

Milestone 17

Anti-CD3: the agonist and the ecstasy

Studies published in the 1960s and 1970s began to solidify the concept that human type 1 diabetes (T1D) is an autoimmune disease (Milestone 2). This was an important conceptual advance because it offered hope of treating the cause of the disease rather than simply controlling symptoms via the provision of insulin (Milestone 1). Initial treatments focused on well-established immunosuppressive drugs such as corticosteroids and cyclosporine. However, the broad immunosuppression caused by these drugs, their associated toxicities and the need for their prolonged use in predominantly young patients ruled them out as a viable therapy for T1D.

An important breakthrough happened in 1985 – namely, the first clinical approval of a monoclonal antibody (mAb), Orthoclone OKT3. This drug was initially used for managing rejection of kidney, heart and liver transplants. Orthoclone OKT3 targets the CD3 molecule that is present exclusively on T cells and depletes them from the circulation, which makes the drug an effective immunomodulator. Unfortunately, its use was frequently accompanied by a severe cytokine release syndrome stemming from its strong initial activation of T cells, which led to its eventual withdrawal from the clinic. Although Orthoclone OKT3 could not fully realize its clinical potential, it did show CD3 to be a rational drug target for treating autoimmune diseases such as T1D.

The 1990s saw key technological advances in the development of modified CD3-specific mAbs that did not stimulate T cells as potently, which meant that they circumvented the harmful cytokine release syndrome that had dogged earlier approaches. Initial pre-clinical studies in mouse models of T1D were encouraging. For example, a 1994 paper by Lucienne Chatenoud, Jean-Francois Bach and colleagues showed that short-term anti-CD3 treatment in recently diagnosed non-obese diabetic mice induced durable remission of disease. Importantly, treated mice seemed to have an otherwise intact immune response, suggesting that only the diabetogenic T cells were targeted.

This new class of CD3-specific mAbs only weakly and transiently depleted their target cells so the mechanisms by which they modulated diabetogenic T cells were rather elusive;

however, some of the first clues were offered by a 1997 paper from the Jeffrey Bluestone lab. Binding of CD3 by modified mAbs seemed to trigger only a partial agonist signal, which led to a lasting state of T cell non-responsiveness. Numerous subsequent studies have expanded on these mechanistic findings and among other things have shown that the CD3-specific mAbs primarily exert their effects on activated cells. This would explain the relative selectivity of anti-CD3 therapy for diabetogenic T cells while leaving the rest of the immune response intact. Later evidence also suggested that the partial agonist signalling of CD3-specific mAbs enhanced the function and/or proliferation of regulatory T cells, which then exerted a dominant suppression on autoreactive cells.

These encouraging animal studies eventually led to the first clinical trial of a partial agonist CD3-specific mAb in T1D. In 2002, Kevan Herold et al. published the results of a small clinical trial of patients recently diagnosed with T1D who received an escalating dose over 2 weeks of the partial agonist CD3-specific mAb teplizumab. There was no evidence of the severe systemic inflammation seen with Orthoclone OKT3, with the most common side effects generally being a transient lymphopenia, rash and mild fever. Most importantly, the patients receiving the mAb showed slower deterioration of β -cell function over 12 months.

Another intriguing aspect of these findings was that there seemed to be a durable effect on the immune response after a single short course of mAb at a relatively low dose, which suggested that it might be possible to ‘rewire’ the immune response into a tolerant state. This initial clinical trial was followed in 2005 by a larger phase II study from Lucienne Chatenoud and colleagues using another distinct CD3-specific mAb, oteelixizumab, in new-onset T1D. This study also showed that a brief course of mAb improved preservation of β -cell function, this time over an 18-month follow-up. CD3-specific mAbs continue to be actively studied in human T1D. For example, Kevan Herold and colleagues completed the first successful prevention trial in 2019. This showed that relatives of patients with T1D at high risk for development of clinical disease who received teplizumab had slower progression to disease than the placebo group.

After some initial false starts, it now seems that anti-CD3 therapy might be starting to realize its full therapeutic potential. Future trials of CD3-specific mAbs, including those in combination with other immunomodulating drugs, could have great potential in protecting β -cell function and restoring immunological tolerance in T1D.

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Milestone study

Herold, K. C. et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N. Engl. J. Med.* **346**, 1692–1698 (2002)

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