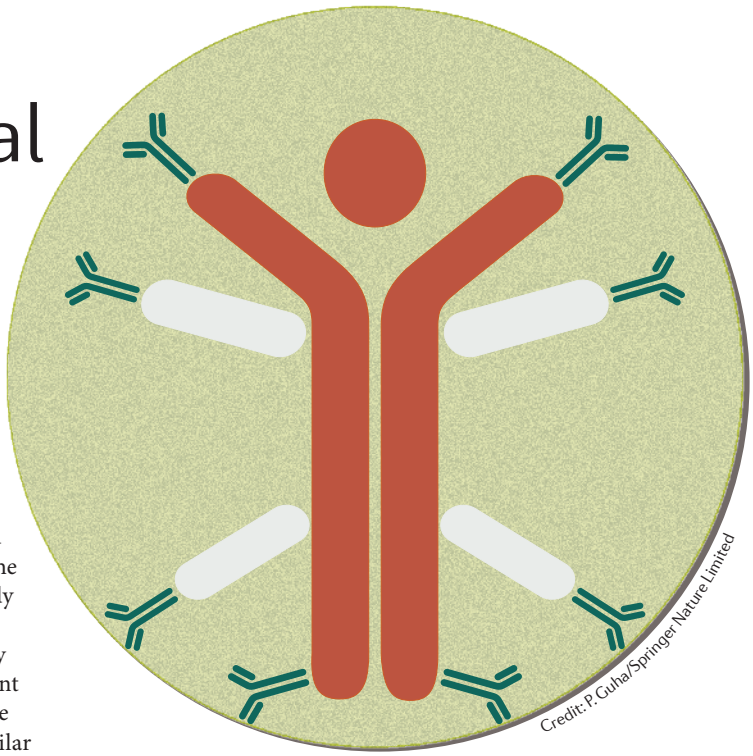
MILESTONE 2

The first monoclonal antibody therapy



Although the injectable therapies (interferon-β (IFNβ) and glatiramer acetate; MILESTONE 1) for multiple sclerosis (MS) were groundbreaking, they were only moderately effective, reducing the annual rate of relapse by approximately one-third. In addition, approximately one-third of patients who receive IFNβ do not respond at all to the treatment. Consequently, efforts continued after their approval to develop more effective treatments, and subsequent work led to the development of the first monoclonal antibody for MS, natalizumab.

The development of natalizumab stemmed from investigations into the therapeutic mechanism of action of IFNβ. Its overall effect is anti-inflammatory, but its exact mechanism of action remains unknown. It is thought to act, in part, by reducing lymphocyte migration across the blood–brain barrier, an important early step in the formation of the inflammatory brain lesions that characterize MS.

While seeking to identify the receptors that mediate attachment of circulating leukocytes to the endothelium in rats with experimental autoimmune encephalomyelitis (EAE; a commonly used animal model of MS), Ted Yednock and colleagues found that their binding was inhibited by antibodies against α4β1 integrin (also known as VLA4), but not by antibodies against various other adhesion receptors. When tested in vivo, the antibody against α4β1 integrin prevented accumulation of leukocytes in the rat CNS and the development of EAE.

The mechanism of action of the antibody was found to be inhibition of the interaction of α4β1 integrin on the surface of lymphocytes with vascular cell adhesion molecule 1, a receptor on the surface of vascular endothelial cells in the brain and spinal cord. Blockade of this interaction reduces the adhesion of lymphocytes and their migration into areas of inflammation.

The work of Yednock and colleagues had been preceded in 1986 by FDA approval of the first ever monoclonal antibody treatment, muromonab-CD3 (anti-CD3), a mouse antibody for the prevention of transplant rejection. This work paved the way for development of a similar therapy to treat MS. However, muromonab-CD3 induced counter-productive immune responses owing to patients producing antibodies against the mouse antibody. For this reason, the antibody that was developed to target α4β1 integrin in MS was a humanized monoclonal antibody — natalizumab.

Results from the initial clinical trials of natalizumab were published in two papers in 1999. These studies indicated that natalizumab was safe and well-tolerated. Among patients with active relapsing–remitting MS or secondary progressive MS, the mean number of new active lesions detected over the first 12 weeks was significantly lower for patients who received natalizumab (1.8) than for those who received placebo (3.6). Similarly, the number of new gadolinium-enhancing lesions was lower (a mean of 1.6 versus 3.3).

Given the promising short-term effects in these initial studies, longer clinical trials were started. Similar results were reported in 2003 in a trial with 213 participants who received natalizumab or placebo every 28 days for 6 months. In 2006, results of a phase III trial that included 942 people who received natalizumab or placebo for more than 2 years showed that natalizumab reduced the relapse rate at 1 year by 68% and the risk of sustained progression of disability by 42% over 2 years compared with placebo.

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In 2005, reports emerged of three patients who had developed progressive multifocal leukoencephalopathy (PML) while receiving natalizumab treatment. These reports led to temporary withdrawal of natalizumab administration until the risks were understood and recommendations were made for their management (MILESTONE 3).

The development of natalizumab had a positive effect on MS treatment and preceded development of further, more effective antibody therapies (MILESTONES 5, 8). However, the only approved therapies at the time required injection, and efforts continued to find suitable drugs for oral administration.

Katharine Barnes, Managing Editor, *Nature Protocols*

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