ACTIVITY REPORT
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Center for Regenerative Therapies TU Dresden

"FROM ORGANISMS TO THERAPY – RESEARCH FOR HUMANS"
Center for Regenerative Therapies TU Dresden
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In the last decade, the DFG Research Center for Regenerative Therapies Dresden (CRTD), Cluster of Excellence at the Technische Universität Dresden, has become an integral part and a major driving force of Biopolis Dresden – a unique research campus focusing on translational research and biomedicine. We leverage Dresden’s cross-campus strengths in medicine, genomics, systems biology, cell and developmental biology, materials science, and bionanoengineering to find innovative products and solutions for regenerative medicines.

Ten years after its foundation, CRTD can boast several outstanding achievements:

• More than 650 peer-reviewed publications from the core research groups.
• Clinical application of novel cell therapies, such as T regulatory cells and immunosuppression-free beta cell transplants.
• Clinical trials in type 1 diabetes prevention strategies.
• Legacy through promotion and placement of core group leaders.
• Graduation of almost 50 doctoral students.
• A new Master’s course in regenerative biology and medicine.
• A modern, state-of-the-art building, offering 7,150 m² of space for research and communication.

Research at CRTD has advanced the frontiers of knowledge in regenerative biology. Several factors essential for faithful tissue regeneration have been identified in model systems, such as the zebrafish brain and the axolotl limb, opening up new possibilities for therapeutic intervention. Our scientists have identified signaling pathways that facilitate the proliferation of neural stem cells in the adult brain and which have consequences in aging and disease. We have developed preclinical models of retinal degeneration, and have created platforms for drug screening in the retina and other target tissues, such as pancreatic islet cells and motor neurons. We have found means to modulate the immune system in conditions, such as Graft versus Host Disease, and in autoimmune diseases, such as type I diabetes.

The first investigator initiated clinical trials based on research carried out in CRTD are being launched and more are planned in the coming years.

This image brochure presents a snapshot of ongoing activities at CRTD. I hope that you will find them interesting and accompany us on a journey into biomedical science and teaching.

Ezio Bonifacio
Director CRTD
As a central scientific unit of the Technische Universität Dresden (TUD), the DFG Research Center for Regenerative Therapies Dresden (CRTD) is supervised directly by the University Executive Board (Rectorate), similar to other faculties of the university.

The CRTD has its own bylaws, organizational structure and decision-making bodies. The organizational structure is composed of the CRTD Board, the Executive Board, the CRTD Member Assembly, the Director, Research Group Leader Assembly, and the Administration. In addition, a Scientific Advisory Board has been appointed. The Technology Platforms provide scientists access to an internationally competitive array of state-of-the-art devices and technologies.

**BOARD**

Members of the CRTD Board are elected every 4 years by the CRTD Member Assembly and include the CRTD Director, elected research area leaders, a representative of non-TU Dresden institutions, the members of the Executive Board and a representative of the core junior group leaders.

**Current CRTD Board members are:**
- All members of the Executive Board
- Prof. Martin Bornhäuser, University Hospital Carl Gustav Carus Dresden (UKD)
- Prof. Triantafyllos Chavakis, University Hospital Carl Gustav Carus Dresden (UKD)
- Prof. Andreas Hermann, University Hospital Carl Gustav Carus Dresden (UKD)
- Prof. Lorenz Hofbauer, University Hospital Carl Gustav Carus Dresden (UKD)
- Dr. Mike Karl, CRTD (representative of independent junior research groups)
The CRTD Board takes the final decisions on all major issues relating to the expansion of the core research institute, group leader appointments, network membership, budget allocation, and major equipment purchases.

EXECUTIVE BOARD

The CRTD Executive Board is comprised of the tenured professors (seniors) of the core research institute and makes decisions on all issues relating thereto. Current CRTD Executive Board members are:

MEMBER ASSEMBLY

The CRTD Member Assembly is composed of all CRTD core group leaders plus the principal investigators of the CRTD network groups of the Dresden campus. Entry into the CRTD Member Assembly must be approved by application to the CRTD Board and membership is renewable annually.

One task of the CRTD Member Assembly is to elect the CRTD Board members and the director of the CRTD. All investigators in the CRTD Member Assembly are eligible to compete for CRTD seed grant awards.

DIRECTOR

The Director is a core research institute professor who represents the CRTD both within and outside of the university and executes the decisions made by the CRTD Board and the Executive Board.

The Director is the chairman of the CRTD Board and the Research Group Leader Assembly and heads the Administration and the Technology Platforms. The current director is Prof. Ezio Bonifacio. Former directors were Prof. Michael Brand (2006-2014) and Prof. Elly Tanaka (2014-2016).

FACTS AND FIGURES

Founded in 2006, the CRTD was the first research center of the Deutsche Forschungsgemeinschaft (DFG) and the first Cluster of Excellence in the new German States. The Excellence Initiative aims to promote top-level research and to improve the quality of German universities and research institutes. In June 2012, the CRTD was reaffirmed as a DFG Research Center and Cluster of Excellence.

In 2017, the CRTD employed 243 staff members, with 184 employees in the core research groups, 40 working in technology platforms and 19 supporting the research center in central administration. Three full professors, 4 associate professors and 12 junior group leaders, as well as one guest group, build the research community at CRTD. CRTD is an equal opportunities employer, and to support our young staff, we provide a family-friendly working environment by providing services, such as child care, to help balance work and family.

Internationality is CRTD’s strength

At CRTD, we work in an international team with ambitious, objective-driven and open-minded colleagues. Our scientific and non-scientific staff work hand in hand to pursue cutting-edge research within a world-class scientific environment. Top scientists from world-leading institutes have been attracted to carry out their research at the CRTD. CRTD’s employees originate from 32 different countries and its 18 core group leaders originate from six different nations: Australia, Bulgaria, Germany, Italy, Turkey, and the USA.
The CRTD is primarily funded by the German Research Foundation DFG. Annual funding amounts to 6 Mio EUR for the DFG Research Center and 2 Mio EUR for the Cluster of Excellence. This funding finances research groups, technology platforms, seed grants, translational grants and the central administration. Furthermore, the DFG provides overheads to cover indirect costs of the research center, which are allocated to the TUD with a certain percentage being transferred to the CRTD.

During the last ten years, CRTD core group leaders have also raised third party funding of 40 Mio EUR through grants from the Federal Ministry of Education and Science (BMBF) and the EU, for their projects.

GEROK POSITIONS

Rotation positions (also called Gerok Positions) enable young physicians working mostly in patient care to be temporarily exempt from their clinical obligations to focus exclusively on new and innovative research projects. The focus of these projects is on clinical problems, incorporation of clinical material and potentially of clinical pilot studies with a focus on translational research with a patient-oriented approach and the investigation of disease mechanisms. CRTD and the Faculty of Medicine at the Technische Universität Dresden are working closely together to enable interested and qualified clinicians fixed-term leave from hospital on the one hand to enable them to work scientifically at CRTD on the other hand for one year. Since 2013, ten physicians have been supported so far.
The CRTD is set up as an interdisciplinary and interconnected network of 18 core groups and 69 principal investigators from 7 research institutes which include the faculty of medicine, the faculty of natural sciences and other internationally outstanding research institutes of the TU Dresden as well as non-TU Dresden research institutions like the Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG), the Leibniz Institute of Polymer Research, the German Center for Neurodegenerative diseases (DZNE) or the Paul Langerhans Institute for Diabetes Research. This network of 87 member labs contributes towards a multidisciplinary approach to multiple disease areas. Members from the Biotechnology Center (BIOTEC) of the TU Dresden, the Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG), the B CUBE – Center for Molecular Bioengineering or the Leibniz Institute for Polymer Research contribute mainly cutting edge technology development to the network. Prof. Martin Bornhäuser (medical clinic I, GMP laboratory for stem cells), Prof. Torsten Tonn (transfusion medicine, German Red Cross), and Dr. Barbara Ludwig as well as Prof. Stefan Bornstein (both medical clinic III; islet transplantations) are members who particularly support CRTD’s translational work. Furthermore, numerous members from the TU Dresden, University Hospital Carl Gustav Carus, Max Bergmann Center and Leibniz Institute of Polymer Research Dresden (IPF), German Center for Diabetes Research at TU Dresden (DZD), as well as the German Center for Neurodegenerative Diseases (DZNE) actively contribute to CRTD’s research. In addition, 12 commercial partners support the CRTD network.

To support and ensure the interaction between all members of the CRTD Network several activities are organized on a regular basis to foster the cooperation and to improve the translation of basic research results into clinical applications. Three main pillars have been set up to support the communication among CRTD Members: monthly research area symposia, the annual summer conference, as well as the yearly CRTD Member retreat. Further information about these measures can be found in the chapter “Communication”.

The CRTD is embedded in a cluster of internationally recognized institutes mainly located in Dresden Johannstadt, at the “Biopolis Dresden” campus. The Dresden biomedical community has undergone major restructuring over the past years. Regenerative medicine and stem cell research are now a key focus in Dresden, ideally positioning Dresden to address a scientific challenge of this magnitude. Such development has been made possible through a unique synergism between the TUD and the non-university research organizations like the Max Planck Society, Leibniz Association, Fraunhofer Society supported by the Free State of Saxony, German Research Foundation (DFG), BMBF, charities, commercial partners, and others.

Internationally outstanding research institutes have developed here as a consequence, like the Biotechnology Center (BIOTEC), the B CUBE, the Max Planck Institute for Molecular Cell Biology and Genetics (MPI-CBG) and the Max Bergmann Center for Biomaterials (MBC) as well as Faculty of Medicine. The expertise provided by these institutes ranges from molecular cell biology and stem cell biology via tissue engineering all the way to clinical applications of cell-based therapies. Most importantly, these institutes form a vibrant research community — accomplished, for instance through common technology platforms, and the largest International PhD program in Germany DIGS-BB. This program currently has more than 200 PhD students from 39 different countries.

The Center for Molecular and Cellular Bioengineering (CMCB) was established in 2016 as an umbrella organization of the three institutions BIOTEC, CRTD and B CUBE. The scientific independently operating institutes are working together under this roof, especially with respect to strategic developments in the university, teaching, administration and provision of scientific infrastructure and services and take advantage of existing synergies.
The aim of research at the CRTD is to gain a fundamental understanding of stem cell biology and tissue regeneration and to use this knowledge to develop better models for diseases, as well as lay the groundwork for new diagnostics and therapies for human health.

CRTD takes advantage of multiple model organisms with varying regenerative capacities from zebrafish, to amphibians, to mammals. This enables comparative biological approaches to identify key pro- and anti-regenerative factors and pathways in a given tissue, and these molecular targets can, in turn, be utilized to develop new therapeutic approaches.

CRTD’s core interests focus on five research areas: Hematology/Immunology, Diabetes, Neurodegenerative Diseases, Bone Regeneration, and Technology Development. In each of these research areas, CRTD and its partners in the CRTD Members group conduct basic research to identify novel therapeutic potential and further develop this in translational research projects. As well as providing the basis for testing in clinical research, these programs also generate innovative research tools and strategies for transfer to commerce.

CRTD’s basic research is focused on elucidating the mechanisms underlying the emergence of tissues from embryonic progenitors in a variety of systems, including the central nervous system and the retina, the hematopoietic system, the pancreas and bone. CRTD researchers investigate lineage commitment decisions, and key regulatory molecules that direct self-renewal and differentiation, tissue homeostasis and repair, as well as the aberrant signaling that occurs in disease.
In order to address basic research challenges in innovative ways, our research groups develop cutting-edge tools. These include induced pluripotent stem cell (iPSC)-derived cellular models of both healthy and diseased human tissues, which are used to identify key processes and potential target proteins, as well as for drug screening. In addition, a range of unique animal models, from genetically tailored zebrafish lines to humanized mouse models is being investigated. Dedicated technology platforms also support our research groups with high-end facilities for microscopy, deep sequencing, single-cell transcriptomics, animal behavior etc.

The aim of translational research is to move the discoveries made in basic research toward clinical application. Specifically, CRTD focuses on the development of cell-based therapies for diabetes and retinopathies, chemical- and peptide-based regenerative medicines for Parkinson’s Disease and Amyotrophic Lateral Sclerosis (ALS), as well as diagnostic tools. The pathway from bench to bedside is technically difficult with many stages of technology maturation, and hence, a multidisciplinary approach is essential, involving many CRTD Member groups, each bringing their specific expertise to the project. Expertise on the BIOPOLIS campus covers early stage in vitro and in vivo disease modeling, GMP cell scaling and production and clinical trial design and execution.

Ongoing clinical activities include the use of cord-blood mesenchymal stromal cells to suppress immune responses of tissue grafts to the host in Graft versus Host Disease (Prof. Dr. med Martin Bornhäuser), and the transplantation of encapsulated pancreatic islets (PD Dr. med. Barbara Ludwig) in type 1 diabetics. The group of Prof. Ezio Bonifacio (Director, CRTD) has conducted ground-breaking research on the early diagnosis of type 1 diabetes and is now running a clinical study aiming to provide early diagnosis of type 1 diabetes in children who have elevated genetic risk (Freder1k study).

CRTD is conducting research in the following research areas: hematology/immunology, diabetes, neurodegenerative diseases, bone degeneration and technology Development. The CRTD Research areas are composed of members from the core institute and the larger CRTD network, and are headed by staff of the Faculty of Medicine Carl Gustav Carus. Some of the CRTD Research areas are particularly strong in basic science (e.g. neurodegeneration) whereas others are more focused on clinical applications (e.g. hematological diseases). In this way, the CRTD as a whole presents a comprehensive basic research through to clinical application pipeline.

All scientists working in these research areas of CRTD are supported by dedicated service technology platforms offering cutting-edge technology and support in a cost-effective way.
HEMATOLOGY/IMMUNOLOGY

The goal of this research area is to improve regenerative therapies for the hematopoietic and lymphatic system, to better regulate immunological rejection and to develop new applications for hematopoietic and mesenchymal stem cells (MSC) for the regeneration of distinct tissues. A major motivation within the research area hematology/immunology is to harness insights obtained in model-system based approaches to develop attractive new adoptive cellular and in vivo targeted therapies. In addition to clinical studies using engineered hematopoietic stem cell (HSC) grafts, clinical use of MSCs has been advanced for Graft-versus-Host Disease, engraftment failure and tissue engineering approaches. Additional cell therapies with antigen-specific T cells and regulatory T cells (Tregs) have been established. Preclinical research in hematology focuses on improving ex vivo culture of HSCs using co-culture systems with MSCs.

In addition to HSC migratory capacity, the regulation of HSC self-renewal and differentiation by intrinsic and microenvironmental cues is a major focus of dedicated research groups. Bioartificial materials are being developed to dissect exogenous signals and mechanisms acting on hematopoietic progenitors to enable successful long-term culture and expansion for therapeutic use. The immunology branch of the CRTD mainly focuses on tolerance as a central mechanism of regeneration and how Tregs interact with hematopoesis and bone regeneration. Novel bispecific antibodies and chimeric-antigen receptor transduced T cells (CAR-T cells) are being developed with the aim of introducing these therapies into the clinic. New emphasis has been put on the comprehensive modelling of steady-state hematopoiesis and leukemia stem cells using innovative mathematical systems.

DIABETES

The goal of this research area is to treat diabetes by transplantation or regeneration of pancreatic islets. The beta-cells of the pancreatic islets are the unique source of insulin, the main hormone for control of blood glucose and its use as an energy source in the body. A reduction in functional beta-cell mass, either due to autoimmunity or prolonged insulin resistance, is a common denominator of different forms of diabetes mellitus. Hence, a main goal of the CRTD is to protect and replace pancreatic islets in order to prevent and cure diabetes.

The research is organized under the themes:
1. Immune therapy,
2. Transplantation,
3. Expansion of beta-cell numbers and function,
4. Disease pathophysiology.

The Diabetes program has a number of synergistic components and extensions that work together to address these areas. Within Dresden, the program includes principal investigators from the CRTD Network at the CRTD core institute as well as the TUD Faculty of Medicine, and the PLID.

NEURODEGENERATIVE DISEASES

This includes the classical neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease, as well as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), spinal cord injuries and retinal degeneration. In addition, cellular mechanisms of cognitive aging are studied.

Neurogenesis in the context of development, adult homeostasis, and after injury has become a particular focus, including all major regenerative and non-regenerative model organisms, including drosophila, zebrafish, axolotl, mouse and man. Furthermore, the induced pluripotent stem cell (iPSC) technology has been adopted to generate cell models of neurodegenerative diseases, set up drug screen for neurodegenerative diseases and to use iPSC-based transplants for cell replacement strategies in Parkinson’s Disease models. A strong community focusing on the retina, spanning basic research up to preclinical cell transplantation models has been established. Molecular pathways and potential drug targets have been defined, and stem cell sources and cell enrichment strategies were identified to improve cell engraftment into the retina.
**BONE REGENERATION**

The focus of this research area is to define the molecular and cellular mechanisms of bone regeneration, as well as the interactions of immune and cancer cells within bone regeneration. Elucidated key factors are tested in preclinical animal models that represent established human bone diseases, as well as in early clinical studies. To accomplish the overall goal and to guide the translational process, CRTD pursues three specific strategies:

1. **A basic research approach** using animal models that have the ability to self-regenerate, including the zebrafish and the axolotl. The intention of this approach is to identify novel targets together with molecular mechanisms for intervention. This will provide the basis for the development of targeted and better-defined therapeutic strategies for bone/cartilage loss and injury.

2. **A systemic targeted approach** using defined factors in bone remodeling as therapeutic targets. These targets include RANK ligand and sclerostin, two regulators of osteoclast and osteoblast biology, respectively. An antibody against RANKL, named denosumab, has been evaluated and upon approval has been used for the treatment of osteoporosis and skeletal metastases. Moreover, an antibody against sclerostin has been evaluated in a bone defect model in diabetic rats and showed superior effects compared to the osteo-anabolic hormone PTH. Current phase II/III studies are ongoing using the promising anti-sclerostin antibody (romosozumab) in humans with bone diseases.

3. **Expanding clinical therapy** by focusing on three topics:
   - Use of GMP-grade adult human MSC from bone marrow and cancellous bone for musculoskeletal tissue regeneration.
   - Understanding of osteocyte biology, as these cells and their products (sclerostin, FGF-23) are increasingly recognized to play a central regulatory role of bone and mineral homeostasis.
   - Development of functional biomaterials and the generation of bone-like structures in bioreactors.

**TECHNOLOGY**

The aim of this area is to develop novel and innovative technologies to support basic and translational Research. Advances in regenerative medicine require the development and ready availability of cutting-edge technologies from many different disciplines, including biochemistry, genetics, genomics, proteomics, metabolomics, biophysics, bioengineering, imaging, and materials sciences. The technology-oriented traditions of TUD and several outstanding independent research institutes, such as MPI-CBG, the MBC and the Helmholtz Zentrum Dresden-Rossendorf, provide an outstanding selection of state-of-the-art instrumentation and contemporary techniques. These provide solutions to the CRTD in addressing essential questions to further advance projects in regenerative biology and medicine. Independent research groups in these institutes, pursuing research in advanced technological fields, also provide their know-how on a collaborative basis.

**Current fields of development include:**

- Cells and tissues prepared under GMP compliant conditions for cell-based therapies and under GLP conditions for preclinical projects.
- Imaging methods for basic science, preclinical and clinical projects, especially for tracking of transplanted cells in vivo.
- Engineered matrices (biomaterials) to exogenously direct cellular fate decisions.
- Regulation of stem cell expansion/differentiation and generation of animal disease models by genetic engineering.
- Development of high-throughput screens for the identification of novel drug candidates, and Bioinformatics for complex data analysis.
- Furthermore, all research groups are supported by a joint service technology platform providing access to the highly specialized instrumentation and know-how essential to support basic and clinical research at the CRTD. Many joint facilities have been established in cooperation with CRTD partner institutions, such as the Faculty of Medicine of the TU Dresden, the Biotechnology Center (BIOTEC) and the Max-Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG).
Vision impairment and blindness caused by the degeneration of the light sensitive photoreceptors and/or the supporting retinal pigment epithelium (RPE), as in macular degeneration or retinitis pigmentosa, represents one of the prime causes for disability in industrialized countries, with no effective treatments currently established. Possible therapeutic options for hindering disease progression or regaining sight include pharmacological interventions, electrical implants, or gene therapeutic approaches. However, although promising, most of these treatment options require an early intervention in disease development before massive cell loss has occurred. Our experimental work focuses on the development of cell-based strategies to replace lost cells in the retina by the transplantation of photoreceptors and RPE cells.

In recent years we provided proof-of-concept studies for photoreceptor survival and maturation following retinal transplantation into mouse models of retinal degeneration, defined the optimal developmental stage for transplantable photoreceptors, identified cell surface markers for efficient enrichment of rod photoreceptors, and demonstrated – in collaboration with Dr. G. Zeck (NMI at the University of Tübingen) – day-light vision repair following transplantation of cone-like photoreceptors into a mouse model with degenerated cones.

Interestingly, our recent results provide evidence that donor photoreceptors actually do not structurally integrate into host retinal tissue, that still contains endogenous photoreceptors, but instead reside between the photoreceptor layer and the retinal pigment epithelium, the so-called sub-retinal space, and exchange intracellular material with host photoreceptors (Fig. 1). These findings contradict the common view that transplanted photoreceptors migrate and integrate into the photoreceptor layer of recipients and therefore imply a re-interpretation of previous photoreceptor transplantation studies. Actually, the observed interaction of donor with host photoreceptors may represent an unexpected mechanism for the treatment of blinding diseases in future cell therapy approaches.

An in vitro expandable cell source for the generation of transplantable photoreceptors and RPE cells will be mandatory for the translation towards clinical application. Therefore, protocols for generating photoreceptor-containing retina organoids and RPE from pluripotent stem cells (mouse and human embryonic and induced pluripotent stem cells) were recently established and used for transplantation studies in pre-clinical retinal degeneration models that are depleted of photoreceptors. Here, stem cell-derived photoreceptors survived for prolonged periods and showed a mature phenotype after transplantation (Fig. 2).

In a complementary approach, we are also studying the transplantation of human ESC/iPSC-derived RPE into degenerative rodent models of retinal degeneration and pre-clinical retinal degeneration models that are depleted of photoreceptors. Here, stem cell-derived photoreceptors survived for prolonged periods and showed a mature phenotype after transplantation (Fig. 2).

Retinal organoids derived from human iPSCs are currently used in the lab for further transplantation studies in severely degenerated mouse models to assess their potential for survival, maturation, connectivity and ultimately vision repair.

Selected Publications:


We are interested in studying mechanisms and turnover dynamics of cell renewal in organ systems with the focus on slowly renewing tissues. Many diseases are thought to affect the generation of new cells, and information about cell turnover in these disease conditions may provide novel insights into the cause and treatments of the disease. We use a technique that is based on the incorporation of nuclear bomb test-derived 14C into genomic DNA, which allows for the analysis of cell and tissue turnover in humans. Using 14C dating we could show that the generation of new cardiomyocytes and neurons in humans is not restricted to development but instead continues throughout life (1-3) (Fig. 1). These findings open up the possibility of augmenting cardiac and neuronal regeneration if the underlying cellular and molecular mechanisms can be revealed.

Furthermore, we use and develop animal models of regeneration to explore novel factors that drive cardiomyocytes into the cell cycle. To examine the generation of heart muscle cells, we use multi-isotope imaging mass spectrometry (MIMS) that combines mass spectrometry and ion microscopy. Cell cycle activity can be monitored using the non-radioactive isotope 15N-thymidine in cardiomyocytes (Fig. 2). Together with other techniques, we could demonstrate that similar to humans, cardiomyocyte proliferation in mice is not only restricted to development, but continues robustly during the neonatal period (Alkass et al. 2015).

Our future research aims to characterize cell turnover in human organs using the 14C birth dating strategy, including the human brain and muscle tissue. Using mathematical modeling, we will establish cell renewal rates and fractions of renewing cells in homeostasis and in disease. Furthermore, we will investigate why tissue regeneration is often restricted, and not sufficient to replace lost parenchymal cells and tissues. We will explore mechanisms that limit cardiomyocyte renewal in the mammalian heart, and we aim to identify factors that can modulate cardiomyocyte proliferation. In this context, one aspect will be to understand the effect of non-productive cell cycle activity (polyploidy) on organ growth and in disease. Our studies aim to provide the grounds for therapeutic strategies that can activate endogenous regenerative pathways to help failing organs to heal from within.
The Bökel Lab study how stem cell niches function, using the Drosophila testis niche as a model. In addition, we want to understand how the underlying signaling pathways are implemented at the cell biological level.

Niche signals appear to directly control separate aspects of stem cell behavior, niche activity is thought to be integrated by the stem cells into a binary fate decision between stemness and differentiation. However, we previously found that inactivation of the Hedgehog (Hh) pathway leads to loss of somatic stem cells from the Drosophila testis niche. In contrast, pathway overactivation leads to overproliferation of the stem cells without, importantly, affecting their differentiation. Similar observations by our lab and others have confirmed that also other stem cell properties such as cell competition or adhesion are directly regulated by the niche signals and can be genetically separated at the level of signaling input.

We therefore propose an alternative, “micromanagement” model of stem cell niche function, whereby niche signals are not integrated into a binary cell fate choice. “Stemness” instead is the sum of many independent instructions and responses which, taken together, make a cell fulfill the job of a stem cell (Fig. 1). This new way of thinking about stemness would have important implications for regenerative medicine.

In parallel, we are interested in cytokine receptor mediated Jak/Stat signaling which is, like Hh, required for stem cell maintenance in the fly testis. Together with Thomas Weidemann at the MPI for Biochemistry, Martinsried, we could demonstrate the mammalian IL-4R subunits are unable to dimerize at endogenous plasma membrane densities due to low affinities between the subunits. Ligand induced dimerization thus requires a subcellular concentration step that is provided by actin mediated, constitutive endocytosis. Intriguingly, equivalent mutations in human and fly Jak kinases that similarly affect subcellular trafficking of the receptor subunits point at the conservation of cytokine receptor endocytosis. We are have just started dissecting this process further using the powerful screening tools of the fly system.

**Selected Publications:**


**Figure 1.**

Traditionally, niches are thought of as signaling microenvironments that are integrated to drive a binary fate decision between stemness and differentiation. However, recent results from several systems question this model. Instead, niche signals appear to directly control separate aspects of stem cell behavior, with “stemness” merely being a functional descriptor.
EZIO BONIFACIO
PRECLINICAL APPROACHES TO STEM CELL THERAPY/DIABETES

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by insulin deficiency. The lack of insulin is primarily caused by the autoimmune-mediated attack and destruction of insulin secreting cells (β-cells) located in the pancreas. Disease is managed by multiple daily insulin injections, but many patients suffer from complications associated with inadequately controlled glycemia such as retinopathy, nephropathy, and neuropathy, leading to blindness, kidney transplantation, and amputation.

A major focus of the research group is in the prevention of T1D. Autoimmunity against the beta cells can be identified by the detection of autoantibodies against the beta cells in the blood. We have developed sensitive and specific assays against the major antigens targeted by these antibodies and have shown that children who have two or more of the autoantibodies have pre-clinical or asymptomatic T1D, and will eventually develop clinical diabetes. More recently, we have found the rate of progression to diabetes is correlated with the rate of progression from single to multiple autoantibodies.

We have also shown that insulin is usually the first antigen targeted by the autoantibodies and that there is a peak incidence of islet autoantibody seroconversion between the age of 6 months and 2 years of life. These findings have led us to investigate the use of autoantigen-based vaccination to prevent the development of autoimmunity in genetically at risk children.

We have completed the first primary prevention trial that actively exposes infants at very high genetic risk for T1DM to autoantigen prior to their seroconversion. This clinical study demonstrates safety and immune efficacy when high doses of insulin are administered orally. We also found evidence that daily oral administration of insulin promotes T-cell responses without inducing hypoglycemia. Importantly, the immune responses observed in insulin-treated children did not display typical features associated with type 1 diabetes. Instead, we identified insulin responsive T-cells that express genes associated with immune regulation in children treated with high doses of oral insulin (Fig. 2), suggesting that this treatment can induce tolerance towards autoantigens. Such a critical observation was made using technology that we have developed to measure immune responses to autoantigen. We combine in vitro stimulation, FACS analysis and single cell T cell receptor sequencing and gene expression to identify phenotypically different antigen-responsive cells.

This technology has not only allowed us to define phenotypes associated with responses to vaccine, but also those associated with active seroconversion and disease, and a unique signature in autoantigen responsive CD4+ T cells prior to autoantibody development.

Our future work in prediction and prevention is focused on extending our clinical trial to younger children as well as introducing public health screening of newborn children as part of the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD). Population-based screening with genetic risk scores genotyping is currently used to identify infants who are genetically at risk for developing type 1 diabetes in the Frederik study. These children will be asked to participate in a randomized controlled trial of primary prevention by oral insulin, and are monitored for autoantibody seroconversion.
MICHAEL BRAND
DEVELOPMENT AND REGENERATION OF THE VERTEBRATE BRAIN

We study vertebrate brain development and regeneration. We ask, for instance, how neural stem cells give rise to and maintain the adult brain, during normal homeostasis and during regeneration of the brain. Since zebrafish have a spectacular ability to regenerate and well-developed genetics and molecular biology tools, they are particularly well-suited for these studies. We have begun to compare our results to mouse brain regeneration.

We focus on understanding the astounding ability of the adult zebrafish brain and retina to regenerate. In contrast to the mammalian brain, adult zebrafish brains retain an amazing number of active neural stem cells throughout, in very discrete spatial domains (right panel), that form the basis of its ability to regenerate. Numerous new neurons of different subtypes are produced in the adult zebrafish brain, providing an ideal genetically and experimentally tractable system for understanding brain repair processes. Using CNS lesion paradigms, transgenics, Cre-loxP and CRISPR technology, we explore by using genome-wide methods what controls the ability of adult neural stem cells to repair damage, and how this works mechanistically. Stem cell based regeneration studies in fish may thus provide clues how CNS regeneration can be stimulated also in mammalian brains.

Future prospects
We are beginning to understand how the zebrafish brain can regenerate. Clearly, mechanisms operating in development are re-deployed also in the adult brain. Good examples are the control of proliferation of cerebellar adult neural stem cells (Kaslin et al., 2009) and ventral telencephalon (Ganz et al., 2010) by Fgfs, or Notch/Delta target gene activation after lesion (Kroehne et al., 2011). Our work on biophysical and cell biological aspects of Fgf signaling (Reifers et al., 1998; Yu et al., 2009; Reis et al., 2009; Nowak et al., 2011; Gupta et al., 2013; review: Boekel and Brand, 2013) helps in this regard. We very successfully use transgenic lines expressing fluorescent reporters in specific progenitor populations for FACS sorting from intact and regenerating brains. This allowed us to detect genome-wide responses to lesion during regeneration of the CNS, and has given us a host of new genes and pathways to work with (Kyritsis et al., 2012; Kizil et al., 2012a, b; reviews: Ganz and Brand 2014; Kyritsis et al., 2014). A formidable challenge is to develop a systems level understanding of these events, and to compare our data with the failing regeneration response in the injured mammalian brain. We have made great progress in identifying and understanding the heterogeneity of adult neural stem and progenitor cells (Grandel et al., 2006; Kaslin et al., 2017, 2008, 2009; Ganz et al. 2010, 2011). By analyzing the molecular anatomy of adult brains, we also develop a better understanding of the adult CNS subdivisions that the progenitor niches reside in, and their counterparts in mammalian brains (Ganz et al., 2007, 2014). A key finding is that regeneration in the adult zebrafish CNS is a stem cell based process (Kroehne et al., 2011, and Kaslin et al., 2017), a claim that is supported by genetic lineage tracing data using the conditional Cre-loxP technology that we developed and which proves essential for our studies (Hans et al., 2009, 2010; Henninger et al. 2017), as are CRISPR knock-out and knock-in studies (Kesavan et al. 2017; Suzzi et al., 2017). The telencephalon, cerebellum and increasingly the retina (Hochmann et al., 2012; Weber et al., 2013; Cimalla et al., 2013; Gaertner et al., 2014) remain excellent systems for studying regeneration events. Surprisingly, adult stem/progenitor cells in the cerebellar stem cell niche seem to be determined to generate specific subtypes of cerebellar neurons even during regeneration (Kaslin et al. 2017). This highlights the need to understand adult stem cell programs for specific subtypes of progenitor cell types in much more detail in the future, also in mammals.

Selected publications:
The Busskamp Laboratory aims to exploit the full potency of human stem cells to generate neural cell types and precise circuits generated from these cells. Previously, our focus was the study of human and mouse retina in health and disease and, in a mouse model of the blinding disease Retinitis pigmentosa, we repaired non-functional cone photoreceptors using optogenetics to restore visual function.

We further expanded this approach to post-mortem human retinas (Busskamp et al. 2010) and this technology now forms the basis for ongoing clinical trials.

Furthermore, our interest covers the study of the basic functions of miRNAs in photoreceptors. Upon cell type-specific knockdown of the miRNA processing machinery, we revealed that the miR-182/183 miRNA cluster maintains the structure of photoreceptor light-sensitive outer segments, and overexpression of this miRNA cluster in mouse embryonic stem cell-derived retinal organs resulted in the formation of light-sensitive outer segments (Busskamp et al. 2014).

Translating these approaches from mice to humans is cumbersome. Hence, we aim to improve these processes by generating functional human neuronal tissues in vitro. We explored the potential of transcription factors (TFs) to induce neurogenesis in human pluripotent stem (iPS) cells and demonstrated that overexpression of two TFs resulted in the homogeneous differentiation of bipolar neurons within four days (Fig. 1). By capturing the coding and non-coding transcriptomes, we identified the rapid molecular differentiation routes at the systems-level (Busskamp et al. 2014).

Currently, the Busskamp lab has two major research goals:

1. Neuronal cell fate engineering: The use of human iPS cells facilitates the study of the genesis of human cell types in an ethically approved setting. However, exploiting the full potency of stem cells is only possible with very few differentiated cell types. In particular, the generation of neurons is in its infancy and of the many neuronal types present in the brain, only a few types have been generated in vitro. So far, neuronal differentiation protocols are multifaceted, tailored to individual cell types, and the molecular events during reprogramming remain enigmatic. Hence, we cannot easily confer these protocols to produce different neurons of interest. Therefore, we plan to induce TFs as differentiation control buttons in human iPS cells in order to explore in vitro neurogenesis systematically. Firstly, we will apply TF libraries to conditional fluorescent iPS reporter lines, facilitating high-throughput isolation and analysis of induced neurons. Secondly, the underlying gene regulatory networks will be revealed using (single cell) RNA-seq over the entire differentiation period and we will combine these in-depth transcriptomic analyses with morphological, anatomical, and functional characterizations. Conceptually, our systems biology approach paves the way for targeted “forward” programming of human iPS cells to neurons.

2. Human neuronal circuit engineering: In order to understand how parts of the human brain function in health and disease, we aim to reverse engineer functional human neuronal circuits from scratch, combining neuroscience with stem cell research and bioengineering. After having generated multiple sets of neurons, we need to understand and control the biology to connect these cells in a reproducible way into precise circuits in vitro. The lab will apply an interdisciplinary approach, combining molecular biology, human stem cell differentiation, 2D neuronal pattern cultures, imaging techniques, optogenetics and electrophysiology to engineer and analyze these human neuronal circuits (Fig. 2). Disease-causing mutations will be introduced to model brain diseases in a human setting to explore novel therapeutic interventions. Furthermore, from an engineering point of view, we aim to create biological computers using living cells to compute signals, as our brain does with extreme efficiency.

Selected publications:


Figure 2. Micro-contact printed laminin pattern for neuronal circuit assembly.

VOLKER BUSSKAMP
NEURONAL CELL TYPES AND CIRCUIT ENGINEERING

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Selected publications:


Our goal is to understand and manipulate the mechanisms controlling the expansion of neural stem cells (NSC) and the generation of neurons in the mammalian brain. This is important, not only to understand brain development and the role of adult neurogenesis in cognitive function, but also to use NSC to promote brain recovery during aging, disease or injury.

The role of time: cell cycle length is a key determinant of stem cell fate

Our strategy to achieve this ambitious goal is based on our previous finding showing that a lengthening of G1 of NSC was sufficient to induce premature neurogenesis while shortening G1 promoted NSC expansion (Lange et al., 2009). In essence, somatic stem cells need time to differentiate and, thus, manipulating G1 length allows us to control their fate during development and adulthood (Borrell and Calegari, 2014). This allowed us to validate the evolutionary role of progenitor subtypes in cortical expansion and gyrification of the mammalian brain (Nonaka-Kinoshita et al., 2013) and given us the means to increase neurogenesis in the adult brain (Artegiani et al., 2011). Ongoing experiments in our laboratory (Fig. 1) will finally demonstrate whether or not this acute increase in adult neurogenesis positively contributes to brain function and cognitive performance including learning, memory and emotional behavior.

Figure 1. Fluorescence picture of the mouse hippocampus upon stereotaxic viral injection to target neural stem cells and neurons with two viral particles carrying GFP (green) and RFP (red) as reporters. Our lab used this approach to expand NSC in vivo (Artegiani et al., 2011) (picture taken by Sara Bragado Alonso)

The Dark Matter of the genome

Beyond G1-expansion of NSC, our group is interested in finding novel mechanisms controlling neurogenesis in physiological conditions. In this context, we generated a transgenic mouse line that allowed us to select specific sub-populations of stem and progenitor cells committed to the neurogenic lineage (Fig. 2). Next-generation, sequencing of these cell types allowed us to identify numerous uncharacterized and previously unknown long non-coding RNAs that we found to be functionally involved in neurogenic commitment. Notably, the role of long non-coding RNAs in several biological processes has just begun to emerge and in fact the overwhelming majority of these elusive transcripts are still unknown and generally referred to as the Dark Matter of the genome (Aprea et al., 2015). The multidisciplinary of the Dresden campus with its new Genome Center and Max Planck Center for Systems Biology synergizes exceptionally well with our expertise on NSC biology and methods to acutely manipulate the developing and adult mammalian brain. We plan to capitalize on these strengths giving us a competitive edge in the exploration of non-coding transcripts in stem cell commitment.

Figure 2. Fluorescence picture of a transgenic mouse embryo expressing RFP (red) and GFP (green) to identify neurogenic progenitors and neurons. Our lab has used this approach to identify lncRNA functionally involved in neurogenesis (Aprea et al., 2013)

Selected publications:


ANTHONY GAVALAS

STEM CELLS IN PANCREAS REGENERATION

We are interested in understanding how extracellular signals and intrinsic genetic programs interact to dictate cell fate decisions in stem and progenitor cells. Our main focus is the development of the endocrine lineage in the pancreas and the conversion of pluripotent stem cells into functional beta cells.

To identify novel players in pancreas lineage specification, we used directed differentiation of mouse embryonic stem cells into pancreas progenitors and screened for downstream effectors of the transcription factor Ngn3, an essential player in the specification of the endocrine lineage. We analyzed one of the candidate genes, Aldh1b1, encoding a mitochondrial enzyme, and shown that it is expressed in all pancreatic progenitors during development and is switched off as soon as cells commit to differentiation. Aldh1b1 elimination during development accelerates differentiation and compromises functionality of the adult beta cells. We have found that the enzyme regulates the metabolism and ROS levels in the embryonic pancreas progenitors and our current hypothesis is that this regulation impacts upon their epigenetic patterning.

Another line of research generated from our candidate screen, concerns GPCR signaling in pancreas specification. We have found that sphingosine-phosphate signaling plays a conserved role in the aggregation of endocrine cells to form islets. Additionally, the same signaling pathway mediates survival of acinar and endocrine progenitors and triggers their differentiation through stabilization of YAP and attenuation of Notch signaling. Extending these findings we have found that downstream components of the GPCR signaling have differential effects on lineage choices during pancreas development. These findings are now used in the conversion of human pluripotent stem cells into functional beta cells.

Taking advantage of other findings in our lab, we identified a marker of putative stem cells in the adult mouse pancreas. Genetic lineage tracing analysis suggested that these are bona fide stem cells contributing to all three pancreatic lineages in homeostasis. Single cell RNA Seq analysis suggested that these cells differentiate using developmental pathways. We demonstrated the self-renewal capacity of these cells by FACS isolating them and expanding them for several passages in vitro as spheroids in a three dimensional matrix and showed that this is the population that gives rise to the mouse adult pancreatic organoids. Importantly, we can now isolate and expand a similar population from the population that gives rise to the mouse adult pancreatic organoids.

Current research concentrates on three axes: (a) to further elucidate signals, signaling components and metabolic requirements that guide specification in the developing pancreas, (b) apply these findings for the efficient conversion of human pluripotent stem cells into fully functional beta cells for diabetes cell therapy and (c) explore the functionality of the putative pancreas adult stem cell population in health and disease using both mouse genetic models and human exocrine tissue.

Selected publications:


The prevalence of age-related degenerative diseases such as osteoporosis and type-2 diabetes is increasing. Particularly in the light of an ageing population in almost all developed countries, it is vital to detect underlying causes and identify potential remedies of degenerative disorders.

Hormonal regulatory networks have been shown to exert a powerful influence on health and disease patterns including the onset (or delay) of degenerative processes. US and others have identified stress hormones (glucocorticoids) as important regulators of health-span and ageing in model organisms. In humans, lifestyle factors including chronic stress have been linked to health outcomes as well, although the underlying causes of this connection are less clear. However, it has recently been acknowledged that a loss of regenerative potential – either systemic or local – is linked to degenerative progression. Through our work we aim to identify novel endocrine regulatory networks, which can be utilized to alleviate degenerative disease such as osteoporosis and type-2 diabetes.

Investigating the role of glucocorticoids in homeostasis and regeneration is another focus area of the laboratory. As endogenous stress hormones glucocorticoids exert powerful effects on virtually all cell populations in the body. However, their role in overall homeostasis is currently not fully understood. Due to their pleiotropic nature, the impact of glucocorticoid signaling on individual tissues and organ systems is inherently difficult to research. In our laboratory we are currently developing molecular techniques, which will allow us to characterize the role of glucocorticoids (and other hormonal regulators) in detail on both the local as well as the systemic level.

These techniques will also enable us to investigate the role of stress-exposure and glucocorticoids in the pathophysiology of degenerative disease such as osteoporosis and type-2 diabetes. Ultimately, we aim to uncover novel regulatory pathways in ageing, degeneration and regeneration.

Prospectively, we aim to identify novel hormonal regulators of regeneration through our work in model organism. Additionally, we are generating testable hypothesis for clinical trials in order to characterize determinants of disease and regeneration in humans.
MIKE KARL

REGENERATION OF THE RETINA

We want to find new ways to prolong neuron lifespan, to prevent tissue scarring and to regenerate neurons. To identify new potential therapeutic strategies our primary aims are to understand and overcome the mechanisms that limit retinal regeneration and cause scar formation in neuro-degenerative diseases of the retina.

Neuronal regeneration versus scar formation in the retina – One major hypothesis of our lab is that glial scar formation in the central nervous system might be a failed regeneration response or separate entity. It is well known that in some species, like fish and chick, the major type of retinal glia cells, Müller glia (MG), have the capacity to regenerate neurons in pathologies, whereas mammals naturally do not. In contrast, mammalian MG respond to all types of retinal pathologies with various functions, summarized as reactive gliosis, which may have positive (e.g. neuroprotection) or detrimental consequences (e.g. cause and contribute to scar formation) for vision. Of note, others and we had found that a very limited number of MG could be stimulated to regenerate few retinal amacrine neurons in the damaged adult mouse retina in vivo (Karl et al 2008, 2012). However, even upon experimental stimulation the overall regenerative response was very limited at multiple levels – e.g. less than 1% of MG proliferating. The underlying mechanisms limiting and regulating regeneration are not understood (Fig. 1). Further, proficient models to dissect the processes limiting regeneration and regulating scar formation in mammals have been missing. In recent years, we made several seminal discoveries, which opened up many new ways to study the mechanisms of retinal regeneration and scar formation in mammals:

The mouse retina regeneration assay: age, damage and stimuli matter – We found that the juvenile mouse retina has a higher regenerative competence, which becomes rapidly restricted with increasing animal age suggesting underlying regulated mechanisms. These findings led to the development of a powerful mouse retina regeneration ex vivo assay (Löffler et al 2015) that enabled studies of distinct processes possibly regulating and limiting regeneration. We developed methods to acutely isolate and study MG at high purity and quality (Schäfer & Karl 2017), and thus performed comparative RNA-Seq studies of MG from various experimental paradigms (unpublished). For example, thereby we identified means to overcome for the first time a major age-dependent limitation in mammalian retina regeneration: effective MG derived progeny generation (unpublished data). Further, using the mouse retina regeneration assay as a phenotypic screen we found that: (1) The type and magnitude of neuronal cell death determines the levels of MG cell cycle re-entry and proliferation (Babu, Münch et al 2017). Our data suggest that mammalian regeneration might not only be limited in MG intrinsically, but also by their environment, e.g. mode of neuronal cell death and neuron derived signals (2). We tested many selected retinal damage dependent factors, which differentially affected MG or elicited novel phenotypes (unpublished).

Modeling neuronal degeneration, regeneration & scar formation in mouse & human retina organoid systems – To ultimately translate findings from regenerative and non-regenerative animal models to the human retina we are developing sophisticated cell-based experimental models. The power of pluripotent stem cells to generate retinal cells in culture had been shown before, and breakthrough discoveries suggested a path to generate human 3D complex retina, so called retina organoids. We recently optimized the pioneering protocol to generate mouse and human retinal organoids efficiently and reliably (Völker et al 2016). For example, comparative gene expression analysis of multiple single retinal organoids and retinal cell birth dating experiments indicated robust and homogenous retinal development superior to previous protocols. Thus, we developed the first mouse organoid system of cone photoreceptor–enriched organoids (Völker et al 2016), which are of interest for basic research and preclinical regenerative medicine, e.g. for cone photoreceptor cell replacement studies. In collaborative projects, we joined forces to utilize pluripotent stem cell derived human retinal cells to develop drug– (Tanaka and Ader labs) and cell-based therapeutic approaches (Adler & Busskamp labs) for retinal diseases (Santos-Ferreira T, Völker et al 2016).

Outlook – We are developing novel robust experimental human organoid models recapitulating retinal neuronal degeneration and scar formation. Our aim is a research platform encompassing the mouse retina regeneration ex vivo assay for the identification of regeneration and scar formation regulators, mouse organoid models for fast-track candidate testing, sophisticated transgenic mouse models for in vivo validation, and human organoid models as well as a human donor retina ex vivo system for preclinical translation.

Selected publications:


Figure 1.

(A) Model of retinal regeneration versus glial scar formation. (B) Age–dependent regenerative competence in the mouse retina. Depicted are immunostained retinal flatmounts and each black dot represents a MG cell nucleus that under- went cell proliferation. Upon stimulation in the injured adult mouse retina in vivo a very low number (7%) of Müller glia are proliferating and some of those gave rise to new neurons (Karl et al 2006). In contrast, in our mouse regeneration ex vivo assay (juvenile mouse retina in organoid culture) we could stimulate more than 50% of MG to proliferate, which resulted in more numerous neuronal progeny compared to adult in vivo (Löffler et al 2019, Schäfer & Karl 2017).

Figure 2.

Mouse and human retina organoid systems. (Left) Our publication of an optimized protocol for the generation of pluripotent stem cell derived retina organoids was featured on the journal cover and in the best of 2015–2016 special issue. (A) Images of growing mouse retinal organoids. Immunostained (B) mouse and (C) human retina organoid tissue sections: (B) photoreceptor neurons (magenta), bipolar neurons (cyan); and (C) progenitors (neurons, glial and immunoexcitable progenitors) in PAX6 reporter (green), respectively (Völker et al 2015, Schäfer & Karl 2017).
We are interested in the role of new neurons in the function of the hippocampus in health and disease and study the interaction of genes and behavioral activity in the regulation of adult hippocampal neurogenesis. Preventing, compensating or reverting loss of hippocampal function is an important target for medicine in an aging society and new neurons might play a critical role in “successful cognitive aging” as new neurons allow the flexible integration of novel information into pre-existing contexts. In a comprehensive approach from molecular to behavioral and functional we are particularly interested in variance, both genetically and behaviorally, and their interacting effects on brain plasticity. The group consists of two units at the Dresden site of the German Center for Neurodegenerative Diseases (DZNE), focusing on the behavioral, epigenetic and functional aspects of adult neurogenesis as well as establishing new methods for the automated quantitative histology and atlasting, and one at the CRTD, where the focus lies on the systems genetics of adult neurogenesis.

Understanding activity-dependent regulation of neurogenesis

We have developed cell isolation strategies to identify precursor cells and other cell types critical to adult neurogenesis and to analyze them ex vivo. We have identified Lysophosphatidic acid receptor 1 (Lpar1) as the best marker of adult hippocampal stem cells so far (Walker et al., Stem Cell Research 2016). We try to understand, how behavioral activity alters the molecular make-up of the cells and how these changes affect adult neurogenesis. We are identifying key factors, systemic or local, that mediate such effects and have a strong focus on immunological factors and T cells in this context (Niebling, F1000 Research 2014). In addition, we try to understand fundamental cellular mechanisms of stem cell activation in response to behavioral stimuli and how their functional states is defined. An important facet of this work takes place in cell culture, where we not only develop improved cell culture protocols (Ehret et al., Stem Cell Research 2015) but also make use of a panel of recombinant inbred strains of mice (EIX) to exploit genetic variance in the culture dish. Using that strategy we identified Wnt pathway member Lrp6 as important regulator of hippocampal precursor cells (Kannan et al., Stem Cells 2016).

Our concept of plasticity as an iterative process, in which function follows form, which is in turn shaped by the behavior itself, knowledge about the specific function of adult-generated neurons becomes critical. We have used a refined version of the classical Morris water maze, explicitly geared towards identifying the function of new neurons (Garthe et al., PLOS One 2009), to dissect the functional contribution of new neurons to the beneficial effects of physical and cognitive activity on learning and memory (Garthe et al., Hippocampus 2016). Ongoing studies focus on the role of dopamine in mediating the critical flexibility that in our view is provided by the new neurons.

Adult hippocampal neurogenesis as individualizing trait

Adult neurogenesis is an individualizing trait. After having found that individual behavioral trajectories explained 22% of the variance in adult hippocampal neurogenesis (Freund et al., Science 2013) we discovered that these behavioral patterns were also associated with more individualistic patterns of social behavior (Freund et al., Neuroscience 2015).

Selected publications:


Tissue regeneration is a fascinating phenomenon, and it manifests differently in animals. We, humans, are rather poor regenerators, but other vertebrates, such as zebrafish, are stunningly regenerative in many tissues including the central nervous system. This regenerative capacity is largely due to the activity of tissue-resident stem cells, which are developmentally and physiologically reminiscent of the stem cells in our brain. However, it is still not clear why the neural stem cells in our brains cannot show a regenerative response in disease states while zebrafish can circumvent this hurdle. Thus, our main goal is to find out the molecular basis of how zebrafish neural stem cells can activate regeneration programs, and whether we can use stem cells for regenerative therapies in diseases of humans, especially in neurodegenerative diseases with what we learn from zebrafish. In addition to zebrafish models, we generated a novel 3D culture system of human cortex for comparative studies. We aim to understand whether we can harness the knowledge we gain from regenerating model organisms such as zebrafish to unlock our brain’s potential to regenerate after disease.

Recently, we have been exploring the potential of zebrafish in circumventing Alzheimer’s disease, where patients progressively lose neurons yet cannot form new ones; namely, they lack proper differentiation/survival response of stem cell-derived neurons. Therefore, inducing a functional “proliferation-differentiation-survival cascade” upon neurodegenerative conditions in mammalian neural stem cells, which otherwise bear neurogenic capacity, could serve as a therapeutic tool (Cosacak et al., 2015; Tincer et al., 2016). Here, the natural competency of regeneration in zebrafish could teach us how to do this. To investigate the molecular programs potentially mediating neurodegeneration-induced stem cell proliferation in regenerating organisms, we generated an Aβ42-dependent neurotoxic model in adult zebrafish brain through cerebroventricular microinjection of cell-penetrating Amyloid-β42 derivatives. Aβ42 deposited in neurons, and caused phenotypes reminiscent of amyloidopathophysiology in humans: apoptosis, microglial activation, synaptic degeneration and learning deficits (Bhattarai et al., 2016; Bhattarai et al., 2017). Upon Aβ42, zebrafish induced neural stem cell proliferation and enhanced its neurogenesis, which is not the case in our brains. We found that Interleukin-4 (IL4) is activated primarily in neurons and microglia/macrophages in response to Aβ42 and is sufficient to increase stem cell proliferation and neurogenesis in fish brain. Our detailed work shows a direct crosstalk of neurons and glia via immune-related molecules, which imposes plasticity to endogenous stem cells in vertebrate brains, and this role is novel and distinct to the known effects of interleukins on immune cells. These findings are important as they suggest (1) neural stem cells can sense the mode of injury by certain specific crosstalk signalling mechanisms, and respond accordingly by eliciting certain molecular programs, (2) zebrafish offers a unique and excellent tool to elucidate these molecular programs.

To investigate the effects of TAU in a regenerative adult vertebrate brain system, we generated a cre/lox-based transgenic model of zebrafish that chronically expresses human TAUP301L, which is a variant of human TAU protein that forms neurofibrillary tangles in mouse models and humans. Interestingly, we found that although chronic and abundant expression of TAUP301L starting from early embryonic development led to hyperphosphorylation, TAUP301L did not form oligomers and neurofibrillary tangles, and did not cause elevated apoptosis and microglial activation, which are classical symptoms of tauopathies in mammals. Additionally, TAUP301L neither increased neural stem cell proliferation nor activated the expression of regeneratively relevant factor Interleukin-4, indicating that TAUP301L toxicity is prevented in the adult zebrafish brain. By combining TAUP301L expression with a novel Aβ42 toxicity model, we found that Aβ42 ceases to initiate neurofibrillary tangle formation by TAUP301L, and TAUP301L does not exacerbate the toxicity of Aβ42. Therefore, our results propose a cellular mechanism that protects the adult zebrafish brain against tauopathies, and our model can be used to understand how TAU toxicity can be prevented in humans (Cosacak et al., 2018).

Our work constitutes a significant interface between basic science and translational research by providing a natural source of regeneration (zebrafish models) and an experimental model for human brain development and neurodegeneration (3D culture system).

Selected publications:
KARSTEN KRETSCHMER

MOLECULAR AND CELLULAR IMMUNOLOGY / FOCUS IMMUNE REGULATION

CD4+Foxp3+ regulatory T (Treg) cells maintain immune homeostasis throughout life and represent promising gain-of-function targets (e.g. in autoimmunity). In this context, our research interests focus on the generation, lifestyle and function of Foxp3+ Treg cells, with a particular emphasis on developmental sublineages of thymic (tTreg) and peripheral (pTreg) origin.

Tolerogenic Vaccination. Targeted antigen delivery to DEC-205+ dendritic cells (DCs) efficiently converts extrathymic naive CD4+Foxp3+ T cells into highly stable and suppressive Foxp3+ pTreg cells (Kretschmer et al., Nat Immunol 2005; Nat Protoc 2006). Such induced pTreg cells have proven to be effective in ameliorating clinical symptoms in various autoimmune mouse models (diabetes, encephalomyelitis, rheumatoid arthritis) (Petzold et al., Rev Diabet Stud 2012; Spiering et al., J Immunol 2015). In ongoing studies, we assess the potential of DC subsets (e.g. DCIR2+ DCs) to confer Foxp3+ Treg cell-mediated autocrine protection (e.g. Tabansky et al., Mol Med, in revision).

 NATURALLY INDUCED pTREG CELLS. Encouraged by the identification of immediate CD4+Foxp3+CD25+ pTreg cell precursors in peripheral tissues of nonmanipulated mice (Schallenberg et al., J Exp Med 2010), we previously established a unique genetic tool to faithfully discriminate mature populations of RFP+GFP+ pTreg and RFP+GFP– pTreg cells (Fig. 1, left) and could show that naturally induced tTreg and pTreg cells represent phenotypically and functionally distinct sublineages (Petzold et al., EJJI 2014). More recently, we succeeded in extending the RFP/GFP model to mice with selective ablation of either pTreg or tTreg cells (Fig. 1, right). Ongoing studies provided first evidence that such ‘tTreg only’ mice (in collaboration with S. Schlenner and A. Liston, Leuven, Belgium) and ‘pTreg only’ mice represent a unique opportunity to delineate the role of developmental sublineages in settings of insufficient (e.g. cancer) and unwanted (e.g. autoimmunity, transplant rejection) immunity.

MOLECULAR MECHANISMS. Extending previous studies on protein-coding genes (Marson*, Kretschmer* et al., Nature 2007), we could now show (in collaboration with R&D, Qiagen, USA) that the transcription factor Foxp3 can act both as transcriptional repressor and stabilizer/amplifier of mRNA genes, with TGF-β and IL-2 fine-tuning cooperatively Foxp3/NFAT-dependent mRNA expression. We addressed various aspects of Foxp3+ Treg cell biology in national and international collaborations, which included molecular pathways of Foxp3+ Treg versus RORγt+ Th17 cell differentiation (Immunity 2014), the essential role of continuous TCR signals in Foxp3+ Treg cell function (Immunity 2014), and the selection of functionally distinct Foxp3+ Treg cell subsets by self-antigen affinity (Nat Immunol 2016). Our own ongoing studies aim to dissect mechanisms of epigenetic regulation by histone methylation and have identified nonredundant roles of individual histone methyltransferases (Mll1-3, Setd1a, Setd1b, etc.) were selectively ablated in Foxp3+ Treg cells by transgenic expression of Cre recombinase (Foxp3, GFP-Cre fusion protein). Representative flow cytometry of CD25 and Foxp3+ GTP-Cre expression among gated CD4+ T cells in lymph nodes of wild-type (left panels) and Mll1/2 fl/fl double-deficient (right panels) mice. In contrast to 12-week-old mice (upper panels), the peripheral compartment of Foxp3+ Treg cells is severely reduced in 12-month-old Foxp3+ GTP-Cre+ x Mll1/2 fl/fl mice (lower panels).

Selected publications:
NIKOLAY NINOV

BETA-CELL BIOLOGY AND REGENERATION

The goal of our group is to make an original contribution towards the cure for diabetes by learning more about the basic biology of the beta-cells, which play a central role in diabetes. To this end, we develop new imaging approaches to better understand how pancreatic beta-cell plasticity and function are controlled in vivo. We complement these studies with molecular approaches to study gene function in individual beta-cells. Finally, we develop new diabetes models and chemical screens in zebrafish in order to find small molecules that promote beta-cell protection and regeneration.

1. Different populations of functional and proliferative beta-cells

We recently developed technologies allowing to track beta-cell proliferation and function during in situ maturation in zebrafish (Singh et al. 2017). The transgenic calcium reporter (GCAMP6s) allowed us to monitor the response of beta-cells to a glucose-stimulation, whereas the Beta-bow system enabled to study beta-cell proliferation and time of differentiation using multicolor imaging (Figure 1). Using these tools, we found that the islet is composed of dynamic sub-populations of beta-cells, which show different capacities for proliferation and for performing functional roles. In particular, we identified a population of “young” beta-cells, which differentiate from tissue-resident stem cells. These beta-cells are primed for proliferation and help to increase the numbers of beta-cells in the islet. In contrast, a second population of “older” beta-cells exhibit reduced proliferative potential, however, these cells respond more efficiently to glucose stimulation (Figure 2). Thus, differences in the age of the beta-cells in an islet lead to the formation of sub-populations of beta-cells, some involved in proliferation and others involved in function (Singh et al. 2017).

Future directions:

We will use our model and new tools to identify the signals that instruct beta-cells to switch from proliferation to function. We found that in zebrafish, this process takes only a few days after the birth of the beta-cells, whereas it is difficult to achieve the formation of functional beta-cells from human stem cells in vitro. Thus, we hypothesize that the in vivo environment in zebrafish provides powerful signals for rapid beta-cell functional maturation. We will now identify these signals, as this knowledge can help to produce functional human beta-cells in vitro for transplantation purposes.

2. The Levels of Reactive Oxygen Species Coordinate Metabolic Activity with Beta-cell Mass Plasticity

The number of beta-cells is under tight metabolic control, as this number increases with higher nutrient intake. However, the signaling pathways matching nutrition with beta-cell mass plasticity remain poorly defined. In our recently published work (Alfar et al., 2017), we used zebrafish as an in vivo model to investigate the role of ROS in the control of beta-cell plasticity. By applying genetic and pharmacological manipulations of ROS levels, we show a critical role for different levels of ROS in beta-cell plasticity (Figure 3). In addition, in collaboration with the group of Joerg Mansfeld (Biotec), we found that glucose-stimulation can lead to a rapid increase in ROS production. Thus, glucose can regulate beta-cell plasticity in part by controlling the intracellular ROS levels.

Future directions:

We will use our model and new tools to understand the nutritional regulation of beta-cell regeneration in zebrafish and the role of ROS in this process. Moreover, using screening in zebrafish, we identified a class small molecules impacting on oxidative metabolism that promote beta-cell expansion. One of this compounds is approved by the Food and Drug Administration (FDA). We will validate these compounds in human beta-cells as a preclinical model of beta-cell regeneration and protection.

Selected publications:


Alfar EA, Kirova D, Konantz J, Birka S, Mansfeld J, and Ninov N. Distinct Levels of Reac-


Our research interest is to understand the mechanisms of developmental and regenerative processes in the vertebrate spinal cord. Specifically, we are investigating the beneficial roles of oligodendroglia in regeneration of the lesioned zebrafish spinal cord.

This includes:
- Identification of novel signals which control glial proliferation and maturation into myelinating oligodendrocytes.
- Assessment of the behavioral impact of de- and re-myelination after CNS injury.
- Development of strategies to utilize beneficial effects of oligodendroglia for functional recovery.

Zebrafish are ideal to study spinal cord injury in an adult vertebrate as they successfully regain function after complete spinal cord transection, accompanied by axonal, neuronal and oligodendroglial regeneration and a complex microglial/immune system response. Over the past ten years, the research has yielded mechanistic insights into the functional regeneration in the zebrafish. I was the first to describe motor neuron regeneration from progenitor cells in the adult spinal cord, highlighting the importance of endogenous progenitor cells in adult regeneration in a vertebrate. Furthermore, I elucidated the role of axon-glia integrity on cognitive function.

The availability of transgenic reporter lines allows small molecule screening in embryos, providing an excellent opportunity to identify pathways involved in neural development. Often these pathways also play a role in adult regeneration.

Therefore, we are using a novel in vivo remyelination assay, which allows us to genetically ablate mature, myelinating oligodendrocytes in the spinal cord of zebrafish larvae. After the ablation, precursor cells remyelinate denuded axons within 4 days. This time window allows testing the pro-myelinating properties of small molecules. In addition to visual confirmation of remyelination, the behavioral impact, like escape response and electrophysiological measures are tested.

The combination of a well-established spinal cord injury paradigm in adult zebrafish with ablation of oligodendrocytes allows then to assess the impact of oligodendroglia on spinal cord regeneration. The newly identified signals which increase neural proliferation and maturation into functionally active oligodendrocytes, are assessed by behavioral measures of functional recovery. This will enabling us to regulate the functional outcome and benefit functional recovery.

Figure 1. Spinal cord injury leads to a massive loss of oligodendrocytes at 3 days post lesion. Tg(olig2:GFP) labels the oligodendroglial lineage. Cross sections of adult spinal cord are shown. (unpublished M. Reimer)

Figure 2. Adult demyelination: Demyelination after ablation of mature oligodendrocytes in the myelinated zebrafish spinal cord with microglial activation (4C4). Images of these mCherry expressing oligodendrocytes (red myelin sheaths) in the cross section of the adult spinal cord (left) and after ablation (right). (unpublished M. Reimer)

Selected publications:
The focus of the lab is to understand how individual tissues respond to an injury, to further understand their interaction during repair and regeneration. The vertebrate limb contains various tissue types including bone, skin, nerves, muscle and blood vessels. After an injury these tissues respond to a plethora of signals driving repair and, in few animal species, regeneration. The fine-tuned coordination of both, the individual tissue regeneration and the interaction with other tissue types could be the key for successful appendage regeneration.

Figuring out how to unlock the inherent regeneration potential in mammals and specifically in humans requires a practical model of regeneration. Axolotl is a powerful model where transgenesis has proven useful for studying molecular and cellular mechanisms of regeneration. Another advantage of this animal model is its semitransparent body, allowing intra-vital imaging of the limb. Axolotl represents a simplified organism in comparison with mammals, yet more complex than other animal models, that is uniquely suited to study bone formation, and appendage phenotypes.

One relevant feature unveiled by studying axolotl limb regeneration is that some mature cells can de-differentiate, a process by which an adult cell acquires a progenitor state. Another mechanism by which a tissue can regenerate is by activating resident stem cells. Recently, we found that muscle fibers do not contribute to new muscle regeneration but rather muscle-specific stem cells differentiate to form new fibers. Although mammalian limb regeneration is far from becoming a reality, with this study we found that axolotls and mammals share a common underlying mechanism for muscle regeneration. In other tissue types, it is unclear the presence of resident stem cells or the multipotency of its progenitors. Such an example is the connective tissue, which plays a critical role in the formation of the regenerating structure called the blastema. Currently, we are using the cre/loxP system to lineage trace connective tissue populations and their descendants during regeneration and wound healing. We study these cell populations during digit tip regeneration of the axolotl and mouse. Rodents and humans can regenerate a digit tip when amputated at the distal end of the third phalanx (P3). In both, mouse and human, the digit fails to regenerate when amputation occurs more proximal or through the second phalanx (P2), resolving by wound healing. Thus, the digit tip provides a common ground for cross-species studies in regenerative medicine.

Our current research program is defined by the following hypotheses: Connective tissue populations differ in their potential to participate in digit tip regeneration and to form bone. And second, that remodeling of the bone at the amputation plane, and a regulated interaction with nerves and blood vessels is necessary for the functional engraftment of the newly regenerating tissue.

Our long-term scope is to find differences and similarities with mammalian regeneration, in order to identify key components that promote or restrict repair and regeneration in mammals. We aim to answer the question of why in these species this potential is not used to regenerate and pattern complex structures.
Neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Parkinson’s Disease (PD) are affecting an increasing percentage of the population. Although many drug candidates have been tested in clinical trials, almost all have failed, and no treatments are available that effectively prevent or delay disease progression. One of the largest challenges is that neurodegenerative diseases seem to be uniquely human disorders, and model organisms, such as mice, which have been so helpful for other diseases, do not recapitulate ALS or PD pathogenesis. Induced pluripotent stem cells (iPSCs) offer a new and powerful approach to studying neurodegenerative diseases, including ALS and PD. Skin or blood cells can be biopsied directly from a patient and, using reprogramming, induced to from iPSCs, which can proliferate and differentiate into the same neurons affected by ALS or PD. As a result, we can use iPSCs to create „diseases in a dish”, which can then be used to understand why patients develop disease pathology. In addition, because iPSCs can generate theoretically limitless numbers of neurons, they are ideal for high throughput screening (HTS) campaigns to identify new and effective drug candidates.

Isogenic iPSC lines provide novel insights into mutant LRRK2-induced PD pathogenesis.

The LRRK2 mutation G2019S is the most common genetic cause of PD. To better understand the link between mutant LRRK2 and PD pathology, we derived induced pluripotent stem cells from PD patients harboring LRRK2 G2019S and then specifically corrected the mutant LRRK2 allele. We demonstrated that neurons with LRRK2 G2019S manifested increased α-synuclein protein, decreased neurite outgrowth, and increased susceptibility to neurodegeneration. We also showed that gene correction resulted in phenotypic rescue in differentiated neurons and uncovered expression changes associated with LRRK2 G2019S. We found that LRRK2 G2019S induced dysregulation of CPNE8, MAP7, UHRF2, ANXA1, and CADPS2. Knock-down with LRRK2 G2019S. We demonstrated that mutant LRRK2-induced inflammation, and direct protection of neurons from nitric oxide–induced degeneration. Currently, we are using data from phospho-proteomics and transcriptomics to better understand the pathways involved in FUS, SOD1 and C9orf72 cases of familial ALS. We confirmed the activity of these compounds using stem cell–derived motor neurons and astrocytes, together with activated microglia as a stress paradigm (24). We discovered hit compounds from a screen of more than 10,000 small molecules. We demonstrated that these compounds act through diverse pathways, including the inhibition of nitric oxide production by microglia, activation of the Nrf2 pathway in microglia and astrocytes, and direct protection of neurons from nitric oxide–induced degeneration. We showed that multiple PD-associated phenotypes were ameliorated by inhibition of ERK. Our results provide novel mechanistic insight into the pathogenesis induced by mutant LRRK2 and enable the development of potential new therapeutics.

Derivation of smNPCs: a novel tool enabling high-throughput screening using iPSC models.

Phenotypic drug discovery requires billions of homogeneous cells for HTS campaigns. Since hundreds of thousands of unique small molecules are often tested in a single HTS campaign, even small variability within the cell populations for screening can invalidate an entire campaign. Neurodegenerative assays are particularly challenging because neurons are post-mitotic and cannot be expanded for implementation in HTS. Therefore, HTS for neuroprotective compounds requires a progenitor cell type that is robustly expandable and able to efficiently differentiate into all of the neuronal subtypes involved in disease pathogenesis. We derived and propagated, using only small mollecules, of human neural progenitor cells (small molecule neural precursor cells; smNPCs). smNPCs are robust, exhibit immortal expansion, and do not require cumbersome manual culture and selection steps. We demonstrated that smNPCs have the potential to directly and efficiently differentiate into neural tube lineages, including motor neurons (MN), and midbrain dopaminergic neurons (mDANs). Unlike iPSCs, smNPCs are committed to the neural lineage and form post-mitotic neurons in a few days, making them ideal for automated screening. Finally, to demonstrate the usefulness of smNPCs we showed that mDANs differentiated from smNPCs with LRRK2 G2019S are more susceptible to apoptosis in the presence of oxidative stress compared to wild type. Most recently, we have improved upon the smNPC design to derive a midbrain floor plate progenitor that is ideally suited to obtaining mid-brain dopaminergic neurons, the main cell type affected in PD.

Stem cell-based phenotypic drug discovery: proof of concept using mouse stem cells.

Stem cells, through their ability to both self-renew and differentiate, can produce a virtually limitless supply of specialized cells that behave comparably to primary cells. We developed an assay to test the neuroprotective properties of compounds using stem cell–derived motor neurons and astrocytes, together with activated microglia as a stress paradigm (24). We discovered hit compounds from a screen of more than 10,000 small molecules. We demonstrated that these compounds act through diverse pathways, including the inhibition of nitric oxide production by microglia, activation of the Nrf2 pathway in microglia and astrocytes, and direct protection of neurons from nitric oxide–induced degeneration. Currently, we are testing hundreds of thousands of unique small molecules are often tested in a single HTS campaign, even small variability within the cell populations for screening can invalidate an entire campaign. Neurodegenerative assays are particularly challenging because neurons are post-mitotic and cannot be expanded for implementation in HTS. Therefore, HTS for neuroprotective compounds requires a progenitor cell type that is robustly expandable and able to efficiently differentiate into all of the neuronal subtypes involved in disease pathogenesis. We derived and propagated, using only small mollecules, of human neural progenitor cells (small molecule neural precursor cells; smNPCs). smNPCs are robust, exhibit immortal expansion, and do not require cumbersome manual culture and selection steps. We demonstrated that smNPCs have the potential to directly and efficiently differentiate into neural tube lineages, including motor neurons (MN), and midbrain dopaminergic neurons (mDANs). Unlike iPSCs, smNPCs are committed to the neural lineage and form post-mitotic neurons in a few days, making them ideal for automated screening. Finally, to demonstrate the usefulness of smNPCs we showed that mDANs differentiated from smNPCs with LRRK2 G2019S are more susceptible to apoptosis in the presence of oxidative stress compared to wild type. Most recently, we have improved upon the smNPC design to derive a midbrain floor plate progenitor that is ideally suited to obtaining mid-brain dopaminergic neurons, the main cell type affected in PD.

Selected publications:


Molecular principles of limb and spinal cord regeneration

Our group seeks to understand the cellular mechanisms underlying salamander limb and spinal cord regeneration as a model for how successful regeneration occurs in a vertebrate. These studies act as a springboard to design novel strategies for regenerating or replacing mammalian tissues. In addition, the model acts as a starting point to rigorously investigate how mammals have lost regeneration capabilities over evolution.

We have recently identified several key signaling molecules that initiate regeneration, and that coordinate limb patterning with limb outgrowth. Using functional expression cloning, we identified a novel role of MARCKS-like protein as an extracellular inducer of proliferation initiation during axolotl appendage regeneration. We further showed that after initial onset of proliferation, that cross induction of anteriorly expressed FGF8 and posteriorly expressed sonic hedgehog are required to sustain limb outgrowth along with patterning to complete regeneration.

The neural stem cells that regenerate the spinal cord

Remarkably the axolotl can regenerate the spinal cord after either tail amputation or spinal cord lesion. We have identified the neural stem cells that rebuild the missing portion of spinal cord as Sox2+ ependymal cells. Recently by implementing CRISPR-mediated targeted genomic deletion of the Sox2 locus we have shown that the Sox2 gene function is required for the acceleration of cell cycle to amplify stem cells during regeneration. Similar to the limb, the neural stem cells maintain a transcription factor code that governs positional identity, and sets a template for the regeneration process. In addition, the spinal cord cells re-express embryonic factors involved in elongating the primary body axis.

CNS organogenesis from ES cells to study and treat spinal cord regeneration

Based on our deep knowledge of regeneration, we have been engineering mouse and human tissues from embryonic stem cells that harbor this kind of positional information. We have engineered three dimensional mouse spinal cord tissue that harbors all of the correct spatial information to produce the different types of neurons of the spinal cord. Our aim is on one hand, to use the system to understand the diversification and spatial patterning of neural tissue. On the other hand, our goal is to promote further growth and morphogenesis of the spinal cord as a structured tissue source for transplantation studies into spinal cord injury, akin to transplantation of fetal spinal cord.

CNS organogenesis from ES cells to study and treat retinal degeneration

In collaboration with the junior groups Marius Ader and Mike Karl, we have also generated eye tissues from human embryonic stem cells. In particular, we have engineered the most efficient means to produce retinal pigment epithelium so far described. In our bodies, these cells perform an important debris clearance function (phagocytosis), which can weaken during aging, leading to blindness. Our HESC derived RPE cells perform such functions in vitro assays, leading us to seek to identify molecular components important for this function that might go awry during aging, and to search for agents that may boost this function. Our retinal pigment epithelial cells have also been transplanted into rodent models of retinal degeneration by Marius Ader, leading to engraftment and amelioration of cell degeneration.

Selected publications:


Our group seeks to understand the mechanisms that govern homeostasis in the intestine and the liver. In particular, we are interested in the role of the immune system, metabolism and the commensal microbiota in the control of intestinal and hepatic regeneration, degeneration, and tumor development.

**Inflammation-associated pathways in intestinal and hepatic regeneration and tumor development**

The intestinal mucosa is covered by a single, rapidly renewing layer of cells termed the intestinal epithelium, which separates a dense luminal microbiota from the largely sterile host tissue beneath. Intestinal immunity as observed in human inflammatory bowel disease (IBD) is associated with ongoing damage to the intestinal epithelium that promotes epithelial regeneration and wound healing but is also a risk factor for the development of colorectal cancer.

Regeneration and tumor development are thus tightly linked processes in the intestine and are influenced by inflammation-associated pathways. In the context of these observations, we could recently describe that calcineurin, a phosphatase that activates a group of transcription factors called nuclear factor of activated T cells (NFAT), and that is well-known for its role in the immune system, is also expressed in intestinal epithelial cells and regulates intestinal stem cell function (Peuker et al., Nat. Med. 2016). This work revealed that calcineurin and NFAT are ubiquitously expressed in the intestinal epithelium but are activated specifically in response to a breach of the intestinal barrier and concomitant translocation of microbial host pattern recognition receptors. This barrier defect was observed in the context of intestinal polyposis and shown to lead to the activation of calcineurin and NFAT in intestinal stem cells, which promoted the incidence and growth of intestinal tumors through NFAT-dependent transcriptional regulation of intestinal stem cells. As such, this work highlighted calcineurin and NFAT as critical mediators of a novel inflammation-associated pathway that is active in the intestinal epithelium and that integrates signals derived from the microbiota to regulate intestinal stem cell function.

Importantly, intestinal barrier dysfunction and microbial translocation are not only observed in the context of polyposis but also in response to intestinal damage, for example associated with IBD, chemotherapy or following allogeneic stem cell transplantation (graft-versus-host disease). Calcineurin and NFAT may therefore not only regulate intestinal stem cell function in the tumor environment but also in the context of damage-associated intestinal regeneration. Furthermore, our description of a molecular pathway driven by the intestinal microbiota and critical for stem cell function suggests that modulation of the endogenous microbiota as well as the development of bacterial strains genetically engineered to activate or inhibit this pathway may provide novel strategies to promote intestinal regeneration and/or prevent tumor development. These concepts are currently being addressed in our group.

In addition, we are investigating whether similar pathways are active in the context of alcoholic and non-alcoholic fatty liver disease, which is associated with ongoing damage to the intestinal epithelium and promotes the incidence and growth of liver tumors through NFAT-dependent transcriptional regulation of intestinal stem cells. As such, this work highlighted calcineurin and NFAT as critical mediators of a novel inflammation-associated pathway that is active in the intestinal epithelium and that integrates signals derived from the microbiota to regulate intestinal stem cell function.

**Lipid antigens in intestinal homeostasis**

In addition to their many roles in metabolism and cellular biology, lipids can serve as antigens and activate lipid-reactive T cells upon presentation by proteins of the CD1 family of atypical MHC class I molecules. We and others have shown that lipid-reactive T cells play critical roles in the intestinal and hepatic homeostasis – a process that is modulated by self lipids as well as by lipids of microbial origin (Olszak et al., Nature 2014, An et al., Cell 2014, Zeissig, Nat. Med. 2012). Current work in the laboratory, which is supported by a Starting Grant of the European Research Council (ERC), focuses on the identification of lipid antigens involved in the regulation of intestinal inflammation and tumor development, whose therapeutic modulation shall target inflammation and carcinogenesis at the origin of these diseases.

**Genetic contributions to inflammation, regeneration, and degeneration in the intestine and the liver**

In ongoing work, our group characterizes the genetic contributions to chronic inflammation, damage, and regeneration in the intestine and the liver. These studies focus on inflammatory bowel diseases (IBD), a group of disorders characterized by chronic intestinal inflammation and damage, and non-alcoholic fatty liver disease, one of the most common disorders in the Western hemisphere that is tightly linked to obesity and associated with liver degeneration, cirrhosis, and hepatocellular cancer in a subset of patients. In recent work, we could contribute to the characterization of the genetic architecture of IBD (Cleynen et al., Lancet 2016; Heap et al., Nat. Genet. 2014, Justins et al., Nature 2012) and alcohol-related liver damage (Buch et al., Nat. Genet. 2015). Moreover, we could identify monogenic forms of IBD, which provided unique insight into the pathogenesis of IBD and opened new opportunities for personalized treatment of patients with IBD (Zeissig S et al., Gut 2015, Zeissig Y et al., Gut 2015).

Selected publications:


NEW RECRUITS AND GROUPS IN 2017

MAXIMINA H YUN
Regeneration of complex structures in adult vertebrates
Humans exhibit rather limited capabilities for tissue repair and regeneration. In contrast, salamanders (such as newts and axolotls) are considered the champions of regeneration, being able to regrow an extraordinary range of complex structures including ocular tissues, tail, jaws, large sections of their heart, parts of their nervous system, and entire limbs throughout their life. Our lab aims to exploit this system in order to determine what cellular and molecular factors underlie the ability to regenerate complex structures and how changes through phylogeny and ageing affect regenerative potential. These are important areas for investigation, progress with which will deliver both fundamental and therapeutic insights.

Our research program focuses on three research topics: the mechanisms underlying the plasticity of the differentiated state, the role and regulation of senescence during regeneration and the role of the immune system in regenerative contexts.

Overall, we seek to expand our knowledge in these areas, as they are central to understanding how adult regeneration can take place, why certain vertebrates can regenerate whereas others cannot, and how to promote regeneration in non-regenerative organisms.

The aims of our ongoing and future research are
- Understanding the molecular basis of cellular plasticity
- Defining the role and regulation of cellular senescence in regeneration and tissue repair
- Unraveling the functions of the immune response in regenerative contexts

FRANZISKA KNOPF
Biology of bone regeneration
Bone fractures in humans heal well, especially at young age. Unfortunately, bone is not replaced after severe injury or upon long term treatment with certain drugs. In order to better understand mechanisms of successful versus impaired bone regeneration, we make use of highly regenerative zebrafish, and evaluate their bone forming capacity in different experimental contexts.

A main focus of the lab is to decipher mechanisms of successful bone regeneration. Zebrafish regenerate bone quickly; however, they do not overgrow bone. Why? To address this question, we will explore ways of positively and negatively influencing tissue regeneration. By using a combined approach of drug treatments, genetic manipulation and state of the art imaging technologies, we aim to identify mechanisms that are involved in growth control of bone and of regenerating tissues in general. This may have important implications for future regenerative therapies targeting bone. Successful bone formation can also be hindered. We investigate adverse effects of certain drugs used in the clinics on bone tissue. As an example, we have analyzed the anti-regenerative effects of immunosuppressive glucocorticoids in zebrafish, and have found that both osteoclast activity and proliferation are reduced by glucocorticoid exposure, while osteoblast apoptosis remains unaffected. In the future, we aim to identify molecules which counteract bone destruction in this context and hope that this will give novel impulses in the treatment of inflammatory diseases.

CRTD PUBLICATION RECORD

Regular evaluation of publication activity helps to analyze the quality of research groups at the CRTD. The sum of journal impact factors, citations and Hirsch factor was calculated from the entire publication record of the group leaders. The Hirsch factor is based on a scientist’s most cited papers and the number of citations that these have received in others publications (e.g. a Hirsch factor of 11 means that the group leader has 11 publications that were each cited by other scientists at least 11 times).

Total Publications*  

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*source : WEB OF Science
Advanced and sophisticated technologies, together with state-of-the-art equipment, are prerequisites for first class research in the fields of biotechnology and biomedicine. The Technology Platform provides access to superior technical and personnel resources through innovative management concepts.

A crucial advantage of the Biopolis Dresden is complementary implementation of technology platforms between participating institutes. This setup provides all scientists on campus and their collaborators with access to an internationally competitive array of state-of-the-art devices and technologies.

A selection of the most frequently used core and joint core facilities available at Biopolis Dresden by CRTD’s scientist is presented below:

• The **Deep Sequencing Facility** offers high quality services for a diversity of Next Generation Sequencing-based applications which include RNA sequencing, especially from ultra-low input down to single cell sequencing, genomic re-sequencing, ChIP sequencing and targeted re-sequencing.

• The **Electron Microscopy and Histology Facility** offers comprehensive services for embedding, sectioning and staining of specimens. Furthermore, it provides expertise and technology to study the histology and ultrastructure of cell and tissue samples using TEM, SEM and correlative light electron microscopy.

• The **Stem Cell Engineering Facility** generates human induced pluripotent stem (hiPS) cell lines and isogenic hiPS cell lines, provides a thorough characterization of the generated/engineered hiPS cells as well as genetic engineering services (seamless gene editing, reporters, knock in/outs) to the scientific community. Consulting and training people to work with pluripotent stem cells as well as genome engineering methodologies (CRISPR/Cas9, TALENS, Lentiv/retroviruses) is another important task.
• **Good Manufacturing Practice (GMP)** compiles guidelines required in order to ensure high standards and reproducibility for the production of drugs. These guidelines provide minimum requirements that a pharmaceutical manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public. GMP is a substantial prerequisite for a successful translation of basic research into clinical applications, like cellular therapies.

• The **Flow Cytometry Facility** offers access to state-of-the-art devices as well as services such as multi-color analysis, cell sorting, flow cytometry training and support in designing and analysing experiments.

• The **Light Microscopy Facility** provides researchers with high-quality imaging systems along with strong support for the design of their experiments. The facility currently comprises more than 20 different systems ranging from high-resolution confocal microscopes to simple fluorescent video microscopes. Sophisticated image processing can be accomplished on high-end graphics machines.

• The **Microstructure Facility** provides cutting edge technologies for the micro-structuring of organic/inorganic materials, offering full set of skills and capabilities within photolithography, soft lithography, polymer micro structuring, thin film deposition and microfluidics.

• The **Single Cell Analysis Unit** offers targeted gene expression profiling or whole transcriptome analysis of single cells. The facility provides assistance in experimental design, technological support and access to state-of-the-art systems or provides the full workflow – from a single cell to expression profiles – as a service.

• **Animal Facility** for housing mice, zebrafish and axolotl serve the scientific community in Dresden.

• **IT infrastructure and support** operates a complex IT infrastructure for 650 active users. The service comprises the full range of server maintenance, storage, network, desktop support and media support.
TECHNOLOGY TRANSFER

The global market for stem cell products, including pluripotent and reprogrammed stem cells, cell culture tools and consumables, disease model systems, and cellular therapeutics, is set to rise to over 100 billion by 2020.

The Center for Regenerative Therapies (CRTD) contributes to this market through its world-leading research in the area of regenerative biology and medicine. Our mission is to translate basic scientific discoveries and know-how into clinically relevant applications and marketable products through alliances with the biotechnology, pharmaceutical and diagnostics industries.

CRTD brings innovative technologies and established expertise to its partnerships with industry, particularly in the areas of neurodegenerative diseases, retina degeneration, type 1 diabetes and pancreatic islet regeneration, and stem cell niches. In its technology transfer endeavor, CRTD works intensively with partners at the Biotech Campus Dresden, including the Biotechnology Center (BIOTEC), B CUBE and the University Hospital Carl Gustav Carus Dresden.

Working across scales from subcellular domains through cellular and organoid models to whole animals, including zebrafish, amphibians and rodents, our core translational focus is in stem cell biology and the elucidation of disease mechanisms, drug screening using innovative disease models and the development of tools for the regenerative medicine industry.

CASE STUDIES

Collaboration between Prof. Federico Calegari and Exiqon A/S (Denmark) for detection of circular RNAs (circRNAs) and their associated molecular complexes using Exiqon’s LNA™ oligonucleotide probes.

Newly discovered circular RNAs (circRNAs) may play many important biological functions, particularly in brain development. To capture circRNAs of interest, as well as their associated molecular complexes, and elucidate their functions and molecular mechanisms, Prof. Federico Calegari’s group and Exiqon A/S (www.exiqon.com) are cooperating to investigate the use of Exiqon’s proprietary oligonucleotide probes (LNA™ technology) for circRNA isolation. Prof. Calegari said, “Current limitations in available research tools and methods for analysing the RNA interactome hinder the understanding of complexity in circRNA functions. Together with Exiqon we will assess the LNA™ technology to overcome these limitations and provide insight into the functions of circRNAs”.

Within a BMBF funded project Prof. Marius Ader is collaborating with Miltenyi Biotec for the identification of cell surface markers allowing enrichment of IPS-derived retinal cells for transplantation.

The groups of Prof. Marius Ader and Dr. Mike Karl at the CRTD are developing protocols for the generation of transplantable retinal cells from human induced pluripotent stem cells (hIPS). In a joined effort with Miltenyi Biotec (http://www.miltenyibiotec.com) cell surface markers for the classification and enrichment of specific donor cells for cell-based treatment approaches in retinal degenerative diseases will be identified as an essential step in therapy development for blinding diseases.

<table>
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<tr>
<th>Patent Title</th>
<th>Inventor(S)</th>
<th>Publication No.</th>
<th>Date</th>
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<tr>
<td>Method for producing polarized retinal progenitor cells from pluripotent stem cells and their differentiation into retinal pigment epithelium cells</td>
<td>Elly Tanaka, Yu Zhu</td>
<td>US 9249390 B2</td>
<td>02/02/2016</td>
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<td>EP 2383333 B1</td>
<td>25/05/2015</td>
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<td>A fluorescence based reporter construct for the direct detection of TGF-beta receptor activation and modulators thereof</td>
<td>Christian Bökel, Thomas Weidemann</td>
<td>EP 2141719 B1</td>
<td>01/12/2010</td>
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<tr>
<td>Methods and compositions for the expansion of somatic stem cells and progenitor cells</td>
<td>Federico Calegari, Benedetta Artegiani, Claudia Waskow, Tatyana Grinenko</td>
<td>EP 2380972 B1</td>
<td>19/09/2012</td>
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An important task for CRTD members is to educate future scientists by engaging in diverse teaching activities. CRTD scientists teach in several faculties of the Technische Universität Dresden.

The Master’s program ‘Regenerative Biology and Medicine’ (RegBioMed) is one of three successful international Master’s programs offered and organized by the BIOTEC for formal reasons, but is represented by CRTD, BIOTEC, the Max Planck Institute of Molecular Cell Biology and Genetics, the Max Bergmann Center for Biomaterials and the Medical Theoretical Center as well as the Faculty of Medicine Carl Gustav Carus. The Master’s program is mainly suitable for students with a background in biology or medicine and received increasing applicant numbers since its first launch in the winter term 2010/11. In 2012 the RegBioMed Master’s Program was awarded with the teaching award sponsored by the Association of Friends and Sponsors of TU Dresden e.V. for its concept of the ‘Lab Rotations’ in which students learn to design and run experiments and thus gain comprehensive experience in experimental work with model organisms, in molecular biology as well as in cell- and organ research.

The Master Program has a connection for outstanding students to enter the Dresden International Graduate School for Biomedicine and Bioengineering (DIGS-BB) through a Fast Track option. The DIGS-BB is a powerful partner dedicated to first-class doctoral training at the frontier of science of the Dresden International PhD Program (DIPP) together with the International Max Planck Research School for Cell, Developmental and Systems Biology. The DIPP provides excellent research opportunities, expert thesis supervision and a structured training curriculum for ambitious and highly qualified university graduates who wish to work towards a PhD in the research areas:

1. Cell, Developmental and Systems Biology (CellDevoSys Program)
2. Regenerative Medicine (RegMed Program)
3. Molecular Bioengineering and Biophysics (BioEng Program)

PhD students in the CRTD can also be independently employed by a professor or group leader and join the network of the Bioscience PhD Students (BiPS). BiPS students have the advantage of accessing Technical University of Dresden and CRTD research communities, international networks, and facilities while completing their PhD. Between 2014 and 2015, 66 BiPS members have been working on their PhD projects at CRTD.

International office
International employees and students will find a point of contact for their questions at the International Office. They can address all concerns regarding visa issues, flat hunting, correspondence with landlords, telephone operators, public authorities, insurances, bank and much more at this information center.

Tenure Track
The tenure track option is an important determining factor in recruiting and supporting top young scientists. As there has been no general legal regulation for the tenure track in Germany, the CRTD established its own tenure track process in 2012. All junior groups are established for a duration of six years. After four years of probation, the junior group leaders get the chance to attend a tenure track evaluation. They are able to pass through an appointment procedure for a permanent W2 professorship under state law a successful evaluation by external and internal boards.

Since 2012, two junior group leaders have successfully passed the tenure track process at CRTD.
COMMUNICATION

Communication between scientists is one of the key components of a successful research center. In this regard, the CRTD hosts regular activities on campus. The main aim of these activities is to support the interaction between the members of the CRTD network including their staff. The events foster cooperation and improve the translation of basic research results into clinical applications. Four main elements constitute the pillars of this international communication system: the research group leader meeting of the core groups, the monthly research area symposia, the yearly summer conference, and the yearly CRTD-retreat with all CRTD members.

Research Area Symposia
Here researchers can present the highlights of ongoing research in one of the five research areas of the CRTD. These symposia foster the exchange of ideas and technologies between research areas.

Company presentations
Several times a year, CRTD offers companies the possibility to present their latest technology to our scientific community. In this way, scientists can also seek out the latest developments on the market. Biotech companies like Becton Dickinson GmbH, Miltenyi Biotec GmbH, Charles River Laboratories and others have been presenting their products already at CRTD, but also Evotec AG and Proago Consulting presented in small workshops.

Summer Conference on Regenerative Medicine
This conference is organized once a year with the purpose of promoting communication on the level of PhD students, Post docs, but also group leaders throughout the campus. Each year internationally distinguished external speakers as well as speakers from the CRTD present their research. Talks chosen from the submitted poster abstracts are added as a communication element for junior scientists. The distinct poster session in the afternoon of the Summer Conference provide ample opportunity for vivid discussions of current research projects.

External Seminar series
The CRTD External Seminar series represents another important element to stimulate communication among researchers on the biocampus. It is part of the joint green seminar that is hosted by the BIOTEC and CRTD. For this seminar series, internationally renowned researchers in regenerative medicine are invited by CRTD after selection by a seminar committee.

International Conferences
International Conferences offer researchers worldwide the possibility to exchange their latest results. From 2006 until 2014 CRTD co-organized together with its partners the International Congress on Stem Cells and Tissue Formation every other year. In 2016 CRTD co-organized with the International Society of Stem Cell Research (ISSCR) an international symposium on “Stem Cell Models of Neural Regeneration and Disease”.

CRTD Group Leader and CRTD Member Retreats
At these retreats group leaders at CRTD as well as CRTD’s members get the opportunity to present their achievements and to discuss strategic issues for future developments of the institute.

PhD/Postdoc Seminar series
At the PhD/Postdoc Seminar series PhD students and Postdocs of the three research institutes BIOTEC, B CUBE and CRTD present the results of their projects. This is a great opportunity to find out what is going on in the research institutions and get valuable feedback on their research projects. It is also a good chance for young scientists to practice lecturing and giving talks.

Internal communication
To strengthen and facilitate the internal flow of information and support the formation of corporate identity, we established an internal newsletter, which saw 27 editions since 2015. It combines organizational with scientific information. The feedback is highly positive.

Since 2009 CRTD has, set up a calendar with microscopic pictures from the CRTD network. It is distributed within the network but is also used for outreach activities.
To raise public understanding and awareness of science, especially about the chances and perspectives, as well as ethical issues in the field of regenerative medicine, CRTD is reaching out to the broader public to share knowledge and scientific discoveries with them. This promotes the transfer of knowledge, allows for public discussions, ensures transparency, addresses current research and its applicability, and makes the quality of research results visible. The CRTD is a committed, involved partner in a dialog with the sciences, the society, the business sector, and the political arena on every level. The PR-office of the CRTD closely interacts with the corresponding offices at the University Hospital Carl Gustav Carus Dresden and the TU Dresden as well as other member institutions of the CRTD network.

General Public
Public events are the main tool to engage in direct communication with the general public. The CRTD offers many different formats for this kind of knowledge transfer. The ‘Long Night of Sciences’ is the biggest public scientific event in Dresden every year, with around 2600 visitors at the CRTD. Each year, research groups of CRTD, BIOTEC and B CUBE prepare information booths, hands-on activities and talks to show and discuss topics of research in regenerative medicine.

The ‘Dresden Seniors Academy’ is a joint CRTD/BIOTEC series of talks and addresses senior citizens.

The public information days ‘Retina-Tag’, ‘Diabetes-Tag’ and ‘Demenz-Tag’ are bringing together basic researchers, clinicians, charities, patients, and the interested public to discuss these diseases and obtain information about recent progress in treatments.

Promotion of young talents
Developing enthusiasm for life sciences among pupils and students is one major aim of CRTD. In the last ten years, several groups of pupils and students visited the CRTD as part of a tailored program including lectures, scientific experiments and educational games. Since 2007, the CRTD participates in the annual ‘Girls’ Day’ and the TU Dresden Summer University. Both events focus on encouraging girls to become interested in biotechnology, cell biology and similar subjects. On March 11, 2016, the CRTD participated for the first time in the ‘UniStem Day’, a European campaign for pupils to acquire knowledge about stem cells and their potential in research and therapies. The Martin-Andersen-Nexö-Gymnasium (MANOS) in Dresden is one of our partner schools with a continuous exchange since 2012.

Political Arena
Due to the demographic change in the global population as well as increasing incidences of so far incurable diseases, novel innovative regenerative therapies are becoming increasingly important. To get an idea of possible applications and the state-of-the-art research, politicians and decision makers need to be informed about the progress in science and politicians take great interest in visiting the CRTD. Since 2010 the Prime Minister of Saxony Stanislaw Tillich visited CRTD three times already and also Saxon State Ministers came several times for a visit. Not only Ministers from Saxony but also from the Federal Republic of Germany as well as from the EU Parliament are interested in interacting with the scientists at CRTD.

Media Relations
An important task of the press office to provide is regular information to the media about the CRTD activities. The access to information for journalists is facilitated by the CRTD press office by preparing press releases, updating a press section on the CRTD website, the Twitter and Facebook account of the CRTD, and promoting contact between journalists and scientists. The CRTD issued about 450 press releases from 2006 to 2016 on topics like recent scientific results, organizational issues, funding or awards. In certain cases, joint or parallel press releases with other local or international institutions are issued. In 2016, the CRTD together with the City of Dresden worked on a campaign showing Prof. Elly Tanaka representing biotechnology. The motif has been used within various activities, for example within an exhibition at Dresden International Airport or at trade fairs.
ACTIVITY REPORT
2013 - 2017
Center for Regenerative Therapies TU Dresden

“FROM ORGANISMS TO THERAPY – RESEARCH FOR HUMANS”
Center for Regenerative Therapies TU Dresden