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WIRTSCHAFT. TECHNOLOGIE. LEBEN.

29. JAHR. № 3. 2023.

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ISSN 1435-5272 | A 49017

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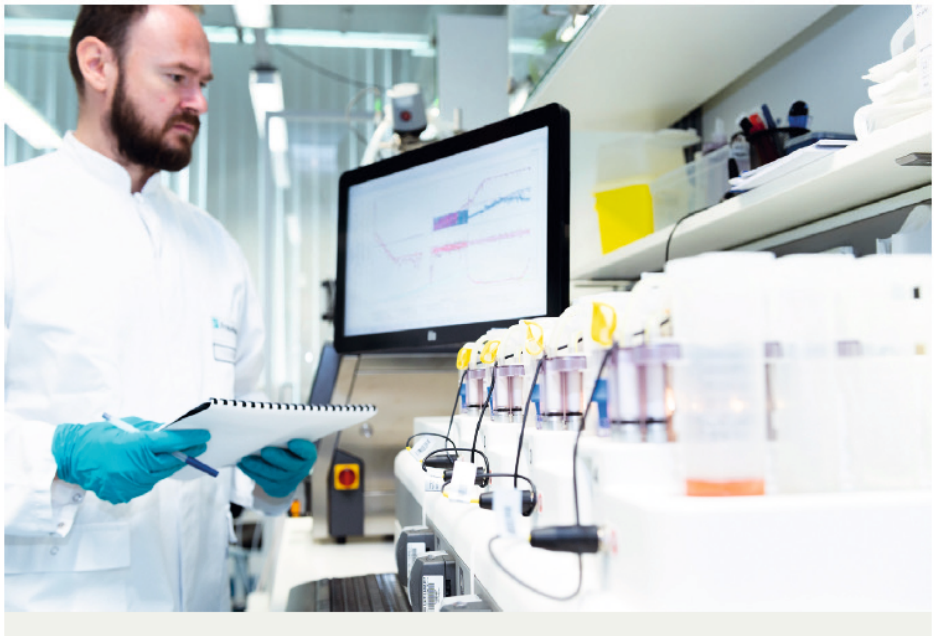
RESEARCH FOR PRACTICAL USE

At the Fraunhofer Institute for Cell Therapy and Immunology (IZI) in Leipzig, innovative cell and gene therapy technologies are being researched and developed for practical use, so that promising approaches can be tested in clinical trials.

by Dominik Schmiedel, Thomas Schmid, Sandy Tretbar, Stephan Fricke, Fraunhofer Institute for Cell Therapy and Immunology (IZI)



Fraunhofer IZI'S GMP process development ensures the transfer of new therapeutic methods and manufacturing technologies for clinical application

Cell and gene therapies have the potential to successfully treat previously incurable diseases. Fraunhofer IZI in Leipzig makes these therapeutic approaches ready for practical use and prepares them for clinical application. The Institute's fields of expertise include research and development, preclinical evaluation, as well as Good Manufacturing Practice (GMP)-compliant process development and optimization. This includes manufacturing clinical trial samples and supporting products across all phases of clinical research until they gain regulatory approval. The Institute operates clean room facilities as well as quality control laboratories and has extensive experience with regulatory procedures and obtaining manufacturing approvals. As a result, more than 3,500 clinical trial samples, including over 500 CAR-T cell products, have been manufactured and shipped to study sites worldwide.

EXPERTISE FROM LEIPZIG

Together with clinical and corporate partners, Fraunhofer IZI is also investigating and testing new technologies for modifying immune cells (viral/non-viral), as well as alternative effector cells such as NK cells and macrophages.

RNA-BASED THERAPIES

By using mRNA molecules, genetic instructions can be introduced into cells in a targeted manner to control the production of specific proteins. This opens up promising possibilities for treating diseases using mRNA. The use of mRNA in cell therapy has great potential in immuno-oncology, where introducing mRNA into the immune cells can trigger patients' endogenous immune system to kill malignant cancer cells.

For example, the mRNA can code for a chimeric antigen receptor (CAR) which is placed on the immune cells as a surface anchor and which, following the lock-and-key principle, specifically recognizes surface structures on the cancer cells. Through the recognition and linkage of cancer and immune cells, the cancer cell can then be killed off.

Although mRNA technology for CAR immune cell therapy is still in its infancy, there are great hopes for the novel approach: mRNAs could usher in a new era of precision medicine. The main challenges in this regard are the stability of mRNA and its efficient re-

lease in different immune cell types, such as T cells and NK cells.

NATURAL KILLER CELLS

All cell therapies which have been approved to treat cancer so far are manufactured from the T cells of patients affected by the disease. But this method is not only extremely costly and time-consuming. There is also an increased risk of manufacturing failure, since the quality of the CAR T cells depends on the condition of the T cells in the cancer patient's blood. However, the T cells' activity can become disrupted, for example by drugs which are used during cancer therapy.

So in the development of new cell therapeutics, research is also focusing on other immune cell types which can be obtained from healthy donors and used to treat multiple patients. In these allogeneic cell therapies, NK cells are of particular interest, because these immune cells can be transplanted between different individuals safely and without severe side effects. Accordingly, NK cell products can be manufactured on a large scale from the blood of a single donor, frozen, and made available to many patients. This would dramatically reduce costs, make the products available to patients more quickly, and standardize product quality.

CAR-NK CELL THERAPIES

Like T cells, NK cells can also be modified with CARs to specifically recognize and kill tumor cells. A first clinical trial with CAR-NK cells in the USA showed promising results in leukemia patients. [1] Thus, curative approaches based on NK cells can be effectively combined with other forms of therapy, such as antibody-based therapies, to target cancer cells even more efficiently.

Despite the great potential of these allogeneic cell products, further research and clinical trials are needed to confirm their safety and long-term efficacy. In addition, after transplantation allogeneic CAR-NK cells don't live as long as autologous CAR-T cells. They also proliferate less and elicit a

Manufacture of a CAR-T cell therapeutic at the Fraunhofer IZI

weaker inflammatory response than T cells, which could be detrimental for fighting tumors.

MORE EFFECTIVE THERAPY

Therefore, new mechanisms need to be developed to further enhance the effect of cell therapies. In addition, there are currently no approved cell therapies to treat patients suffering from e.g. lung or colorectal cancer. So one focus of research at Fraunhofer IZI is the establishment of CAR-NK cells to treat further types of cancer, as well as the enhancement of the efficacy of these cells. For example, new CAR constructs and additional genetic engineering methods are helping make NK cells more long-lived, resistant and tumor-reactive.

OPPORTUNITIES THROUGH AAV

Patients with severe genetic diseases may also benefit from new gene therapeutics. For example, hereditary blindness, muscular dystrophy and hemophilia can be treated with gene therapies based on adeno-associated viruses (AAV). These viruses aren't pathogens. Instead, they replace defective human genes by transporting healthy genes.

About 7,000 genetic diseases could potentially be treated through the use of AAV. However, although the use of AAV is one of the most successful and safest gene therapy methods to date, only five AAV-based drugs have been approved in Europe (Luxturna®,Zolgensma®, Upstaza®, Roctavian®, Hemgenix®). The manufacture of the necessary investigational drugs is extremely demanding – and resources for it are very limited. Therefore, a new clean room facility for the GMP-compliant production of AAV-based gene therapies is being built at Fraunhofer IZI.

SAXOCELL: STRONGER IN A NETWORK

Excellent research infrastructure, a sound research and development base, expertise in process development and more than ten years of experience in the pharmaceutical manufacture of cell and gene therapeutics make the Fraunhofer IZI in Leipzig a pivotal partner in cell and gene therapy development. The Institute's close cooperation with the University Hospitals of Leipzig and Dresden as well as Chemnitz Hospital ensures a seamless transfer into clinical practice. Due to these fields of expertise, Fraunhofer IZI plays an key role within the innovation cluster SaxoCell. This alliance of Saxon research institutes, hospitals and corporate partners aims to provide safer, more effective and more affordable therapies to improve patients' lives in the long term.

Fraunhofer IZI and Leipzig University Hospital are jointly organizing the annual Leipzig Immune ONcology Conference LION (www.lion-conference.com). Interested readers are cordially invited to attend on November 8th and 9th, 2023.

[1] Liu E et al. Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. N Engl J Med. 2020 Feb 6;382(6):545-553..