

Off-the-shelf T cell therapies for multiple myeloma

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Although a source of much hope among 'multiple myeloma' (MM) patients, adoptive T cell therapies are still held back by expensive, lengthy, individual-tailored approaches. However, an EU-funded project is aiming to shake things up with off-the shelf solutions of its own.

There are currently three main approaches for obtaining therapeutic T [cells](#): the isolation, expansion and reinfusion of tumour-infiltrating lymphocytes (TILs); the ex vivo generation and expansion of tumour antigen-specific T cell lines; and the genetic engineering of autologous T cells with tumour antigen-specific T cell receptors (TCRs) or chimeric antigen receptors (CARs). But whilst the feasibility and effectiveness of these approaches have all been proven in clinical settings, all these approaches have to be tailored to the patient before they can be applied.

With this in mind, the CARIPSCTCELLS (Generation of safe and efficient, off-the-shelf, chimeric antigen receptor (CAR)-engineered T cells for broad application) project has developed technology that will enable in vitro, unlimited, safe and broadly applicable T cells targeting MM. Dr Maria Themeli, coordinator of the project, discusses its results.

Why are T cell therapies so rarely used?

Current strategies for obtaining therapeutic T cells have limitations. Their use is restricted to specialised institutes and specific patient populations. The isolation and ex vivo manipulation of autologous cells

require expensive specialised equipment, good manufacturing practice (GMP) facilities and trained personnel. In many cases, the autologous T cell isolation and expansion would be problematic or impossible, for instance in immunosuppressed patients after chemotherapy or immune-deficient patients presenting malignancies.

Moreover, the production of autologous therapeutic cancer-specific T cells requires processing times which can be critical for the patient's health. Sometimes the patient dies before receiving the therapy. This all makes the production of therapeutic T cells an expensive process, which is difficult to be broadly applied.

How did your project aim to solve these problems? How did such solutions come about?

We thought that the development of broadly applicable cellular therapeutics, which have been manufactured, functionally validated and banked in advance, and can be applied beyond histocompatible Human leukocyte antigen (HLA) barriers, would improve the consistency and availability while reducing the cost of adoptive T cell therapy. With this goal in mind, we explored the feasibility of a novel strategy for generating unlimited, 'off-the-shelf', safe, antigen-specific T lymphocytes with optimised features.

We propose the use of induced [pluripotent stem cells](#) (iPSC) as a source of T lymphocytes. These cells can be cultured in the lab without limit and can be differentiated to T lymphocytes. In addition, they can be genetically manipulated easily, so that the final T cell product will possess specific desirable immunotherapeutic characteristics. For example, we can provide cancer antigen specificity through an artificial CAR and delete the expression of HLA molecules to make them histocompatible.

Why did you decide to focus specifically on MM?

The department of haematology at VUmc Amsterdam is one of the biggest European centres for MM patient care. What makes us so interested in this disease is that although there has been much progress in delaying the course of the disease, it still remains incurable. Therefore, we focus our research on finding novel, potentially curative therapies. To this end, we have developed and preclinically evaluated the use of CD38-targeting CAR-T cells for the treatment of MM.

How was the CRISPR/Cas9 system beneficial to your research?

The CRISPR/Cas9 technology has revolutionised the field of gene therapy over the last few years. With this technology, modifying the genome has become easier and safer, since it allows for highly specific gene editing. We use this system in order to genetically modify the cells in the iPSC stage and achieve specific optimised features when they differentiate into therapeutic T cells.

What would you say are the most important achievements of the project?

We have succeeded in generating genetically-modified iPSC, which give rise to broadly applicable 'off-the-shelf' T cells bearing an anti-myeloma CAR and eliciting anti-myeloma function without having histocompatibility restrictions.

What do you hope will be the long-term impact on MM treatment?

The development of 'off-the-shelf', applicable immunotherapeutic tools will lift immunotherapy from an individual basis and will allow the availability of controlled, validated and safe immunotherapeutics for a broad patient population.

MM is the second most common haematologic malignancy. Thus, a broadly applicable adoptive T cell immunotherapy would be of benefit for many patients. But most important, this project will lay the foundation for a new strategy for the broad application of iPSC-derived T cells, not only for targeting MM, but also for all CAR-based T cell therapies, since the results obtained from our studies could also be translated to other malignancies.

What are your follow-up plans, if any?

We aim to further pursue the goal of generating potent therapeutic T cells from iPSC. We will focus on further improving the therapeutic properties of the generated T cells from human iPSC by influencing and refining the in vitro differentiation mechanisms of phenotypic determination and by enhancing their persistence and effector function.

More information: Project page: cordis.europa.eu/project/rcn/195614

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