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Maintenance of regulatory T cell phenotype by expression of IL-2 fusion protein

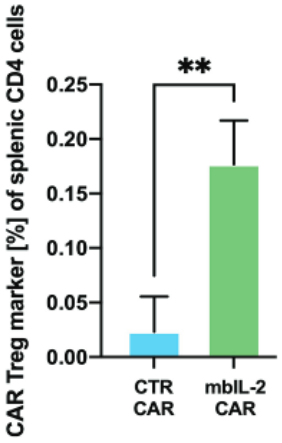
Keywords: IL-2, Treg cell, immune response, Treg phenotype

INVENTION NOVELTY

A new and promising approach for the treatment of transplant patients and for autoimmune diseases is the adoptive transfer of tissue- or graft-specific regulatory T cells (Tregs). In the medium term these modified cells can specifically control the immune response of the body and prevent an unwanted or excessive (auto-)immune responses. Nonetheless, Treg survival, phenotype, and function are critically dependent on IL-2, and rely therefore on IL-2 producing cells.

This property may have a negative impact on the persistence of therapeutic Treg products, especially adoptive Treg therapy. The regimen by immunosuppressive drugs (e.g., administration of calcineurin inhibitors) after solid organ transplantation generate "IL-2 cytokine sinks." Therapeutic Tregs compete with endogenous cells for growth-promoting factors in these sinks, resulting in a negative loop by neutralizing their therapeutic effect.

Artificially induced autocrine IL-2 signaling may therefore enhance the therapeutic benefit of adoptively transferred cells by establishing IL-2 independence.



Expression of IL-2 fusion protein enhanced CAR-Treg survival in an IL-2-limiting environment (Kremer et al., 2022).

VALUE PROPOSITION

Tissue- or graft-specific Tregs represent novel therapeutic approaches for organ transplantation and autoimmune diseases. However, maintenance of their cell phenotype is a major hurdle for the successful application of antigen-specific Tregs in patients. In view of this, the newly developed technology provides an IL-2 fusion protein for expression in Tregs to prevent the loss of cell phenotype and to maintain their therapeutic potential.

TECHNOLOGY DESCRIPTION

IL-2 is produced and secreted by T effector cells (Teff). Simultaneously, these cells are at the forefront of initiating rejection reactions in allogeneic transplanted organs. Mandatory immunosuppressive treatment after transplantation or during therapy for severe autoimmune diseases results in an environment in which IL-2 is low or absent. The new technology involves a membrane-bound IL-2 protein that is expressed as a separate protein or with CAR as a common fusion protein in Tregs and anchored to the cell membrane. Interaction with the endogenous IL-2 receptor results in autocrine IL-2 signalling and thus IL-2 independent and CNI resistant Tregs.

COMMERCIAL OPPORTUNITY

In-licensing is possible.

DEVELOPMENT STATUS

In vivo studies in a mouse model have successfully demonstrated proof of concept of the novel technology.

PATENT SITUATION

International PCT-application (PCT/EP2023/065631) with priority of June 2022 is pending.

FURTHER READING

Kremer J, Henschel P, Simon D, Riet T, Falk C, Hardtke-Wolenski M, Wedemeyer H, Noyan F, Jaeckel E. Membrane-bound IL-2 improves the expansion, survival, and phenotype of CAR Tregs and confers resistance to calcineurin inhibitors. Front Immunol. 2022 Dec 23;13:1005582. doi: 10.3389/fimmu.2022.1005582. PMID: 36618378; PMCID: PMC9816406.

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