DEAL WATCH

IL-2 focus switches to stimulating T_{regs}

Recombinant interleukin-2 (IL-2) has been used since the early 1990s for the treatment of renal cell carcinoma and melanoma, as high-dose IL-2 has immune-stimulating properties. A spate of deals in 2017 — including Eli Lilly's acquisition of co-development rights to Nektar's NKTR-358, the acquisition of Delinia by Celgene, and a co-development agreement between ILTOO Pharma and Servier (Supplementary information S1 (table)) — illustrate growing interest in another potential therapeutic use for IL-2. This cytokine stimulates regulatory T (T_{reg}) cells and therefore could have applications in numerous autoimmune diseases.

Two nearly simultaneous discoveries in the 1990s catalysed research on IL-2 as an immunosuppressive agent, rather than an immune stimulant. "I think the people who do mouse studies deserve all the credit for this," says Abul Abbas, a professor at the University of California, San Francisco, USA, who has advised ILTOO and Celgene. IL-2 was known to promote effector T (T_{eff}) cell function (hence its anticancer properties), but when scientists knocked out *Il2* or components of its receptor in mice, they unexpectedly developed spontaneous autoimmunity. This observation coincided with the discovery of T_{reg} cells — a marker of which is constitutive expression of the high-affinity IL-2 receptor α-chain (IL-2Rα) — and their primary role in dampening T_{eff} cells and resolving inflammation. Eventually, IL-2 was found to be a key cytokine in T_{reg} cell development, thus explaining the mouse phenotypes (*Nat. Rev. Immunol.* **15**, 283–294; 2015). "That's when the field of IL-2 therapeutics got turned on its head," says Abbas.

The IL-2R can be composed of different combinations of the α- and β-chains together with the common γ-chain, leading to receptors with varying affinity for IL-2. Whereas T_{reg} cells constitutively express high levels of IL-2Rα, T_{eff} cells express this chain only transiently after stimulation and also express the lower-affinity IL-2Rβ. David Klatzmann, a professor at Pierre and Marie Curie University, Paris, France, reasoned that low-dose IL-2 could preferentially stimulate T_{reg} cells over T_{eff} cells. A pioneering phase I/IIa trial that he led showed that low-dose IL-2 promoted T_{reg} cell development in patients with hepatitis C virus (HCV)-induced vasculitis, which is characterized by a low number of T_{reg} cells (*N. Engl J. Med.* **22**, 2067–2077; 2011). "When I saw the results of this first trial, and knowing that you can find IL-2 on the shelves of most hospitals, I thought that people would immediately realize its potential, because there is a T_{reg} insufficiency in many settings," he says. ILTOO Pharma was spun out from his work. Simultaneously, another group investigating the same hypothesis — led by John Koreth at the Dana-Farber Cancer Institute, Boston, USA — reported a positive trial of low-dose IL-2 in graft-versus-host disease (*N. Engl J. Med.* **365**, 2055–2066; 2011). Subsequent trials of low-dose IL-2 have reported positive results in diseases including type 1 diabetes (T1D) (*Lancet Diabetes Endocrinol.* **4**, 295–305; 2013) and systemic lupus erythematosus (SLE) (*Nat. Med.* **22**, 991–993; 2016). And in an ongoing 'disease-finding trial' led by Klatzmann that is investigating low-dose IL-2 in 14 different autoimmune, T cell- or antibody-based diseases (NCT01988506), he has found a biological response in all patients treated with the cytokine so far, leading him to describe IL-2 as "the corticosteroids of the 21st century".

Using a low dose of IL-2 is one way to bias responses to activate T_{reg} cells; another is to modify IL-2 to preferentially target IL-2Rα. Delinia's lead candidate, DEL106, is a mutated version of IL-2 that preferentially binds to IL-2Rα, fused to an antibody Fc domain, whereas Nektar developed a polyethylene glycol (PEG)-conjugated version of IL-2, known as NKTR-358. Although PEGylation is normally used to extend protein half-life, Nektar recently presented data suggesting that NKTR-358 preferentially binds to IL-2Rα. These candidates are in preclinical development.

George Tsokos, a professor at Harvard Medical School, Boston, USA, highlights some potential hurdles for IL-2 therapies. Patients with SLE, a disease high on the list of potential uses for IL-2, are clinically heterogeneous, and the same is likely to be true for the molecular pathways governing T_{reg} cell development in these individuals. Moreover, his group found that T cells from patients with SLE have reduced sensitivity to IL-2 (*Arthritis Rheumatol.* **4**, 808–813; 2017). Klatzmann agrees that biomarkers could be necessary and that not all patients with a biological response will necessarily have a clinical response. Nevertheless, it seems that harnessing T_{reg} cells could lead to much-needed new therapies for diseases such as T1D and SLE.

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SUPPLEMENTARY INFORMATION
See online article: S1 (table)
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