Technical University of Denmark

Popular science summary of the PhD thesis

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Title of the PhD thesis	Peptide-MHC directed expansion of antigen-responsive CD8 T cells using antigen-presenting scaffolds
PhD school/Department	Life Science/Health Tech

Science summary

* Please give a short popular summary in Danish or English (approximately half a page) suited for the publication of the title, main content, results and innovations of the PhD thesis also including prospective utilizations hereof. The summary should be written for the general public interested in science and technology:

The immunotherapeutic approach, adoptive cell transfer (ACT) have in malignant melanoma studies showed clinical durable responses in more than 50% of patients. However, the expansion of tumor infiltrating lymphocytes (TILs) requires extensive *ex vivo* culturing often at the cost of T cell differentiation and functional capacity. Most current strategies involve non-specific expansion of bulk TILs, often providing growth preference to co-infiltrated virus-specific T cells and driving an exhausted phenotype of the T cell product.
The aim of this thesis is to develop a new technology to expand tumor-reactive T cells, through use of Major histocompatibility complex (MHC)-loaded artificial antigen-presenting scaffolds (Ag-scaffold) to provide the T cells with specific functional stimulation to obtain phenotypic and functional properties to mediate tumor regression. These scaffolds are built on a dextran-based polysaccharide backbone associated with streptavidin molecules where biotinylated peptide-MHC class I molecules are attached to govern the specific interaction with a specific T cell, and a combination of biotinylated cytokines and co-stimulatory molecules are co-attached to provide stimulation to the T cell to achieve increased functional properties. The Ag-scaffolds interacts specifically with T cells based on recognition of the peptide-MHC molecule and effectively expand and functionally stimulate specific T cells, while leaving all other T cell specificities untouched.
We found that the Ag-scaffold expansion strategy support antigen directed T cell proliferation while retaining a favorable functional profile of the expanded T cells, as the T cells express a multifunctional cytokine profile upon antigen challenge, high CD28 expression, and reduced PD-1 expression. Importantly, numerous different antigen-specific CD8 T cell populations can be stimulated in a single culture, as each T cell specificity is expanded with individual Ag-scaffolds carrying MHC class I molecules comprising one peptide specificity. In this way, broad tumor target recognition can be obtained, leading to a T cell product with increased tumor-cell killing potential.
This expansion technology could with great advantage be used in ACT, to increase the anti-tumor effect of the transferred T cell product, as all of the achieved T cell characteristics are of significant importance for *in vivo* tumor cell recognition following ACT of expanded T cell products.