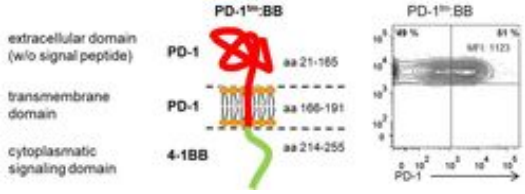
Technology Offer

Empowering T and NK cells for ACT through engineering with PD-1:4-1BB

Reference Number 01-00937

Challenge

The adoptive transfer of selected highly tumor-reactive T and NK cells (ACT) and checkpoint inhibitors achieve remarkable tumor regression in patients. Experimentally generated high-affinity T cell receptors (TCR), CAR constructs and NK cells have been advantageous by boosting effector function and proliferation, but they may bear an increased risk of unwanted toxicities. Loss of function following tumor infiltration occurs independently of T cell avidity. Functional inactivation may occur due to inter alia blockade of TCR signaling and upregulated inhibitory checkpoint receptors on activated T cells and their respective ligands expressed on tumor cells. To break the immunosuppressive axis in ACT, costimulation and coinhibition signals controlling the strength and duration of the T cell response should be considered to improve the efficacy and safety of ACT.



Design of the chimeric costimulatory receptor PD-1:4-1BB and surface expression after T cell activation.

Technology

Costimulation can provide pivotal survival signals to the T cell and can prolong effector functions. Tailored costimulation, when and where it is required, can be achieved by engineered costimulatory proteins that are activated by locally expressed ligands. PD-1:BB chimeric protein is one those engineered proteins which is designed to turn the native PD-1 inhibitory signal into a costimulatory signal for T cell activation and optimal T cell function. The object of the invention was therefore to provide a fusion construct comprising the native coinhibitory PD-1 receptor extracellular domain and the transmembrane domain operably linked to the intracellular domain of the costimulatory 4-1BB (CD137) receptor. The PD-1:BB chimeric receptors, in a first set of experiments, upgraded low-avidity T cells and enhanced TCR-triggered cytokine secretion. In an human melanoma xenograft model, PD-1:BB fostered intratumoral T cell proliferation and enabled better tumor control with reduction of tumor volume.

Commercial Opportunity

The features of 4-1BB signaling apparently apply in the context of CAR-T cell engineering and NK cells. With this respect, the costimulatory receptors may add a considerable improvement of CAR-T as well as NK cell therapies. In addition, checkpoint inhibition therapies may benefit from a combination with PD-1:BB engineered T and NK cells. The supportive effect of PD-1:BB on T and NK cell function make it an attractive tool for ACT.
The technology is open for licensing in the fields of CAR-T and NK cell therapies, further co-development is highly welcomed.

Development Status

So far, the development for PD-1:BB has been tested in the context of TCR-engineered T cells. Actually, experiments are performed whether coengineering of T cells with a chimeric antigen receptor (CAR) and the costimulatory construct is as effective as with TCR-engineered T cells. The same will be true for NK cells.
Further costimulatory constructs consisting of PD-1:CD28 and CD40L:CD28 have also been developed and characterized.

Patent Situation

Patents are pending in US, EP, CA, CN, JP, NZ and AU, with priority from March 2016.

Further Reading

Schlenker et al. (2017), Cancer Res. 77:3577-3590

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Licensing Contact:
Dr Hubert Müller
Technology Manager
T: +49 89 318814-32
mueller@ascenion.de

Ascenion GmbH
Herzogstraße 64
D-80803 München
T: +49 89 318814-0
info@ascenion.de
www.ascenion.de