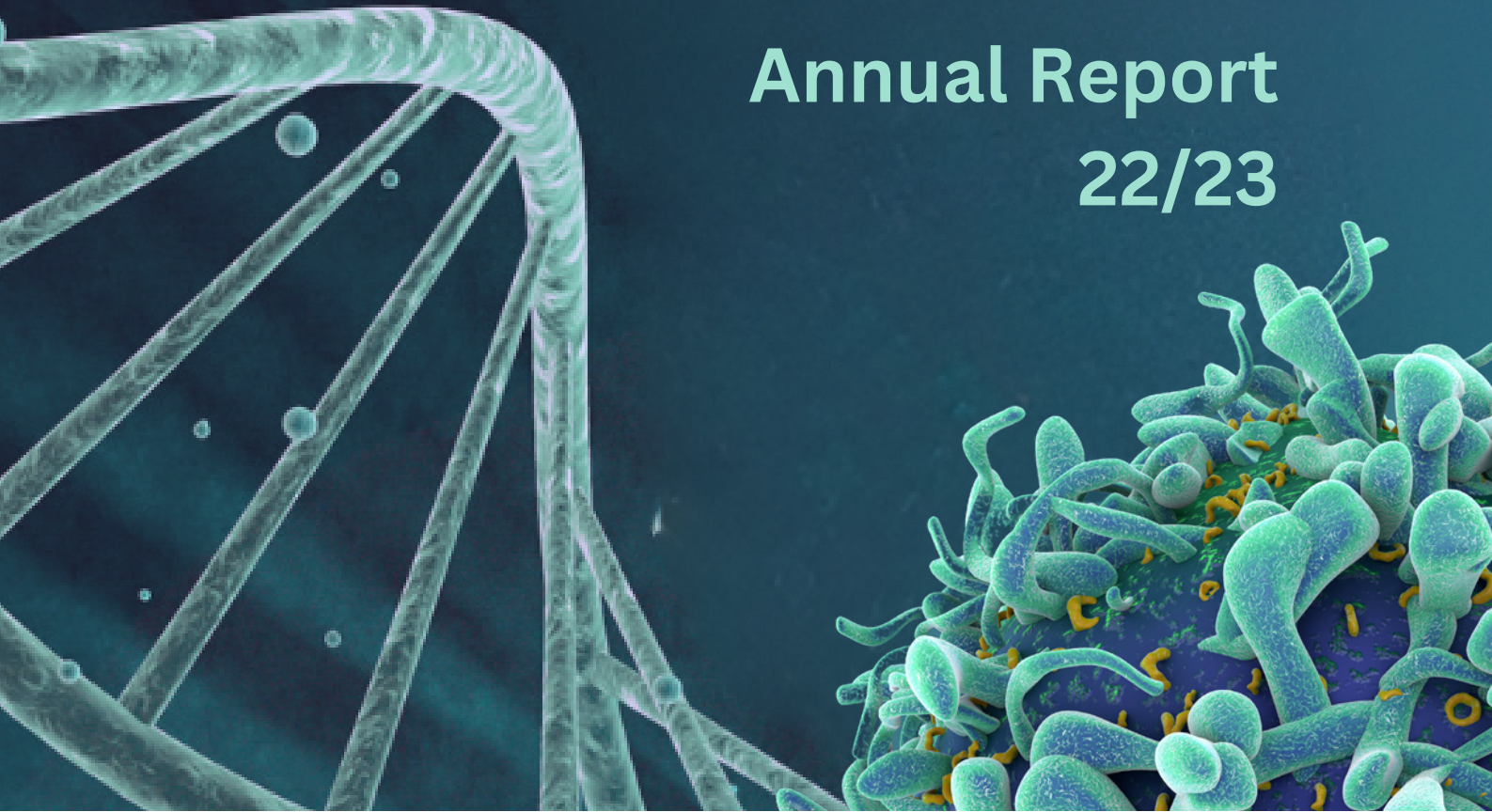
SaxoCell®

Living Drugs

Saxonian Precision Therapy Cluster

Annual Report 22/23




CTD
Center for Regenerative
Therapies TU Dresden

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Foreword

An eventful, successful and inspiring 2022/23 and thus the first half of SaxoCell's first funding period is now behind us and we are happy about the many different tasks and challenges we have already overcome together within the cluster.

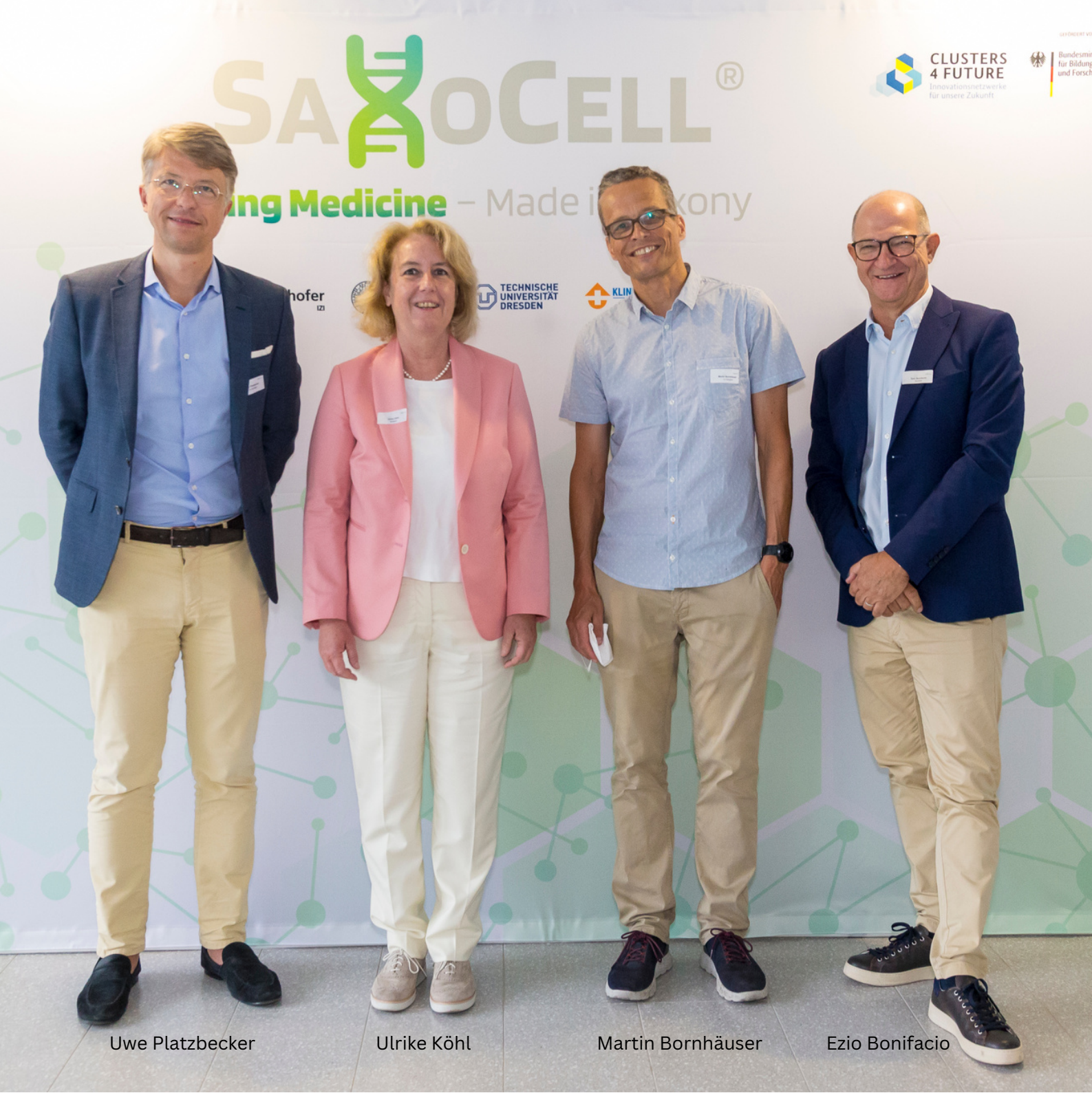
Our 12 projects are in the midst of their first implementation phase. We have successfully spun out one **start-up** from our project HemRec and our other project xMac has been rewarded with the **Science4Life Venture Cup** (Business plan competition). Not only has there been these exploitation successes, the projects have also produced a lot of **interesting data**, some of which is clearly visible in **high-ranking publications**. The platforms work closely with the projects to accompany and support them in the best possible way. Opportunities to get a glimpse of how our projects and platforms are working were at our **consortium meeting** in Dresden in June 2022 and at our first **Scientific Advisory Board Meeting** in October 2022 at Fraunhofer IZI Leipzig. There was also an **exchange with the other Future Clusters** (Clusters4Future) at the BMBF meetings in Berlin and Bonn in 2022 and 2023, respectively.

The 2022/23 period was accompanied by numerous **workshops, lectures and seminars**, which were tailored and led by our Hub team. In addition to workshop series on transfer and GMP, there were specialized events, such as the Thymus symposium or the Nextflow workshop from our industry partner ecSeq, as well as popular science lectures on medical topics related to cell and gene therapies from speakers within the cluster. The Hub's transfer team was active in positioning projects toward industry goals and scouting for the next phase, as well as attending a number of partnering conferences with the **BIO-Europe 2022 in Leipzig** a key highlight in spreading SaxoCell's mission and attracting new industry partners. We also enjoyed **public relations** work with events such as the Long Night of Science and the "Türen auf mit der Maus" action day, which vividly brought the future of personalized medicine closer to a broad audience of young and old.

SaxoCell speakers Ulrike Köhl (left) and Ezio Bonifacio (right) at the first SAB meeting in Leipzig in October 2022.

We are delighted with the many events and projects that have been realized, which collectively embody a **vibrant and progressive cluster**. Thank you to all the PIs, scientists, clinicians, all their teams, our industry partners, our Scientific Advisory Board, our partners at the project management Jülich, and all who have worked with us to make this first stage so exciting and successful. This is what makes such an **innovative large-scale project** like SaxoCell possible in the first place.

Ulrike Köhl & Ezio Bonifacio
SaxoCell Spokespersons



Uwe Platzbecker Ulrike Köhl Martin Bornhäuser Ezio Bonifacio

The SaxoCell speakers

Ulrike Köhl - Speaker

Director of Fraunhofer Institute for Cell Therapy and Immunology Leipzig; Head of Clinical Immunology at the University of Leipzig

Ezio Bonifacio - Speaker

Professor for Preclinical Stem Cell Therapy & Diabetes at the Center for Regenerative Therapies Dresden, TUD Dresden University of Technology

Uwe Platzbecker - Co-speaker

Director of the Clinic and Polyclinic for Hematology, Cell Therapy and Hemostaseology, Leipzig University Hospital

Martin Bornhäuser - Co-speaker

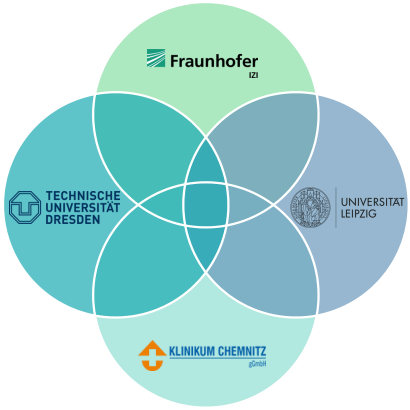
Director of the Medical Clinic I, University Hospital Carl Gustav Carus Dresden

SaxoCell in portrait

Achieving more together

SaxoCell - the Saxon precision therapy cluster aims to provide effective, safe and affordable autologous and allogeneic cell and gene therapies to patients suffering from difficult-to-treat diseases.

In doing so, we bring together excellent basic as well as applied research expertise within Saxony with industrial resources and the know-how of other national and international partners to become a **beacon for cell and gene therapy** in Europe.



Core institutions of SaxoCell

Industry partner of SaxoCell

Our **core partners** are the TUD Dresden University of Technology, the University of Leipzig, the Fraunhofer Institute for Cell Therapy and Immunology and the Chemnitz Hospital. In addition, eight **industrial partners** are already working closely with SaxoCell.

SaxoCell is one of seven winners of the nationwide **Clusters4Future initiative of the BMBF** and is funded with approximately EUR 15 million for the first implementation phase 2021 - 2024.

With its **12 innovative research projects** on CAR-T and (CAR-) NK cell therapies, gene therapies based on designer recombinases as well as regenerative approaches, SaxoCell offers a broad spectrum of therapies that are tailored to the needs of patients.

SaxoCell's core competencies

These innovative cell and gene therapies are developed and optimized in Saxony and are to be brought to automated production and finally to application with the help of our adjacent **technology platforms** (OMICS, CLINICS us SYSTEMS) as well as industrial partners via preclinical and clinical studies. Thus, the entire **value chain is mapped in Saxony**. In the long term, we want to reduce the costs of such forms of therapy for patients and health insurers and strengthen Saxony as a business location.

Vision and objectives

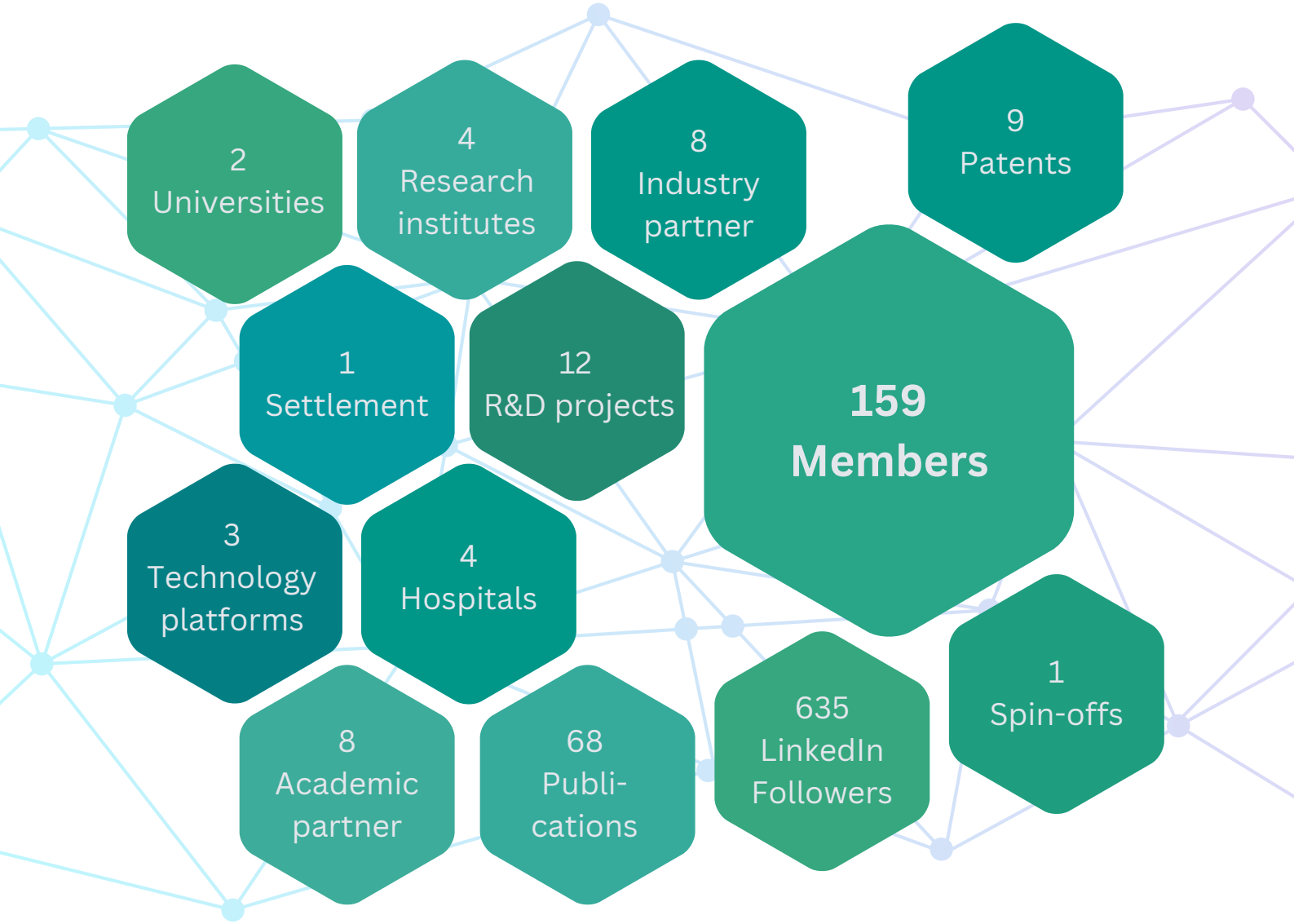
SaxoCell will continue to substantially improve **regional networking in Saxony** in the field of cell and gene therapy, integrate further partners and initiatives nationwide - and close corresponding gaps in the **value chains**. In this way, **synergy potentials** are to be raised and realized.

Long term goals

In addition, the cluster will massively increase the **visibility** of the activities of Saxonian and nationwide partners in the field of cell and gene therapy - both at the level of research and with regard to the R&D activities of industrial partners. In this way, access to funding for the players is to be facilitated and expanded, and structures are to be created to **accelerate clinical translation** (network of clinical players and cooperation with regulatory authorities).

Through these and other activities, SaxoCell will significantly increase the attractiveness for investments of national and international companies in the industry and contribute significantly to the development and further strengthening of an innovative cell and gene therapy industry in Saxony and Germany.

SaxoCell in numbers



Important successes

From SaxoCell in the period 2022/23

Settlement: In December 2022, the Taiwanese company HAN Biomedical settled in BioCity Leipzig due to the close cooperation with the SaxoCell project ZellTWund.

Spin-off: TU Dresden spin-off Seamless Therapeutics launches in March 2023 with $12.5M seed funding to expand a transformative gene editing platform based on programmable precision designer recombinases at the Dresden site in close collaboration with the SaxoCell project HemRec.

Awards: In January 2023, SaxoCell member Michael Hudecek (UltraCAR-T) was awarded the Schelling Prize (endowed at 25,000 euros) by the Bavarian Academy of Sciences for innovative cancer research in the field of CART cell research. In addition, our project xMac was awarded for the concept and business plan phase of the Science4Life Venture Cup. In addition, SaxoCell spokesperson Ulrike Köhl was elected to the Saxon Academy of Sciences in Leipzig.

New partners: In the current funding phase, we received several partner requests from companies, which is why we decided to found SaxoCell e.V. to integrate them. In addition, we are in close exchange with other clusters, such as BioRN and the Cluster4Future ProxiDrugs (networking meetings planned for the end of 2023). Furthermore, we have been a network partner of the Tagesspiegel since 2023 in connection with the Future Medicine Science Match in November 2023.

Public relations: In order to offer low-threshold information on the topic of personalized medicine to a broad public and to consolidate acceptance of innovative cell and gene therapies, we participated in public, popular science events such as "Türen auf mit der Maus" and the "Lange Nacht der Wissenschaften" in Leipzig and Dresden.

Patents: Since the beginning of the first SaxoCell implementation phase, nine patent applications have been filed, one by the CAR-NK4.0 project, one by the NK4Therapy project, five by the xMac project and two by the OPTIX project. Another five patents were filed with the support of SaxoCell employees. In addition, one more patent from OPTIX is pending.

Publications: In the SaxoCell context and with the assistance of SaxoCell PIs and collaborators, numerous, high-profile publications have been published in journals such as: Nature Communication, Frontiers in Immunology, Frontiers in Pharmacology, Blood, JAMA Oncology, Lancet Hematology and Leukemia.

Press releases: Several SaxoCell-related press releases were published during the reporting period, e.g. from Leipzig University Hospital "First in Europe - All CAR-T cell therapy products available in Germany for cancer patients will be available at Leipzig University Hospital in the near future" and from Chemnitz Hospital "Chemnitz Hospital introduces CAR-T cell therapy". In addition, announcements were published on EU grants acquired and the Seamless Therapeutics spin-off.

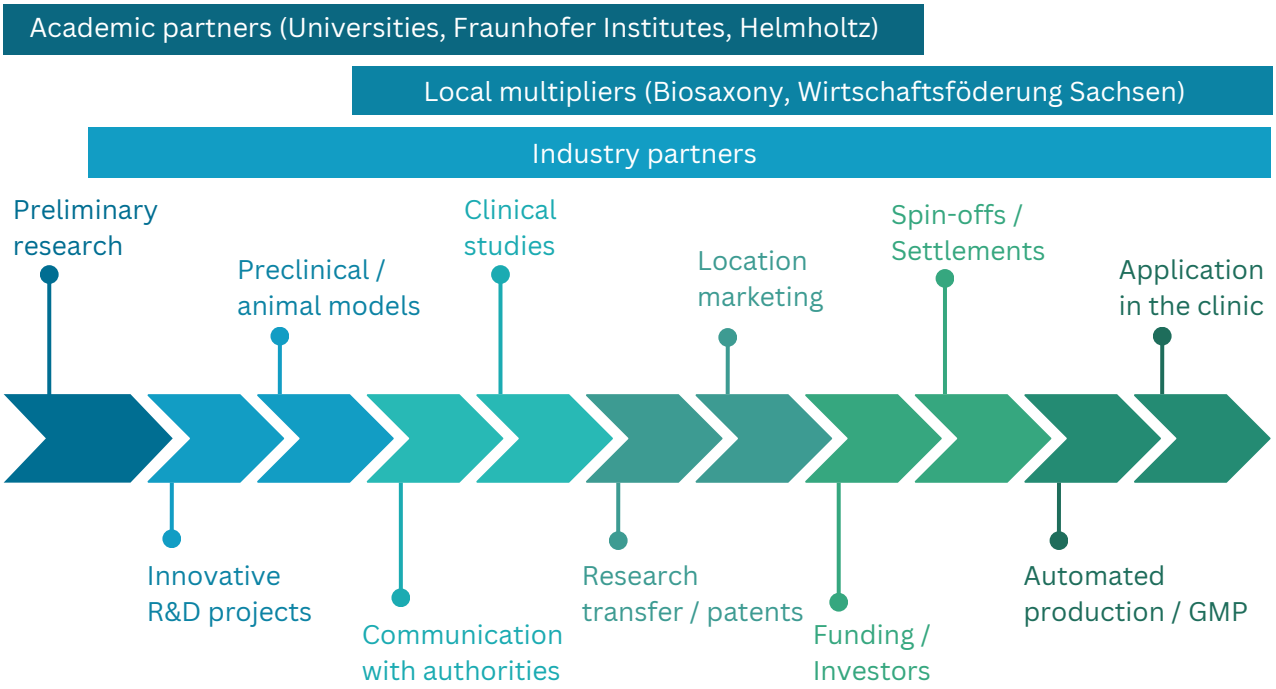
Visibility: The visibility of the cluster is strengthened by a series of public lectures and workshops, cooperation with partners from industry and public relations, participation in national and international conferences and trade fairs, our SaxoCell website as well as social media appearances.

Additional funding: In the cluster, additional funding was obtained with the participation of SaxoCell members, e.g. the GO-Bio *initial* funding for the xMac project, EU funding for Leipzig and Dresden projects, as well as another BMBF funding for a project by Michael Hudecek in cooperation with the Fraunhofer IZI.

SaxoCell partners

A strong cluster is more than the sum of its individual players. SaxoCell pursues a **regional development approach** with nationwide and international reach. Through an extensive network of **local and supra-regional partners** from science and industry, we plan in the long term to establish, if possible, the **complete value chains** for the field of cell and gene therapy development in Saxony.

Value chain for the development of innovative cell & gene therapies in Saxony



SaxoCell partners

AFFIMED

CRTD
Center for Regenerative Therapies TU Dresden

CELLPEDIA
Experience Cell Selection

DKMS
Life Science Lab

ECSEQ BIOINFORMATICS

Fraunhofer IZI

HAN
HAN BIOMEDICAL INC.

HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

HELMHOLTZ MUNICH

iccas

imise.

IZBI

KKS Dresden

KLINIKUM CHEMNITZ gGmbH

MDTB CELLS

Miltenyi Biotec

NCT
NATIONAL CENTER FOR TUMOR DISEASES
PARTNER SITE DRESDEN
UNIVERSITY CANCER CENTER UCC

Saxony Center for Feto/neonatal Health

ScaDS.AI
DRESDEN LEIPZIG

DER TAGESSPIEGEL

Personalized Cancer Immunotherapy
T-CURX

TECHNISCHE UNIVERSITÄT DRESDEN

Universitätsklinikum Carl Gustav Carus

Universitätsklinikum Leipzig
Medizin ist unsere Berufung.

UNIVERSITÄT LEIPZIG

Tcell Tolerance

Zentrum für Klinische Studien Leipzig

Your logo

Advantages for new partners

The Saxocell future cluster is a beacon for **personalized medicine** in Saxony with national and international appeal. The number of new academic and industrial partners is growing steadily. The integration of new partners can take place at the beginning of the new implementation phase in 2024 as well as at any time via **SaxoCell e.V.**. SaxoCell offers **exclusive advantages** to new partners:

Access to innovative **ATMPs** from basic and applied research, **platform technologies, infrastructure, patients** for clinical trials, and comprehensive ATMP expertise

Access to potential **customers** and **end users** (e.g., for equipment and service solution providers) as well as **skilled personnel**

Participation in joint **educational activities** and **training of specialists**, support in **regulatory issues** and **communication with the authorities**

Investment opportunities for **VC** through increased **spin-off** activities of SaxoCell partners, access to **financing options for cost-intensive development steps** (public funding)

Increasing the **visibility** of the respective company

Become a key member of our growing network by contacting us at info@saxocell.de.

Scientific Advisory Board

The SaxoCell Scientific Advisory Board (SAB) is a scientific advisory board and consists of **experts from the fields of research and industry as well as representatives from patient advocacy** who advise the SaxoCell cluster in general and support the projects with their experience.

Discussions are currently underway to **include further members** on the SaxoCell Scientific Advisory Board.

The SAB meets once a year with the project leaders of the SaxoCell projects and technology platforms and provides valuable advice based on its individual expertise from different areas.

SAB Meeting 2022

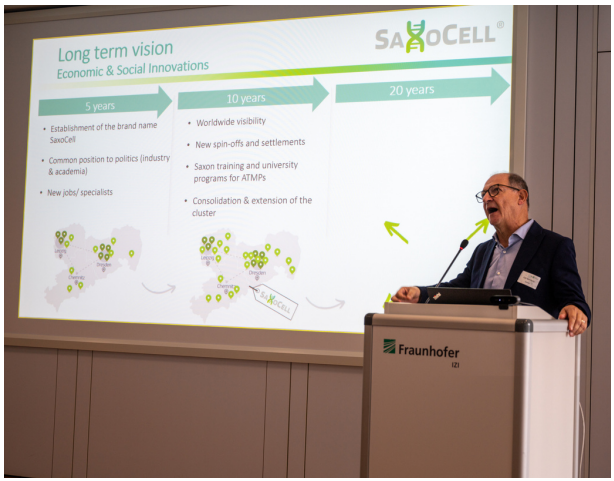
The SAB meets for a first exchange in Leipzig

In October 2022, the first meeting of our scientific advisory board took place at Fraunhofer IZI in Leipzig. For all SaxoCell members and speakers involved, it was an excellent opportunity to share **project progress** with the SAB and discuss further goals for the future.

Many thanks to all participants of our SAB for the **excellent advice** and the **enriching exchange**.

SaxoCell PIs and Hub members in conversation

The SaxoCell SAB pursues the presentation of projects and platforms



SaxoCell spokesman Ezio Bonifacio on the long-term goals of the SaxoCell Cluster.

Funding

SaxoCell is one of seven **winners of the Clusters4Future initiative of the BMBF** and prevailed against a total of 137 applicants in the first round of the 2021 competition. Under the motto "Clusters4Future", research-intensive regions throughout Germany are taking innovative approaches to **knowledge and technology transfer** with the aim of creating the next generation of **regional innovation networks**. The clusters of the future are intended to bring excellent research results more quickly into application and thus into people's everyday lives.

A total of 14 future clusters, seven from the **first** and seven from the **second** competition phase, have been selected and funded by the BMBF so far. SaxoCell is in close contact with the other clusters, which focus on communication, mobility, quantum technology and medicine, among others.

The amount of funding is approximately EUR 15 million for the first three years (corresponds to the first implementation phase). However, a total of three implementation phases with a total funding amount of EUR 45 million are planned over nine years.

CLUSTERS 4 FUTURE
Next generation innovation networks

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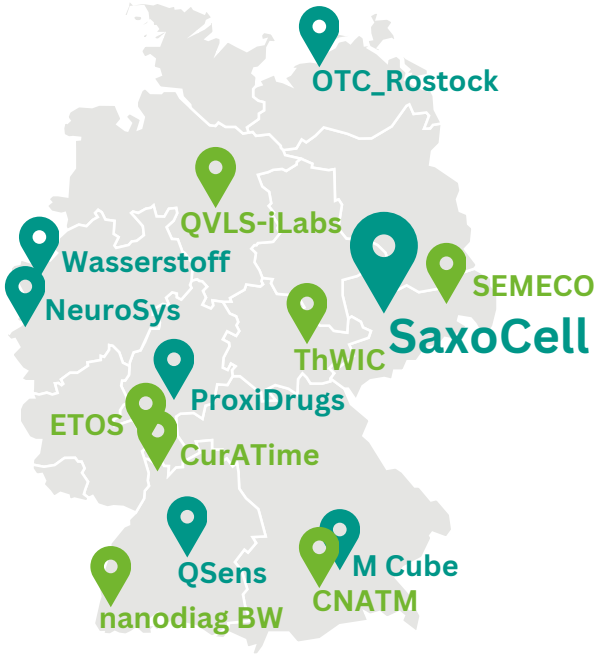
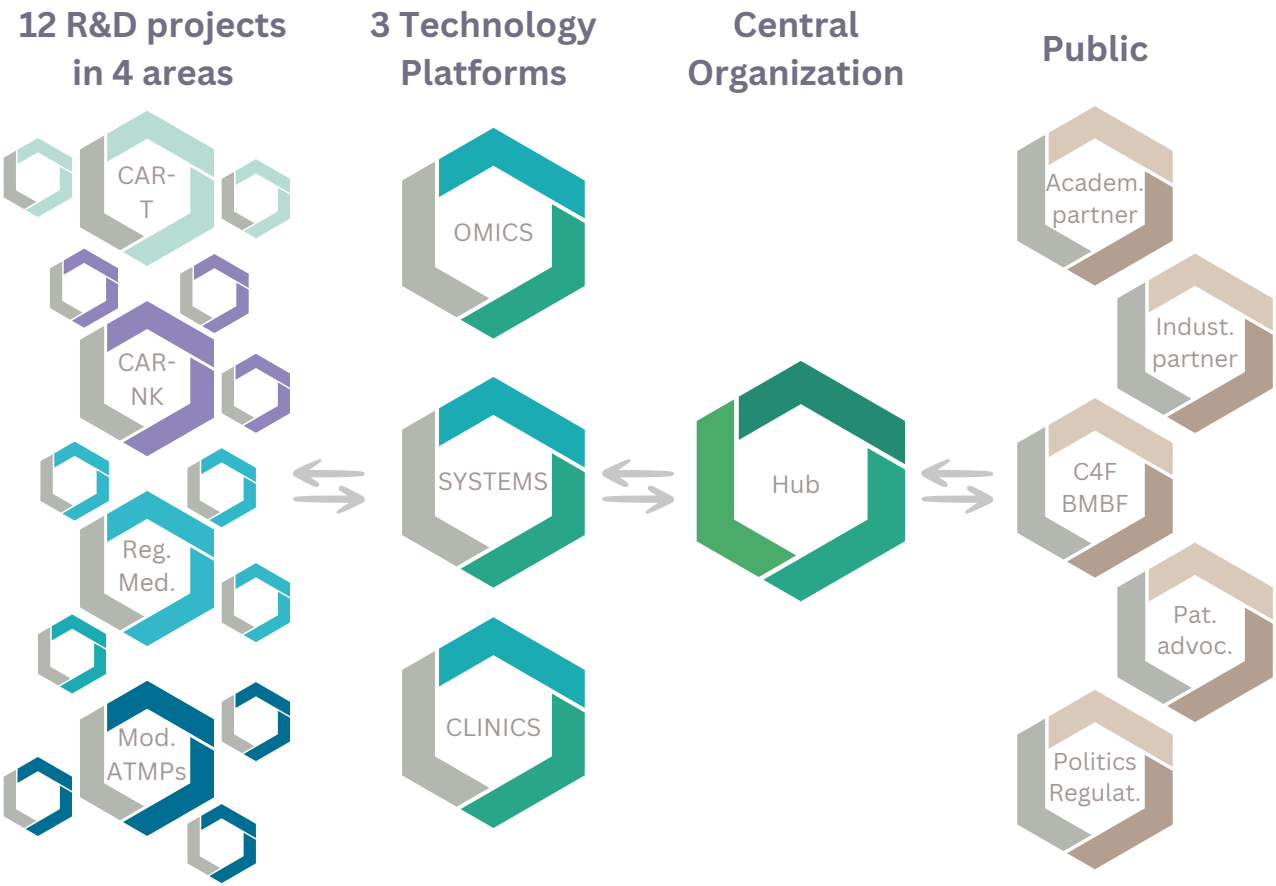


Future clusters of the first (dark green) and second (light green) BMBF competition round.

Cluster profile

Linking science and industry

SaxoCell consists of several mutually supporting entities. The **12 research projects** are organized into **four areas** around the overarching foci of CAR T cell therapies, (CAR) NK cell therapies, Regenerative Medicine and Modulated Cell and Gene Therapies. These projects are supported by **three adjacent technology platforms** OMICS (data collection and analysis), SYSTEMS (automation, AI) and CLINICS (clinical trials, consulting). Assistance in project management, transfer and marketing is provided by the Hub, which also represents the **central interface** to the public.



SaxoCell projects

Allo-CAR-Treg	Genetically modified regulatory T cells for the treatment of autoimmune diseases
UltraCART	CAR-T cell approach with novel target molecules and innovative technology

CAR-NK4.0	AI-assisted CAR-NK cell platform with fully automated manufacturing process
CAReNK-AID	CAR-NKs for the treatment of severe autoimmune diseases
NK4Therapy	Memory NK cell subset for tumor immunotherapy

HemRec	Designer recombinases for regenerative therapy of hemoglobinopathies
ZellTWund	Regenerative wound dressing from fibroblasts & biopolymers for chronic wounds
xMac	Macrophages for allogeneic transplantation in solid tumors
MSC-PreStiGe	Immunomodulatory mesenchymal stromal cells against GvHD after transplantation

OPTIX	Antibody-modified stem cell transplantation for the prevention of GvHD
ECP-CAR	Extracorporeal photophoresis as a modulatory adjunct in CAR-T cell therapy
TheraSTAR	Switchable Uni-CAR receptors for therapy & diagnostics

Allo-CAR-Treg

AlloCARTreg is developing a universal immunosuppressive cell product for the treatment of autoimmune and inflammatory diseases through innovative site-specific adapter CAR technologies.

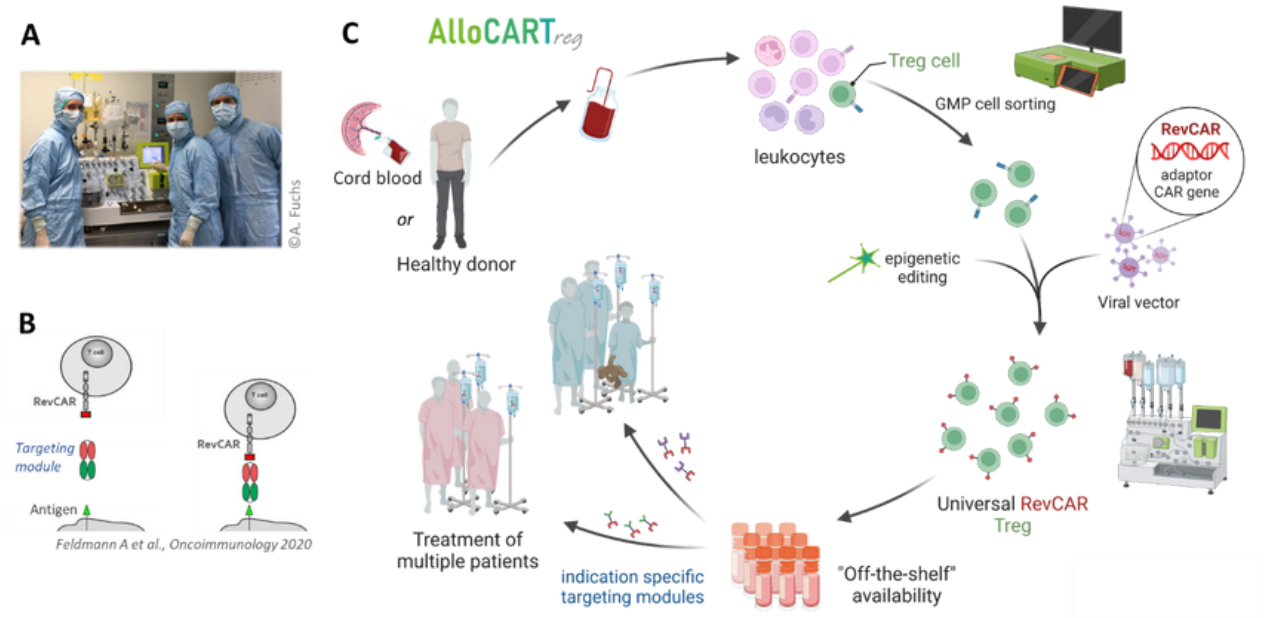
Project lead: Martin Bornhäuser & Anke Fuchs

Partner: Helmholtz Center Dresden Rossendorf, Technical University Dresden

The projects bundles expertise with clinical scale fully automated polyclonal Treg manufacturing using the CliniMACS Prodigy (Fig 1A; Fuchs), Treg cell therapy for cGvHD (Bornhäuser), state-of-the-art universal adaptor RevCAR technology (Fig. 1B; Feldmann) and pioneering genetic engineering methodology (Buchholz). The project involves comprehensive investigation into the phenotypic and functional characterization of regulatory T cells (Treg) derived from apheresis and cord blood as starting population for next generation site specific Treg cell therapy.

It includes the development of improved GMP Treg isolation to reach high purity, optimization of Treg expansion and integration of CAR transduction into the automated manufacturing process (Fig. 1C). Furthermore, enhanced specificity and persistence of allogeneic Treg will be realized by smart genetic engineering towards an off-the-shelf cell product.

Overall, our results to date provide a promising foundation for our vision of allogenic off-the-shelf immunosuppressive cell therapy with switchable site-targeting that holds the potential to advance clinical practice in the field autoimmunity and severe inflammation.



Schematic representation of AlloCARTreg vision. A) Closed system automated polyclonal Treg manufacture in the GMP clean room. B) RevCAR adapter CAR concept for antigen-specific targeting developed by A. Feldmann. C) Schematic of the AlloCARTreg vision – advanced universal Treg manufacture for organ-targeted off-the-shelf Treg treatment by co-infusion of indication-specific targeting modules.

UltraCAR-T

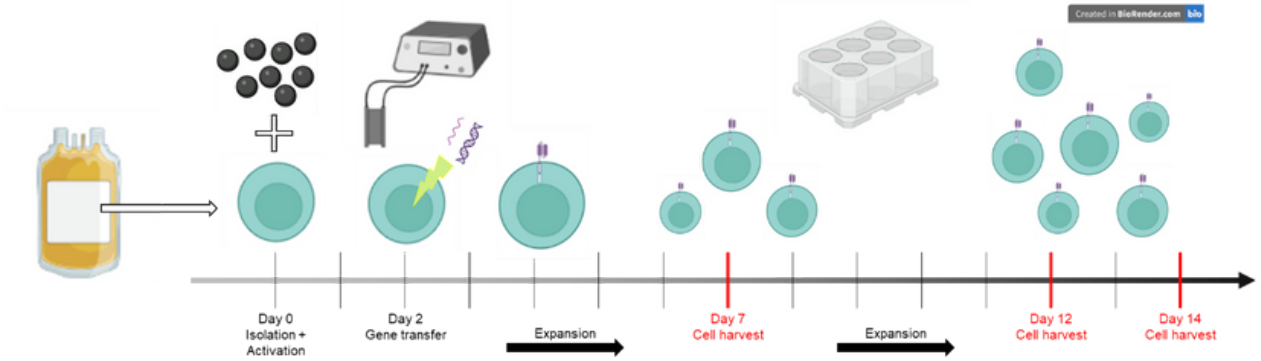
The goal of the UltraCAR-T project is the development, clinical testing and economization of innovative CAR-T cell products for the treatment of oncological diseases. The focus is on the optimization of development and manufacturing processes with regard to production time & production costs, as well as product quality & product functionality.

Project management: Michael Hudecek

Partners: Fraunhofer IZI, T-CURX GmbH

Prior to the start of the project, the project partner T-CURX had already evaluated a number of different target antigens for the execution of the project. Among other things, comprehensive going-to-clinic and going-to-market analyses were performed and it was decided to use a target antigen in acute myeloid leukemia (AML) as the lead target antigen for the UltraCAR-T project. The antigen shows an advantageous expression pattern, as it is highly expressed on malignant cells in AML and Chronic Lymphocytic Leukemia (CLL) CLL on the one hand, and is undetectable or barely detectable in healthy tissue on the other hand. In previous experiments, T-CURX had already produced and tested different CAR constructs. The different CARs were expressed in T cells and their efficacy against antigen+ AML cell lines was tested. In the course of the UltraCAR-T project, confirmatory experiments were performed with the most promising CAR construct. The data confirm previous work and demonstrate the efficacy of CAR-T cells against AML cell lines and primary AML blasts.
Furthermore, the manufacturing time of the CAR-T cells should be significantly reduced. This was initially tested using a semi-open, non-automated GMP manufacturing process. For this purpose, alternative clinical manufacturing protocols were compared, which differ, among other things, in the type of T cell activation and in the process length. The protocols were compared in terms of cell yield, CAR expression level, functionality and gene expression. An SOP for a 7-day manufacturing process was then developed and tested (see Figure).
Furthermore, the manufacturing time of the CAR-T cells should be significantly reduced. This was initially tested using a semi-open, non-automated GMP manufacturing process. For this purpose, alternative clinical manufacturing protocols were compared, which differ, among other things, in the type of T cell activation and in the process length.

The protocols were compared in terms of cell yield, CAR expression level, functionality and gene expression. Subsequently, an SOP for a 7-day manufacturing process was developed and tested (see figure).



Optimization and shortening of CAR T cell production. T cells are isolated and activated on day 0. On day 2, gene transfer is performed by sleeping beauty transposition. Cells are then expanded until harvest. Protocols tested included differences in activators, electroporation devices, and expansion time. The manufacturing process optimized in UltraCAR-T achieves the desired target dose of CAR-T cells as early as day 7.

The CAR-T cell product was also targeted at the genome and proteome levels, particularly to determine intrinsic T cell fitness. For this purpose, T cells were examined at the days of T cell isolation, electroporation, and harvest using nanostring analysis. Nanostring analysis is a standardized and relatively inexpensive "entry-level" technology that we used to prepare for the more elaborate analyses on the OMICS platform. It was found that the use of different manufacturing protocols resulted in single significant differences in the gene expression profile of the harvested T cells. The changes in gene expression profile were also reflected in protein expression, which was confirmed using flow cytometric measurements. These results indicate that manufacturing time in particular influences T cell fitness and differentiation.
As a key result, UltraCART presents a new, innovative CAR-T cell product for the treatment of AML, and an optimized GMP manufacturing template for CAR-T cells, which will also be used for further product candidates from T-CURX's pipeline.

CAR-NK4.0

The project is developing an AI-assisted CAR-NK cell platform (CAR-NK4.0) and a fully automated manufacturing process for the phase I trial of an allogeneic target-specific CAR-NK approach for the treatment of myeloid neoplasms, using innovative technologies such as biospecific targeting, AAV and lentiviral gene transfer, and novel cell activation.

Project Lead: Ulrike Köhl

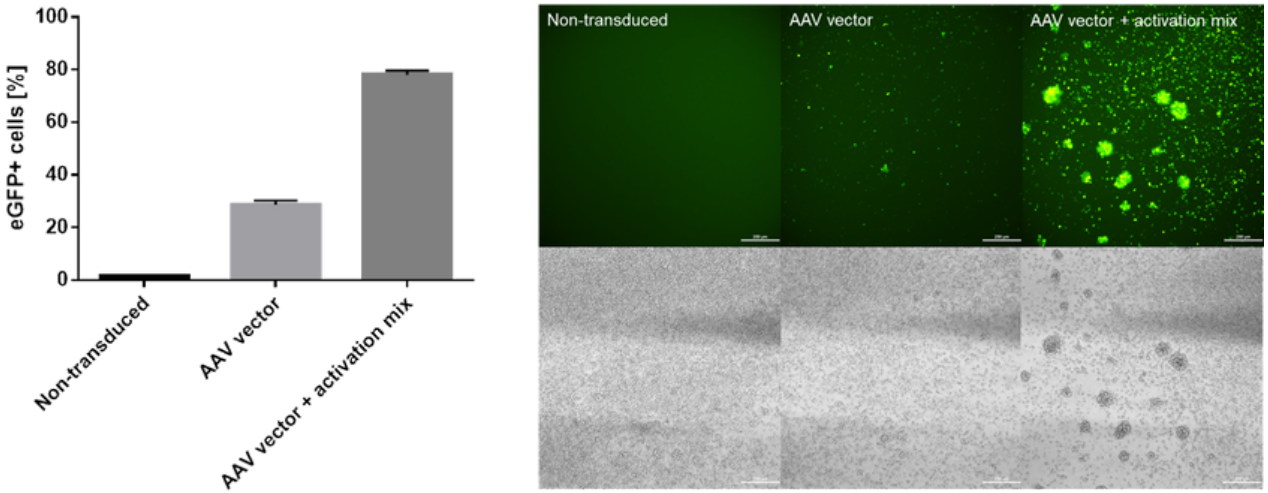
Partners: Fraunhofer IZI, Leipzig University Hospital, Leipzig University, Chemnitz Hospital, Affimed GmbH, Miltenyi Biotec B.V. & Co. KG

In a proof-of-concept study, a digitally controlled, automated production of CAR-NK cells with targeted CARs was established. Here, primary Natural Killer Cells were isolated from leukocyte concentrates to supply project partners with NK cells. The Natural Killer Cell Transduction (NKCT) process was transferred and quality control was implemented. In addition, a first production run of targeted CAR-NK cells with preclinical vector is planned.

A protocol was established for the clinical trial "Bridging to Transplantation" in myeloid diseases. Patients with unfavorable prognosis and without transplantation option will receive target-specific CAR-NK cells here. The study includes design, endpoints, patient selection and monitoring. Biobanking will support the research during the study. The implementation of CAR-T cell therapy has also created a suitable infrastructure for ATMP testing. In addition, the cell therapy expertise of all project partners strengthens the planned study quality.

In the field of multiple myeloma, bi-specific CARs could be developed. Antibody fragments were cloned into CARs suitable for NK cells and tested on target cells. Optimized CAR-NK cell production using retroviral transduction and bispecific targeting against CD19 was successfully tested on tumor cell lines.

Efficient transgene expression of AAV vectors in primary NK cells was demonstrated for the first time. Different AAV serotypes and capsid variants were compared and optimized, with approximately 80% eGFP transgene expression. Initial AAV-CAR vectors in NK cells showed increased cytotoxicity. Further characterization and optimization steps, including intracellular processing of AAV vectors, are in progress.



Transduction of primary human natural killer (NK) cells with adeno-associated viral (AAV) vectors. AAV vectors could be successfully and efficiently used for transduction and transgene expression of human primary NK cells. The basic transgene expression level of AAV vectors is very low and highly donor-dependent (see AAV vector). The addition of an activation mix increases the level of transgene expression to ˜80%, donor-independent (see AAV vector + activation mix).

CAReNK-AID

The goal of the CAReNK-AID project is to develop innovative cell-based therapies for the treatment of autoimmune diseases, such as Systemic Lupus Erythematosus (SLE), type 1 diabetes and pemphigus vulgaris, for which there are currently no suitable treatments. In this project, natural killer (NK) cells are genetically engineered with chimeric antigen receptors (CAR) to target and eliminate autoreactive B cells, which are the primary cause of certain autoimmune diseases, via their surface molecule CD19.

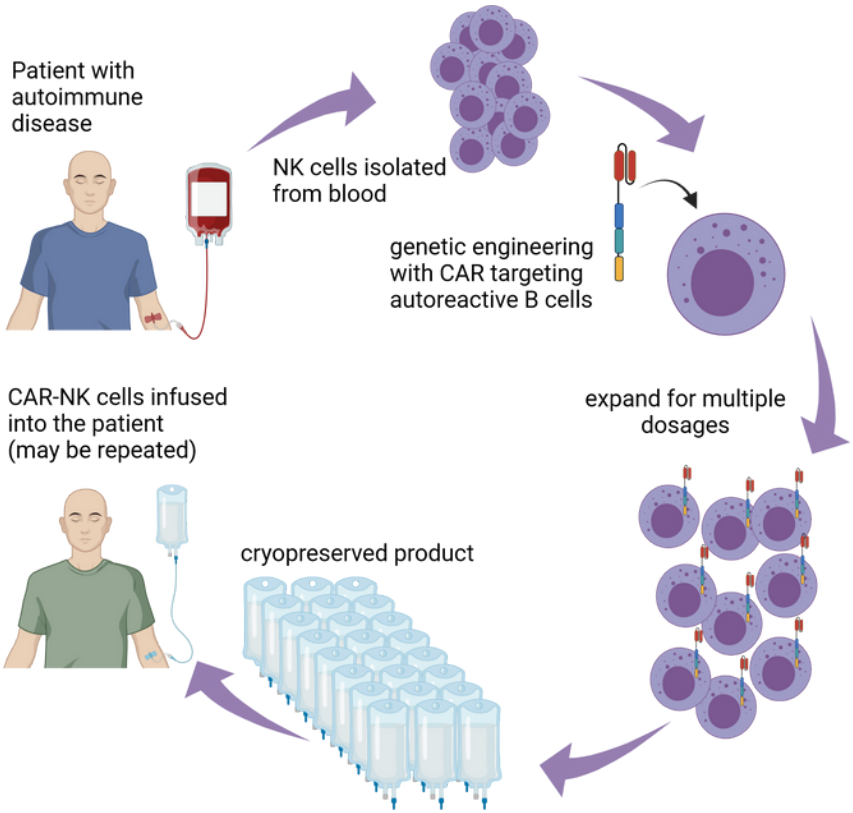
Project lead: Torsten Tonn

Partner: TUD Dresden University of Technology, University Hospital Dresden, University of Leipzig

A CAR targeting CD19 (CD19.CAR) was constructed and stably transduced into the NK cell line NK-92. After confirming the activity of CD19.CAR against CD19+ B cells in vitro, primary NK cells were transduced with CD19.CAR and the transduction efficiency and cytotoxicity were compared. A GMP procedure for the production of activated, unmodified primary NK cells on a clinical scale has been established, validated and forms the basis for the implementation of genetically modified primary NK cells in patients with severe autoimmune diseases. A study protocol is currently being developed to evaluate safety and efficacy in patients with various autoimmune diseases in which depletion of CD19-based B cells may hold promise for therapeutic benefit.

In addition, process optimizations focusing on NK cell expansion as well as non-viral gene transfer are being carried out to enable standardized and automated manufacturing for later phases of clinical development. Here, a CD19-expressing feeder cell line was successfully established to enable selective expansion of CD19.CAR NK cells. Various mutations in the CD19.CAR binding site of the CD19 molecule were introduced to improve expansion properties. For non-viral CAR delivery, DNA-based constructs for mRNA production have been developed, including mutagenesis to exploit the natural cap-1 structure with reduced immunogenicity. Self-amplifying mRNAs (sa-mRNAs) were added to the range of mRNA candidates, and optimal nanoparticle candidates for mRNA transfection were identified based on studies in standard cell lines.

In parallel, a second-generation CAR was developed that allows specific targeting of autoimmune-reactive B cells without destroying B cells that do not contribute to disease progression. To this end, autoreactive epitopes associated with type 1 diabetes and pemphigus vulgaris were identified, cloned into lentiviral CAR vectors, and expressed in NK-92 cells. The functionality of the CARs for specific autoreactive B cells was confirmed by degranulation and cytotoxicity assays.



Therapeutic approach based on CD19.CAR-NK cells for the treatment of autoimmune diseases

Based on recent publications on the clinical breakthrough of CAR-T cells in autoimmune diseases, the consortium is currently preparing a clinical trial protocol aimed at using autologous primary CD19. CAR-NK cells in patients with severe autoimmune diseases. While development to eliminate disease-specific B cells is ongoing, we plan to enter the clinic with autologous CD19.CAR-NK cells in parallel with clinical and preclinical development. As described above, the Phase I trial, which is expected to start in the second half of 2024, will combine different autoimmune diseases.

NK4Therapy

The project aims to develop a manufacturing process of memory-like NK cells for tumor immunotherapy leveraging patented technologies for commercialization.

Project lead: Achim Temme

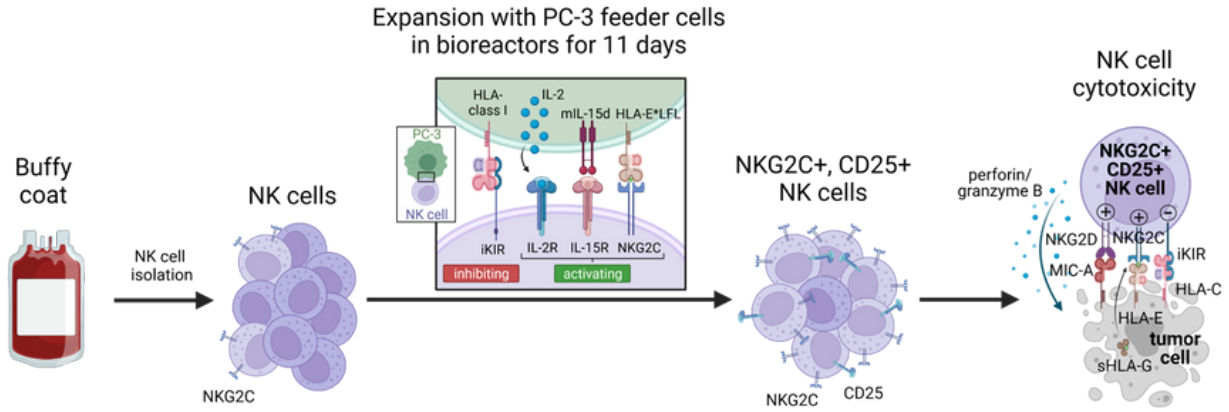
Partner: University Hospital Dresden, Technical University Dresden, Cell.Copedia GmbH Leipzig

The "NK4Therapy" project pursues immunotherapy of cancer using memory-like NK cells characterized by expression of NKG2C. These NK cells have potential for the treatment of leukemia and solid tumors. The objectives of the project include a GMP-compliant NK cell isolation using a new proprietary technology and GMP procedures to generate memory-like NK cells on a clinical scale using patented genetically modified feeder cells.

A functional feeder cell clone was identified and adapted to growth conditions without animal components to further minimize risk of transmitting animal spongiform encephalopathy agents. Lethal irradiation of the feeder cell clone with 30 Gy eliminated tumorigenicity but still enabled selective expansion of NKG2C-positive NK cells which showed no signs of exhaustion.

Further studies identified an optimal ratio of feeder to NK cells for large-scale expansion in disposable bioreactors. Expanded NKG2C-positive NK cells showed effective elimination of leukemia and glioblastoma cells which was tunable by picomolar amounts of IL-2 and enhanced by TIGIT blockade.

Key milestones achieved include next-generation sequencing of the feeder cell clone, establishment of test systems for identity testing, and development of a GMP-compliant device and kit for NK cell isolation.



Workflow of a large-scale expansion of NKG2C+ NK cells with PC-3 feeder cells at a ratio of 10:1 in bioreactors with gas-permeable soil membrane. 5 x 10^5 PC-3 feeder cells were fed on the day of isolation, day 3 and day 7

The "NK4Therapy" project contributes to advancing a NKG2C-positive NK cell-based immunotherapy of cancer through an optimized GMP-compliant manufacturing process for clinical use.

HemRec

Hemoglobinopathies are one of the most common inherited diseases worldwide. The HemRec project aims to develop a universal cure strategy for ß-chain hemoglobinopathies. To this end, a designer recombinase produced in the Buchholz laboratory is being developed to correct genetic defects in hematopoietic stem cells.

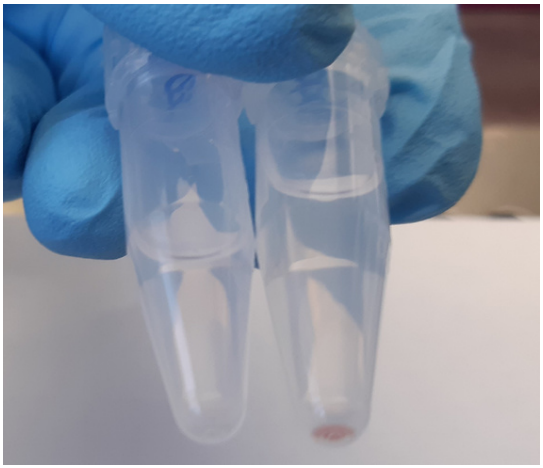
Project lead: Frank Buchholz

Partners: TUD Dresden University of Technology, DKMS Life Science Lab gGmbH

By deactivating a gene that affects the regulation of hemoglobin, the production of fetal hemoglobin can be stimulated. This genetic correction has the potential to reduce the devastating effects of diseases such as sickle cell anemia and ß-thalassemia, among others. The cooperation partners TU Dresden and DKMS Life Science Lab GmbH have the common goal of making this therapeutic option available worldwide at low cost. The scientific vision is to develop an innovative genome editing therapy for hemoglobinopathies. Current treatments carry high risks or are not available to all patients. The targeted recombinase technology promises to provide an effective and safe treatment for these diseases.

The recombinase technology was pioneered over decades by Frank Buchholz and offers important advantages over other genome editing methods such as the CRISPR-Cas system. For example, designer recombinases enable more precise and safer genome editing. Great successes in the development of designer recombinases led to the foundation of the company Seamless Therapeutics at the Dresden site in 2022. Start-up funding of 11.8 million euros is intended to support the further development of the technology platform in order to establish a selection of therapeutically applicable recombinase candidates and prepare them for clinical use. The company's know-how could therefore be useful for various projects of the SaxoCell cluster.

The experimental work within the project has made significant progress and achieved first promising results. An important milestone was the identification of the appropriate target sequence to successfully deactivate the gene BCL11A, which affects hemoglobin regulation, in human cells. With the help of SLiDE, first versions of recombinases with activity at these target sites were developed. Furthermore, reporter cells could be generated and first knock-out experiments were performed, which yielded promising results. In addition, assays were established in a relevant cell line for the activation of fetal hemoglobin (see figure).



Activation of fetal hemoglobin by recombinase technology

In addition, initial data from a well-founded business case analysis are available, shedding light on the promising conditions for a possible market entry. The results of this study support the research efforts in this field and confirm the potential of this innovative approach.

Overall, the progress made so far in the project is extremely promising and gives hope that the project will be a success. The results and data obtained encourage the team to continue research and development with the ultimate goal of developing an effective and innovative therapeutic option for hemoglobinopathies.

ZellTWund

The ZellTWund project focuses on the generation and utilization of purified pro-regenerative cells from human skin, in particular fibroblast subpopulations, for the purpose of skin regeneration in chronic, non-healing wounds, involving degradable biopolymers.

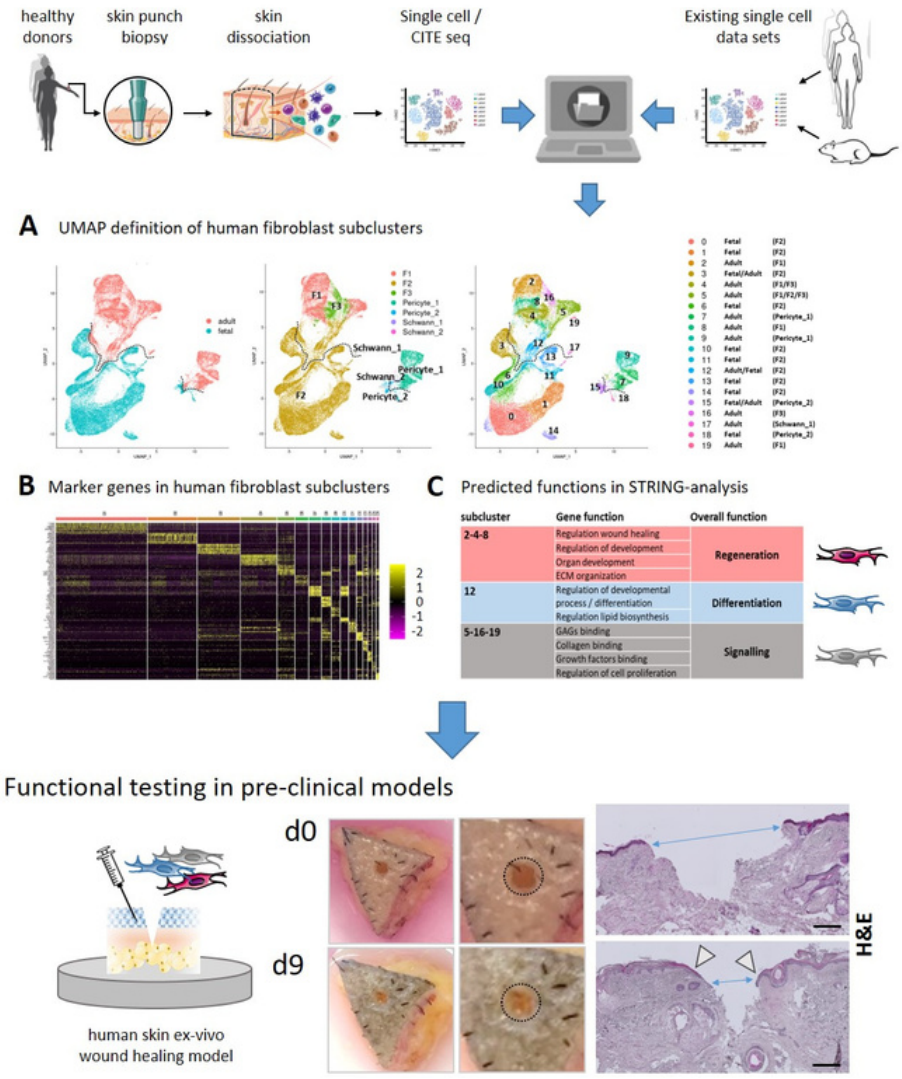
Project lead: Jan-Christoph Simon & Sandra Franz

Partners: University Hospital Leipzig, University of Leipzig, Helmholtz Center Munich

Fibroblasts are a diverse population of cells with different functions that adapt to environmental signals. Several fibroblast subtypes have been identified in mouse studies, some of which are associated with regenerative processes in development and wound healing.

To identify pro-regenerative fibroblasts in human skin, existing single cell sequencing data from human skin were analyzed and compared with known data from mouse studies. This resulted in three fibroblast clusters that differed between fetal and adult cells. Assignment of marker genes from mouse studies demonstrated that certain fetal subclusters resembled mouse fibroblast populations. Pro-regenerative marker genes identified in reindeer antler fibroblasts were also included in the analysis and found in fibroblast subclusters of human fetal skin. Furthermore, different expression profiles were identified in fibroblast subclusters of adult human skin, indicating possible different functions.

In addition, skin culture models were developed to test the tolerability, integration and efficacy of a pro-regenerative wound dressing. This includes a new ex-vivo wound healing model from human skin samples that includes all three layers of the skin and can be maintained in long-term culture by special media. The ex-vivo wound healing model using human skin will be used for preclinical testing of the wound dressing. We entered into a new industry collaboration with HAN Biomedical, who is already providing us with clinically used biomaterials for the incorporation of the pro-regenerative fibroblasts. As a result of this collaboration, HAN established a European research office in Leipzig. Further studies are needed to characterize the fibroblast clusters and confirm the integration of the cells into the skin tissue.



Identification and characterization of human regenerative fibroblasts. Skin is taken from healthy human donors by biopsy and the different fibroblast subpopulations are identified by single-cell sequencing and compared with existing data sets. The fibroblast subpopulations are then divided into functional groups based on their properties (including surface markers). The regenerative properties of the corresponding populations will then be tested and verified in preclinical models.

MSC-PreStiGe

The project objective of MSC-PreStiGe is to develop an industrial value chain for mesenchymal stromal cells (MSCs), including active ingredient production, drug production and clinical application.

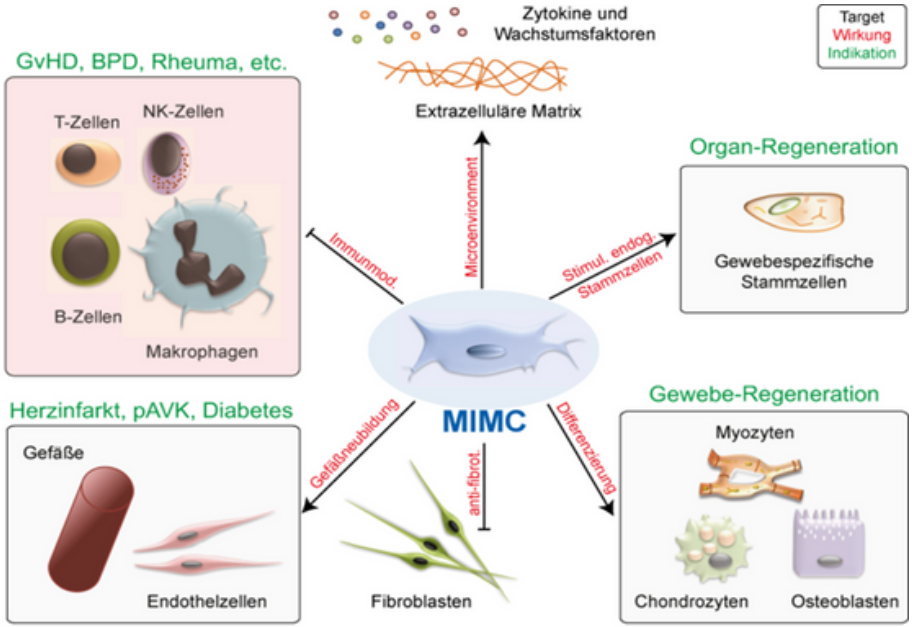
The newly developed active ingredient Desacell® exploits the immunomodulatory capabilities of MSCs from umbilical cord tissue. Due to their enormous expansion potential, cell products from one umbilical cord can be used to treat several patients, with the initial focus on severe acute graft-versus-host disease (GvHD) following allogeneic stem cell transplantation.

Project lead: Mario Rüdiger

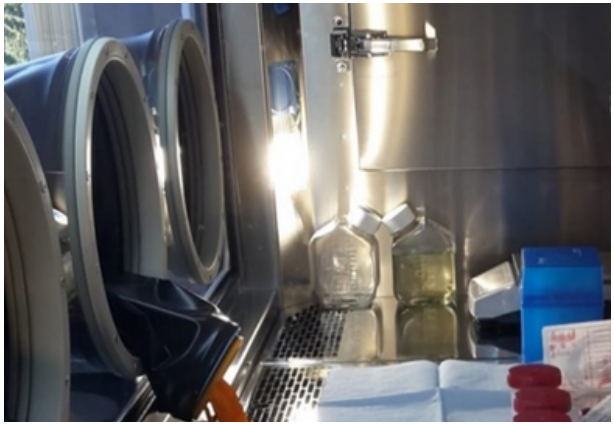
Partners: TUD Dresden University of Technology, Dresden University Hospital, DKMS Stammzellbank gGmbH, MDTB Cells GmbH

In order to establish Desacell® as a novel MSC-based therapeutic, the entire target process was first extracted from the established proof-of-concept and the differences to the future manufacturer were identified. Furthermore, GMP-compliant approaches to resolve these differences were developed and the specifications for industrial scaling as well as an implementation plan for the process transfer were elaborated. The implementation including the necessary accompanying investments could consequently be started.

In addition, the prerequisites for a potentially targeted clinical intervention with Desacell® as well as complementary activities for further value-adding stages and products were created to prepare for the international use of Desacell® in large-scale studies and subsequent regulatory submissions for indications with high medical need. This includes research and development activities to predict the potential success of the clinical use of Desacell® as well as the characterization of the mode of action of Desacell® by establishing and validating an effector cell-free, highly reproducible, standardized and automatable quality control assay based on Fas ligand stimulation, which allows the determination of the anti-inflammatory capacity of MSC from umbilical cord tissue (UC-MSC).



Mechanisms of action, target cells, and indications of MSC (after Raynaud et al., The Necessity of a systematic approach for the use of MSCs in the clinical setting. Stem Cells Int, 2013. 2013: p. 892340.)



Example pictures from the production

xMac

The xMac project focuses on the development of a GMP-compliant manufacturing process for self-renewing human macrophages from induced pluripotent stem cells for clinical investigational drugs against solid tumors, infectious diseases and lung diseases. The focus is on broadly applicable macrophage preparations for allogeneic transplantation.

Project lead: Michael H. Sieweke

Partner: TUD Dresden University of Technology

The xMac project develops self-renewing human macrophages for allogeneic transplantation. Activation of self-renewal in human macrophages removes a major obstacle to their therapeutic application, since macrophages, in contrast to T cells, could not be propagated ex vivo until now. With our protocol, we succeeded in increasing the yield of these cells by at least a factor of 50.

Macrophages are also a very plastic cell type and can adopt a pro-inflammatory, an anti-tumor state, or, especially in tumors, a tumor-promoting polarization state. We have removed specific transcription factors in self-renewing macrophages that play an important role in this process. These self-renewing, genetically modified macrophages are resistant to tumor-induced, pro-tumorigenic M2-like polarization and will be particularly useful for cancer therapy.

Bioinformatic and functional analyses of these modified self-renewing macrophages show that they retain M1 polarization and are resistant to tumor-induced M2 polarization. Our data suggest that these cells will have potent antitumor activity and formed the basis for a new patent application.

In addition, we made progress in developing a macrophage production process in xeno-free medium up to harvesting on day 15 after induction of the embryoid body (an intermediate in our macrophage production).

Why macrophages?

Tumor encapsulates itself | Macrophages invade tumor... | ...but are reprogrammed by the tumor | Tumor continues to grow

DKO macrophages can no longer be reprogrammed

Macrophages in which transcription factors involved in the self-renewal process have been knocked out (double knockout macrophages, DKO macrophages) can no longer be reprogrammed by the tumor environment.

At the Science4Life Venture Cup - the most important business plan competition for the life sciences in Germany - we came fourth in the business plan phase (out of 87 participating teams), beating strong competition! This is an important boost for our ambitions to found a company based on self-renewing human macrophages.

OPTIX

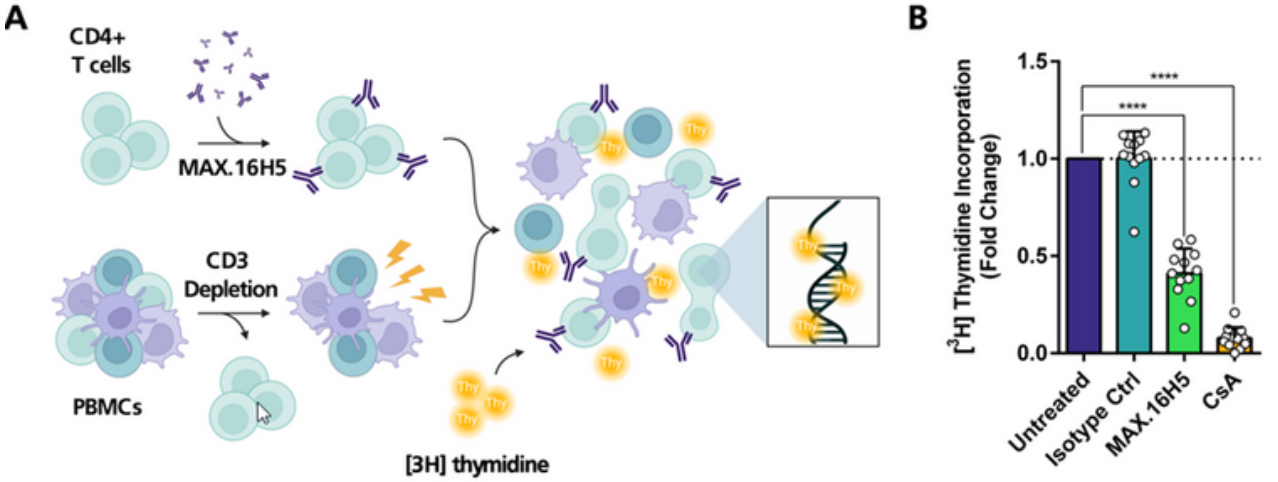
Within the OPTIX project, an optimized manufacturing process for antibody-modified cell transplantation (Palintra®) will be developed and clinically implemented. The aim is to reduce graft-versus-host disease (GvHD) in the treatment of hematological neoplasms while preserving the graft-vs-leukemia effect.

Project lead: Tcell Tolerance GmbH, Lilly Stahl

Partners: Fraunhofer IZI, Leipzig University Hospital, Dresden University Hospital, Chemnitz Hospital

Palintra® is a novel therapeutic strategy for GvHD prevention by ex vivo incubation of an allogeneic cell transplant with the anti-CD4 antibody MAX.16H5 to an Advanced Therapy Medicinal Product (ATMP). Within the OPTIX project, several milestones for the clinical use of Palintra® will be developed:
For the GMP-compliant production of the MAX.16H5 antibody, a Master Cell Bank (MCB) was first successfully produced by the Fraunhofer IZI's AG GMP-Biopharmaceuticals. Currently, the production of the first GMP batch of the MAX.16H5 antibody is being prepared in order to use it for process development and validation of the production of the ATMP Palintra® as well as a GLP safety study.
With previously available antibody material from GMP sample batches, the Palintra® production process could be optimized. The elucidation of the mechanism of action of the MAX.16H5 antibody is largely complete, for which a proliferation assay was developed as an in vitro functional assay using primary donor material. Incubation of the antibody with the cell graft saturates CD4+ T cells and inhibits their proliferation, which is the principal mechanism of action for GvHD reduction.
Here, biomarkers were identified that are downregulated upon incubation of T cells using the MAX.16H5 antibody. This work is currently under review at Frontiers in Immunology. For potential use as a release-relevant assay, the proliferation assay was also transferred to cell lines for better validation.

To improve the quality control of cell-based drugs (e.g. Palintra®), a functional software demonstrator "AI Flow Software Algorithm" for the automated analysis of flow cytometric measurements has also been developed.
Furthermore, data regarding the use of the MAX.16H5 antibody to avoid a potential cytokine release syndrome in CAR-T cell therapy in vitro have already been generated.



Inhibition of CD4+ T cell proliferation by MAX.16H5 in a functional in vitro assay (from Roth et al., Frontiers in Immunology, under review).
A) Experimental design: CD4+ T cells were stimulated with cells from a second donor in a coculture assay. Analysis of CD4+ T cell proliferation was based on incorporation of the radioactive nucleoside [3H]-thymidine into the genome of proliferating cells. B) [3H]-thymidine incorporation is significantly reduced after MAX.16H5 and ciclosporin A (CsA) treatment of CD4+ T cells. Shown is the relative change in [3H]-thymidine incorporation compared with the untreated group (mean ± SD, N = 12).

ECP-CAR

In the ECP-CAR project, the analysis of cellular subpopulations including their molecular profiles and effector functions in a cell therapeutic real-world system of a clinical study on the effects of an implemented extracorporeal photopheresis (ECP) is performed. The procedure of ECP, which is well known from other indications, such as the treatment of graft-vs-host disease after allogeneic stem cell transplantation, in terms of efficacy, safety and mechanism of action, currently does not present itself as a regular component of the sequence of therapeutic application of CAR-T cells. As an innovative intervention, ECP as a preparative, immunomodulatory component of CAR-T cell treatment is now being preempted here. In addition to positive effects on clinical endpoints, such as a reduction in inflammatory side effects, positive effects on in vivo expansion, persistence and functionality of CAR-T cells are also hypothesized.

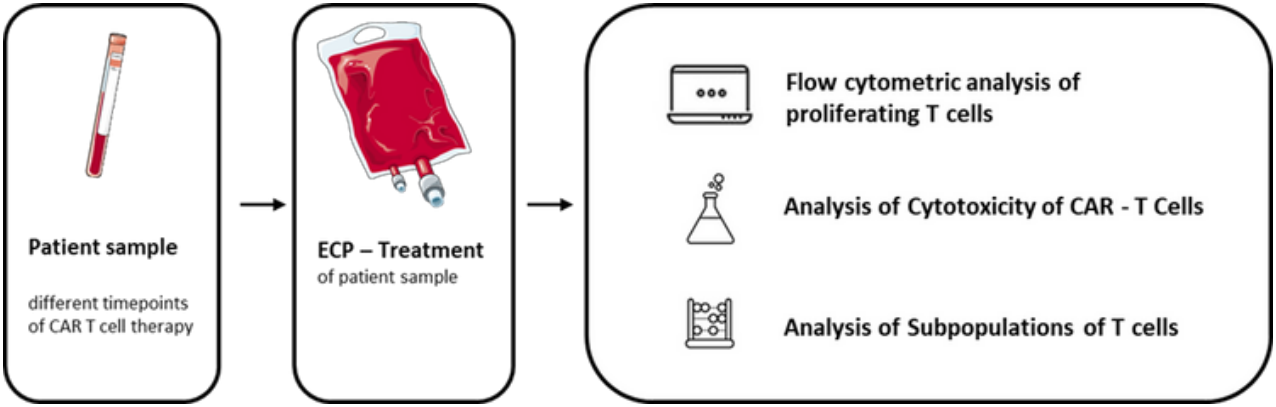
Project lead: Vladan Vucinic

Partners: University Hospital Leipzig, University of Leipzig, University Hospital Dresden

The core of the work was originally a study-by-study analysis of the effects of ECP treatment in combination with CAR-T cell therapy on cellular subpopulations including their molecular profiles and effector functions. As an innovative intervention, ECP should precede CAR-T cell infusion as a preparatory immunomodulatory component. This novel clinical procedure was to be used as part of a nonapplicant-funded prospective intervention study (PhotoCAR, phaseI/II) in CAR T-cell therapy.

Unfortunately, the Photo-CAR study could not start as planned because the ECP procedure was classified by the PEI as an ATMP and in combination with CAR-T cells as an investigational product. We worked closely with the PEI for clarification and discussion, and the submission of literature data and our own results from the aforementioned assays should increase the chances of conducting and starting the PhotoCAR study. Unfortunately, the PEI requirements exceed the available capacity to conduct an academic study.

Therefore, a project amendment of the ECP - CAR project was created. The project will be used to prospectively apply an ECP procedure prior to CAR-T cell administration by generating data and elucidating the exact mechanism of action of ECP. Samples from different time points will be taken from patients currently treated in the clinic and subjected to ECP treatment. Cell populations, proliferation of T cells, apoptosis and cytotoxic competence of CAR-T cells will be investigated.



Procedure to study the immunomodulatory effect of ECP treatment before and during CAR-T cell therapy

TheraSTAR

TheraSTAR develops theranostic target molecules, i.e. target molecules that are important for therapy and diagnostics, which can be used in a variety of ways for tumor immunotherapy based on adapter RevCAR technologies, modulation of the tumor microenvironment, tumor and therapy monitoring by diagnostic imaging methods, and radionuclide therapy.

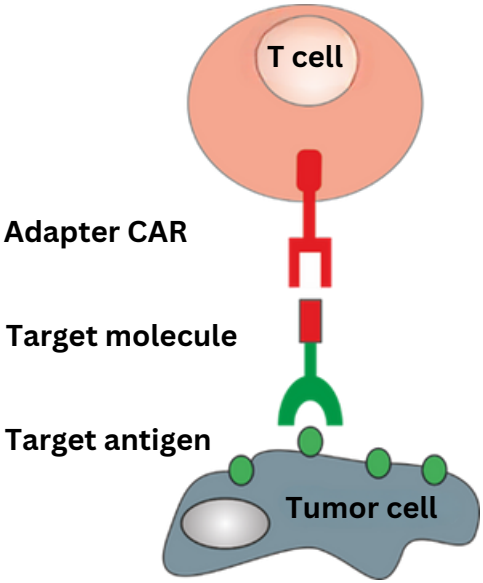
Project lead: Anja Feldmann

Partners: TUD Dresden University of Technology, Helmholtz-Zentrum Dresden-Rossendorf

For effective and safe tumor detection and therapy, we are developing "gated positive" (GP) and "gated inhibitory" (GI) adapter CAR (RevCAR) platforms consisting of two main components: the target molecules (TMs) and the GP/GI-CAR T cells. The unique feature is that GP/GI-CAR T cells can recognize and kill tumor cells exclusively mediated by the soluble TMs. The TMs determine the tumor specificity of the GP/GI-CAR-T cells and allow their activity to be turned on and off as needed.

The development of the platforms involves the generation of novel, bispecific target molecules (bsTMs) that specifically target the adapter CAR-T cells against tumor-associated antigens or "immune checkpoint" molecules. This is done to modulate the tumor microenvironment to favor immunotherapies.

To date, novel TMs have been successfully constructed, eukaryotically expressed and purified by affinity chromatography. In addition, GP/GI-CAR-T cells were successfully generated by lentiviral transduction at cell culture scale. Both components were manually prepared in sufficient quantity and quality for preclinical studies. For preclinical feasibility studies, we used tumor cell lines presenting the target antigen natively on their surface as well as established reproducible cell culture models recombinantly expressing the target antigen after genetic modification by lentiviral transduction.

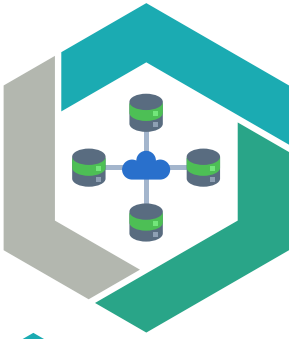


Schematic representation of the gated positive (GP) and gated inhibitory (GI) Adapter CAR (RevCAR) platform for tumor cell killing and modulation of the tumor microenvironment. T cells are genetically modified to express adapter CARs. These GP/GI-CAR T cells require a target molecule to recognize and kill tumor cells that present a specific target antigen (e.g., tumor-associated antigens or "immune checkpoint" molecules).

So far, we have successfully demonstrated in cell culture experiments that GP/GI-CAR-T cells in combination with the new TMs can specifically and efficiently destroy antigen-expressing tumor cells. The activity of GP/GI-CAR-T cells is strictly dependent on the presence of appropriate TMs.

Technology Platforms

The three technology platforms provide **technical and regulatory support** to the 12 R&D projects.



OMICS

State-of-the-art cellular and molecular measurement techniques as well as data processing and interpretation, biomarkers, patient stratification

SYSTEMS

Integrated processes, machine learning and artificial intelligence for automated manufacturing

CLINICS

Bundling and networking of clinical expertise, consulting on clinical studies, translation of therapeutic products into clinical practice

OMICS

The mission of SaxoCellOMICS is to provide a common platform incorporating state-of-the-art cellular and molecular measurement techniques, data processing as well as interpretation. This platform will support the development and manufacturing of gene and cell therapeutics by providing efficient methods for monitoring therapies, identifying mechanisms of action and novel targets, and developing quality criteria for manufacturing and predictive biomarker development. By working closely with other SaxoCell partners, SaxoCellOMICS contributes to strengthening the competitiveness of companies in the SaxoCell region.

Project lead: Kristin Reiche & Ezio Bonifacio

Partners: Fraunhofer IZI, TUD Dresden University of Technology, Leipzig University, ecSeq GmbH

In 2022/23, a comprehensive list of relevant methods and technologies was compiled and made available to all SaxoCell partners via the website in the members' area. This process was carried out in collaboration with the SaxoCellOMICS partners and the SaxoCellHub.

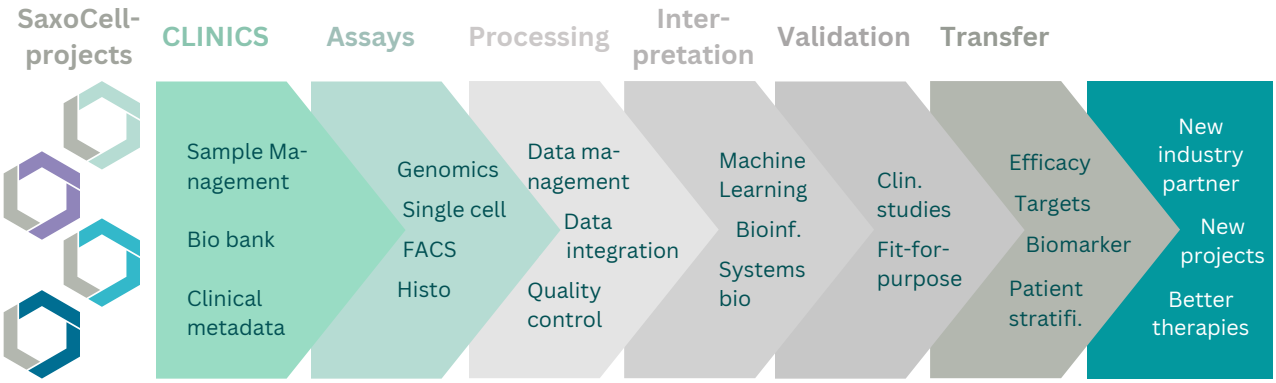
In addition, recommendations and standard operating procedures (SOPs) for sample collection and processing were developed and harmonized. Existing workflows such as flow cytometry and transcriptome sequencing were used as templates. Harmonization will be performed between the TUD and IZI production sites in collaboration with SaxoCellCLINICS. In addition, SOPs and guidelines for data generation and analysis of selected assays are being developed.

Another important step was the preparation of a description of available experimental workflows and analysis types as well as a cost matrix. This matrix will provide guidance and costing for SaxoCell projects.

A major focus of the project is to coordinate and harmonize the methods available at the different sites, e.g., flow cytometry (FACS) or RNAseq, by performing interlaboratory comparisons between SaxoCellOMICS partners to determine and, if necessary, improve the agreement of measurements between sites. Planning for these interlaboratory comparisons has already begun, and samples have been identified and methods for sample processing established.

Concrete processes for integrating SaxoCellOMICS into selected projects such as ECP-CAR, UltraCAR-T, MSC-PreStiGe and CAR-NK4.0 were also developed. Contacts were made with eight SaxoCell projects to discuss project plans and identify needs. In addition, successful pilot experiments with single cell technologies were conducted in collaboration with a local research group. The data management plan developed in SaxoCellOMICS governs the GDPR-compliant collection, storage and handling of data.

Another important aspect is the collaboration with the NFDI consortium GHGA (German Human Genome Phenome Archive). SaxoCellOMICS will benefit from the GHGA infrastructure and serve as a bridge to manage project data according to GHGA guidelines. In addition, SaxoCellOMICS has offered courses to train scientists in (single cell) transcriptomics. Moerover, a Galaxy Server has been set up to allow scientists to analyze their transcriptome sequencing data.



Presentation of the technologies and competences bundled in SaxoCellOMICS as well as their interaction with SaxoCell projects in order to accompany the development and production of gene and cell therapeutics and to create new fields of action for industry and science.

Overall, SaxoCellOMICS has made significant progress by identifying a broad range of methods and technologies, developing SOPs, coordinating collaboration among partners, and promoting integration into specific projects.

SYSTEMS

The goal of SaxoCellSYSTEMS is to build an automation platform for the production of cell therapeutics (ATMPs) in the SaxoCell cluster.

Project lead: Stephan Fricke & Ulrich Blache

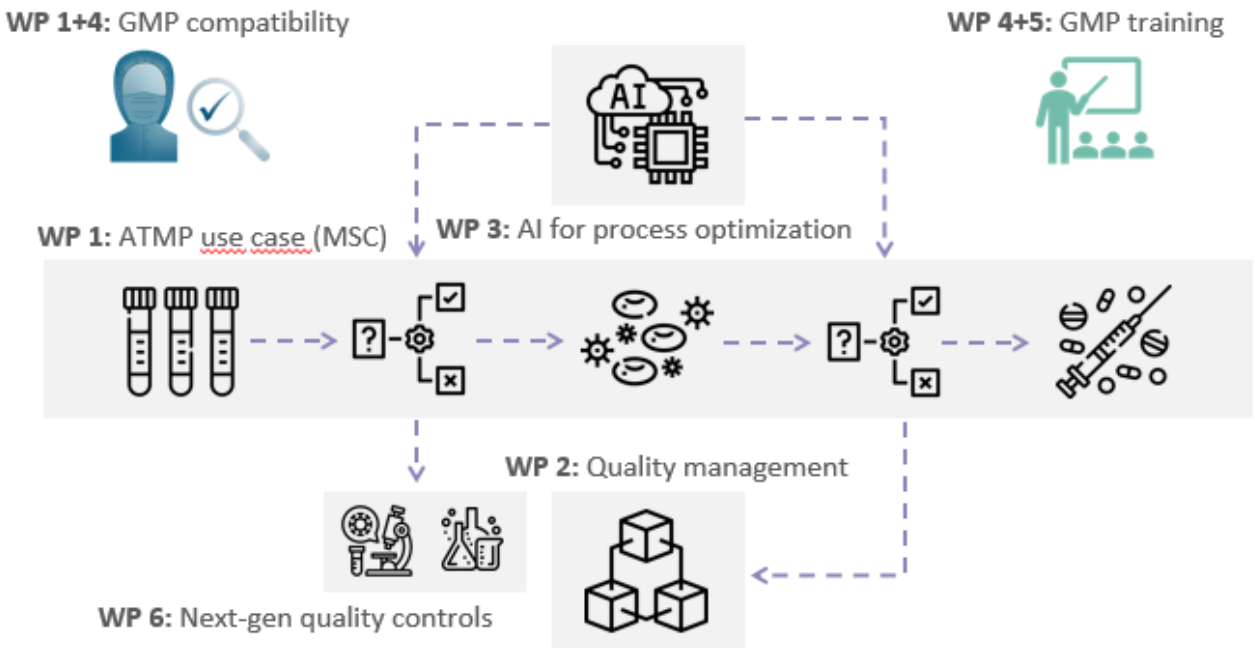
Partners: Fraunhofer IZI, ICCAS University of Leipzig, TUD Dresden University of Technology

SaxoCellSYSTEMS has the long-term goal of establishing an automation platform for the manufacturing of cell products (ATMPs) of the SaxoCell cluster. In the current implementation phase (2021-2024), the focus is on the development of a concept for automated manufacturing of cell therapeutics, the evaluation of artificial intelligence (AI) methods for automation, the integration of intelligent quality management and the development of new quality controls. Furthermore, the consortium is developing GMP training concepts.

Among the results achieved so far are the mapping of GMP-compliant automation challenges, the development of a training concept for GMP personnel, the creation of a competence atlas, the publication and submission of scientific papers, and the clarification of system architecture aspects.

Currently, the use case for the production of Mesenchymal Stromal Cells (MSCs) in particular is being considered in close cooperation with the SaxoCell project MSC-PreStiGe. In this context, a generic thinking and design model was formulated and critical digital interfaces were identified. In addition, progress was made in developing AI models for determining confluence and analyzing impedance measurements of MSCs in 3D cultures. Monitoring parameter requirements for the MSCs expansion use case were determined and appropriate cell culture models were identified. Microcavity arrays for 3D cell culture models were fabricated and initial test measurements were performed.

The creation of GMP training modules has taken place and a collaboration with SaxoCell Hub to use the education portal has been established.



Schematic of SaxoCellSYSTEMS task areas in the form of Work Packages (WPs).

Overall, SaxoCellSYSTEMS has made significant progress in the current implementation phase and has laid a solid foundation for building an automation platform. Collaboration with other partners and the development of practical solutions are the focus in order to implement the concept in the coming phases and transfer it to other ATMPs.

CLINICS

SaxoCellCLINICS was founded to provide resources and services for innovative research projects with clinical relevance in the SaxoCell cluster in the best possible way. The platform acts both as a clinical contact for project partners and as an interface between research institutions, authorities, industry and other platforms in the cluster.

Project lead: Uwe Platzbecker & Silke Gloaguen

Partners: University Hospital Leipzig, University Hospital Dresden, Center for Clinical Studies Leipzig (ZKS), Coordination Center Clinical Studies Dresden (KKS)

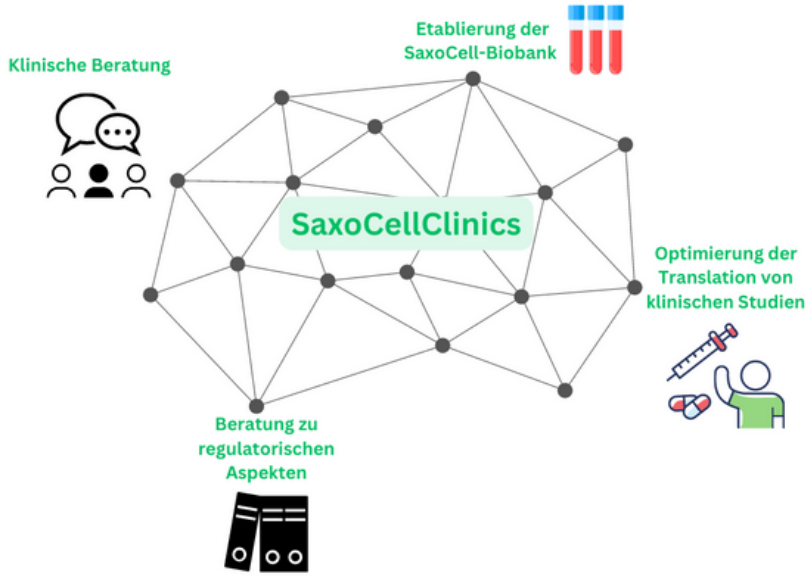
The specific **objectives of the platform** are defined as follows:

1. Establishment of a central coordination structure for clinical and regulatory aspects in the field of gene and cell therapy in the SaxoCell cluster.
2. Optimization of translation of phase 1-3 clinical trials in the field of cell and gene therapy.
3. Consulting and establishment of networks.
4. Establishment of a registry and harmonization of biobanking (SaxoCell-Bio) for cell and gene therapies in Saxony.

The SaxoCellCLINICS platform has already made important progress. Fixed contact persons with clear tasks have been appointed, including Uwe Platzbecker as scientific director, who is primarily responsible for clinical-scientific issues and study designs. Silke Gloaguen leads the coordinative activities of the platform, while Janine Kirchberg is an important link between specific cluster projects and the platform.

SaxoCellClinics platform staff regularly attend cluster meetings and are available as contacts for projects and working groups in the cluster. The platform focuses on training and advising partners in clinical trials as well as providing support in later preclinical phases. It works closely with the Paul Ehrlich Institute (PEI), the state directorate and other authorities.

With regard to the concrete preparation of clinical work, the SaxoCellCLINICS platform has already taken various measures. It is cooperating closely with the SaxoCell project "ECP-CAR", which is working on the development of a clinical trial with CAR-T cells and is also providing patient samples for translational analyses in the context of CAR-T cell therapies in order to understand the effect of ECP treatment in the context of such a therapy. The platform is also supporting the design of a CAR-NK cell therapy trial in myelodysplastic neoplasia (MDS)/acute myeloid leukemia (AML). For the ECP-CAR project, the platform is working on the application for manufacturing authorization for the ECP procedure and corresponds regularly with the PEI.



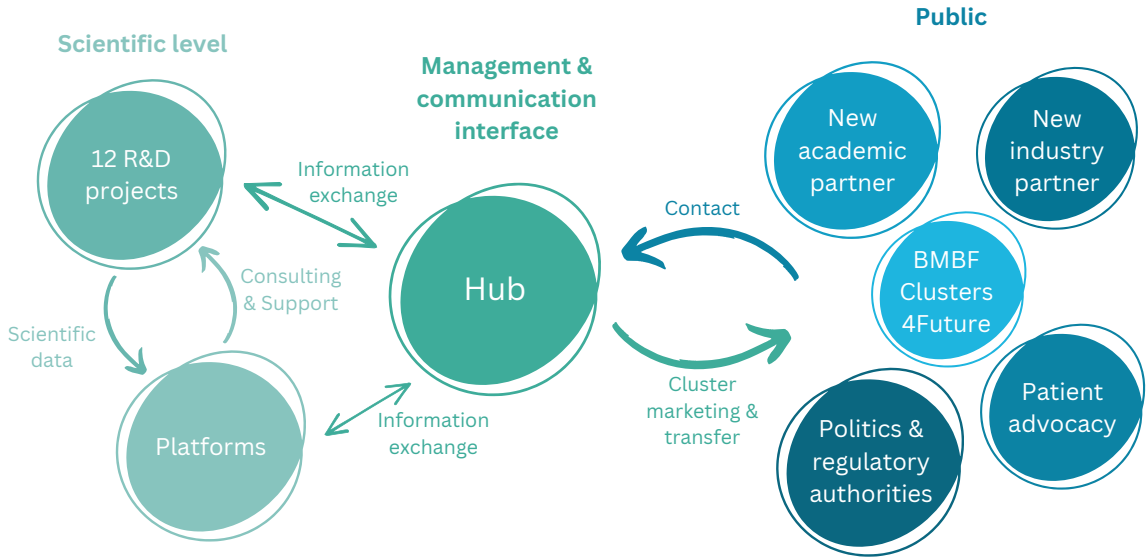
The fields of activity of SaxoCellCLINICS

Overall, the SaxoCell Clinics platform has made significant progress in supporting and coordinating clinical trials in the Saxo Cell Cluster. It helps to improve the translation of research results into clinical application and to provide a solid basis for future cli-nical projects.

Hub

Interface and support

The SaxoCell Hub is the **central interface** between the SaxoCell projects, the technology platforms and the public. It supports SaxoCell members in organizational and regulatory matters and offers assistance in all aspects of technology transfer.



The SaxoCellHub's field of activity consists of **three core programs**:

- The **Pipeline Accelerator Program** (PAP), which is mainly concerned with project management, the identification of new projects and the coordination of existing and new projects.
- The **Innovation Culture Program** (ICP), which deals with press and public relations, marketing and technology transfer. It offers support in contract and patent management, organizes education and training events, and strengthens the innovation culture.
- The **Cluster Matching Program** (CMP), which promotes the cluster strategy in the long term and creates a joint research infrastructure.

The SaxoCell Hub is also structured in such a way that contact persons for projects and platforms are available from the core institutions **TU Dresden, Fraunhofer IZI Leipzig and the University of Leipzig** in order to create a low-threshold offer for SaxoCell members of the respective organization. Discussions are currently underway to recruit representatives from Chemnitz Hospital for the hub.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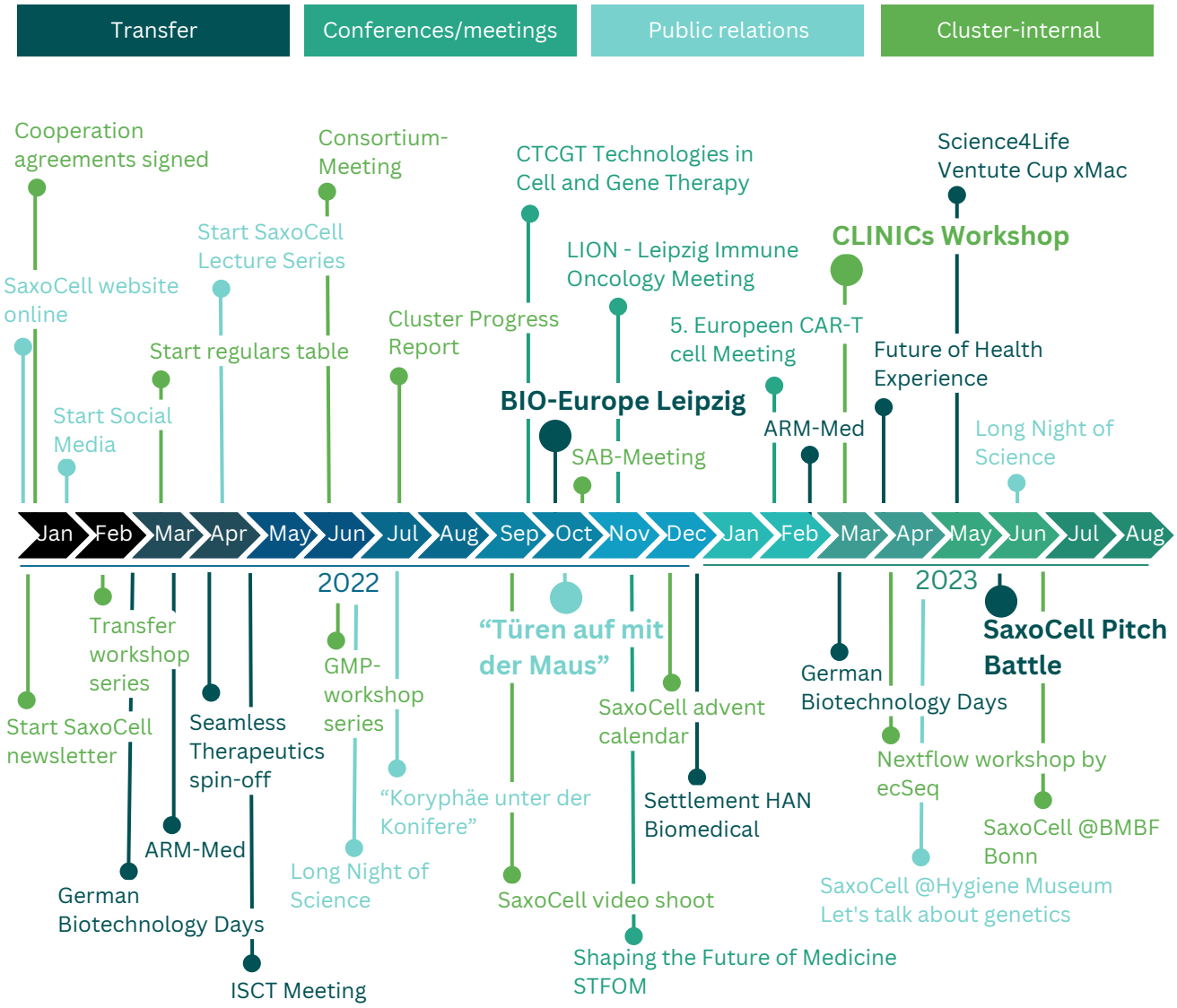
Through weekly Hub-internal, digital meetings, current tasks are discussed and solutions are developed, whereas long-term, strategic tasks are discussed once a quarter in person in either Leipzig or Dresden.

SaxoCell events

Through support of the Hub in the period 2022/2023



In the following, we would like to briefly portray four SaxoCell events from the areas of **Transfer**, **Public** and **Cluster-internal**.

BIO-Europe 2022

Europe's largest partnering event as guest in Leipzig

BIO-EUROPE is **Europe's largest industry and partnering trade fair** in the life science and biotechnology sector. In 2022, BIO-EUROPE took place for the first time in Leipzig with more than 5000 visitors from 66 countries, which offered SaxoCell an excellent opportunity to present itself on the mainly international stage.

Sophia Kolbe (right) and Stephanie Wieneke (center) from the SaxoCell Hub team in conversation with Thomas Kalinski (left), State Secretary of the Saxon Ministry of Economics.

With the support of the trade fair organizers Biosaxony e.V. and the EBD Group, we were able to set up a **SaxoCell booth** as part of the Saxon joint stand, where interested trade fair participants could find out about our activities in direct conversation with our hub members as well as by means of **print material** (flyer, annual report) and the **SaxoCell image film**. The Saxon community stand was located in the **center of the exhibition**, which offered us many contact opportunities.

In addition to our SaxoCell booth, we organized a **SaxoCell symposium** on the main stage in the exhibitor area on day 2 of the 3-day BIO-EUROPE to present SaxoCell in a wide-reaching way and to bring our scientists from the projects and platforms but also our transfer staff and speakers into conversation with the participants. Cluster speaker Ezio Bonifacio opened the well-attended symposium, which was moderated by Dorit Teichmann and Thomas Tradler (both Hub / Transfer). We heard interesting presentations from Anke Fuchs (AlloCAR-Treg), Sandy Tretbar (OPTIX) and Ulrike Weirauch (SaxoCell OMICS).

SaxoCell speaker Ezio Bonifacio opens the SaxoCell Symposium

An essential component of BIO-EUROPE is also the lively **partnering activity**, which enables an enormous number of different players to network in order to explore cooperation opportunities. In more than 60 partnering meetings with international (Johnson & Johnson, Moderna, CureVac, EliLilly) and national (BioNTech, PharmAI, Evonik, IDT Biologica) companies, our SaxoCell transfer team was able to inquire about the needs of the respective companies in the field of current cell and gene therapy activities and to explore possibilities for cooperation.

The on-site discussions resulted in a concrete collaboration between the Israeli company Aposense and scientists from the SaxoCell project CARe-NK-AID. The industry contacts made at BIO-EUROPE 2022 will be regularly maintained in order to identify further cooperation opportunities in the future and to allow the network to grow steadily and organically.

The Hub team at the SaxoCell booth

“Türen auf mit der Maus”

The mouse visits SaxoCell at the CRTD

“Die Sendung mit der Maus” is one of the best-known German television programs for children. Many of us remember it as a program that not only explained the world to us, but also awakened a love of science and research.

Every year in October, Die Maus invites institutions, museums and companies to open their doors to the public at **“Türen auf mit der Maus”**!

The mouse visits SaxoCell

Full house at the event Türen auf mit der Maus. SaxoCell invited young and old scientists to the CRTD in Dresden to explore the topic of personalized medicine in a playful and easy-to-understand way.

Under the motto **"Exciting Connections",** SaxoCell took part in Türen auf mit der Maus last year, on October 3, 2022 - with great success. At the Center for Regenerative Therapies Dresden (CRTD), we counted around 170 visitors in four hours, about half of them children.

SaxoCell Hub member Luisa Brückner (center) training future scientists

We offered pipetting stations, microscopy workshops, lectures, games and much more and it was great fun, with clearly **positive feedback** from all sides.

SaxoCell Hub member Anette Bartsch in cleanroom clothing with the mouse

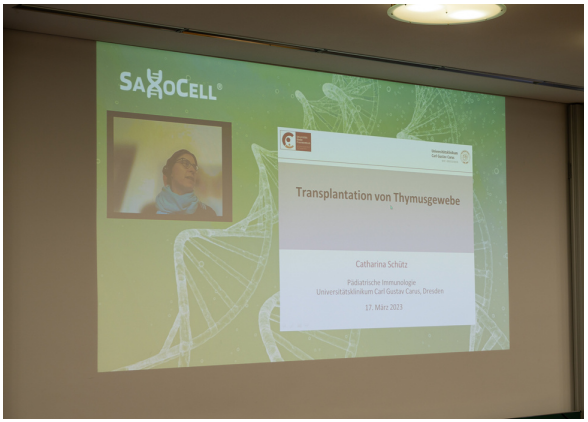
CLINICS Workshop

Clinical studies with ATMPs

The SaxoCell CLINICs workshop on March 16 and 17, 2023 was a great success. With about 30 participants in Leipzig and about 100 online accessors, we were able to reach a large audience who wanted to learn how to set up and run a **clinical trial**, especially with regard to ATMP first-in-human studies.

The workshop was organized by Silke Gloaguen, Janine Kirchberg and our SaxoCell speaker Uwe Platzbecker, who together form the CLINICs team.

Coffee break and networking discussions of the approx. 30 participants of our SaxoCell CLINICs workshop at the study center of the University Hospital Leipzig



Exciting presentations and attentive audience at the lectures of our SaxoCell-CLINICs workshop

Organizer Silke Gloaguen during moderation

The workshop covered all important topics from biostatistics (Dirk Hasenclever) to GMP-compliant ATMP production (Jörg Schäffner, IDT Biologika GmbH) and regulatory requirements. With experts from the **Paul Ehrlich Institute** PEI (Bettina Ziegele), the **Landesdirektion Sachsen** (Anne Lewerenz), the Koordinierungszentrum für Klinische Studien KKS Dresden (Xina Grählert) and the Zentrum für Klinische Studien ZKS Leipzig (Peggy Houben) we spent two intensive days with very valuable input. An important further step to support the translation of our cell and gene therapy projects into the clinic has been taken.

Many scientists from the cluster, such as Vladan Vucinic (SaxoCell project ECP-CAR, PhotoCAR study), but also from outside, such as Catharina Schütz (transplantation of thymus tissue) and Ralf Henkelmann (solutions for cartilage damage) presented their projects clearly in the form of case studies and were thus able to give the participants a good insight into current clinical issues. In addition, the workshop provided ample opportunity for discussion and networking both within and outside the sessions. Afterwards, the discussions could be deepened at the **SaxoCell regulars' table**.

SaxoCell regulars' table at the end of the CLINICs workshop

Pitch Battle

Dresden selects innovative concepts

On June 22, 2023 SaxoCell hosted the first Pitch Battle, with **five teams** presenting their start-up ideas at the conference location Prezel 1724 in the heart of Dresden-Neustadt.

Participating teams were Stefanie Hartmann with MicroAcoustiX, Anthony Gavalas with ISLET-poiesis, Barbara Ludwig with ISLET-poiesis Kalyptos, Markus Badstübner with Cancilico and Jiri Eitler with SMART NK Therapeutics.

Stephanie Wieneke from the SaxoCell Hub welcomes the participants

Exciting pitches on innovative start-up ideas as well as an attentive audience at our SaxoCell Pitch Battle

Five 10-minute pitches were followed by feedback from our jury members Dorit Teichmann, Martin Bornhäuser, Felix Lansing and Dejan Husman. In a relaxed atmosphere and after a small snack, the jury cast their vote.

The **winner of our Pitch Battle 2023** is the **startup Cancilico**, which emerged from the research group "AI in Cancer" of the University Hospital Dresden and develops state-of-the-art artificial intelligence-driven tools for cancer diagnostics.

Group picture of all participants of our SaxoCell Pitch Battle after the award ceremony

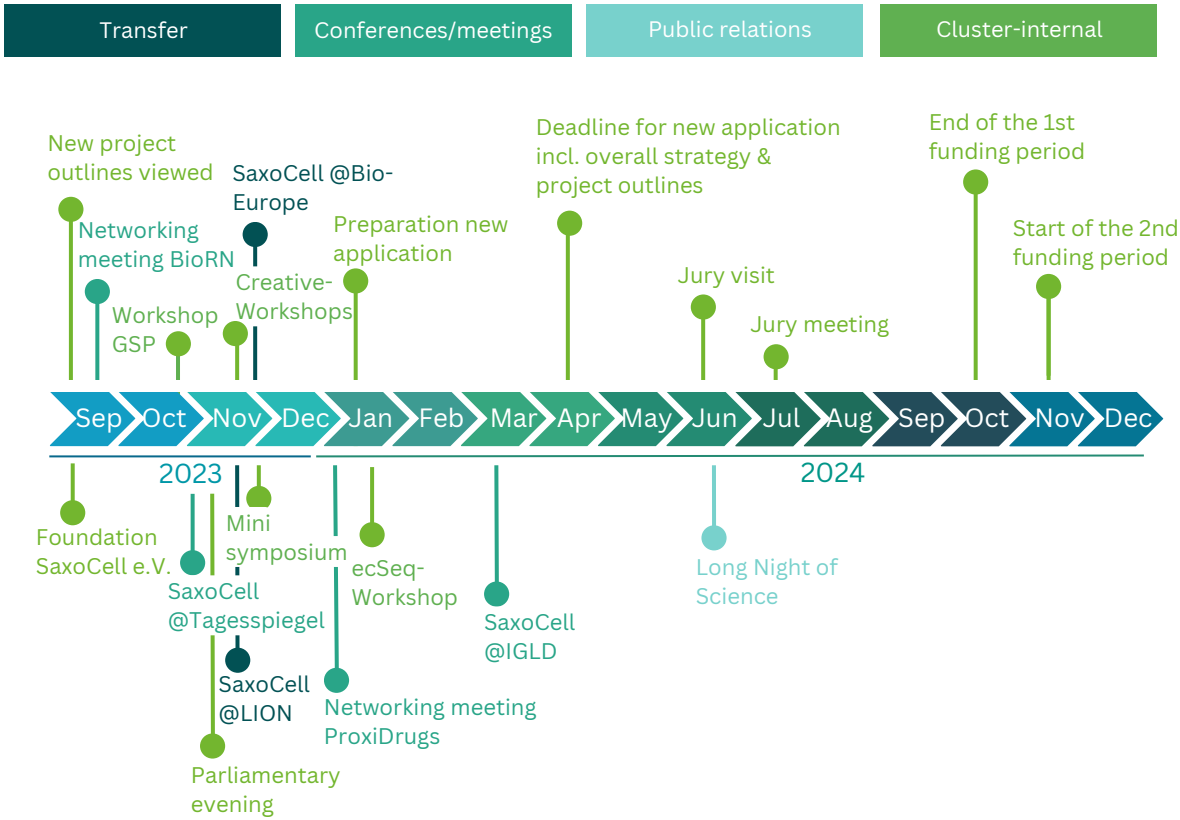
Outlook

To the end of the 1st and the beginning of the 2nd funding phase

The first funding phase of SaxoCell covers the period from October 2021 to the end of September 2024. In the **first part of this first phase**, almost all projects were able to start as planned and generate the first important results in collaboration with their cluster partners. Framework programs around the research activities, such as continuing education events, marketing and transfer events, and networking meetings with other German clusters of similar, thematic focus, have also been established.

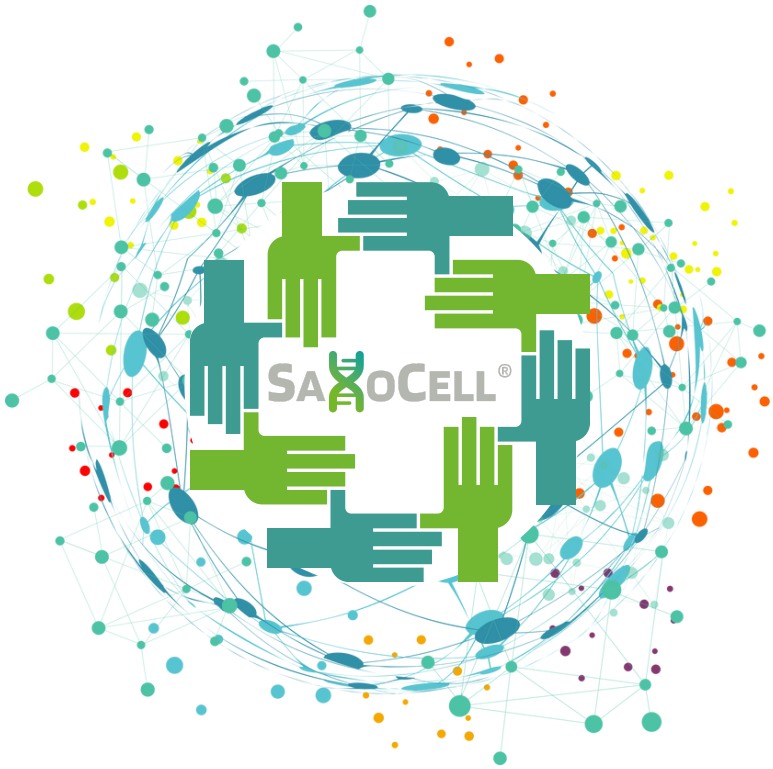
The upcoming **second half of the first funding period** is now fully dedicated to the successful completion of the projects and the achievement of the set milestones as well as, of course, the preparation of the new funding period. In order to complete the projects as planned, they will be surveyed by the Hub team on a quarterly basis and support will be offered or arranged as needed. The **Scientific Advisory Board** also supports the projects and platforms in an advisory capacity. The founding of **SaxoCell e.V.** following this year's 2023 consortium meeting will also enable us to involve interested companies and stakeholders in the cluster in the future, even during the course of the funding period.

In addition, the Hub is planning **numerous events** in which SaxoCell members will participate, such as Bio-Europe 2023 in Munich and the Leipzig Immunoncology Conference (LION). Networking meetings with other collaborative projects, such as BioRN, the science and industry cluster around Heidelberg, and ProxiDrugs, the future cluster from Frankfurt, are also scheduled for late 2023. A Parliamentary Evening will also be organized for networking and as a discussion platform between SaxoCell PIs and members from politics and regulation. In addition to numerous specially organized workshops, including on Good Scientific Practice (GSP), we will present two joint sessions at the annual meeting of the Interdisciplinary Group for Flow Cytometry and Laboratory Medicine IGDL in Leipzig in March 2024, where SaxoCell will present itself to a national audience.



In preparation for the **next funding phase**, 35 new project ideas have already been submitted and reviewed by the spokespersons in the first step. This forms the basis for preparing the new overall application for the cluster by the end of 2023. This must then be submitted to the BMBF in April of the coming year. An official inspection of our cluster by a jury commissioned by the BMBF will then take place before the summer break in 2024. The application, the inspection and the various reports of the cluster (cluster progress reports & SAB reports) are included in the evaluation and are decisive for the approval of the second implementation phase.

With **innovative ideas**, new, interested project partners from science and industry, and the **continuation of successful projects** and studies from the first funding phase, we are meticulously and full of anticipation preparing the upcoming, second funding period and look forward confidently to a **sustainably growing network** with the overarching goal of further expanding the cell and gene therapy sector in Saxony and continuously improving the treatment of serious diseases at the level of efficacy, tolerability and accessibility.



List of abbreviations

AAV	Adeno-Associated Virus
ATMP	Advanced Therapy Medical Product
BMBF	Federal Ministry of Education and Research
C4F	Clusters4Future
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GvHD	Graft-versus-Host-Disease
PEI	Paul Ehrlich Institute
PI	Principal Investigator
PtJ	Project management Jülich
USP	Unique Selling Point
VC	Venture Capital
WFS	Wirtschaftsförderung Sachsen, Saxony Economic Development
CGT	Cell- and gene therapy

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