Next generation of Immune Therapy: HLA-independent T-cell receptors against the Urokinase Receptor

Project Status

Modified T cells have been comprehensively characterized. Further preclinical studies are planned to validate the therapeutic potential.

Benefits

- HLA-independence enables broader applicability
- Alternative to chimeric antigen receptor (CAR) constructs
- Potential for improved efficacy and reduced side effects
- Potential to better deal with tumour heterogeneity and antigen escape mechanisms
- Potential for allogeneic therapies

Patent Applications

Priority Patent Application EP23198276 filed on Sept. 19, 2023 and corresponding PCT/EP2024/076097 (pending)

Offer

- Joint further development and clinical trials
- The technology can be licensed or assigned

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Contact us for more information on this promising technology:
Innovectis Gesellschaft für Innovationsdienstleistungen mbH
Altenhöferallee 5
D – 60438 Frankfurt am Main
E-Mail: kirstin.schilling@innovectis.de

Background T cell-based immunotherapy has become a key pillar of cancer treatment. Identifying new target antigens is essential to further advance this field. The urokinase receptor (uPAR) is an attractive candidate target. It is involved in tumor cell invasion and metastasis. uPAR is overexpressed in many solid and hematologic malignancies, in tumor cells as well as in non-malignant stromal cells and its expression correlates with poor prognosis. In addition, uPAR has been described as a marker of senescent cells that contribute to therapy resistance in tumors and to tissue damage in metabolic and inflammatory diseases. Current anti-tumor and senolytic approaches targeting uPAR mainly rely on monoclonal antibodies or CAR-T cells.

Innovative Technology Researchers at the University Medical Center Mainz (Germany) have developed an alternative approach: HLA-independent T-cell receptors (TCRs) with specific reactivity against uPAR. These TCRs were isolated from healthy blood donors and show the following properties:

Specificity

- TCRs directly recognize uPAR and do not require presenting molecules or antigen processing
- TCRs that recognize both cell surface forms of uPAR have been identified (see figure).

Functionality

- TCR sare functional both in CD4 and CD8 Tcells
- their avidity appears comparable to neoantigen-specific, HLA-restricted TCRs
- Robust cytolytic activity of anti-uPAR TCRs

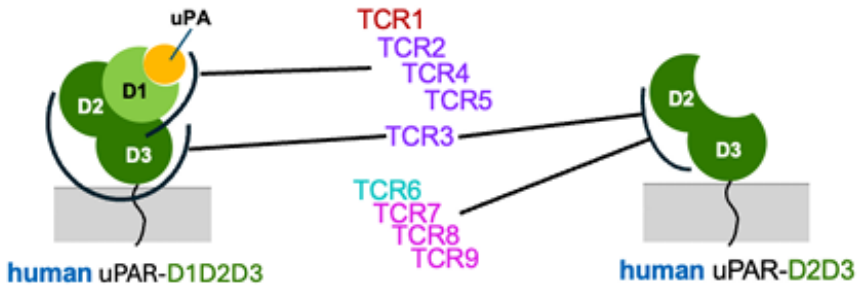

Figure: uPAR consists of three extracellular domains (D1, D2 and D3). The natural ligand uPA binds to domain D1. D1 with its ligand is physiologically cleaved off on uPAR-expressing cells. We have cloned nine distinct anti-uPAR TCRs from four distinct healthy blood donors. Four TCRs recognize D1 on the intact molecule and five TCRS are directed against the truncated version consisting of D2 and D3.

The TCRs seem ideally suited to develop new treatment strategies for uPAR overexpressing malignancies and senescence-associated disease. Among these are:

1. Adoptive TCR-T cell therapies
2. the development of novel soluble multispecific constructs containing uPAR specific binding sites of the HLA-independent anti-uPAR TCRs
3. the development of vaccination protocols to intermittently induce natural, HLA-independent anti-uPAR T-cell responses.blockade.