properties of CAMPATH-1 through class switching (MILESTONE 8) and humanization (MILESTONE 12). In 1998, CAMPATH-1H (humanized IgG1), which was manufactured in an academic facility in Cambridge, was the first humanized monoclonal antibody to be injected into humans. Lymphoma cells were cleared from the blood and bone marrow of two patients with non-Hodgkin lymphoma and from a single patient with life-threatening vasculitis.

> "[CAMPATH-1H] could potentially be of use in any situation where depletion of lymphocytes is required"

Following those initial findings, Cambridge scientists explored the potential of CAMPATH-1H as short-term therapy for kidney transplantation and a range of autoimmune diseases. In the latter category, most notably in collaboration with the neurologists Alastair Compston and Alasdair Coles, CAMPATH-1H was investigated as a short-course therapy for the autoimmune disease multiple sclerosis. In 2006, this academic study reported that CAMPATH-1H reduced inflammation and improved disability in patients with relapsing–remitting disease. That study paved the way for industry-sponsored phase II and III clinical trials of CAMPATH-1H that eventually showed that short-term antibody therapy was more effective at preventing disease relapse than was standard interferon-β therapy.

In the three decades that it took CAMPATH-1H to reach regulatory approval for the treatment of multiple sclerosis, many other humanized monoclonal antibodies joined the market, often overtaking but forever in credit to the original.

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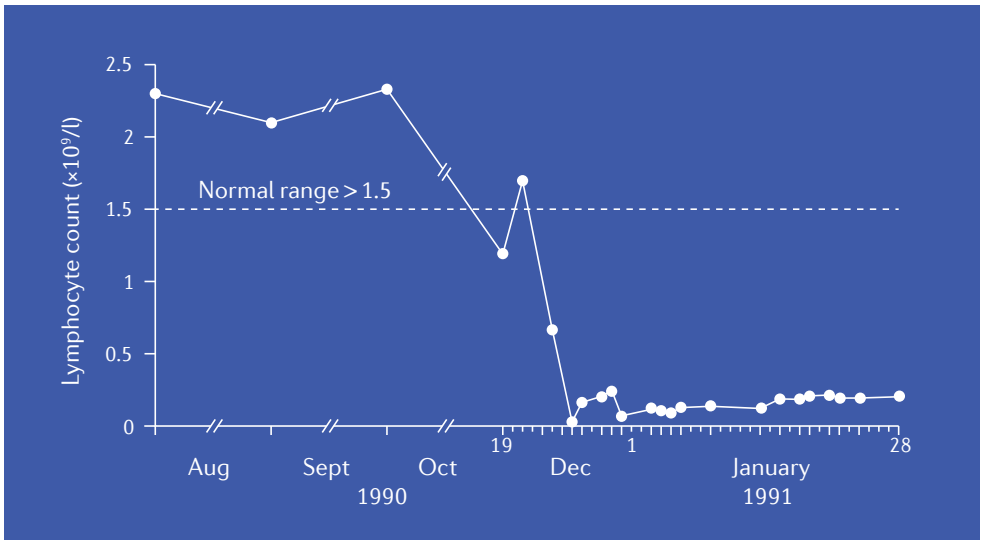

This analysis of lymphocyte depletion to achieve remission in a patient with severe vasculitis shows the effect on lymphocyte counts of a short course of treatment with the first manufactured batch of CAMPATH-1H. Adapted from data provided by the late Martin Lockwood and courtesy of Herman Waldmann.

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FURTHER READING Waldmann, H. & Hale, G. CAMPATH: from concept to clinic. *Phil. Trans. R. Soc. B* **360**, 1707–1711 (2005)