Large-scale urology project: cell therapy for the treatment of stress incontinence

The first and so far only clinical DFG research group on urology is being coordinated by a team from Tübingen. The team is developing a cell-based therapy for the regeneration of the urethral sphincter. Clinicians, life scientists and engineers are working together to try and find a causal therapy of stress incontinence.

In July 2012, a DFG-funded clinical research unit (KFO) was established in Tübingen with the aim of developing a cell-based therapy for the treatment of urinary incontinence, or more specifically, stress incontinence, a disorder that results from a weak or malfunctioning urethral sphincter. The bladder leaks urine during physical activity and in the worst case, it even leaks when sneezing or coughing. The involuntary release of urine is not only extremely uncomfortable for the sufferer, but can also have health consequences such as urinary tract infections.

A number of treatment options are available for keeping the problem at bay, with differing success rates. Current treatment options are the training of the pelvic muscles and electrostimulation, medical treatment and the implantation of ribbons, slings or artificial sphincters. These measures can lead to considerable improvements, but they do not provide causal treatment. KFO 273 is now investigating different aspects of cell-based treatment in order to find a causal treatment, i.e. one that is able to strengthen the weakened urethral sphincter. The DFG is providing around 3.4 million euros for the first funding period, which ends in June 2015.

The KFO 273 team is headed up by Prof. Dr. Wilhelm K. Aicher from the Department of Urology at the University of Tübingen. The department’s medical director, Prof. Dr. Arnulf Stenzl, is the spokesperson of the KFO. It also involves groups outside the University Hospital on the basis that it is now accepted that such an ambitious goal can only be achieved by pooling expert knowledge and skills.

Regeneration-competent stem cells are removed from the patient and re-integrated into the sphincter to improve its occlusive force and restore as much function as possible. The first stage is identifying the most suitable cells, and the researchers are specifically looking at stem cells from the bone marrow, the placenta and the fatty tissue. The cells are isolated, processed and turned into precursor and muscle cells in the laboratory. They are then studied electrophysiologically to test whether certain cells develop into contractile muscle cells. This part of the project is being carried out by Prof. Dr. Elke Guenther and her team at the NMI.

Difficult precision work: placing living cells into the sphincter using a minimally invasive procedure

In addition to looking for optimal cells, another project involves the development of a method that enables the endoscopic, target-specific and dosed application of the cells into the sphincter. This needs to be done with the highest possible precision as the sphincter is only a few millimeters thick. In addition, the aim is not to inject the cells, but rather to deposit them at the target destination using an innovative endoscopic procedure that does not require a needle.

The researchers from Tübingen are working on the development of this technology with a group led by Prof. Dr. Jan Stallkamp at the Stuttgart-based Fraunhofer Institute for Manufacturing Engineering and Automation (IPA). A novel sensor technology is being developed (by Prof. Dr. Oliver Sawodny, University of Stuttgart)
to enable the non-invasive verification of the outcome of the procedure directly in the body. Moreover, researchers from the Department of Radiology at the University of Tübingen are working on the development of innovative imaging modalities that are specifically adapted to the sphincter area (Prof. Dr. Konstantin Nikolaou).

Since muscular strength can only be exercised if the "new" cells receive appropriate signals from the nervous system, a group of researchers are working with a team led by Dr. Simone Di Giovanni from the Hertie Institute for Clinical Brain Research (HIH) to examine whether the applied cells physiologically integrate into the muscle, whether they connect with the neural control mechanism and how neural connection can be improved.

Meanwhile, the researchers have made good progress and have shown that the planned therapy is feasible in principle. The team's aim is therefore to obtain funding for a second period. "The subprojects are all on schedule, but we have not been able to substantiate all assumptions," says Aicher. The team initially studied how the sphincter responded to the introduction of the cells, whether this led to rejection reactions, inflammation or scarring. "We applied human cells that were expanded in the laboratory into normal, healthy sphincters and did not observe any adverse reactions in xenobiotic large-animal models. The animals tolerated the cells well. In the next step, we want to show in the incontinence model that the sphincter defect can actually regenerate and that the urethral sphincter can achieve an improvement in occlusive force," says Aicher. There will be some changes in the plans for the next three-year period. Two new subprojects will be integrated. First, Prof. Dr. Katja Schenke-Layland from the University Women's Hospital wants to study whether Raman spectroscopy is suitable for monitoring the success of cell therapy. "Raman spectroscopy is commonly used in chemistry. Although it is less well known in the field of biology, it is extremely interesting as it allows non-contact measurements. We want to study whether the method is suitable for finding out whether certain tissue areas display muscle-cell type activity," says Aicher. Second, a team led by PD Dr. Melanie Hart from the Department of Urology at Tübingen University Hospital aims to investigate whether the addition of growth factors enhances the integration of the cells into the target tissue. The plan is to package growth factors such as cytokines into microbeads from where defined amounts will be gradually released.

Project consortium hope that their findings will be applied before the end of the decade

Urinary incontinence – an urgent problem: given an increasingly ageing population, urinary incontinence is likely to become more frequent and generate higher healthcare costs.

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If the DFG decides to fund the project for another funding period as the project partners hope, then it is very likely that they will be able to carry out a feasibility study and clinical studies. If everything goes to plan, a cell therapy will enter clinical testing in 2018. With this in mind, the KFO team applied for and was granted a COST (European Cooperation in Science and Technology) project which commenced in 2013 under the leadership of Prof. Stenzl. This project aims to foster international exchange of scientific information on stress incontinence, pelvic weakness and similar defects of the urogenital tract. "We will exchange our knowledge and staff with partners from 16 EU countries, and hope that the transfer of know-how will accelerate the projects," says Aicher.

The KFO team presented the current state of their work at a conference held to celebrate the 50th anniversary of the Department of Urology in Tübingen on 21st and 22nd November. The anniversary programme bore the slogan "L.I.F.E." (L for quality of life, Lebensqualität, I for intervention, F for research (Forschung) and E for excellence), which summarises the services and topics dealt with at the Department of Urology. The KFO team organized a half-day symposium on 22nd
November that focused on clinical and scientific aspects of the application of stem cells in the field of urology. A major focus was cancers of the kidney, prostate and bladder. There were other sessions on stone treatments and bladder function. The anniversary programme also featured a workshop entitled “European Prosthetic Urology”, which dealt with urological implants and technologies for the treatment of urethral, penile and sphincter diseases.

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