MILESTONE 13

Targeting cytokines in disease

Monoclonal antibodies that specifically block cytokines (soluble mediators of cell communication) have revolutionized the treatment of autoimmune diseases. The staggering potential of this approach followed a small clinical trial in 1992 that used a chimeric monoclonal antibody to tumor-necrosis factor (TNF) to treat patients with therapy-resistant rheumatoid arthritis. Today, TNF inhibitors are the world's leading drug class, with sales of more than US $30 billion and use in more than 7 million patients.

The hypothesis that cytokines might be important in autoimmune disease first came from immunohistological data in the early 1980s showing upregulated expression of major histocompatibility complex class II in autoimmune tissues, such as the thyroid in Graves' disease and rheumatoid joints. Marc Feldmann (an Australian immunologist trained in medicine and working in London, UK) speculated that cytokines might control this effect and hence be of pathogenic importance. To help test his hypothesis, Feldmann approached Ravinder Maini (a UK-based rheumatologist who had studied soluble factors involved in lymphocyte activation), and a very fruitful collaboration ensued. With the help of Fionula Brennan, they and other groups demonstrated the presence of multiple pro-inflammatory cytokines in inflamed joints. In 1989, they showed that in cultures of human rheumatoid tissue, if TNF was blocked by the addition of various antibodies, the production of interleukin 1 (IL-1β) and other pro-inflammatory cytokines ceased. This suggested that TNF might be a 'master regulator' and led to the concept of a 'TNF-dependent cytokine cascade' that drives the manifestations of rheumatoid arthritis. Tony Cerami and others had encouraged the industry to make TNF-specific antibodies to treat bacterial sepsis, but they were unsuccessful.

In 1993, Feldmann and Maini gained assistance from the emerging biotechnology company Centocor, which had a chimeric (human–mouse; MILESTONE 12) TNF-specific monoclonal antibody known as 'cA2' (subsequently registered as infliximab or Remicade), to perform a small proof-of-principle clinical trial of 20 patients with active rheumatoid arthritis. After infusion of the antibody, nearly every patient reported rapid and remarkable improvement in pain, fatigue and mobility. They also showed a reduction in inflammation, as indicated by loss of joint swelling and decreased serum concentrations of C-reactive protein and IL-6. Unfortunately, the improvements were short-lived and disease activity recurred after 12–16 weeks. Consequently, a subset of these patients were re-treated with cA2, and they showed subsequent responses of equal magnitude. Efficacy and durability were proven in further longer term clinical trials, and beneficial effects were extended through the use of lower doses of the antibody in combination with the anti-rheumatoid drug methotrexate.

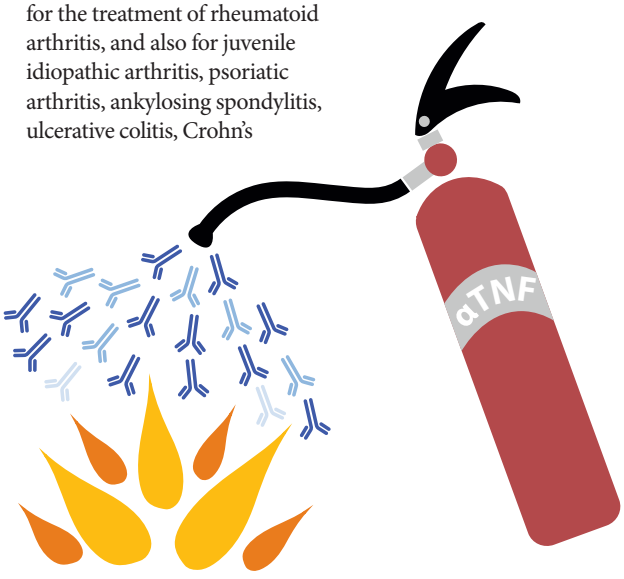
There are currently five antibody-based TNF inhibitors licensed for the treatment of rheumatoid arthritis, and also for juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and psoriasis. Common to these diseases, and possibly others, is the role of TNF in orchestrating the recruitment of leukocytes to target tissues and upregulating the expression of adhesion molecules and chemokines. However, this approach has limitations and is not beneficial in all patients. For example, some patients with juvenile idiopathic arthritis do not respond to TNF blockade, but a monoclonal antibody specific for the IL-6 receptor (tocilizumab; Hoffmann–La Roche and Chugai) from Tadamitsu Kishimoto's laboratory is effective in treating these children.

> "After infusion of the antibody, nearly every patient reported rapid and remarkable improvement"

More recently, antibodies specific for IL-17A have been developed for the treatment of psoriasis. IL-17A, which is produced by T cells and other cells, is thought to function as a 'master cytokine' in the pathogenesis of psoriasis by stimulating keratinocytes to secrete chemokines and other pro-inflammatory mediators that recruit additional inflammatory cells to the skin. The first IL-17A-specific antibody to gain approval (in 2015) for the treatment of psoriasis was secukinumab (Novartis), and now several others are also approved or in development.

The remarkable success of TNF blockade has inspired the development of an ever-expanding toolbox of cytokine-targeted antibody drugs that are bringing real hope to patients with autoimmune diseases and beyond. Indeed, nearly half of all medicines in clinical trials are monoclonal antibodies or their derivatives (MILESTONE 14).

Lucy Bird,
Senior Editor, *Nature Reviews Immunology*



Targeting cytokines such as TNF with antibody-based drugs can quench harmful immune responses in patients with chronic inflammatory diseases. Image credit: P. Guha/Nature Publishing Group.

ORIGINAL RESEARCH PAPERS Elliott. M. J. *et al.* Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor-α. *Arthritis Rheum.* **36**, 1681–1690 (1993) | Yokota, S. *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* **371**, 998–1006 (2008) | Langley, R. G. *et al.* Secukinumab in plaque psoriasis—results of two phase 3 trials. *New Engl. J. Med.* **371**, 326–338 (2014)

FURTHER READING Feldmann, M. & Maini, R. N. TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nat. Med.* **9**, 1245–1250 (2003) | Chan, A. C. & Carter, P. J. Therapeutic antibodies for autoimmunity and inflammation. *Nat. Rev. Immunol.* **10**, 301–316 (2010)