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Reduced immunosuppression possible in transplantations

Modified immune cells produce donor-specific tolerance

Traditionally, transplant recipients have had to take immunosuppressive medication for life to prevent organ rejection. However, there are considerable side effects involved. Using modified immune cells (MICs), TolerogenixX GmbH from Heidelberg has now managed to generate donor-specific tolerance in recipients of living kidney transplants without suppressing the overall immune system. In the long term, this innovative cell therapy could conceivably be used for treating autoimmune diseases.

When a vital organ fails, organ replacement procedures such as dialysis, extracorporeal membrane oxygenation (ECMO) or various heart support systems are employed. These are technically complex procedures that are very demanding for the individuals that undergo them. They also carry the inherent risk of serious infections. These devices cannot fully replicate the complex functions of a natural organ. Therefore, in the long term, transplantation remains the most viable option for ensuring a better chance of survival.

Living kidney donation



Under the leadership of Prof. Dr. Christian Morath (CSO), Prof. Dr. Matthias Schaier (CEO) and Prof. Dr. Anita Schmitt (CTO) (from the left), TolerongenixX GmbH develops individual cell therapeutics that can lead to specific and lasting immune tolerance to donor organs.
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In 2021, a total of 2,979 organs obtained from deceased persons were transplanted in Germany[1)], with kidneys accounting for half of these. However, by the end of the year over 7,000 patients were still waiting for a new kidney; the current waiting time for a kidney via Eurotransplant exceeds eight years. In light of these challenges, living kidney donation from relatives or close friends is considered in certain cases. Healthy individuals possess two kidneys and can lead an almost normal life even after donating one kidney. "The percentage of living kidney donations varies between institutions, ranging from 30 to 50 percent," explains Prof. Dr. Matthias Schaier, senior physician at the Heidelberg Kidney Centre (NZH). "Patients undergoing dialysis to filter out waste products experience accelerated ageing due to the accumulation of toxic substances in their blood. In contrast, transplant recipients, despite the need to take multiple medications with severe side effects, demonstrate lower mortality rates than patients on dialysis. These mortality advantages become apparent as soon as six months after transplantation."

HLA molecules generate individual tissue signature

In all transplantations, matching the blood group and tissue characteristics of the donor(s) and recipient(s) as closely as possible is crucial to minimise the risk of organ rejection. While the ABO blood group system has only four main blood groups (A, B, AB and 0), individual characteristics (antigens) on the surface of tissue cells vary significantly. These proteins, known as HLA (human leukocyte antigen) molecules, are present on every cell in the body and can be easily detected on white blood cells called leukocytes. They create a characteristic signature that allows the immune system to distinguish between the body's own cells and foreign cells. HLA molecules that are foreign to the body are primarily recognised by T lymphocytes, which initiate an immune reaction that can lead to rejection of the transplanted organ.

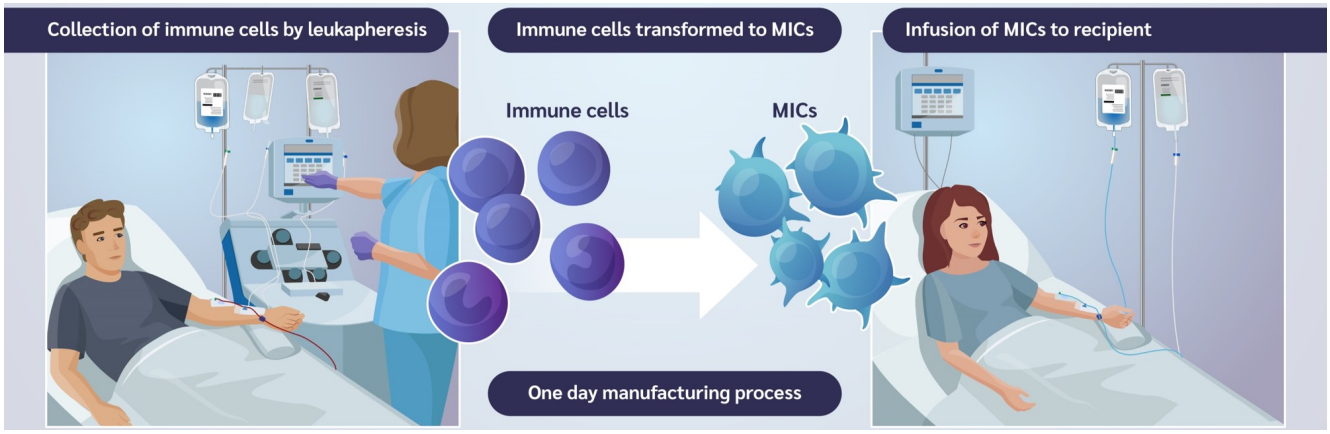
To date, several thousand different tissue characteristics are known. The typing process focuses on the major representatives of HLA molecules, including HLA-A, HLA-B, HLA-C, HLA-DR and HLA-DQ. There are countless possible combinations since every person inherits one variant from their father and another from their mother. The goal is to achieve the best possible tissue compatibility between donor and recipient. A complete match of all tissue characteristics is only possible in twins, which is why transplant recipients are required to take immunosuppressive drugs for the rest of their lives to prevent organ rejection. However, these medications also suppress the immune system's basic mechanisms, leading to a range of potential side effects, including increased susceptibility to infections and tumours, gastrointestinal issues, osteoporosis, kidney damage, nervous tissue damage and high blood pressure.

Donor-specific tolerance through MICs

"TolerogenixX GmbH has developed a novel cell therapy that has the ability to selectively suppress unwanted immune reactions to the transplanted organ without compromising the body's immune defences against bacteria, viruses or tumour cells," explains Prof. Dr. Matthias Schaier, CEO of the Heidelberg-based company founded in 2016. Together with Prof. Dr. Anita Schmitt (CTO) from Heidelberg University Hospital and Prof. Dr. Christian Morath (CSO) from the NZH, the physician aims to translate this ground-breaking therapy from academic research to clinical application.

The curative approach developed by TolerogenixX involves using modified blood cells from the organ donor to establish long-lasting and specific tolerance in the organ recipient. One week before the scheduled kidney transplant, peripheral blood mononuclear cells (PBMCs) are collected from the donor's blood using a process called leukapheresis. PBMCs consist of blood cells with only one nucleus, including lymphocytes and monocytes but not multinucleated granulocytes or anucleate erythrocytes. The isolated cells are then treated with the chemotherapeutic agent mitomycin C for a duration of thirty minutes. "In oncology, it has been observed that this treatment induces changes in the surface characteristics of the cells," says Schaier. "The HLA molecules remain intact, but the co-stimulatory signals for an immune response are replaced by inhibitory signals. As a result, the modified cells acquire an 'immunologically tolerant' state, as if they were wearing a 'tolerance jersey'."

The modified immune cells (MICs) are administered to the transplant recipient on the day they are prepared. However, due to the permanent damage caused by mitomycin C, the MICs undergo programmed cell death (apoptosis) in the days that follow. The resulting cell fragments not only promote a donor-specific tolerance of the T lymphocytes in the recipient, but also stimulate the formation of regulatory B lymphocytes, which also help prevent immune reactions against the transplanted organ[2)]. The patient receives the kidney transplant one week after the MICs have been administered. In a phase I study, conducted to assess the therapy's safety and efficacy, it was demonstrated that this approach is well tolerated by patients. The induced tolerance was found to be durable, lasting for at least five years despite the dosage of immunosuppressive medications typically required after transplantation being significantly reduced. The kidney specialist explains: "The transplant patients who received MICs in advance are experiencing improved outcomes compared to those in the control group, primarily due to the reduced need for immunosuppressive medication. These patients experience hardly any side effects, show no rejection reactions, and are less susceptible to opportunistic infections." To provide optimal protection for the transplanted organ, patients initially receive standard immunosuppressive drugs immediately after transplantation. The dosage of these medications is gradually decreased over time. The goal is to reduce the medication to only one tablet of calcineurin inhibitor, a medication that inhibits the release of immunostimulatory substances. Based on the promising results obtained so far, a phase II study involving 62 donor-recipient pairs was initiated in Munich, Stuttgart and Heidelberg in 2022.



One week before the planned kidney transplant, white blood cells are collected from the donor by means of leukapheresis. Modified immune cells (MICs) are generated by treating the white blood cells with mitomycin C. These MICs are administered to the recipient by infusion on the same day.
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New perspectives for autoimmune diseases

Autoimmune diseases are triggered by excessive immune reactions to the body's own antigens. Preclinical data show that MIC cell therapy also has huge potential in these cases. The patients' own PBMCs are collected, treated with mitomycin C and then returned to the patient. These MICs help instruct the immune system which HLA molecules (i.e. the body's own HLA molecules) to tolerate. TolerogenixX is currently also exploring the potential of this therapy for treating lupus erythematosus (SLE), an inflammatory rheumatic disease characterised by autoantibodies targeting nuclear components, and potentially affecting multiple organs. "We believe our therapy has major potential for treating other autoimmune diseases and we are open to research collaborations in this field," says the CEO.

Large cost savings possible

Compared to other cell therapeutics, MICs are much gentler for the recipient. Additionally, TolerogenixX has optimised the production process of MICs in clean rooms, making it more efficient and less time-consuming than other cell therapies.

"Depending on the indication, there will be adaptations, but in principle it is a comprehensive platform technology," the entrepreneur explains. "The therapy is not only highly effective, but also comparatively inexpensive. And in the long run, further costs can be saved through the reduction of immunosuppressants and the fact that patients may experience a reduced risk of secondary diseases associated with immunosuppressive treatment."

References:

1) German Organ Procurement Organisation (DSO)

2) Morath C, Schaier M, Ibrahim E, et al. (2023): Induction of Long-Lasting Regulatory B Lymphocytes by Modified Immune Cells in Kidney Transplant Recipients.*J Am Soc Nephrol.*, 34(1):160-174. doi:10.1681/ASN.2022020210

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