An Engineered Soluble Human IL-17A Receptor for Treatment of Auto-Immune Diseases (BGN)

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Interleukin 17 (IL-17) represents a family of pro-inflammatory cytokines consisting of six members, termed IL-17A-F. IL-17A is expressed by a unique lineage of CD4 T cells (Th-17) and is known to stimulate fibroblasts, endothelial cells, epithelial cells and macrophages to produce multiple pro-inflammatory mediators, including IL-1, IL-6, TNF-alpha, NOS-2 and chemokines, resulting in the induction of inflammation. Previous studies have shown that IL-17 is actively involved in a range of pathologic conditions in humans, ranging from common asthma to several autoimmune diseases, such as rheumatoid arthritis (RA), psoriasis and inflammatory bowel disease, as well as allergen-specific immune responses. Three anti- IL-17 monoclonal antibodies have shown initial promise in recent Phase II clinical trials for treatment of psoriasis. We have inhibited the same target, IL-17, using a different agent we have developed, namely a soluble IL-17 receptor, sIL-17R.

The Technology

Using a directed evolution approach, we have generated novel soluble IL-17RA mutants exhibiting increased IL-17A binding affinity and thermostability, relative to the wild type enzyme. A human fibroblast cell-based assay and in vivo analysis in mice indicated that two improved IL-17RA mutants efficiently inhibited the secretion of IL-17A-induced pro-inflammatory cytokines. Examination of one of these mutants in a psoriasis mice model showed the efficacy of that mutant in promoting recovery of psoriasis plaques. This mutant can thus be used as a promising drug candidate for the treatment of psoriasis and can be tested as a therapeutic agent for various other auto-immune diseases.

Applications

Our novel proteins may be useful as therapeutic agents for the treatment of auto-immune diseases, including RA, psoriasis and inflammatory bowel disease.

Advantages:

Higher affinity to IL-17 than natural IL-17R (6-fold increase)
Higher stability than natural IL-17R
No observed toxicity

Status of Development:

Directed evolution of the IL-17A receptor results in improved IL-17A affinity
The engineered receptors efficiently inhibit IL-17A-induced cytokine secretion in vitro and in vivo
The engineered receptor promotes recovery of psoriasis plaques in a mouse model

Patent Status

Pending

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