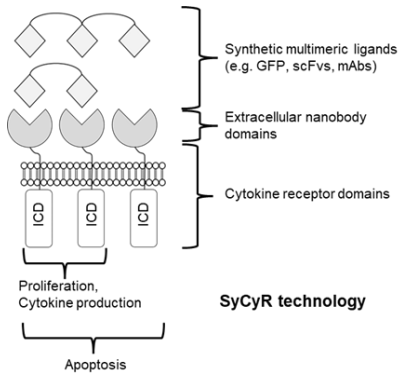


Synthetic Cytokine Receptors

Synthetic cytokine receptors to control cellular activity

Invention

Engineered immune cells such as Chimeric Antigen Receptor (CAR) T cells are used in novel therapeutic approaches against several types of cancer. To tune the activity of these cells, further artificial or synthetic receptors are inserted into these cells. Cytokines and their receptors constitute a large family of such tuning signals for the regulation of immune responses and have thus been in focus of research for additional immune cell engineering.



Synthetic cytokine receptors (SyCyR) consist of an extracellular nanobody-domain and an intracellular signaling domain taken from a natural cytokine receptor. The nanobody-domain is directed against an artificial ligand, including recombinant proteins and antibodies, that can be added in a controlled fashion. Thereby, the cytokine receptor signal can be switched on and off as required.

Natural receptors incorporated in SyCyRs can include a broad variety of receptors mediating activating functions including proliferative effects or cytokine secretion as well as inactivating effects as induction of apoptosis. Hence, a variety of effects can be mediated through addition of defined extracellular ligands.

SyCyR - Schematic composition. SyCyRs contain intracellular domains of endogenous cytokine receptors.

Extracellular domains are replaced by single domain antibodies (VHH) against synthetic ligands. Artificial ligands bind to SyCyRs and activate signal transduction.

Commercial Opportunities

The invention offers a toolbox to dissect signal transduction in vitro and in vivo e.g. with regards to receptor composition, cross-talk and stoichiometry of

receptors and ligands. The invention further provides a solution to ongoing challenges in the field of CAR technology. Specific amplification or deactivation of CAR cells can be challenging. Often cytokines with severe side-effects like IL-2, IL-7 or IL-15 are required to sustain viability and activity of CAR cells. In addition, it remains difficult to deactivate or remove CAR cells in patients in the case of on-target, off-tumor effects. The SyCyR technology allows the activation of distinct cellular events including proliferation or apoptosis specifically on engineered cells expressing SyCyRs without affecting endogenous cells.

Current Status

A broad range of synthetic cytokine receptors has been developed by the researchers, and a proof of concept has been shown in T cells and in mice. International patent applications are pending.

Relevant Publications

Engelowski, E., et al. (2018) Synthetic cytokine receptors transmit biological signals using artificial ligands. *Nat Commun* 9(1): 2034.

Floss, D.M., and Scheller, J. (2019) Naturally occurring and synthetic constitutive-active cytokine receptors in disease and therapy. *Cytokine Growth Factor Rev* 47: 1-20.

Mossner S, Floss DM, Scheller J. Pro- and anti-apoptotic fate decisions induced by di- and trimeric synthetic cytokine receptors. *iScience*. 2021 Apr 24;24(5):102471.

An invention from the Heinrich-Heine-University of Düsseldorf.

Advantages

- Enables defined cellular responses through addition of synthetic ligands
- Compatible with a broad variety of receptors
- Synthetic ligands are highly specific for SyCyR target cells
- SyCyRs can be activated by nanomolar ligand concentrations
- Can be utilized as amplification or eradication switch for engineered cells as for e.g. CAR cells

Technology Readiness Level

1 2 3 4 5 6 7 8 9

Experimental proof of concept in vitro and in vivo research models

Sector(s)

- Biotechnology
- Research
- Pharmaceutical industry

Ref.-No.

5182



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