GLYKO-ENGINEERED INTERLEUKIN-4 BASED ANTAGONISTS

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HINTERGRUND

Interleukin-4 (IL4) and IL13 are crucial mediators in the onset and progression of chronic inflammatory diseases. Thus, over the past 10 years IL4 and IL13 became central targets in novel therapy strategies directed against atopic dermatitis, allergy and allergic asthma. Most of them are based on neutralizing antibodies. Due to compensatory functions of IL4 and IL13 antibodies targeting either one of the cytokines or receptors gamma chain or IL-13Rα1 act as partial antagonists, only reducing IL4 or IL13 activity. In contrast, targeting the IL-4Rα receptor has been shown to be a successful treatment strategy inhibiting both IL4 and IL13. Pitrakinra, an IL-4 mutant (R121DY124D) inhibits IL4 and IL13 signalling through blockade of the shared IL4Rα receptor. However, due to pitfalls, like a rather short serum half-life of three hours, Pitrakinra failed to meet the endpoints in a clinical phase 2b trial.

LÖSUNG

This technology here provides an new strategy for the generation of a novel IL4-based IL4/IL13-inhibitor that firstly blocks signaling of endogenous IL4 and IL13 with an IC50 value five times lower than Pitrakinra, that secondly exhibits an increased serum lifetime and that thirdly shows no or an ultimately low immunogenic potential allowing longterm application. This was achieved by inducing a sterically demanding group into a central position of the receptor-interacting epitope of IL4. Introducing steric hindrance is much more efficient in abrogating an interaction between two binding partners than creating an electrostatic mismatch (Pitrakinra). For reducing the immunogenic potential, mono- and oligosaccharides that can mimic N-glycan structures naturally found in glycoproteins such as IL4 were added by inducing multiple specific mutations. This modifications with complex oligosaccharide groups also enhance protein stability by strongly reducing renal and endocytotic protein clearance.
Figure: An IL4-based antagonist can be generated by designing an IL4 protein (ligand) that can still bind to IL4Rα (receptor 1) but is incapable to recruit either one of the two receptors (receptor 2). This competes with endogenous IL4 (and IL13) for binding to IL4Rα and shut down IL4 (and IL13) signaling.

**VORTEILE**

- New strategy for the generation of a novel IL4-based IL4/IL13-inhibitor
- Innovative application of N-glycan structures for development of receptor antagonists
- Applicable for following areas: atopic dermatitis, allergy and allergic asthma