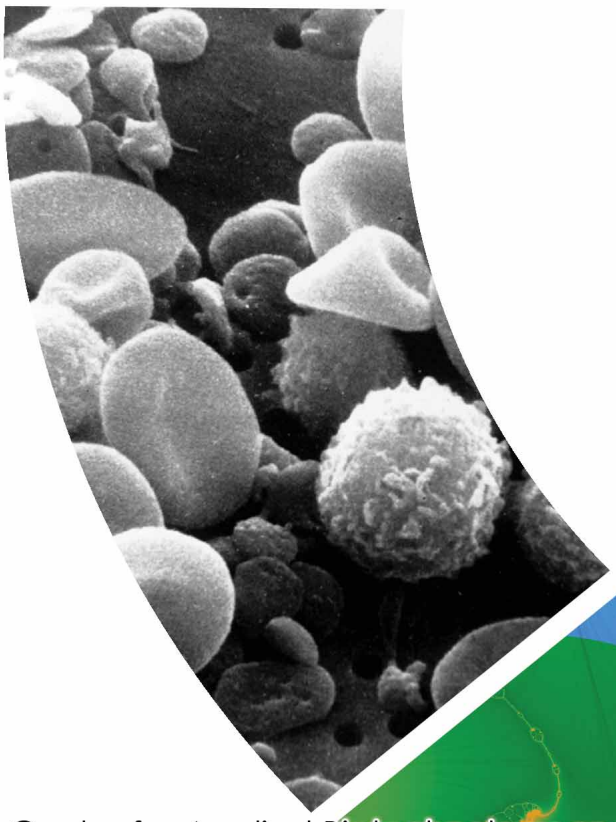
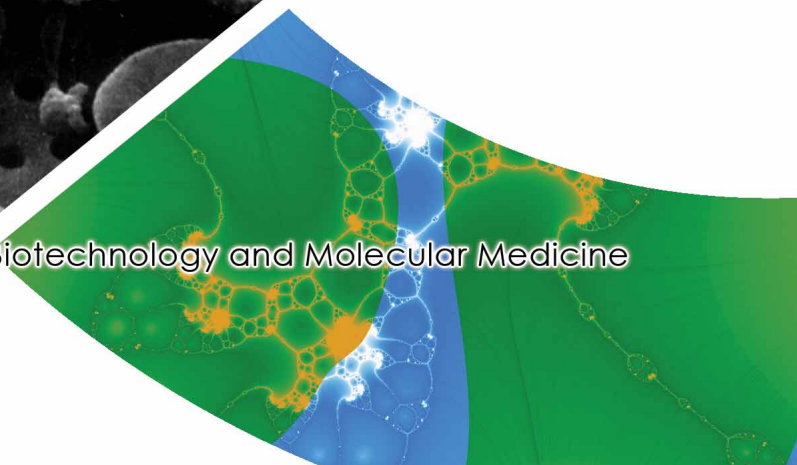
cabmm

center for applied biotechnology and molecular medicine





The Competence Center for Applied Biotechnology and Molecular Medicine

The CABMM celebrates its 10th anniversary in 2018. What began with a small nucleus of three innovative groups (the Musculoskeletal Research Unit (MSRU), the Institute of Veterinary Biochemistry and Molecular Biology (IVBMB) and the Institute of Regenerative Medicine (IREM)) is now a large network dedicated to Applied Biotechnology and Molecular Medicine, currently consisting of 77 CABMM members and their teams of more than 200 postdocs, PhD and Doctorate Students – all of whom are an important part of the whole. Not only has the network increased but the intensity of collaboration between partners, representing true translation between basic research and clinics.

The dynamics of the CABMM are also documented by changes within the founding institutions. The IREM has become a large institute of several groups and is no longer associated with the clinical centre of the University Hospital; the IVBMM has broadened its scope and has become the Department of Molecular Mechanisms of Disease (DMMD); and since 2017, the MSRU has become part of the DMMD.

Furthermore, the MSRU has expanded its expertise and no longer invests research in musculoskeletal diseases alone. In collaboration with other CABMM members, we have broadly extended our animal work to vascular diseases, skin replacement, and scaffold applications for regenerative medicine in other organ systems. Along that line, Professor Hoerstrup has also become the Founding Co-Director of Wyss Zurich, a translational centre for regenerative medicine and robotics, in a joint venture between the University of Zurich and the Federal Institute of Technology (ETHZ) that is sponsored by the philanthropist Hansjörg Wyss.

The mantra 'from bench to beside and back again' has become reality by including highly innovative research in all fields pertinent to the CABMM and also by fulfilling the regulatory aspects. The latter is an integral part of true translation since the best product will not make it to the patient if the regulatory authorities of all countries don't make it free for clinical studies. For this, new medical products and devices have to be produced according to Good Manufacturing Practice (GMP) and then tested under Good Laboratory Practice (GLP). Both accreditations are available at the CABMM and together with the accreditation of Good Clinical Practice (GCP) at the Center for Clinical Studies at the University Hospital Zurich, the university is in the privileged position to offer the entire regulatory path to the benefit of the patient.

The 10th anniversary of the CABMM shows a success story of scientists who are capable of working together with a true mission of improving medicine for the patients – humans and animals alike. The dream became true thanks to the dedicated work of many members of the network, but mainly with thanks to its sponsors for believing in our goals and work. Hansjörg Wyss helped to start our network in 2008, and the Mäxi Foundation gave us continuity over the past decade. In 2018, we were able to get permanent positions for running the CABMM, giving us a prosperous future for the coming years.

It's time for me to step aside and leave the leadership to younger members of the CABMM. This booklet summarises the success story of the CABMM during my time of leadership. Thank you, and please enjoy it.

Brigitte von Rechenberg
Prof. Dr. med. vet., Dipl. ECVS

Concept of the CABMM

The Center for Applied Biotechnology and Molecular Medicine (CABMM) is an official competence centre of the University of Zurich that was founded in 2008 by a small group of highly motivated and successful scientists, namely Professor Dr Brigitte von Rechenberg, Professor Dr Dr Simon P Hoerstrup, and Professor Dr Dr Michael O Hottiger. Under the slogan 'From bench to bedside … and back', the CABMM provides a stimulating environment for interdisciplinary and translational research, promoting scientific exchange and collaborations between basic and clinical researchers.

Structure of the CABMM

Administratively, the CABMM is assigned to the Vetsuisse Faculty of the University of Zurich and consists of the Plenum as highest decision-making body, the Steering Committee as operating body, and the managing director heading both the Coordinating Office as central contact and co-ordination point and the Platform Organization Team, dealing with all aspects connected to the CABMM Research Platform. Additionally, a Scientific Advisory Board (SAB) was established as controlling body.

Aim of the CABMM

The fundamental idea behind the CABMM is to perform, co-ordinate, and promote interdisciplinary and clinically oriented translational research. By definition, translational medicine is the interface between preclinical research and clinical development, 'translating' basic research results into clinical practice as well as clinical observations into scientific hypothesis in the laboratory. In order to fulfil these goals, it is essential that basic researchers and clinicians from various fields work closely together.

The CABMM aims to foster those collaborations between basic researchers and clinicians from human and veterinary medicine and, thus, to function as a bridge between disciplines as well as between basic and applied or clinical research. Therefore, it demonstrates a unique structure, in that it combines:

1) A network of existing research groups interested in exchanging scientific information and creating collaborations; and
2) A working platform for collaborative research.

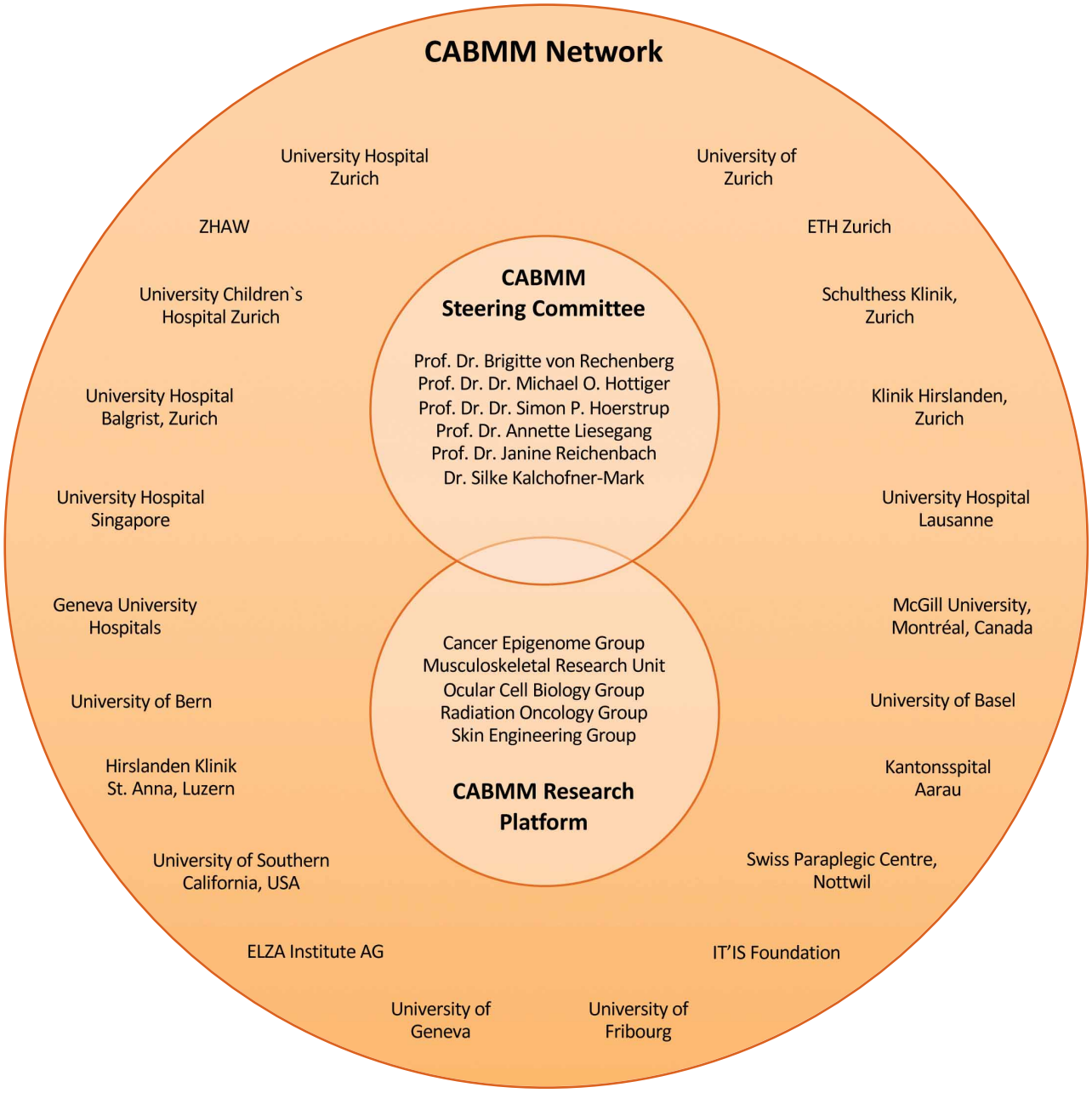
CABMM Research Platform

The CABMM Research Platform is accommodated within the Department of Molecular Mechanisms of Disease ((DMMD) director: Hottiger), and, provides not only lab space but also expert assistance in the form of technical support and scientific advice. On the CABMM Research Platform, basic scientists, clinicians and veterinarians can discuss their research and ideas, and work shoulder to shoulder for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissues.

CABMM Member Network

The CABMM network consists of member groups from various institutions. Although the majority of associated scientists belong to institutions in Zurich, we also have strong affiliations with other institutions located elsewhere in Switzerland (e.g.

Organigram of the CABMM



The unique structure of the CABMM consists of an extensive network of existing research groups from various institutions as well as a research platform providing lab space and support (Status: May 2018)

Bern, Lausanne, Lucerne, Basel, etc.), as well as in other countries (e.g. Singapore, Canada, and the USA).

The CABMM aims to continuously strengthen this network by promoting scientific exchange and collaborations. One of the most important instigators for starting a new collaboration is the yearly CABMM Spring Seminar and the CABMM Symposium, allowing for the fruitful exchange of scientific knowledge and ideas. Additionally, the CABMM Start-up Grant has been created, a peer-reviewed funding programme designed to support collaborations within the CABMM Network.

And it seems to pay off, as our network is very active. Basic researchers and clinicians from both human and veterinary medicine are working together on numerous joint research projects, thus reflecting the multifaceted work within the CABMM, and the number of collaborations between clinicians and basic researchers is very high.

Areas of expertise

Another special feature of the CABMM is the fact that we do not focus on only one particular medical field but rather on the translational and interdisciplinary character of research projects. Thus, the research conducted within the CABMM addresses various medical problems and is assigned to the following applications fields:

- Experimental medicine and surgery;
- Molecular medicine;
- Regenerative medicine; and
- Applied biotechnology.

Promotion of young scientists

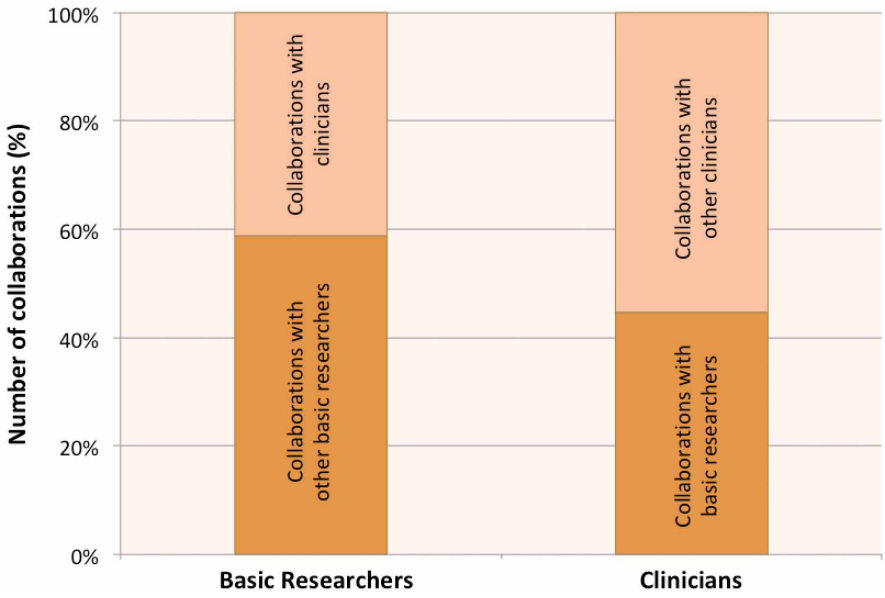
Furthermore, the CABMM aims to promote and support young scientists as they represent our future, and we think that they should be introduced to the importance of translational research early in their career. Places on our research platform are preferentially given to young researchers, and young academics also have the opportunity to discuss scientific questions with the experienced members of our Scientific Advisory Board and to ask for their advice during the regular SAB meetings. Moreover, the CABMM is involved in teaching activities. Beside our weekly CABMM Scientific Seminar, where young academics from the CABMM Research Platform and network have the opportunity to discuss their research with more experienced researchers and are trained in presenting their scientific projects, the CABMM is involved in existing teaching programmes at the University of Zurich.

Regulatory affairs

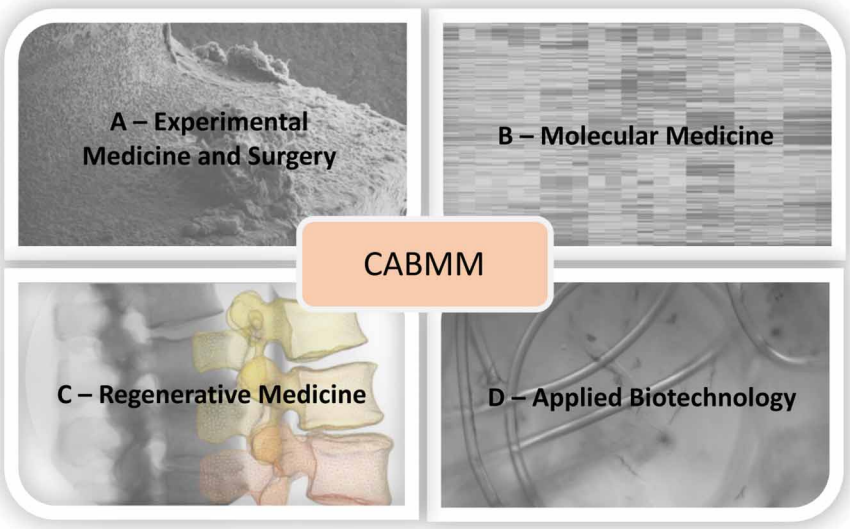
Moreover, the CABMM is involved in generating and providing the regulatory background needed for the efficient translation of basic research findings into the clinical environment. Regulatory affairs play an important role in the development of new drugs and therapies and, with thus, in translational medicine, regulatory requirements have to be taken into consideration in the preclinical phase in order to prevent unnecessary loss of time and money. Now, through efforts within the CABMM, the University of Zurich is one of the first European universities combining all regulatory requirements for the development, production, and first clinical trials of new drugs and therapies under one roof. Whereas GCP has already been running at the University Hospital for several years, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) have recently been established at the Institute for Regenerative Medicine (IREM) and the Musculoskeletal Research Unit (MSRU), respectively, through two founding members of the CABMM, Professor Dr Dr Simon P Hoerstrup and Professor Dr Brigitte von Rechenberg.

In summary, the CABMM promotes interdisciplinary and translational research by:

- Fostering collaborations between its members, in particular between basic researchers and clinicians from veterinary and human medicine;
- Providing a working platform where basic researchers, clinicians, and veterinarians work closely together;
- Focusing on translational and interdisciplinary aspects of research; and
- Promoting and supporting young scientists.



Collaborations of basic researchers with other basic researchers or clinicians, as well as clinicians with other clinicians or basic researchers. Status: 31 December 2013

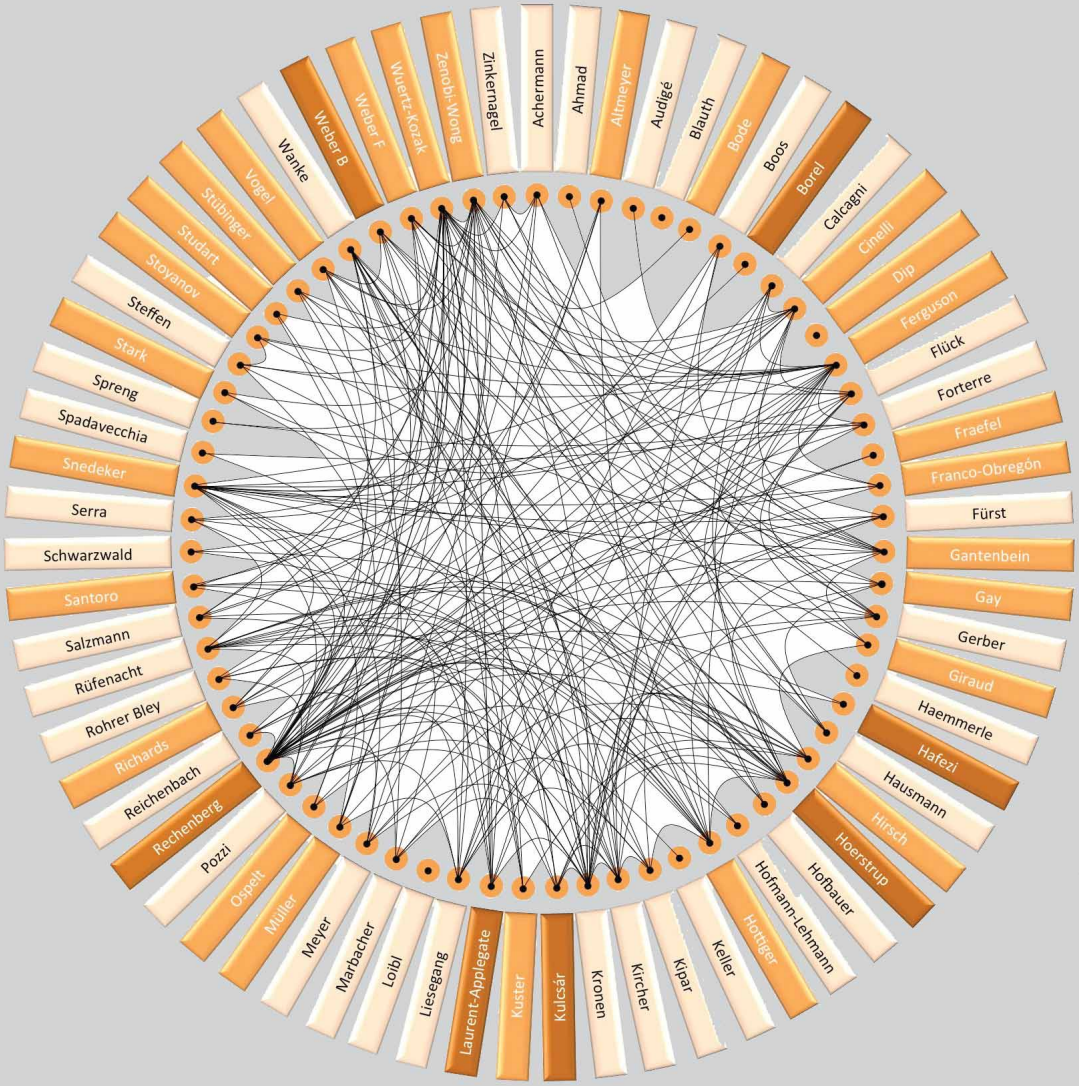


Application fields within the CABMM

Aims of the CABMM

- Promotion of scientific exchange and collaboration, in particular between research groups in clinical and basic research in the fields of (applied) biotechnology, experimental medicine and surgery, regenerative medicine, and molecular medicine;
- Planning and performance of joint projects in order to increase knowledge in the research fields described above;
- Transfer of gained project knowledge to sustainable further development by filing patent applications;
- Extension of the network to other research centres, universities, and industry in Switzerland as well as abroad;
- Set up and promotion of joint training programmes in order to specifically promote young academics, particularly at the postgraduate level;
- Establishment of a university research priority programme for the acquisition of research funds;
- Joint use of specific infrastructure (facilities, organisation, equipment); and
- Promotion of public relations.

CABMM network



Active networking between CABMM members: each line represents a collaboration between the indicated member groups.

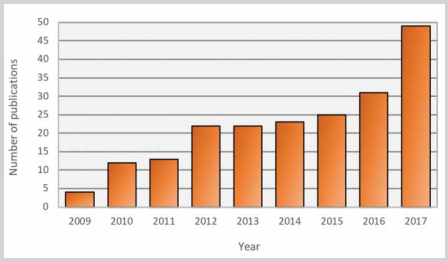
Status: 31 December 2017

Since its foundation in 2008, the CABMM has gained acceptance and reputation in the field of interdisciplinary and translational research, which is illustrated by a continuously growing number of CABMM members. Starting with 16 members in the founding year, our network consisted of 74 members at the end of 2017 and keeps growing. Considering the number of team members behind every person, this makes an impressive network!

However, not only is our network continuously growing, but it is also very active and shows an impressive number of collaborations.

On a quick glance, due to the different professional backgrounds of our members, the connection between them may not be obvious. But on a second, more profound look, common interests can be detected and result in a large number of collaborations between members from different application fields, as well as between basic researchers and clinicians, reflecting the interdisciplinary and translational aspect of the network.

The impressive number of collaborations and joint research projects is also reflected by the continuously increasing number of publications affiliated with the CABMM.



CABMM-affiliated publications

As we do not focus on only one particular medical field, but rather on translational and interdisciplinary research aspects, our network is dedicated to fostering advances in the following applied and clinically oriented research fields.

Experimental medicine and surgery

In this application field, the experimental application of biotechnology products in animal models, as a basis for human clinical trials, is addressed. Integration and adaptation at the systemic, organ, and cellular level are investigated, allowing for product optimisation.

In parallel, analytical techniques are improved and animal models, as well as anaesthesia and analgesia procedures, optimised, respecting high ethical standards.

Members of this application field in alphabetical order

Audigé, Laurent PD Dr (DVM), PhD
Blauth, Michael Professor Dr med
Boos, Alois Professor Dr med vet
Flück, Martin Professor Dr (PhD)
Forterre, Franck Professor Dr med vet
Fürst, Anton Professor Dr med vet
Gerber, Christian Professor Dr med
Hafezi, Farhad Professor Dr med, PhD
Hämmerle, Christoph Professor Dr med dent
Hausmann, Oliver PD Dr med
Hirsch, Sven PhD
Hofbauer, Günther Professor Dr med
Keller, Emanuela Professor Dr med
Kipar, Anja Professor Dr med vet
Kircher, Patrick Professor Dr med vet, PhD
Kronen, Peter Dr med vet
Kulcsár, Zsolt PD Dr med, PhD
Kuster, Niels Professor Dr (PhD)
Laurent-Applegate, Lee Ann Professor Dr med
Liesegang, Annette Professor Dr med vet
Marbacher, Serge PD Dr med, PhD
Meyer, Dominik Professor Dr med
Pozzi, Antonio Professor Dr med vet
Rechenberg von, Brigitte Professor Dr med vet
Rüfenacht, Daniel Professor Dr med
Schwarzwald, Colin Professor Dr med vet, PhD
Serra, Andreas Professor Dr med
Spadavecchia, Claudia Professor Dr med vet, PhD
Spreng, David Professor Dr med vet
Steffen, Frank Professor Dr med vet
Stübinger, Stefan PD Dr med vet
Wanke, Isabel Professor Dr med

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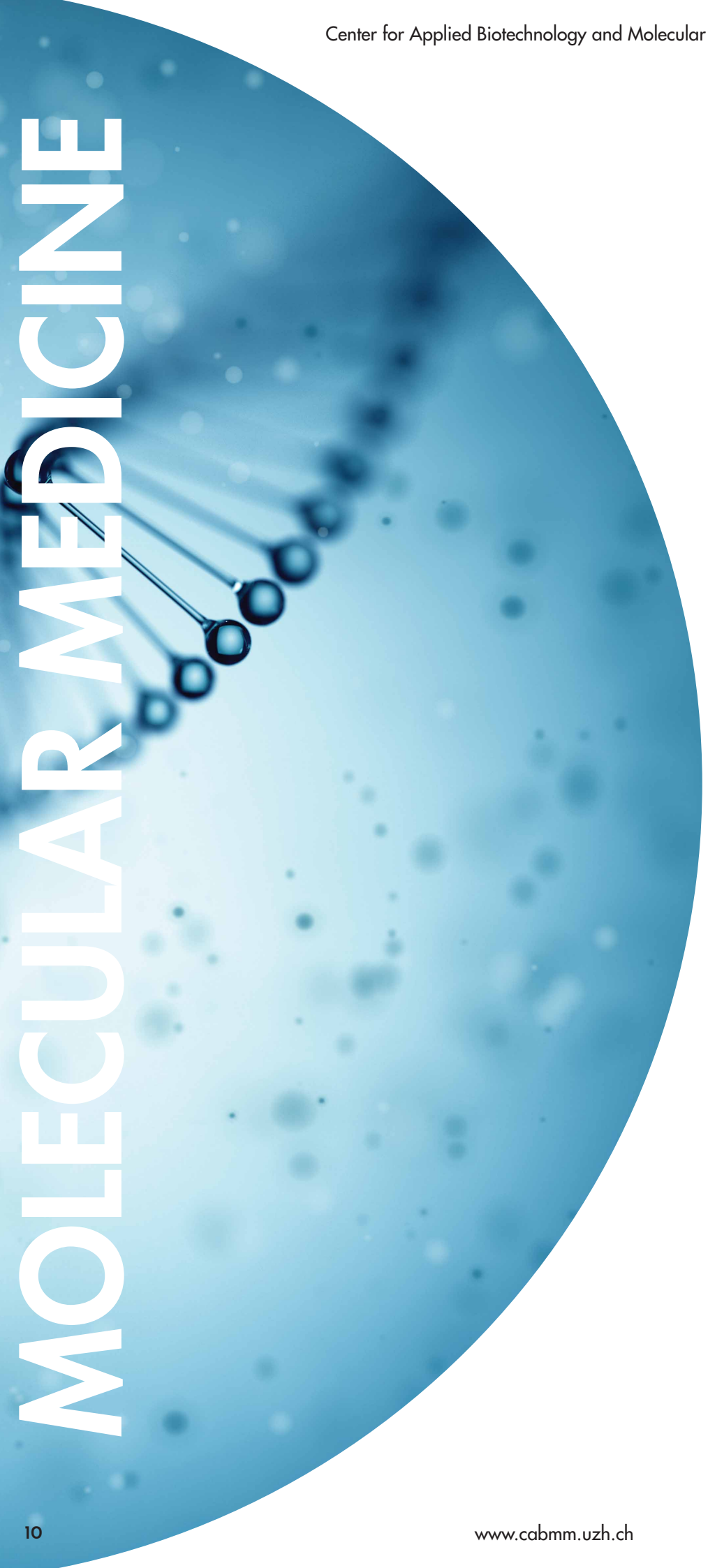


Molecular medicine

In this application field, the molecular control mechanisms that should be replaced, supported or modulated by biotechnology products in diseased organs are investigated. Understanding of the functionality and local molecular needs of organs in different states of diseases may lead to the development of new treatment strategies using replacement tissues or biotechnology products.

This application field also comprises research on release mechanisms such as local drug delivery systems, targeting local and systemic control mechanisms as well as gene therapy.

Members of this application field in alphabetical order

Achermann, Yvonne PD Dr med

Altmeyer, Matthias Professor Dr (PhD)

Borel, Nicole Professor Dr med vet

Cinelli, Paolo PD Dr (PhD)

Dip, Ramiro PD Dr med vet, PhD

Fraefel, Cornel Professor Dr (PhD)

Gay, Steffen Professor Dr med

Hofmann-Lehmann, Regina Professor Dr med vet

Hottiger, Michael Professor Dr med vet, PhD

Ospelt, Caroline PD Dr med, PhD

Reichenbach, Janine Professor Dr med

Rohrer Bley, Carla Professor Dr med vet

Santoro, Raffaella PD Dr (PhD)

Zinkernagel, Annelies Professor Dr med

Status: 31 December 2017

Regenerative medicine

In this application field, research focuses on the generation and optimisation of replacement tissues *in vitro* and their subsequent surgical implantation *in vivo*.

Research includes determination of the optimal living conditions of replacement tissues, set up and optimisation of bioreactor and cell culture conditions, as well as investigation of suitable scaffolds and matrices as structural basis.

Additionally, the regeneration of organs by cell transplantation is investigated (e.g. organ regeneration after injection of mesenchymal stem cells).

Members of this application field in alphabetical order

Ahmad, Sufian Dr med

Calcagni, Maurizio PD Dr med

Ferguson, Stephen Professor Dr (PhD)

Franco-Obregón, Alfredo Dr (PhD)

Gantenbein, Benjamin Professor Dr (PhD)

Giraud, Marie-Noëlle PD Dr (PhD)

Hoerstrup, Simon Professor Dr med, PhD

Loibl, Markus PD Dr med

Müller, Ralph Professor Dr (PhD)

Richards, Peter PD Dr (PhD)

Salzmann, Gian Professor Dr med

Snedeker, Jess Professor Dr (PhD)

Stoyanov, Jivko PD Dr (PhD)

Vogel, Viola Professor Dr (PhD)

Weber, Benedikt PD Dr med, PhD

Würtz-Kozak, Karin Professor Dr (PhD)

Zenobi-Wong, Marcy Professor Dr (PhD)

Status: 31 December 2017

Applied biotechnology

This application field comprises the design and development of 'intelligent biotechnology products' for tissue engineering. For this purpose, material science is mainly employed, but approaches based on nanotechnology and pharmaceutics are also used. Molecular surface structures of implant materials and scaffolds are modified and, subsequently, their effect on the induction and conduction of the body's own cells is investigated.

Furthermore, local drug release and drug targeting systems are developed.

Members of this application field in alphabetical order

Bode, Jeffrey Professor Dr (PhD)

Stark, Wendelin Professor Dr (PhD)

Studart, André Professor Dr (PhD)

Weber, Franz Professor Dr (PhD)

Status: 31 December 2017

CABMM Research Platform

Amongst other strategic goals, the CABMM aims to promote scientific collaborations, in particular between clinicians and basic research, and to extend and optimise methodological knowhow and use of specific infrastructure. Therefore, the CABMM has its own research platform accommodated within the DMMD at the University of Zurich.

The CABMM Research Platform consists of two laboratories and one cell culture lab. All CABMM members have the possibility to rent a place on the CABMM Research Platform for one or more of their group members – preferably for young scientists – and, thus, to offer them the possibility to actively collaborate, share, and improve their knowledge by using the interdisciplinary research network and expertise of the CABMM.

On the CABMM Research Platform, basic scientists, veterinarians and clinicians are working closely together and discussing their research projects. In order to optimise collaborations between platform users, we are organising platform meetings and scientific seminar series to get valuable insights into the research and methodology of other research groups. This creates a stimulating environment and builds a bridge between basic science and clinical problems, resulting in applied and translational research.

The CABMM Research Platform has been intensively used since the creation of the CABMM in 2008. Overall, 14 research groups from different fields of natural sciences, human medicine or veterinary medicine have used our research platform for different time periods. In summary, almost 50 people – among them group leaders, postdocs, PhD students, veterinary doctoral students, diploma students, technicians, veterinarians, and others – conducted or still conduct their research projects on the CABMM Research Platform.

The quality of the research performed is evidenced by eight successful completed PhD theses, ranging from topics related to human diseases (like intervertebral disc degeneration or bone development and osteoporosis) to problems in veterinarian medicine, e.g. equine tendon healing. Furthermore, more than 90 peer-reviewed research articles were published in scientific journals describing projects that were investigated on the CABMM Research Platform.

Research groups

Due to the diversity of the research topics investigated on the CABMM Research Platform, we would like to briefly introduce all the groups that have used our platform during the previous years:

Bone and Stem Cell Research Group (PD Dr Peter J Richards (PhD))

The main interest of the Bone and Stem Cell Research Group is related to musculoskeletal biology and disease (e.g. bone, cartilage, tendon, spine) with a main focus on bone research. Additionally, the group specialises in multipotent stromal cell (MSC) research, investigating the regulatory mechanisms controlling osteogenic, chondrogenic and adipogenic lineage commitment. One of the main focuses has been on the functional role of the serine protease HtrA1, which is thought to play an important role in a variety of normal and pathological conditions. To date, the group has confirmed HtrA1 as being centrally involved in modulating MSC osteogenesis and adipogenesis and may, therefore, be of relevance when considering the underlying processes governing adipose and bone tissue disease.

Cancer Epigenome Group (Professor Dr med vet Michael O Hottiger, PhD)

Disruption of the epigenome, as a result of alterations in epigenetic regulators, is a fundamental mechanism in oncogenesis. Elucidating the networks of these regulators in different cancer types will provide further understanding of the interplay between genetic and epigenetic alterations and, with thus, allow for the development of epigenome-targeted therapeutic strategies. The goal of the Cancer Epigenome Group is therefore to investigate epigenetic regulators by performing a high-throughput drug screen on patient-derived cancer cells with epigenetic inhibitors alone or synergised with first-line anticancer drugs. Pharmacological profiles will then be linked to detailed epigenetic characterisation to describe the molecular mechanisms of drug response,

as well as to allow for the identification of predictors of drug sensitivity.

Cranio-Maxillofacial Surgery and Implantology Group (Professor Dr med vet Brigitte von Rechenberg)

The group's main research interest and expertise is in dental implantology and laser medicine in oral and maxillofacial surgery. Current research activities focus on the development and biological analysis of new and innovative treatment options and techniques for bone regeneration and reconstruction. The influence of laser osteotomy and piezoelectric bone cutting on bone remodelling, inflammatory processes and bone resorption is evaluated to gain further insight into basic tissue interaction mechanisms and to define the best parameters, as well as advantages/limitations of each technique. The final aim is to attain newly arranged and self-stabilising osteotomies, not only in oral and maxillofacial surgery but also in orthopaedics and other medical disciplines.

Equine Research Group (Professor Dr med vet Anton Fürst)

Orthopaedic injuries account for the majority of career-limiting diseases in horses used for athletic purposes, ranging from pleasure riding to high-performance sport endeavours. Unfortunately, successful outcome in equine orthopaedics is commonly hindered by the slow regeneration or even incomplete reparation of mesenchymal tissues. For example, equine fracture patients commonly suffer from delayed bony union, horses with subchondral cystic lesions often show incomplete regeneration of the bony defect, even after surgical debridement, and horses with tendon injuries require a very long phase of convalescence and still have a high risk of re-injury because of insufficient/minor-quality repair tissue. Therefore, the group aims to study and develop regenerative methods to improve healing of injured musculoskeletal tissue.

Genome Accessibility and Modification Group (Professor Dr Matthias Altmeyer (PhD))

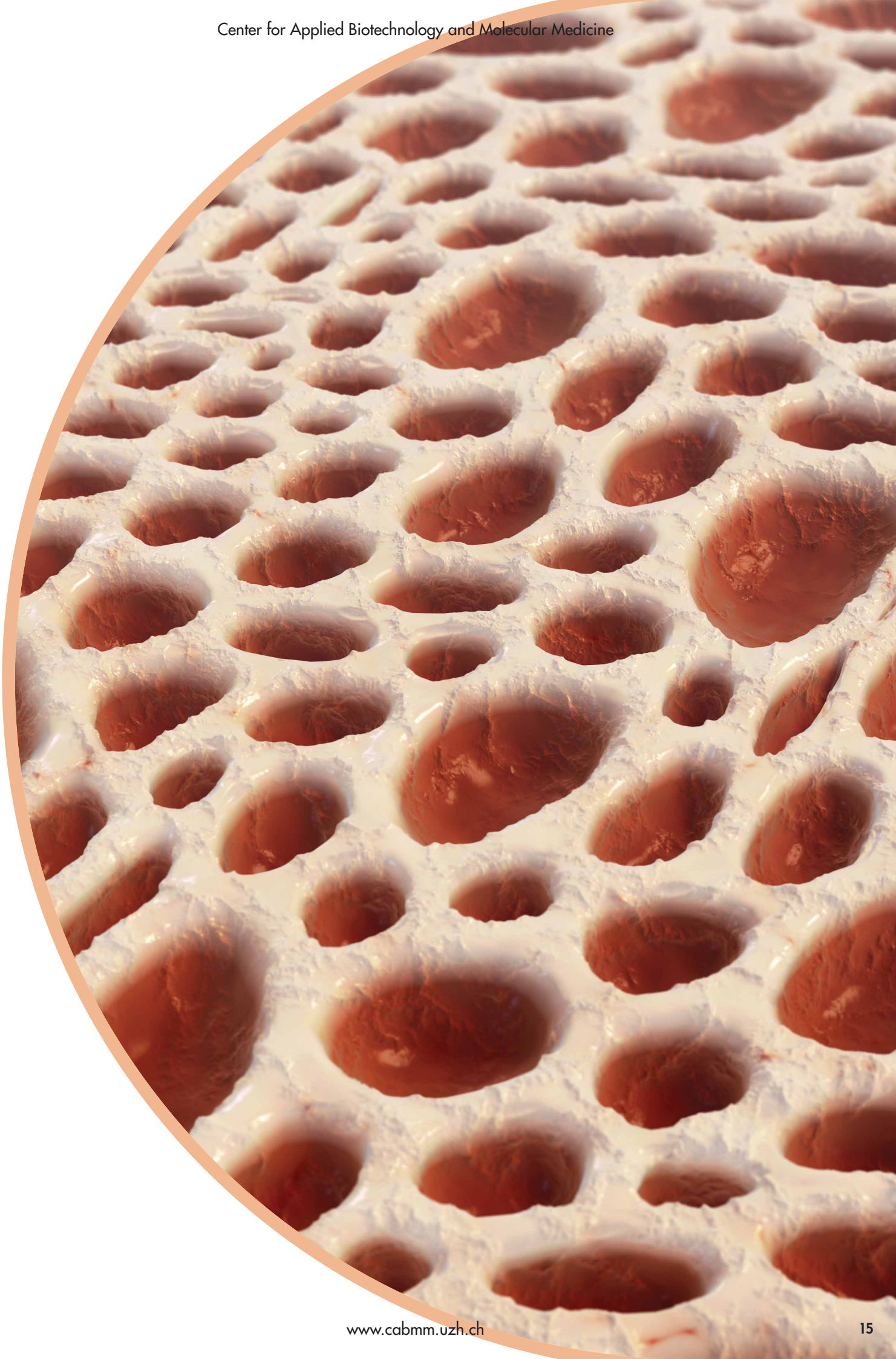
Gene therapy holds the possibility to revolutionise the way otherwise incurable genetic diseases are treated. In principle, it allows for the DNA within a cell to be changed. With the dawn of new gene editing technologies such as CRISPR-Cas9, repairing mutations within human cells has become reality. Our ability to programme this bacterial defence mechanism with human target sequences has unlocked unprecedented possibilities for gene therapy and personalised medicine. While CRISPR-Cas9 has made gene editing by homologous recombination easier, its efficiency remains poor. The focus of the Genome Accessibility and Modification Group is to increase the efficiency of gene editing using CRISPR-Cas9 by making the cell's genome more accessible to the editing machinery to enhance the rate of genome integrations.

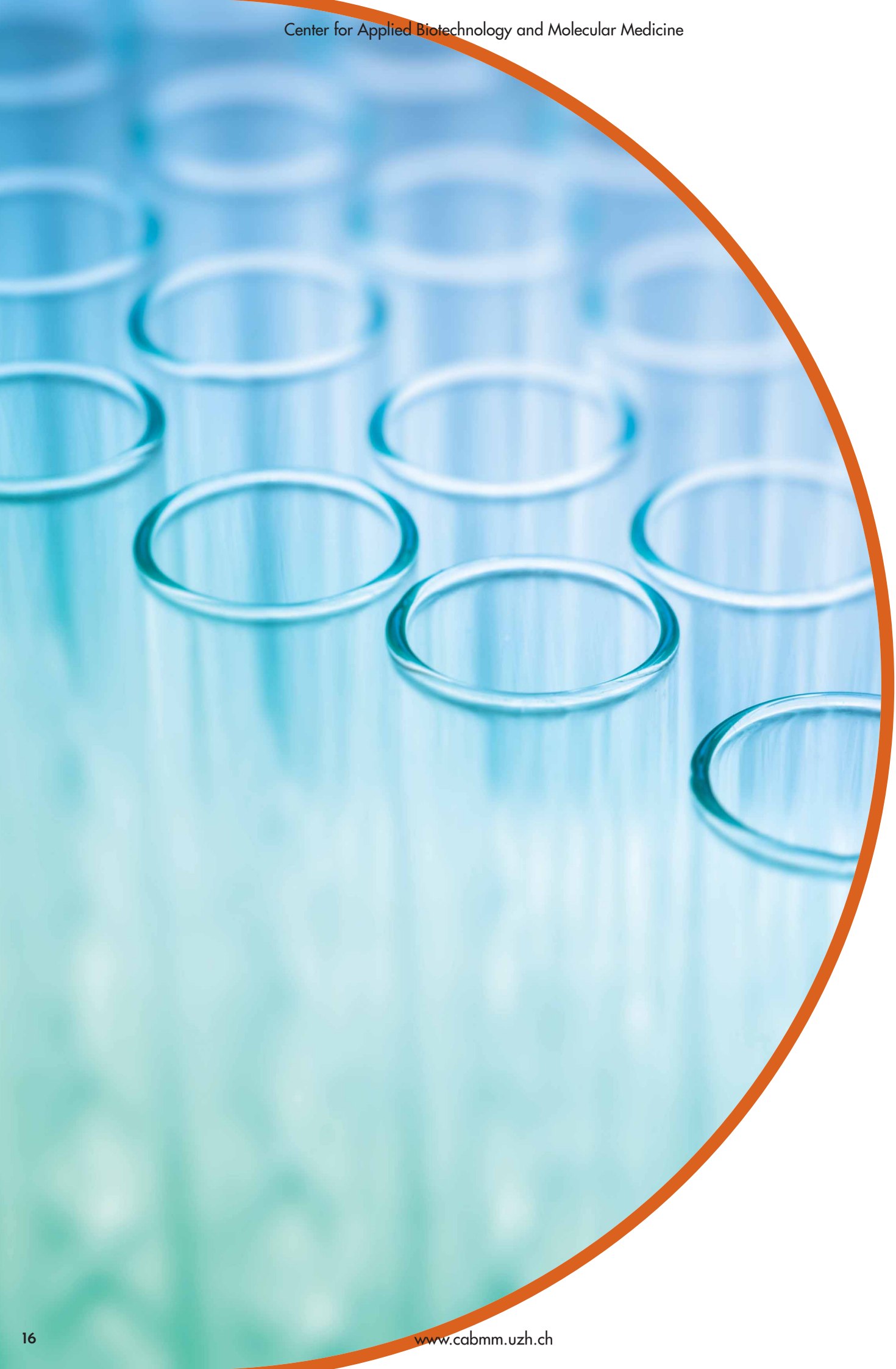
Interventional Work Research (Professor Dr med Daniel A Rüfenacht)

The Interventional Work Research (IWR) group is interested in the understanding, imaging and visualisation of neurovascular diseases and their minimally invasive treatment options. Research focuses on vessel wall pathologies, in particular on intracranial aneurysms, arteriovenous malformation and vascular dementia. The biological pathways of interest include cellular regulation chains concerning angiogenesis and degeneration. Translational research efforts comprise the support of exploratory workshops, multiscale modelling and methods connecting biomechanics with biological effects at the cellular and organ system level. Furthermore, the group supports the establishment of a sustainable databank for neurovascular diseases (AneuX, SwissNeuroFoundation).

Musculoskeletal Research Unit (Professor Dr med vet Brigitte von Rechenberg)

The Musculoskeletal Research Unit (MSRU) is specialised in the design, implementation and evaluation of *in vivo* preclinical investigations, particularly in large animal models. The areas of investigation centre on the musculoskeletal system but also extend to cardiovascular and wound healing applications. The group has also established expertise in histology processing and analysis, including non-decalcified plastic embedded ground and thin sections, cryosections, paraffin embedded sections, as well as immunohistochemistry. The MSRU was confirmed to be GLP compliant by Swissmedic in 2014. Thus, together with GMP at the Institute for Regenerative Medicine (IREM) and GCP at the University Hospital, the University of Zurich is now able to offer the complete quality chain for research and development of new therapeutics.





Ocular Cell Biology Group (Professor Dr med Farhad Hafezi, PhD)

The Ocular Cell Biology Group works on a number of clinical and experimental research projects, with the aim to develop new and innovative therapeutic approaches for ocular diseases, mainly related to the cornea. Main research interests are corneal wound healing, corneal infection, ocular biomechanics, and progressive myopia. The common link among these interests is the treatment modality of corneal cross-linking (CXL). CXL mechanically stiffens the cornea by photopolymerisation: the combination of UV light to deliver energy and riboflavin (vitamin B2) as a substance inducing cross-links in collagen has been established clinically in the early 2000s. The aim of the OCB group is to optimise currently used treatment parameters to make the treatment more efficient and accessible outside of the operating theatre.

Radiation Oncology Group (Professor Dr med vet Carla Rohrer Bley)

Radiotherapy remains one of the major treatment options in human and veterinary cancer treatment. However, many solid tumours are radiation resistant. Thermoradiotherapy combines radiotherapy with hyperthermia (41-43°C) and is used clinically in particular cases of human and canine cancer. Hyperthermia is provoking changes in the tumour microenvironment by increasing perfusion and oxygenation and at the cellular level by the induction of cell death and the inhibition of DNA repair mechanisms. These changes increase the efficacy of radiation treatment towards a better tumour response, but the underlying molecular mechanisms have not yet been fully elucidated. The aim of the Radiation Oncology Group is to investigate the sensitivity of human and canine cell lines towards thermoradiotherapy and to determine involved molecules.

Skin Engineering Group (PD Dr med Maurizio Calcagni)

Standard treatment of large burn wounds is based on the pioneering work of Rheinwald and Green in the 1970s, where small areas of the patient`s intact skin are used to cultivate cultured epidermal autografts. Nevertheless, disadvantages of the procedure include the use of several animal components during cultivation and a very short time window for transplantation. The Skin Engineering Group aims to produce reliable, safe, traceable autologous keratinocyte sheets, without using feeder cells of animal origin and bovine serum to treat patients in the burn unit, all the while providing the surgeons with a window of flexibility in order to optimise the grafting date to the health of the patient. The project also aims to characterise and better understand how keratinocyte sheets can enhance the wound bed and accelerate wound healing.

Spine Research Group (Professor Dr Karin Würtz-Kozak (PhD))

Back pain is one of the most cost-intensive health problems in the world, with an extremely high prevalence. One specific form of back pain is called discogenic back pain, which can arise under certain degenerative conditions. Disc degeneration is a complex process, but a common feature is the accumulation of specific matrix degradation products (e.g. fragmentation products), although quality and quantity of degeneration products can differ in a group with a similar degree of degeneration. Based on this observation, the overall interest of the Spine Research Group is to elucidate cellular mechanisms during degeneration that may underlie the development of discogenic back pain; this knowledge could be used to develop novel treatment options, e.g. the use of bio-drugs in a minimally invasive manner.

Tendon Repair Group (Professor Dr med vet Anton Fürst)

Tendon injuries are a common cause of lameness and wastage in horses. The conventional and most widely spread therapy for tendonitis in the horse involves administration of anti-inflammatory drugs and introduction of a controlled exercise programme adjusted by regular ultrasonographic examinations. However, the healing process is very slow and results in the formation of scar tissue, which is functionally inferior compared to normal tendon tissue. This has important consequences for the animal in terms of reduced performance and a substantial risk of re-injury. The aim of the Tendon Repair Group is to develop cell-based treatment strategies to enhance tendon healing in the horse, resulting in a shorter convalescence period and an improved quality of repaired tissue, thereby reducing the risk of relapse.

CABMM Start-up Grant

The CABMM Start-up Grant is a peer-reviewed funding programme designed to support collaborative research projects and, thus, to strengthen the CABMM network and to promote new collaborations between CABMM members.

The establishment of the CABMM Start-up Grant was made possible through the generous financial support of the Mäxi Foundation. It supports novel projects within the musculoskeletal and the cardiovascular field, with emphasis being placed on proof-of-principle, high-risk studies, which would most likely not be supported by other more competitive funding agencies. It is expected that the findings generated from these initial studies should be sufficient to enable further applications to be submitted to other funding agencies.

We offer the opportunity to all CABMM members to apply twice a year for such preliminary studies. The applicants can receive a maximum amount of CHF 40,000 (~€33,838) over a period of one year.

The peer-review process of grant proposals involves pre-review for compliance with the general and structural requirements, and initial scientific screening by the CABMM Steering Committee, followed by expert evaluation by the CABMM Scientific Advisory Board. The evaluation criteria include, amongst other things, originality of the problem(s) addressed; scientific and technical excellence of the proposal and the team; as well as relevance to the objectives of the CABMM, e.g. translational character of the proposal, collaborations between CABMM members; and creation of additional value for our network.

Since its conception in 2010, the CABMM Start-up Grant has funded a total of 43 projects with an overall amount of nearly CHF 1.5m (CHF 1,453,222.40). So far, 20 associated articles have successfully been published in peer-reviewed scientific journals, illustrating the importance of our funding programme as well as the scientific excellence of the supported projects. Additionally, the results obtained in those preliminary studies have allowed in several cases for the support of continuative studies by larger funding agencies, proving our strategy successful.

Because of the multifaceted research of our members it is impractical to summarise all projects supported by a CABMM Start-up Grant, and, due to the high number of funded studies, it is also not possible to describe all of them in detail. That is why we decided to provide short descriptions of two selected projects supported by our funding programme – one of the first funded projects and one that was published in the high-ranked journal *Nature Communications*. In addition, you will find a list of all publications associated with the CABMM Start-up Grant.

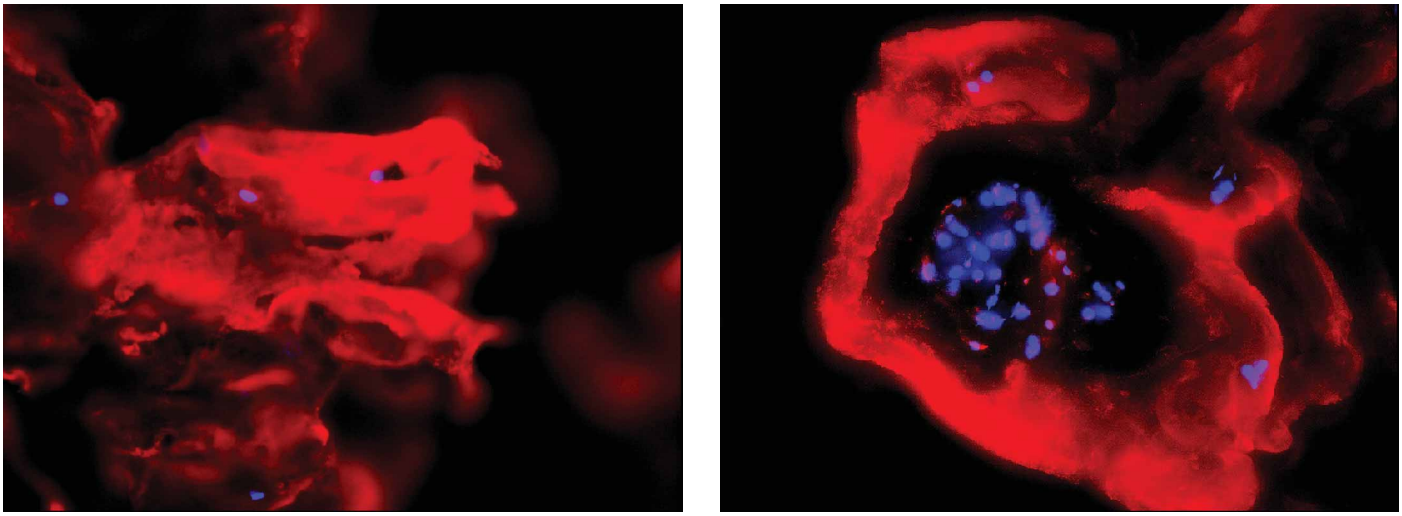
CABMM Start-up Grant project: 'Role of serine protease HTRA1 in spinal disc degeneration'

Principal investigator:
PD Dr Peter Richards

Collaborator:
Professor Dr Karin Würtz-Kozak

Human HTRA1 is a highly conserved secreted serine protease that degrades numerous extracellular matrix (ECM) proteins. We have previously identified HTRA1 as being upregulated in osteoarthritic patients and as having the potential to regulate matrix metalloproteinase (MMP) expression in synovial fibroblasts through the generation of fibronectin fragments.

In the present report, we have extended these studies and investigated the role of HTRA1 in the pathogenesis of intervertebral disc (IVD) degeneration. HTRA1 mRNA expression was significantly elevated in degenerated disc tissue and was associated with increased protein levels. However, these increases did not correlate with the appearance of rs11200638 single



Immunofluorescence staining of HTRA1 in degenerated IVDs

nucleotide polymorphism (SNP) in the promoter region of the HTRA1 gene, as previously suggested. Recombinant HTRA1 induced MMP production in IVD cell cultures through a mechanism critically dependent on MEK, but independent of IL-1β signalling. The use of a catalytically inactive mutant confirmed these effects to be primarily due to HTRA1 serine protease activity. HTRA1-induced fibronectin proteolysis resulted in the generation of various sized fragments which, when added to IVD cells in culture, caused a significant increase in MMP expression.

Furthermore, one of these fragments was identified as being the amino-terminal fibrin- and heparin-binding domain, and was also found to be increased within HTRA1-treated IVD cell cultures as well as in disc tissue from patients with IVD degeneration.

Our results therefore support a scenario in which HTRA1 promotes IVD degeneration through the proteolytic cleavage of fibronectin and subsequent activation of resident disc cells.

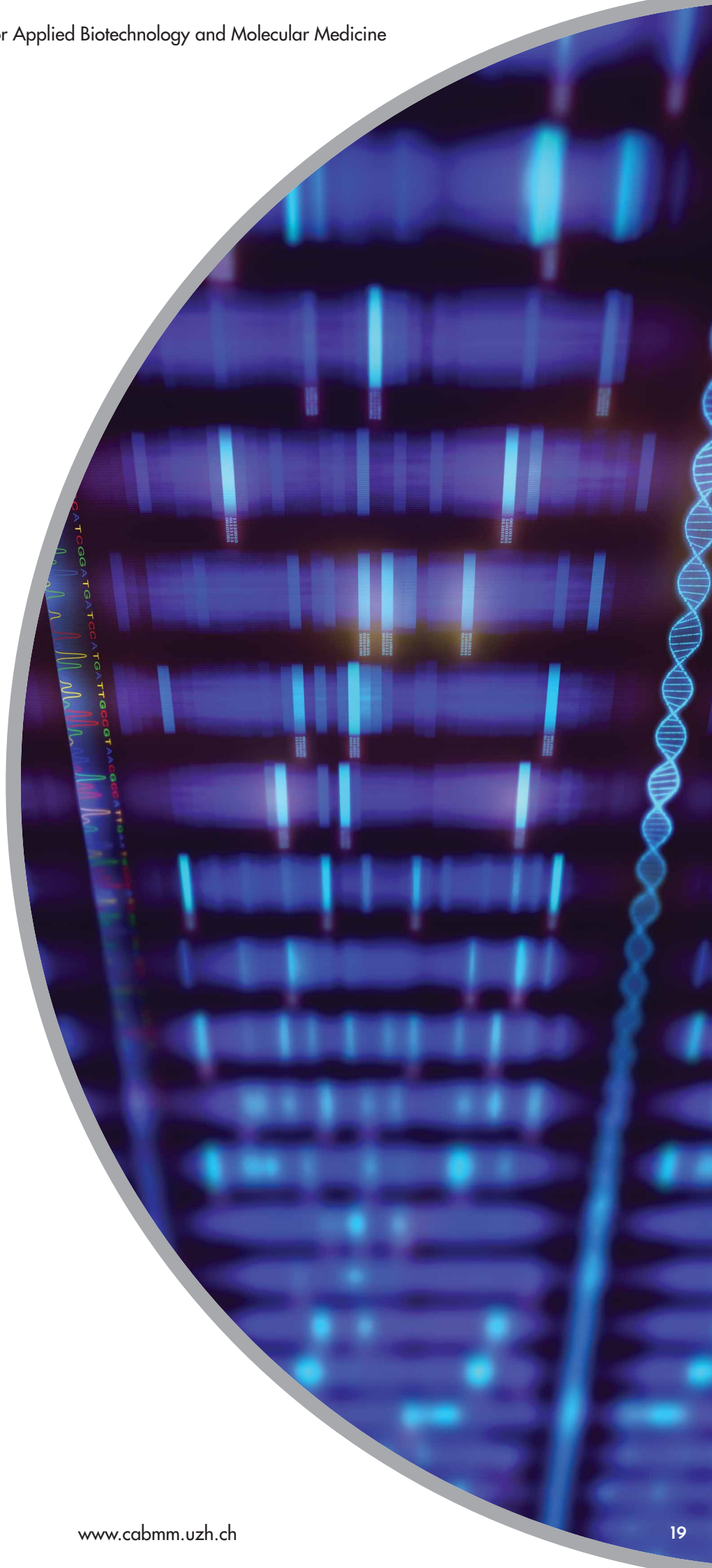
Associated publication: Tiaden AN *et al.* A detrimental role for human high temperature requirement serine protease A1 (HTRA1) in the pathogenesis of intervertebral disc (IVD) degeneration. *J Biol Chem.* 2012;287(25):21335-45.

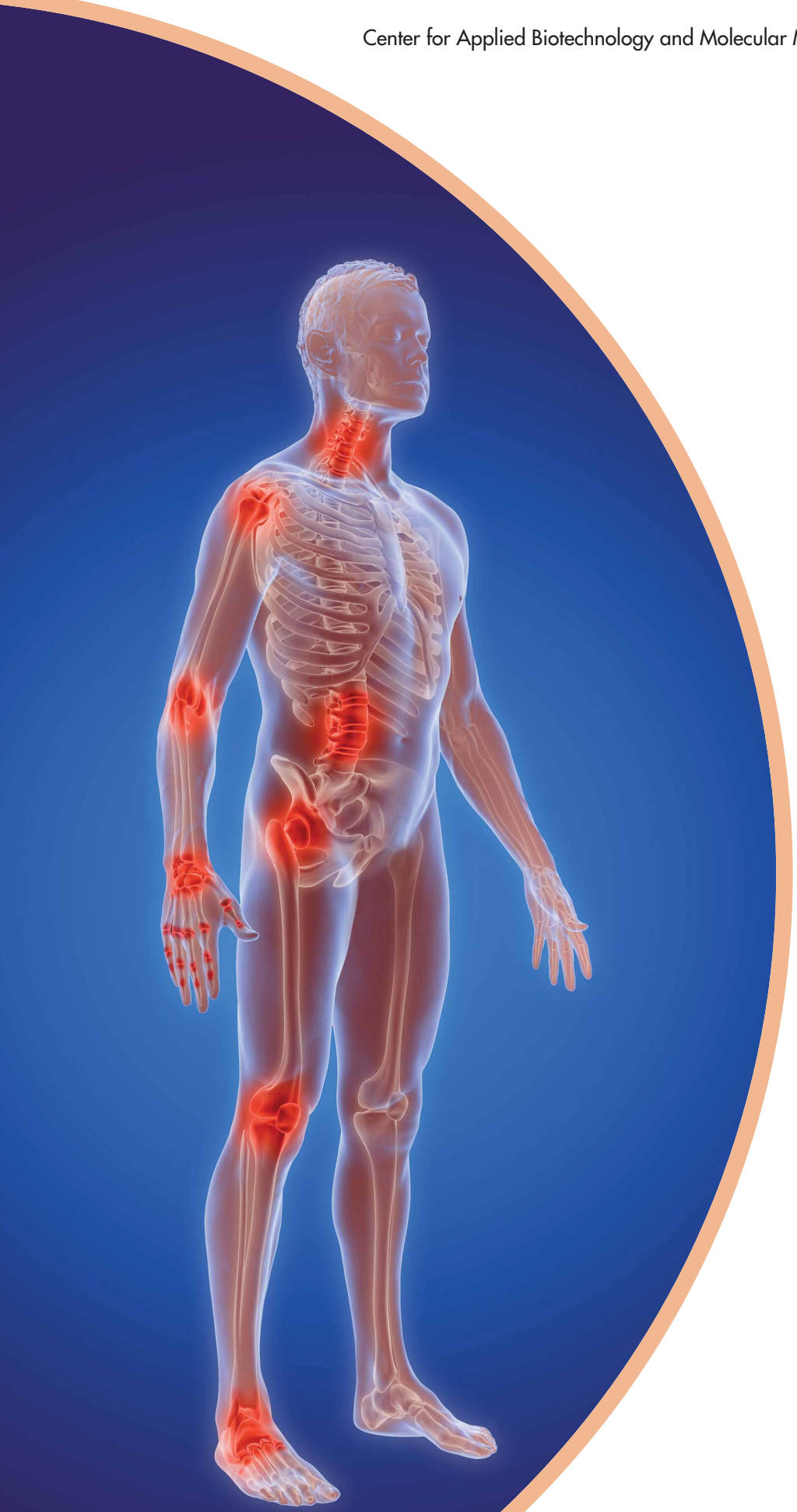
CABMM Start-up Grant project: 'Analysis of topographic differences in synovial fibroblasts'

Principal investigator:
PD Dr Dr Caroline Ospelt

Collaborator:
Professor Dr Dr Michael Hottiger

Background: Most forms of arthritis occur with a distinctive pattern of joint involvement. Molecular mechanisms explaining the predominance of certain forms of arthritis in specific joint locations are, however, not known. Synovial fibroblasts (SFs), the resident stromal cells of the synovium, are major effectors of joint inflammation and destruction by producing pro-inflammatory mediators and matrix-degrading enzymes.



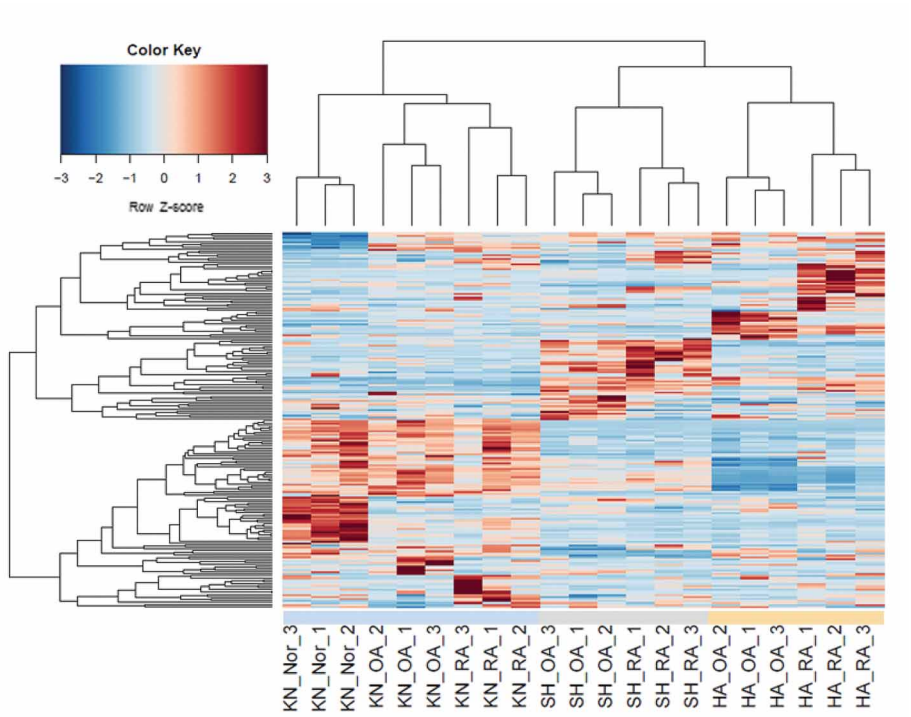


Aim: We hypothesised that SFs taken from different joints show a site-specific gene expression pattern, which could explain why some joints are more likely to be affected by certain arthritides than others.

Results: By using RNA sequencing we could detect significant differences in gene expression in SFs cultured from knee, shoulder or hand joints. Unsupervised, hierarchical cluster analysis showed clustering of human SFs, first according to joint location and then according to disease (rheumatoid arthritis (RA), osteoarthritis (OA), and non-arthritic joint pain). Positional expression was mainly evident in transcripts encoded in the HOX clusters, which are well known for their role in embryonic limb development. The expression of this positional HOX code could be confirmed in more human joints (elbows, hips, ankles) in SFs, as well as in whole synovial tissues and also in mouse joints. We could show that the expression of the positional HOX code is maintained via DNA methylation and histone modifications, in particular histone acetylation and H3K27me3 repressive marks. In functional assays, we found differences in chemotaxis, cell adhesion and proliferation between SFs from different joints. Also, different expression of matrix-metalloproteinases being responsible for matrix-degradation by SFs could be confirmed by real-time PCR measurements.

Conclusion: SFs from joints of different anatomic sites exhibit substantial differences in gene expression, suggesting that functionally distinct subsets of SFs populate different joints. These joint-specific SF phenotypes probably create a unique microenvironment in each joint, which determines the susceptibility of certain synovial joints to develop specific forms of arthritis.

Associated publication: Frank-Bertoncelj M *et al.* Epigenetically-driven anatomical diversity of synovial fibroblasts guides joint-specific fibroblast functions. *Nat Commun.* 2017 Mar 23;8:14852.



Supervised cluster analysis based on the top 25 non-redundant, most differentially expressed transcripts in pair-wise comparisons between joint locations (knee, shoulder, hand) and diagnosis (RA, OA, norm)

CABMM Start-up Grant-associated publications (in chronological order)

1) Guetg C *et al.* Inheritance of silent rDNA chromatin is mediated by PARP1 via noncoding RNA. *Mol Cell.* 2012 Mar 30;45(6):790-800.

2) Tiaden AN *et al.* Detrimental role for human high temperature requirement serine protease A1 (HTRA1) in the pathogenesis of intervertebral disc (IVD) degeneration. *J Biol Chem.* 2012 Jun 15;287(25):21335-45.

3) Tiaden AN *et al.* Human serine protease HTRA1 positively regulates osteogenesis of human bone marrow-derived mesenchymal stem cells and mineralization of differentiating bone-forming cells through the modulation of extracellular matrix protein. *Stem Cells.* 2012 Oct;30(10):2271-82.

4) Lindtner RA *et al.* Osteoanabolic effect of alendronate and zoledronate on bone marrow stromal cells (BMSCs) isolated from aged female osteoporotic patients and its implications for their mode of action in the treatment of age-related bone loss. *Osteoporosis Int.* 2014 Mar,25(3):1151-61.

5) Klawitter M *et al.* Expression and regulation of toll-like receptors (TLRs) in human intervertebral disc cells. *Eur Spine J.* 2014 Sep;23(9):1878-91.

6) Gantenbein B *et al.* Activation of intervertebral disc cells by co-culture with notochordal cells, conditioned medium and hypoxia. *BMC Musculoskelet Disord.* 2014 Dec 11;15:422.

7) Robaszkiewicz A *et al.* ARTD1 regulates osteoclastogenesis and bone homeostasis by dampening NF-κB-dependent transcription of IL-1β . *Sci Rep.* 2016 Feb 17;6:21131.

8) Krupkova O *et al.* An inflammatory nucleus pulposus tissue culture model to test molecular regenerative therapies: validation with epigallocatechin 3-gallate. *Int J Mol Sci.* 2016 Sep 27;17(10).

9) Kuemmerle JM *et al.* Identification of Novel Equine (Equus caballus) Tendon Markers Using RNA Sequencing. *Genes* (Basel). 2016 Nov 10;7(11).

10) Broguiere N *et al.* Factor XIII Cross-Linked Hyaluronan Hydrogels for Cartilage Tissue Engineering. *ACS Biomater Sci Eng.* 2016;2(12):2176-2184.

11) Krupkova O *et al.* The Natural Polyphenol Epigallocatechin Gallate Protects Intervertebral Disc Cells from Oxidative Stress. *Oxid Med Cell Longev.* 2016;2016:7031397.

12) Ghayor C *et al.* N,N Dimethylacetamide a drug excipient that acts as bromodomain ligand for osteoporosis treatment. *Sci Rep.* 2017 Feb 8;7:42108.

13) Frank-Bertoncelj M *et al.* Epigenetically-driven anatomical diversity of synovial fibroblasts guides joint-specific fibroblast functions. *Nat Commun.* 2017 Mar 23;8:14852.

14) Mirsaidi A *et al.* Prostaglandin E2 inhibits matrix mineralization by human bone marrow stromal cell-derived osteoblasts via Epac-dependent cAMP signaling. *Sci Rep.* 2017 May 22;7(1):2243.

15) Öztürk E *et al.* Hypoxia regulates RhoA and Wnt/β-catenin signaling in a context-dependent way to control re-differentiation of chondrocytes. *Sci Rep.* 2017 Aug 22;7(1):9032.

16) Studer D *et al.* Human chondroprogenitors in alginate-collagen hybrid scaffolds produce stable cartilage in vivo. *J Tissue Eng Regen Med.* 2017 Nov;11(11):3014-3026.

17) Öztürk E *et al.* RhoA activation and nuclearization marks loss of chondrocyte phenotype in crosstalk with Wnt pathway. *Exp Cell Res.* 2017 Nov 15;360(2):113-124.

18) Krismer AM *et al.* Biologic response of human anterior cruciate ligamentocytes on collagen-patches to platelet-rich plasma formulations with and without leucocytes. *J Orthop Res.* 2017 Dec;35(12):2733-2739.

19) Monchaux M *et al.* Inflammatory Processes Associated with Canine Intervertebral Disc Herniation. *Front Immunol.* 2017 Dec 4;8:1681.

20) Bertolo A *et al.* Increased motility of mesenchymal stem cells is correlated with inhibition of stimulated peripheral blood mononuclear cells in vitro. *J Stem Cells Regen Med.* 2017 Dec 18;13(2):62-74.

CABMM key people

Brigitte von Rechenberg
Professor Dr med vet,
Dipl ECVS
Founder, CABMM and
chairwoman, CABMM
Steering Committee

Institution:
Musculoskeletal Research
Unit (MSRU), Vetsuisse
Faculty, University of Zurich

Our main interest is in musculoskeletal research, focusing on bone and cartilage. We investigate fracture and defect healing with or without the application of biomaterials/biomimetics, the influence of inflammation in bone and cartilage healing, and the importance of physiological remodelling of subchondral bone and cartilage. At the same time, we have embarked in wound healing of deep and infected skin wounds. Furthermore, as an experimental animal facility, we have received GLP accreditation by the Swiss Medic in 2014 and, in this capacity, we have broadened our scope to other fields of experimental medicine, as well.

Simon P Hoerstrup
Professor Dr med Dr rer nat
Founder, CABMM and
member, CABMM Steering
Committee

Institution:
Institute for Regenerative
Medicine, University of
Zurich; and Wyss Zurich,
ETH and University of Zurich

The research expertise of Professor Simon P Hoerstrup lies in the fields of: 1) tissue engineering, including engineered blood vessels, heart valves, and microscale strategies for myocardial regeneration; (2) regenerative medicine, e.g. development of cell-based implants out of *in vitro* generated microtissues to improve myocardial functionality of the diseased heart; and 3) disease modelling, e.g. studying inflammatory processes that occur in the early development of arteriosclerosis.

Michael O Hottiger
Professor Dr med vet Dr Phil II
Founder, CABMM and
vice-chairman, CABMM
Steering Committee

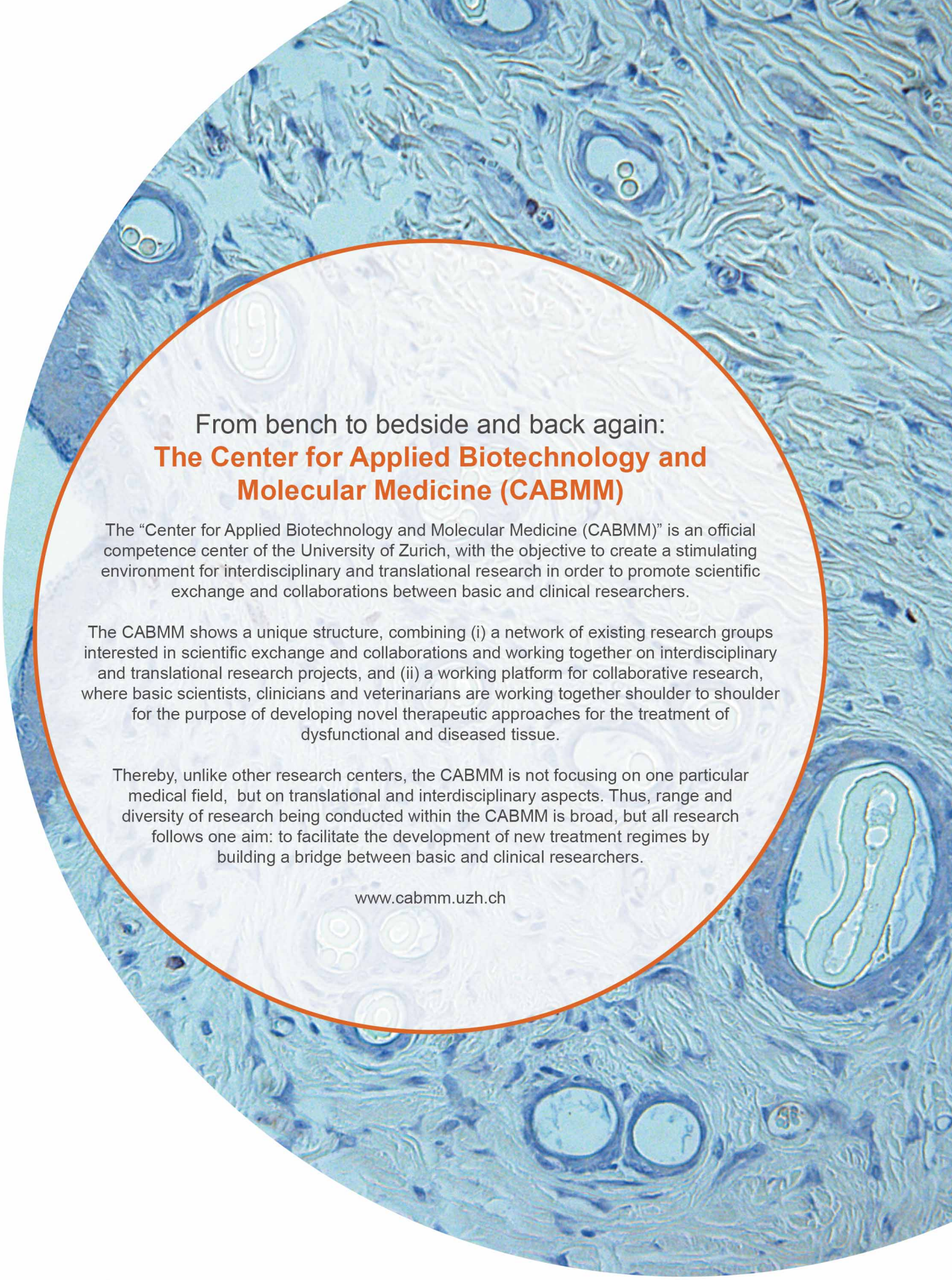
Institution:
Department of Molecular
Mechanisms of Disease,
University of Zurich

Inflammation is the biological response of tissues to harmful stimuli such as pathogens, damaged cells or irritants. It is a protective attempt of the organism to remove the injurious stimuli and to initiate the healing process. My laboratory is interested in the molecular mechanisms that regulate inflammation. In particular, we investigate the regulation of inflammation by post-translational modifications of proteins. Our current work focuses on the activation and function of the enzymes that catalyse these protein modifications (e.g. ADP-ribosylation) and the identification of their target proteins.

Silke Kalchofner-Mark
Dr rer nat
Managing director,
CABMM

Institution:
CABMM, University of Zurich

Silke Kalchofner-Mark is a biochemist with profound expertise in protein biochemistry and a particular interest in bone and spine research. In her position as managing director of the CABMM, she takes care of all administrative and managerial tasks. This includes management of the CABMM Research Platform, financial and personnel administration, as well as support of the member network. Furthermore, she is responsible for the organisation and moderation of scientific conferences and teaching events, as well as all concerns regarding public relations.



From bench to bedside and back again:

The Center for Applied Biotechnology and Molecular Medicine (CABMM)

The “Center for Applied Biotechnology and Molecular Medicine (CABMM)” is an official competence center of the University of Zurich, with the objective to create a stimulating environment for interdisciplinary and translational research in order to promote scientific exchange and collaborations between basic and clinical researchers.

The CABMM shows a unique structure, combining (i) a network of existing research groups interested in scientific exchange and collaborations and working together on interdisciplinary and translational research projects, and (ii) a working platform for collaborative research, where basic scientists, clinicians and veterinarians are working together shoulder to shoulder for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissue.

Thereby, unlike other research centers, the CABMM is not focusing on one particular medical field, but on translational and interdisciplinary aspects. Thus, range and diversity of research being conducted within the CABMM is broad, but all research follows one aim: to facilitate the development of new treatment regimes by building a bridge between basic and clinical researchers.

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center for applied biotechnology and molecular medicine

University of Zurich[UZH]

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