Website address:
https://www.gesundheitsindustrie-bw.de/en/article/dossier/cell-and-gene-therapies-from-bench-to-bedside

Cell and gene therapies: from bench to bedside

While cell therapy has become standard treatment for a number of blood cancers, most cell and gene therapy approaches for the treatment of hereditary and metabolic diseases, neurodegenerative disorders and cancer are still in the experimental phases or early clinical trials. However, recent successes give rise to the hope that cell and gene therapies will in future make important contributions to previously incurable diseases.

Cell and gene therapies are regenerative medicine tools with which intact cells or the genetic information (DNA) of vital substances are transplanted into a patient either to replace malfunctioning or defective cells or to promote processes that enable the regeneration of missing or misdirected functions in diseased tissue. Many patients with previously incurable diseases, including severe hereditary and metabolic diseases, neurodegenerative disorders or cancer are very hopeful about these innovative therapy methods.

Autologous and allogeneic haematopoietic stem cell therapies

The scientific breakthrough for cell therapy came with the successful transplantation of haematopoietic stem cells in leukaemia patients. Adult haematopoietic stems cells can be isolated from bone marrow or umbilical cord blood. Ever since Professor Anthony Ho from Heidelberg University Hospital successfully treated a patient with highly malignant Burkitt lymphoma in 1985 by transplanting haematopoietic stem cells from the patient's peripheral blood, this method has become standard treatment for aggressive non-Hodgkin lymphomas, Hodgkin's disease and multiple myeloma. Prof. Ho's Department of Medicine V at Heidelberg University is now one of the largest stem cell transplant centres in Germany and among the most renowned research institutions in the field of cell therapy worldwide.

Bone marrow smear of a patient with acute myeloid leukaemia.

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Autologous stem cell therapy is an innovative therapy in which stem cells are removed and later returned to the same person. Growth factors (mainly granulocyte colony stimulating factor, G-CSF) are used to stimulate the growth of new stem cells so that they spill over into the blood. The stem cells are collected in a process known as apheresis (used to separate stem cells from blood) and stored in liquid nitrogen until required. The patient then undergoes high-dose chemotherapy before the frozen stem cells are returned and start to restore the formation of blood.

Meanwhile, allogeneic stem cell therapy can be effectively carried out with cells from the patient's relatives or unrelated donors. Ideally, cells are taken from a donor with a matching HLA tissue type in order to prevent incompatibility reactions. HLA (human leukocyte antigen) molecules are presented on the surface of cells and used by the human immune system to differentiate the patient's own/healthy cells from foreign cells. However, 100% tissue matches are rare, and the transplanted donor cells therefore are not only able to replace the malignant cells destroyed by chemo- or radiotherapy, but also detect and kill residual cancer cells. Nowadays donor cells can be transplanted without having to completely shut down a patient's defective immune system. Allogeneic stem cell therapy, which can be applied to many indications, is thus in principle also an immunotherapy.

Professor Michael Schmitt, who holds an endowed professorship in cellular immunotherapy at the University Hospital in Heidelberg, is further developing such immunological cell therapy approaches. His research involves different T-cell subpopulations, including natural killer cells, mesenchymal stromal cells and myeloid-derived suppressor cells. A particular focus is on dendritic cells, which are cells that take up and process antigens of cells that have been labelled "defective" (e.g. tumour cells) and present them to the T cells of the immune system. Clinical trials are being carried out to assess the safety and efficacy of dendritic cell vaccines for the treatment of cancers, including glioblastoma, which is a highly aggressive brain tumour.

Regeneration of cartilage and liver cells

Dendritic cell that is in direct contact with two T lymphocytes.

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Prof. Schmitt explains that in vitro studies and studies involving animal models have led to high expectations for the use of cell therapy approaches in the treatment of haematological and oncological diseases. In 2014, the German Society for Haematology and Medical Oncology established a cell therapy workgroup in which leading German experts have been developing guidelines for the implementation of preclinical research results in clinical trials as well as criteria for the production of relevant cellular products. Pharmaceutical and biotech companies are also working with hospitals and research institutions to develop cell therapy approaches involving cells other than haematopoietic stem cells and immune system cells. For example, Reutlingen-based TETEC AG is working with the NMI Natural and Medical Sciences Institute (NM) in Reutlingen at the University of Tübingen in a project aimed at developing methods for the regeneration of intervertebral discs with autologous cartilage cells (see article entitled "Cells and biomaterials for the treatment of intervertebral disc defects"; see link on the right-hand side).

In cooperation with the Children's University Hospital in Heidelberg, Weinheim-based Cytonet GmbH & Co. KG has developed a liver cell therapy for the treatment of newborn babies and infants with congenital urea cycle defects. In multi-centre clinical trials involving hospitals from Europe and North America, Cytonet has successfully used healthy human liver cells for the treatment of the young patients. The cells were isolated from non-transplantable donor livers (see article entitled "Cytonet cooperates with Hamad Medical Corporation in Doha, Qatar"; see link on the right-hand side).

In early 2014, Cytonet submitted a European approval application for its liver cell therapy to treat this life-threatening metabolic disease; the company has already been listed four times as one of the hundred most innovative SMEs in Germany.

Liver cell infusion through the portal vein.
© Cytonet GmbH & Co. KG

There are great expectations for induced pluripotent stem cells, i.e. cells that are derived from adult tissue (skin cells, for example) and that can give rise to cells such as nerve or heart muscle cells with the potential to successfully treat diseases such as Parkinson's, paraplegia, amyotrophic lateral sclerosis (ALS), heart attack and other degenerative diseases. However, promising research results have so far only been obtained with animal models and cell cultures; clinical trials with human patients are not likely to take place in the foreseeable future.

Gene therapy trials

Clinical phase I trials are currently being carried out to investigate the efficacy of gene therapy for the treatment of Parkinson's as well as Alzheimer's. The patients involved in the trials receive functional glutamate decarboxylase and neuronal growth factor (NGF) genes that are transferred into the cells using adeno-associated viral vectors. These trials, as well as the only gene therapy currently approved for application in human patients in Europe (for the treatment of lipoprotein lipase deficiency), use modified viruses as gene shuttles that are applied directly into the target organ. In other cases, gene therapy approaches are combined with cell therapy approaches in which patient cells with high regenerative potential (preferably stem cells) are genetically modified ex vivo and later transplanted back into the patient.

Moreover, researchers are experimenting with the possibility of silencing disease-causing mutated genes using RNA interference, especially for the treatment of diseases caused by a mutated gene that leads to the overproduction of the relevant protein, thus damaging cells. This approach has already been successfully used in the mouse model for treating a specific type of ALS that is caused by a mutation in the superoxide dismutase gene 1 (SOD1). However the approach is unsuitable for the treatment of human ALS due to more than a hundred ALS-causing mutations that might occur in the SOD1 gene.

The various gene therapy approaches were initially mainly directed at the treatment of hereditary genetic diseases. However, cancer has since become the major focus of clinical gene therapy trials. Several articles in this dossier address these new developments and the successes, opportunities and risks associated with them.

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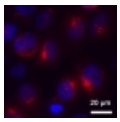
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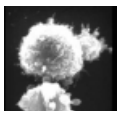
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