Il-6 Receptor Alpha-Binding Protein And Its Use In Controlling Cytokine Release Syndrome In Immunotherapy

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SUMMARY

UCLA researchers in the Department of Chemical and Biomolecular Engineering have developed a novel protein that binds to and inhibits human IL-6 receptor alpha (IL-6Rα), which can be used to modulate and/or prevent cytokine release syndrome in immunotherapy.

BACKGROUND

Severe cytokine release syndrome (CRS), or a sudden and dramatic increase in cytokine production caused by an intensely overstimulated immune system, has been implicated in the death of multiple patients treated with adoptive T-cell therapy. In particular, IL-6 has been shown to be highly upregulated in patients experiencing severe CRS, and tocilizumab—an anti-IL-6Rα antibody—is an effective treatment for CRS in many patients. However, real-time detection of cytokine levels remains unfeasible at this time. As a result, clinical decisions on when to treat a patient with tocilizumab or other pharmaceutical interventions such as corticosteroids must be made based on indirect symptoms such as fever and rising blood pressure. Consequently, the treatment timing of CRS is imprecise and susceptible to missing the optimum treatment window.

INNOVATION

The inventors developed a single-chain variant of tocilizumab that efficiently binds to and inhibits human IL-6 receptor alpha (IL-6Rα). This synthetic protein can be used to modulate and/or prevent cytokine release syndrome in immunotherapy, particularly adoptive T-cell therapy. When stably expressed in tumor-targeting T cells, this invention can potentially increase the precision and effectiveness of CRS intervention by enabling T cells to perform real-time modulation of cytokine signaling, within the cellular milieu where CRS originates. The invention could regulate cytokine signaling in both engineered T cells and the surrounding endogenous immune cells, which are also important contributors to CRS.

APPLICATIONS

- Prevent and/or ameliorate cytokine release syndrome
- Suppress undesirable inflammatory responses

ADVANTAGES

- Self-regulating
- Real-time detection
- Effective and precise

STATE OF DEVELOPMENT

Primary human T cells that constitutively express an anti-CD19 chimeric antigen receptor (CAR) and the anti–IL-6Rα protein have been shown to significantly reduce cytokine production upon antigen stimulation, without compromising target-cell lysis or T-cell proliferation *in vitro*. It has also been shown that constitutive anti–IL-6Rα protein production does not alter CD19 CAR-T cells' subtype differentiation pattern, nor does it trigger premature exhaustion of the CAR-T cells. Finally, it has been confirmed that CD19 CAR-T cells that stably express the anti–IL-6Rα protein retain equally robust anti-tumor functions *in vivo* compared to conventional CD19 CAR-T cells.

PATENT STATUS

Country	Type	Number	Dated	Case

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OTHER INFORMATION

KEYWORDS

Immunotherapy, T cell therapy, sequence, modulate, cytokine release syndrome, single-chain variable fragments, IL-6 receptor alpha

CATEGORIZED AS

- **Medical**
  - Disease: Cancer
  - Therapeutics

RELATED CASES

2017-453-0

United States Of America	Issued Patent	11,701,384	07/18/2023	2017-453

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Single-Chain Bispecific Chimeric Antigen Receptor Targeting BCMA And CS1 For The Treatment Of Multiple Myeloma
- Transforming Growth Factor-Beta (TGF-β)-Responsive Single-Chain Variable Fragments And Chimeric Antigen Receptors
- Intracellular-Ligand-Responsive Cytotoxic Molecules For Selective T-Cell Mediated Cell Killing

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