BIOBUSINESS BRIEFS

DEAL WATCH

Boosting TRegs to target autoimmune disease

Abbott Laboratories and Biotest Pharmaceuticals have entered into an agreement to co-develop BT-061, a humanized CD4-specific monoclonal antibody that is currently in Phase II trials for psoriasis and rheumatoid arthritis (RA). Under the agreement, Biotest will receive an upfront fee of US$85 million, with additional milestone payments potentially adding up to a total of $395 million, plus royalties on the sales of BT-061, if the drug is approved. The two companies will co-promote BT-061 in the five major European markets (Germany, France, the United Kingdom, Italy and Spain), and Abbott will have exclusive global rights to commercialize BT-061 outside these countries.

The target, CD4, is a surface glycoprotein that functions as a co-receptor for the T cell receptor (TCR) on $CD4^+$ T helper cells and regulatory T (T_{Reg}) cells. Several different CD4-specific antibodies have entered clinical trials for autoimmune diseases so far, and fall into two main categories: depleting and non-depleting. Depleting CD4-specific antibodies function by targeting autoreactive $CD4^+$ effector T cells, but can suppress general immunity. By contrast, non-depleting antibodies such as BT-061 are thought to act by activating T_{Reg} cells, which have been found to malfunction in autoimmune diseases such as psoriasis and RA. As only natural regulatory mechanisms are activated in this process, BT-061 is thought to be particularly safe, as the immune system as a whole remains functional to fight infection.

Michael Ehrenstein, Professor of Rheumatology at University College London, UK, expresses his excitement about the fact that a non-depleting CD4-specific approach has shown promising results in RA and psoriasis. "Inducing tolerance in autoimmune diseases is an attractive proposition, as it raises the possibility of administering the therapy for only a short period of time, until balance is restored. This contrasts with currently available conventional or biological therapies, which need to be administered continuously for conditions like RA."

How BT-061 works, and why it appears to affect T_{Reg} cells differently to other $CD4^+$ T cell subsets, is not yet entirely clear. Ehrenstein points out that: "In an inflammatory milieu, TCR signalling is likely to be intense. Targeting CD4 would dampen TCR signalling and it is possible that in this context, T_{Regs} are less sensitive than effector T cells to this inhibitory effect." Alexander Rudensky, Professor at Memorial Sloan Kettering Cancer Center, New York, USA, explains that we now also know that a particular 'suboptimal' mode of T cell activation results in the generation of T_{Reg} cells. "In this regard, it is possible that during the ongoing recruitment of naive T cells into the chronic inflammatory response, BT-061 might facilitate the differentiation of new auto-antigen-specific T_{Reg} cells." A further hypothesis is that the antibody selectively stimulates preformed T_{Reg} cells, at the expense of pathogenic effector T cells, but the mechanistic underpinnings of such a mechanism are not clear.

The selective expansion or activation of T_{Reg} cells is a promising strategy in a range of autoimmune settings, and preclinical studies with BT-061 are underway to study its potential in immune-related disorders other than RA and psoriasis.