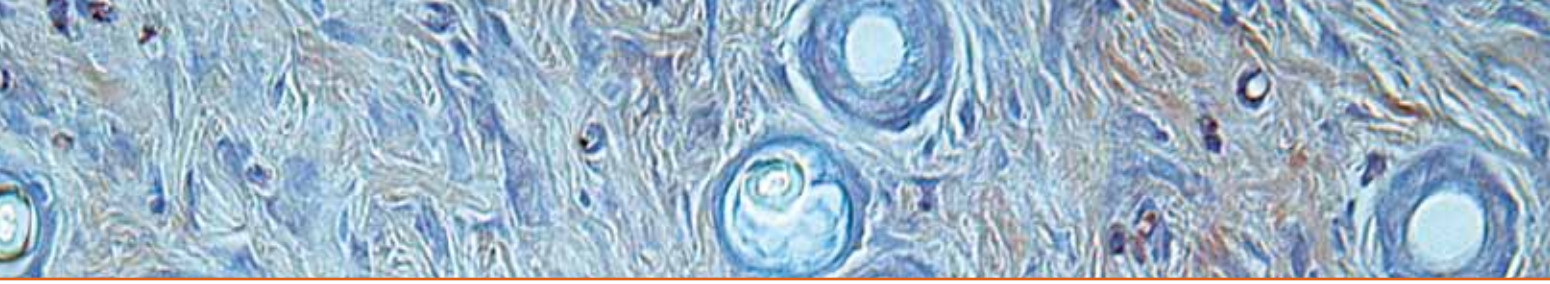
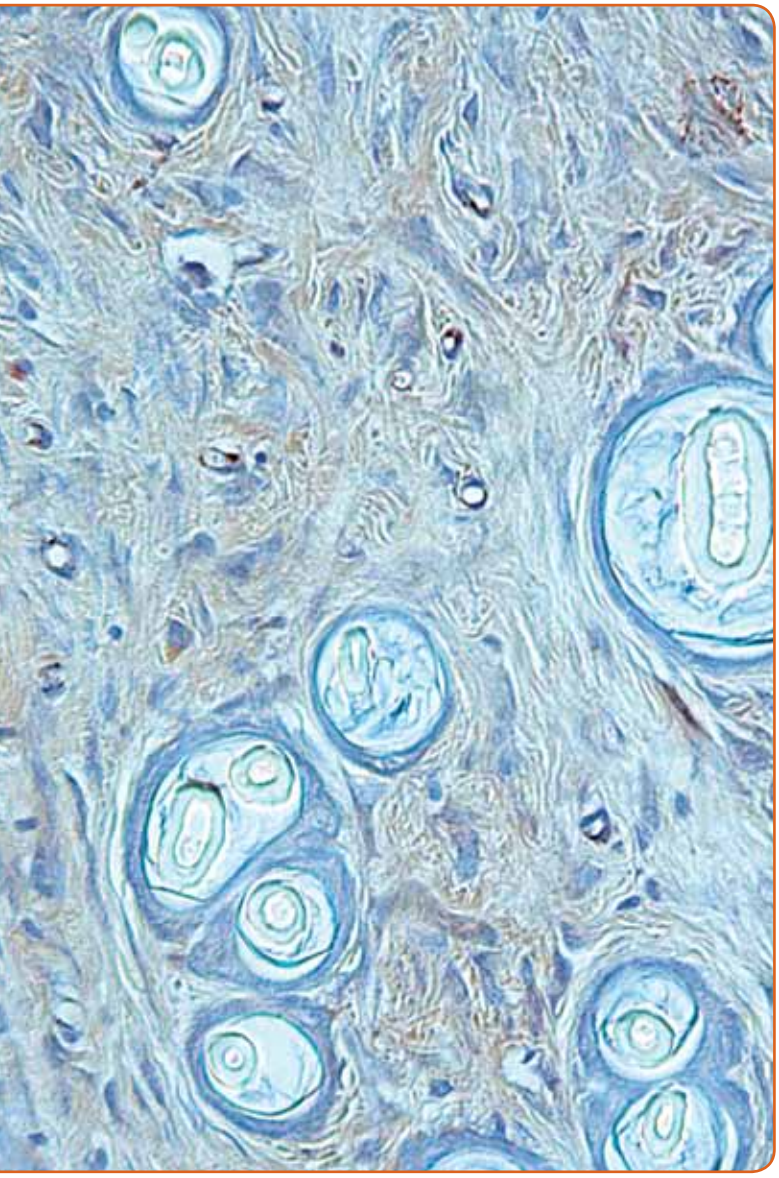
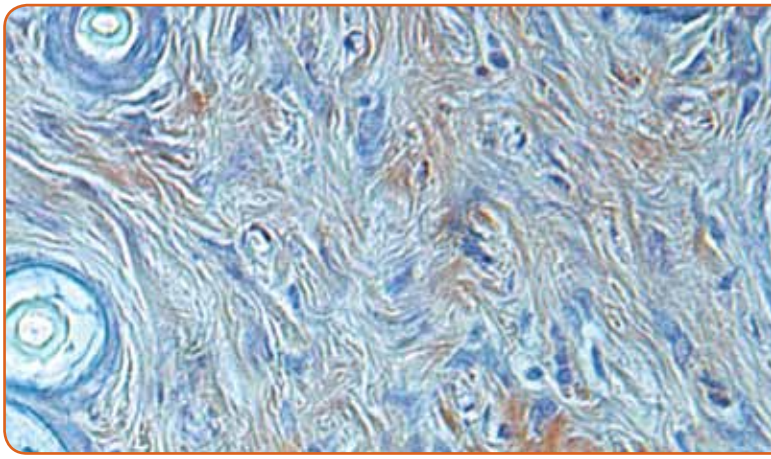


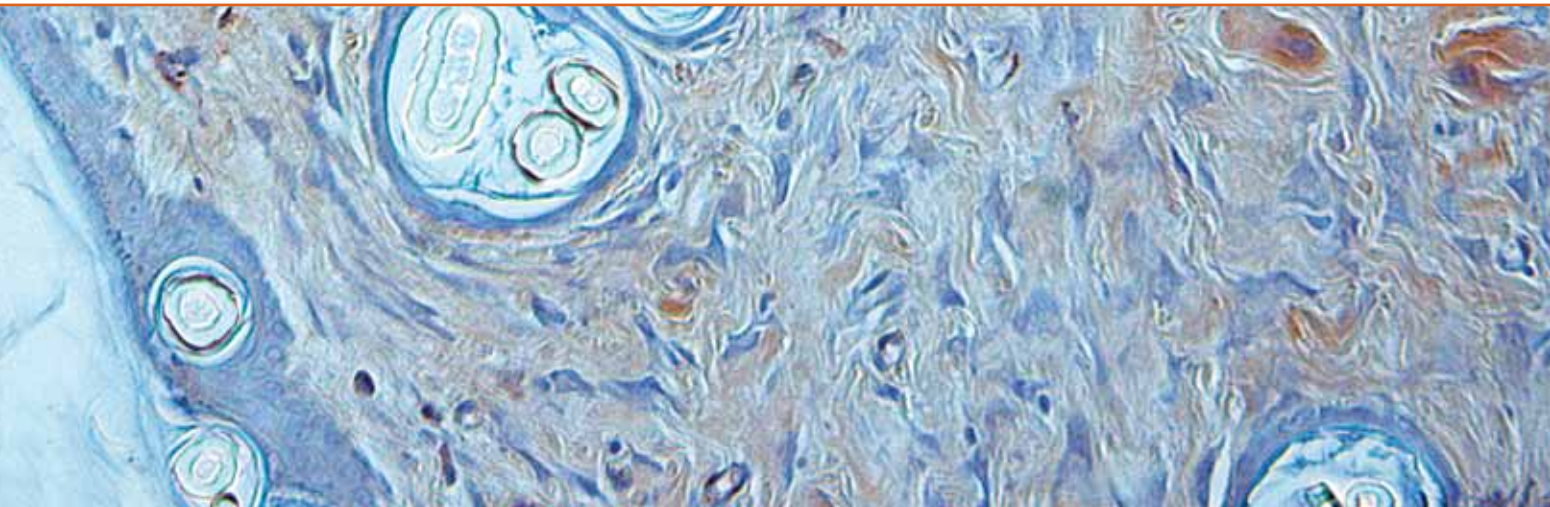




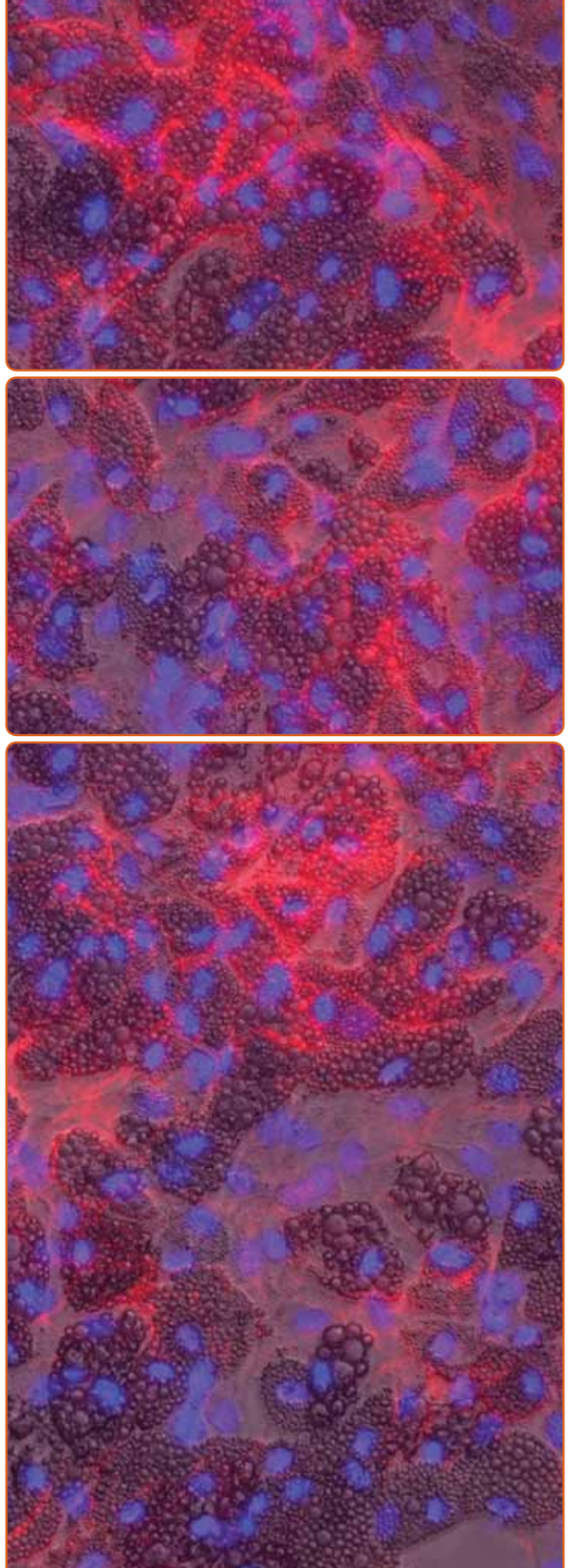
cabmm

center for applied biotechnology and molecular medicine

report 2014 / 2015



cabmm report
2014 / 2015



CONTENTS

Preface 6

About Us 8
- Steering Committee 10
- Scientific Advisory Board 12
- 4th CABMM Spring Seminar 14
- 5th CABMM Symposium 16
- 5th CABMM Spring Seminar 18
- 6th CABMM Symposium 20

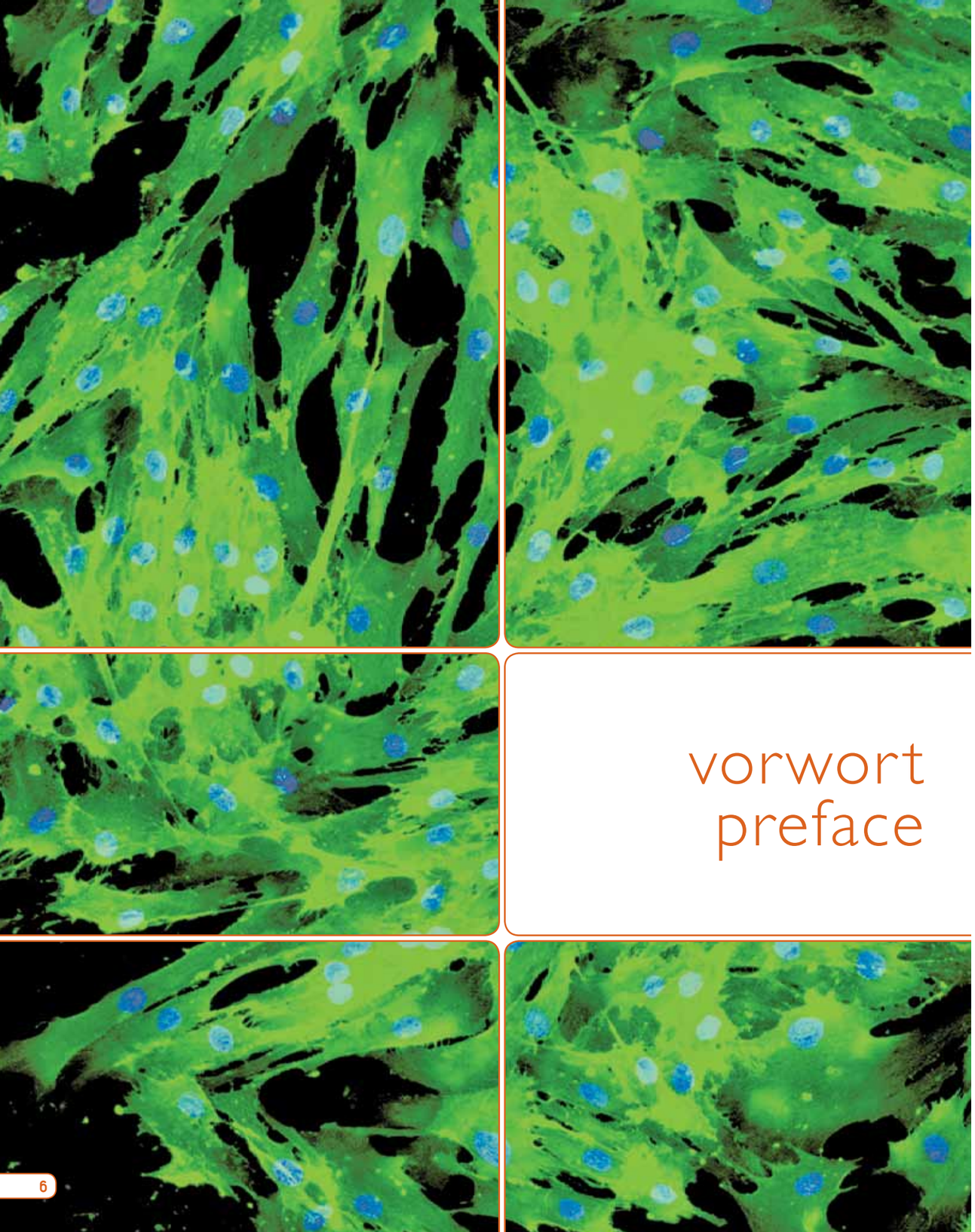
Portraits 22
- Prof. Dr. Jörg Goldhahn 24
- Dr. Silke Kalchofner-Mark 28
- Prof. Dr. Marcy Zenobi-Wong 32

Research Reports 36
- Leading article „Gene therapy" / Leitartikel „Gentherapie" 38
  Prof. Dr. Janine Reichenbach, University Children's Hospital Zurich
- Overview CABMM Research Platform:
  Bone & Stem Cell Research Group 46
  Cranio-Maxillofacial Surgery and Implantology Group 50
  Equine Research Group 52
  Musculoskeletal Research Group 54
  Tendon Repair Group 57

CABMM Start-up Grant 60
- Overview CABMM Start-up Grant 62
- Description of selected projects 64

Facts and Figures 70
- Member profiles 72
- Joint research projects 92
- Publications 100
- Public relations 106

Impressum 108



vorwort
preface

Liebe Leserin, lieber Leser

„Let's make sure the one and only CABMM is fit for the future!"

Ja, das Netzwerk ist gefestigt und kann sich nach den Aufbaujahren – über sieben Brücken musst Du gehn – auf eine annähernd zeitgemässe Infrastruktur, seine ForscherInnen und die Nachwuchskräfte verlassen.

Innerhalb von sieben Tagesmärschen muss nun aber schon die nächste und grösste aller Brücken geschlagen werden. Der Bach, nein, der Fluss – eigentlich ist der Mississippi nur ein Rinnsal – der zu überschreiten ist, ist zum einen das Ende der Unterstützung durch die Mäxi-Stiftung, welche nur noch bis 2018 dauern wird, und zum anderen der Rücktritt von Brigitte von Rechenberg, die im Jahr 2019 in den Ruhestand treten muss. Danach muss das CABMM-Boot alleine den Mississippi überqueren, einen neuen Kapitän oder Kapitänin finden und vor allem nachhaltig von der UZH unterstützt werden.

Alle beteiligten Kräfte und auch Aussenstehende, die an dieses Bündnis glauben, müssen an die Arbeit und helfen, Lösungen zu finden. Ein CABMM, das fit für die Zukunft ist, muss jetzt angedacht, besprochen und geregelt werden.

Denken Sie mit ....!

Die Hoffnung stirbt zuletzt ...

Bruno Bonin
Mäxi Stiftung

Dear reader,

„Let's make sure the one and only CABMM is fit for the future"!

Yes, the network is strengthened and after the consolidation period – "you have to cross seven bridges" – one can rely on its up-to-date infrastructure, its researchers and its young employees.

But within a seven-day's march, the next and biggest of all bridges has to be built now. The stream, no, the river to be crossed – actually, the Mississippi is only a trickle – is on the one hand the end of the support by the Mäxi foundation that will last only until 2018 and on the other hand the resignation of Brigitte von Rechenberg, who will retire in 2019. Thereafter, the CABMM boat has to pass the Mississippi alone, to find a new captain and particularly, it has to be sustainably supported by the UZH.

All forces involved as well as outsiders believing in this alliance, have to get down to business now in order to find solutions. A CABMM fit for the future has to be contemplated, discussed and arranged.

Let's think about it!

Hope always dies last ...

Bruno Bonin
Mäxi Foundation

about us

cabmm bodies and events

The "Center for Applied Biotechnology and Molecular Medicine (CABMM)" is an official competence center of the University of Zurich and was founded in 2008 by a small group of highly motivated and successful scientists, namely Prof. Dr. Brigitte von Rechenberg, Prof. Dr. Dr. Simon P. Hoerstrup and Prof. Dr. Dr. Michael O. Hottiger. With the creation of the CABMM, they gave rise to a stimulating environment for interdisciplinary and translational research, promoting scientific exchange and collaborations between basic and clinical researchers.

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 coordination point and the Platform Organization Team dealing with all aspects connected to the CABMM Research Platform. Additionally, a Scientific Advisory Board was established as controlling body.

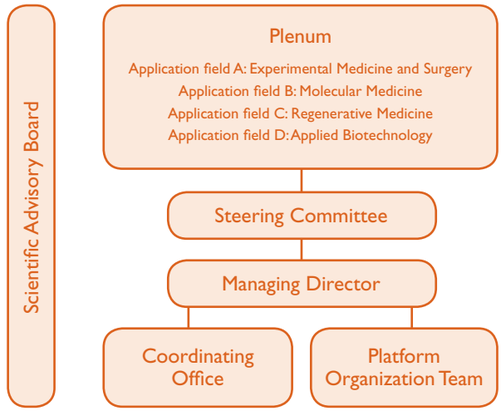
The CABMM demonstrates a unique structure, in that it combines (1) a network of existing research groups interested in exchanging scientific information and creating collaborations and (2) a working platform for collaborative research, where basic scientists, clinicians and veterinarians are able to work together shoulder to shoulder for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissues.

Another special feature of the CABMM is the fact that we do not focus on only one particular medical field, but rather on translational and interdisciplinary aspects. Thus, under the slogan "From bench to bedside … and back", the CABMM is dedicated to fostering advances in applied, clinically oriented research in the fields of (A) experimental medicine and surgery, (B) molecular medicine, (C) regenerative medicine, and (D) applied biotechnology.

Furthermore, the CABMM offers expertise in regulatory affairs: Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) were established at the Institute for Regenerative Medicine and the Musculoskeletal Research Unit, respectively, through two founding members of the CABMM, Prof. Dr. Dr. Simon P. Hoerstrup and Prof. Dr. Brigitte von Rechenberg. As Good Clinical Practise (GCP) has already been running at the University Hospital for several years, the University of Zurich now combines all regulatory requirements for the development, production and first clinical trials of new drugs and therapies under one roof.

In terms of scientific exchange and public relations, two major events are organized every year: the CABMM Spring Seminar and the CABMM Symposium. During these meetings, all CABMM members and their research groups, as well as non-members who are interested in the work of our center, have the opportunity to discuss ideas and experiences. Both events play essential roles in strengthening the CABMM network and enhancing collaborations between CABMM members from a variety of research disciplines.

In this chapter, the Steering Committee represented by Prof. Dr. Brigitte von Rechenberg and the Scientific Advisory Board are looking back on the achievements and obstacles that have been overcome within the reporting period. Additionally brief summaries about our main events during the years 2014 and 2015 can be found.



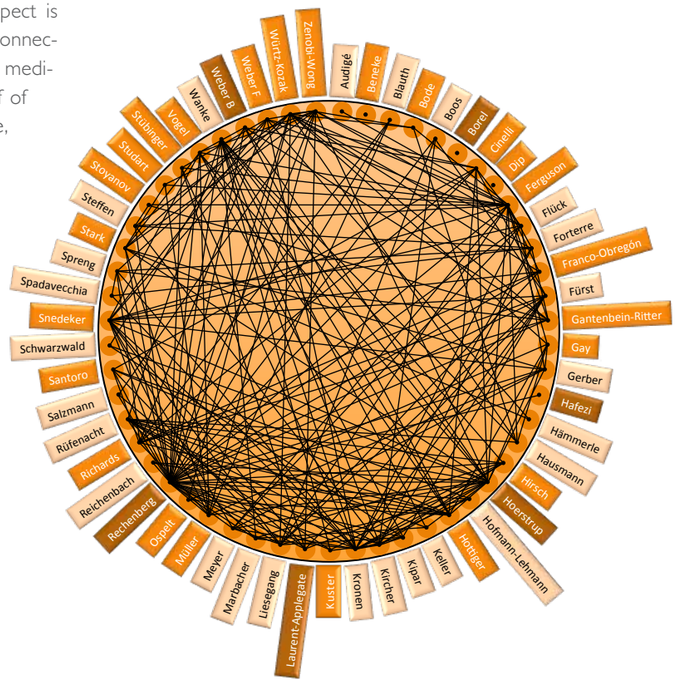
from the cabmm steering committee

The CABMM network is further growing. In the reporting period the number of active members climbed from 52 to 61 at the end of 2015, and new applications are already pending. The uniqueness of the CABMM is still the fact that it provides a network of many different groups from a great variety of professional backgrounds. On a quick glance, the connection between them may not be obvious, but on a second and more profound look, common interests can be detected and represent the true interdisciplinary as well as translational aspect of the network. The impressive connections and actual collaborations between the different fields of the CABMM (molecular medicine, applied biotechnology, regenerative medicine, and experimental medicine and surgery) as well as between basic researchers and clinicians are visualized in the figure below reflecting true interdisciplinarity and translation. The translational aspect is also represented such that a concentration of these connections is gathered around the groups of experimental medicine, where preclinical studies demonstrate the proof of principle for further translation into clinics and there, into human and veterinary medicine.

The importance of this translational approach is also reflected by changes in the institutes of our two co-founders and members of the CABMM Steering Committee, Michael O. Hottiger and Simon P. Hoerstrup.

Under the leadership of Michael, the former "Institute of Veterinary Biochemistry and Molecular Biology (IVBMB)" changed its name and focus. The new name "Department of Molecular Mechanisms of Disease (DMMD)" indicates the new focus of the institute. Biochemistry and molecular biology still are the main targets, but viewed in the light of disease, where possible biotechnical applications to change diseased molecular events may be the future.

Simon became the director of the newly formed "Institute of Regenerative Medicine" as well as the "Wyss Translational Center Zurich", where the focus is placed on crossing the death valley between innovations and the real market for the benefits of society. In case of medical innovations, this always means that the death valley consists of passing the various hurdles of regulatory affairs. Regulatory affairs in production (Good Manufacturing Practice, GMP), conduction of preclinical studies (Good Laboratory Practice, GLP) and finally clinical trials (Good Clinical Practice, GCP) are the prerequisite for true translation, where innovations finally can be applied to the benefit of the patients. The University of Zurich is the only University at least in Europe, which has it all under one roof. GMP (Institute for Regenerative Medicine) and GLP (MSRU) competences are embedded within the CABMM network.



cabmm steering committee

Name and affiliation	Application field
Prof. Dr. med. vet. Brigitte von Rechenberg (Chairwoman) Vetsuisse Faculty, University of Zurich	A – Experimental Medicine and Surgery
Prof. Dr. med. vet. Dr. phil. II Michael O. Hottiger (Vice-Chairman) Vetsuisse Faculty and Faculty of Science (MNF), University of Zurich	B – Molecular Medicine
Prof. Dr. med. Dr. rer. nat. Simon P. Hoerstrup Medical Faculty, University of Zurich	C – Regenerative Medicine
Prof. Dr. med. vet. Annette Liesegang Vetsuisse Faculty, University of Zurich	A – Experimental Medicine and Surgery
Prof. Dr. med. Janine Reichenbach University Children`s Hospital Zurich	B – Molecular Medicine
Dr. rer. nat. Silke Kalchofner-Mark Vetsuisse Faculty, University of Zurich	Managing Director

Our Network is not only growing, but our members are also very successful. Quite a few groups received awards with their outstanding interdisciplinary work, but two of our female members were especially successful: Karin Würtz-Kozak received an SNF professorship and Raffaella Santoro was appointed as a new member of the European Molecular Biology Organization (EMBO). She was the only female scientist this year as being elected and she is only the third woman of the UZH overall. What a great achievement, we are really proud of you both. Let's take this as a stimulus for our network!

Zurich, June 2016
Brigitte von Rechenberg,
Chairwomen of the CABMM Steering Committee

from left to right:
Prof. Dr. Dr. Simon P. Hoerstrup, Prof. Dr. Annette Liesegang, Dr. Silke Kalchofner-Mark, Prof. Dr. Brigitte von Rechenberg, Prof. Dr. Janine Reichenbach, Prof. Dr. Dr. Michael O. Hottiger

the scientific advisory board of the cabmm

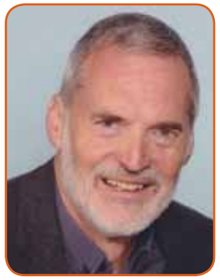
The aim of the Scientific Advisory Board (SAB) of the CABMM is to critically evaluate the quality of the CABMM and to review grant applications for a CABMM Start-up Grant. Therefore, regular meetings take place at the University of Zurich to assess scientific issues on site and to discuss research proposals directly with the applicants. Furthermore, all SAB members offer general support in all scientific questions and participate in the training and promotion of young academics.

The participation in the yearly CABMM Spring Seminar and CABMM Symposium allows the SAB to get insights into the quality of the network and to contribute to fruitful discussions.

The SAB consists of wellknown scientists representing the different application fields of our center as well as representatives from industry and the Mäxi Foundation. Additionally, the Deans of the Medical and the Vetsuisse Faculty of the University of Zurich are part of the SAB *(ex officio)*.

cabmm scientific advisory board

Name and affiliation	Representing
Prof. em. Dr. med. vet. Felix R. Althaus (chairman) University of Zurich	Application field A – Experimental Medicine and Surgery
Prof. Dr. med. Jörg Goldhahn Novartis Institutes for Biomedical Research, Basel (until 2016), ETH Zurich	Industry
Prof. em. Dr. Walter Schaffner (PhD) University of Zurich	Application field B – Molecular Medicine
Prof. Dr. med. Dr. med. dent. Dr. h.c. Hans-Florian Zeilhofer University Hospital Basel	Application field C – Regenerative Medicine
Dr. med. Bruno Bonin Meilen	Mäxi Foundation
Prof. Dr. med. vet. Brigitte von Rechenberg Dean of the Vetsuisse Faculty, University of Zurich	(ex officio)
Prof. Dr. phil. nat. Jean-Marc Fritschy Deputy dean of the Medical Faculty, University of Zurich	(ex officio)



From the CABMM Scientific Advisory Board

We have seen some major changes in the Scientific Advisory Board during the reporting period. First, Prof. em. Dr. A. Robin Poole, PhD, from McGill University, Montréal, Canada, stepped down as the chair. We thank him for his relentless engagement and excellent advice. As the founding chair of the Board, he has helped shape its profile from the very beginning. The chair now goes to Prof. em. Dr. med. vet. Felix R. Althaus, former Dean of the Vetsuisse Faculty, ex-director of the Institute of Veterinary Pharmacology and Toxicology and a member of the CABMM ever since its foundation.

Another prominent resignee is Prof. Dr. ir. Frank P.T. Baaijens, Eindhoven University of Technology, The Netherlands. He has been appointed *Rector Magnificus* of his University. We are proud that he was a member of our board and we congratulate him on his election to the highest office. His position was taken by Prof. Dr. med. Dr. med. dent. Dr. h.c. Hans-Florian Zeilhofer, head of the Department for Oral and Maxillofacial Surgery, University Hospital Basel. He is also a founding partner and member of the board of directors of MedTech Innovation Partners AG (MTIP), a startup company focusing on bringing medical technology innovations to the market.

The Scientific Advisory Board has held several meetings in the new composition and worked out recommendations for the CABMM Steering Committee.

Zurich, July 2016
Prof. em. Dr. med. vet. Felix R. Althaus
Chair of the CABMM Scientific Advisory Board

4. spring seminar

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Im Anschluss an die bereits 7. CABMM Vollversammlung fand am 16. Mai 2014 das 4. Spring Seminar unseres Zentrums am Tierspital Zürich statt. Den zahlreichen Teilnehmern wurde ein klinisch orientiertes Programm geboten, welches vor allem Vorträge aus dem Bereich der experimentellen Medizin und Chirurgie umfasste.

Das 4. CABMM Spring Seminar wurde von Prof. Dr. Brigitte von Rechenberg, der Vorsitzenden des CABMM Leitungsausschusses, eröffnet. Nach ihrer Begrüssung übergab sie das Wort an PD Dr. Peter J. Richards, den wissenschaftlichen Direktor des CABMM, der die Veranstaltung moderierte.

Die erste Vortragsreihe hatte Forschung über Krankheiten der Blutgefässe und des Herz-Kreislauf-Systems zum Schwerpunkt. Zunächst stellten zwei Neumitglieder ihre Forschungsbereiche dem CABMM Netzwerk vor: Dr. Serge Marbacher vom Kantonsspital Aarau sprach über intrakraniale Aneurysmen und dadurch verursachte subarachnoidale Blutungen. Prof. Dr. Isabel Wanke von der Hirslanden Klinik in Zürich führte das Thema mit ihrem Vortrag über bild-basierte Bewertung von Aneurysmen anhand ihrer Form und Grösse fort. Danach berichtete Dr. Benedikt Weber vom Universitätsspital Zürich von verschiedenen Ansätzen, Gewebe für den Ersatz von Herzklappen zu züchten, und anschliessend in präklinischen Studien zu testen.

Die zweite Vortragsreihe über Forschung im Bereich des Bewegungsapparates wurde wiederum von einem Neumitglied eingeleitet, Prof. Dr. Martin Flück vom Universitätsspital Balgrist in Zürich. Er referierte über die Möglichkeit, der Degeneration von Muskelgewebe mittels zielgerichteter Zellverbindungen entgegenzuwirken. Als nächster Redner sprach Prof. Dr. David Spreng von der Universität Bern über die möglichen Ursachen von Kreuzbandrissen bei Hunden. Abschliessend gab Dr. Karin-Würtz-Kozak von der ETH Zürich einen Übersichtsvortrag über neue Forschungsansätze zur Regeneration von unterschiedlichen Geweben des Bewegungsapparates mit Fokus auf Bandscheiben- und Muskelregeneration.

Mit den zusammenfassenden Worten von Prof. Dr. Brigitte von Rechenberg wurde schliesslich ein weiteres, erfolgreiches Meeting beendet. Sie erwähnte, wie wichtig die translationale Forschung sei, und dass diese durch das Wachstums unseres Zentrums auch weiterhin ermöglicht und gefördert würde.

Zum Abschluss des 4. CABMM Spring Seminars gab es bei einem gemütlichen Apéro die Gelegenheit, sich über Gehörtes auszutauschen, neue CABMM Mitglieder kennenzulernen und gemeinsame Forschungsinteressen zu diskutieren.

4th spring seminar

of the center for applied biotechnology and molecular medicine (cabmm)

Following the 7th Plenary Meeting of the CABMM, the 4th Spring Seminar of our center took place on May 16th, 2014, at the Animal Hospital in Zurich. Numerous participants had the opportunity to follow a clinically-oriented program mainly including presentations from the field of experimental medicine and surgery.

The chairwomen of the CABMM Steering Committee, Prof. Dr. Brigitte von Rechenberg, opened the 4th CABMM Spring Seminar. After welcoming the audience, she made way for the Scientific Director of our center, PD Dr. Peter J. Richards, who chaired the event.

The main focus of the first session was on vascular and cardiovascular diseases. The meeting kicked off with two of the newest members presenting their area of research to the CABMM network: Dr. Serge Marbacher from the Kantonsspital Aarau talked about intracranial aneurysms and their contribution to subarachnoid hemorrhage. Prof. Dr. Isabel Wanke from the Hirslanden Klinik in Zurich continued this topic with her presentation on image-based evaluation of aneurysms based on their size and shape. Thereafter, Dr. Benedikt Weber from the University Hospital Zurich gave an in-depth account of his ongoing pre-clinical studies within the field of tissue engineering and heart valve replacement.

The second series of lectures dealt with research in the field of musculoskeletal tissues and again began with a presentation from a new CABMM member, Prof. Dr. Martin Flück from the Balgrist University Hospital. He talked about focal-adhesion-targeted approaches against the degeneration of muscle tissue. The next speaker, Prof. Dr. David Spreng from the University of Bern, talked about possible causes of canine cruciate ligament ruptures. Finally, Dr. Karin Würtz-Kozak from the ETH Zurich gave an overview of new approaches for the regeneration of disc and muscle tissue.

Following the concluding remarks of Prof. Dr. Brigitte von Rechenberg, another successful meeting was brought to a close. She mentioned the importance of translational research and the increasing possibilities provided by the growing network of our centre.

The after meeting Apéro offered participants the opportunity to exchange new ideas and to reflect upon the presentations given. It also allowed new members the possibility to introduce themselves in an informal atmosphere.

5. symposium

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Das Kompetenzzentrum für Angewandte Biotechnologie und Molekulare Medizin (CABMM) hat am 13. November 2014 zu seinem 5. Symposium an die Universität Zürich geladen. Ein abwechslungsreiches Programm mit zwei hochinteressanten Hauptvorträgen zog ein grosses Publikum an und machte diese Veranstaltung zu unserem bis dato erfolgreichsten Event. Darüber hinaus wurden Projekte präsentiert, die entweder durch einen CABMM Start-up Grant gefördert und/oder auf unserer Forschungsplattform durchgeführt wurden. Eine zusätzliche Posterausstellung gab weitere Einblicke in die CABMM-assoziierte Forschung.

Nachdem CABMM-Mitbegründer Prof. Dr. Dr. Simon P. Hoerstrup die Veranstaltung eröffnet hatte, gab Prof. em. Dr. Walter Schaffner von der Universität Zürich den ersten, sehr sympathischen Hauptvortrag. Hochrangige wissenschaftliche Publikationen, die Erfindung von Laborequipment, eine Doktorarbeit im Guinessbuch der Rekorde und viele – nicht nur wissenschaftliche – Anekdoten belegen seine erfolgreiche Karriere im Bereich der Genregulation. Im Anschluss präsentierte Deborah Studer von der ETH Zürich die Ergebnisse ihrer Doktorarbeit zum Thema Knorpelregeneration. Sie untersuchte die molekularbiologischen Eigenschaften verschiedener Zelltypen, um diese als Ersatz für defektes Knorpelgewebe einzusetzen. Die Identifizierung von Sehnen-spezifischen Markerproteinen im Pferd wurde im letzten Vortrag von PD Dr. Paolo Cinelli der Universitätsspital Zürich thematisiert. Das durch einen CABMM Start-up Grant geförderte Projekt konnte mit der Identifizierung zweier neuer Kandidaten aus einer Vielzahl möglicher Gene erfolgreich abgeschlossen werden. Die folgende Kaffeepause bot nicht nur Gelegenheit für wissenschaftlichen Austausch in entspannter Atmosphäre, sondern auch Raum für die Begutachtung und Diskussion der ausgestellten Poster.

Im zweiten Teil der Veranstaltung hiess der Moderator und wissenschaftliche Direktor des CABMM, PD Dr. Peter J. Richards, unseren zweiten Hauptredner, Prof. Dr. Christian Gerber, vom Uniklinikum Balgrist in Zürich herzlich willkommen.

Unter dem Titel „From bedside to bench" erläuterte er am Beispiel von Verletzungen des Schultergelenkes eindrucksvoll, wie wichtig es ist, wissenschaftliche Antworten auf Patienten-basierte Fragestellungen zu finden. Als Mitglied der Forschungsgruppe von Prof. Dr. Michael Blauth von der Medizinischen Universität Innsbruck, Österreich, sprach Dr. Hannes L. Ebner anschliessend über die Methodik der Herstellung von gelatine-basierten Nano-Faser-Netzen in einem elektrischen Feld. Mit Hilfe dieser Strukturen lässt sich die Differenzierung von mesenchymalen Stammzellen zu Knochenzellen erhöhen. Im letzten Vortrag berichtete Prof. Dr. Dr. Michael O. Hottiger von der UZH über die molekulare Regulation der Reifung von Vorläufer-Zellen zu Osteoklasten. Im Speziellen erörterte er die Rolle von Proteinmodifizierungen durch das Anheften bestimmter Zuckerreste in diesem komplexen System.

Prof. Dr. Dr. Simon P. Hoerstrup bedankte sich zum Abschluss bei allen Rednern sowie den Organisatoren des Meetings und entliess alle Teilnehmer in einen Apéro. In diesem gemütlichen Rahmen konnten gemeinsame wissenschaftliche Interessen entdeckt werden.

5th symposium

of the center for applied biotechnology and molecular medicine (cabmm)

The 5th CABMM Symposium was held on November 13th, 2014, at the University of Zurich. An interesting program with two exciting keynote lectures attracted a large number of participants resulting in our most successful event so far. The program also comprised presentations about projects that were either supported by a CABMM Start-up Grant or performed on the CABMM Research Platform and, for the first time, a poster exhibition providing for further insight into CABMM-associated research.

After CABMM co-founder Prof. Dr. Dr. Simon P. Hoerstrup opened the meeting and welcomed the participants, Prof. em. Dr. Walter Schaffner from the University of Zurich gave the first, very appealing keynote speech. He talked about his career in gene regulation including top-ranking publications, inventions of lab equipment, a PhD thesis published in the Guinness World Records and numerous anecdotes – not only from the field of science. Subsequently, Deborah Studer from the ETH Zurich presented the results of her doctoral thesis concerning cartilage repair. In order to find the most suitable cell source for cartilage replacement, she compared different characteristics of mesenchymal stem cells as well as adult and fetal chondrocytes. In the next talk, PD Dr. Paolo Cinelli from the University Hospital Zurich spoke about the identification of tenocyte specific markers in the horse. Out of a large number of possible candidates, two new tendon specific markers could be identified in native equine tissue.

The following coffee break provided not only the opportunity for scientific exchange, but also the chance to visit the poster exhibition.

After the coffee break, the Scientific Director of the CABMM, PD Dr. Peter J. Richards, introduced our second keynote speaker, Prof. Dr. Christian Gerber from the Balgrist University Hospital in Zurich. In his presentation entitled "From bedside to bench" he highlighted impressively the importance of transferring questions from the patient into the lab using the example of tendon tears in the shoulder. Afterwards, representing the research group of Prof. Dr. Michael Blauth from the Medical University Innsbruck, Dr. Hannes L. Ebner spoke about the manufacturing process of electrospun nano-meshes and their subsequent use to enhance the osteogenic differentiation potential of mesenchymal stem cells. In the last presentation, Prof. Dr. Dr. Michael O. Hottiger talked about the molecular regulation of osteoclast development, focusing on the role of protein modifications by ADP-ribosylation in this complex system.

In his concluding remarks, Prof. Dr. Dr. Simon P. Hoerstrup thanked all speakers and the meeting organizers for their contribution. Subsequently, he released the audience into a nice Apéro, where all participants had the opportunity to discover common interests for future collaborations.

The 5th CABMM Symposium was kindly supported by

5. spring seminar

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Zahlreiche Interessierte nahmen am 12. Juni 2015 an unserem 5. CABMM Spring Seminar an der Universität Zürich teil. Gruppenleiter, welche schon seit mehreren Jahren mit uns vernetzt sind, und auch neue Mitglieder nutzten die Gelegenheit, ihre Arbeit zu präsentieren. Zudem wurde ein Forschungsprojekt vom neu gegründeten Wyss Translational Center Zurich vorgestellt.

Zum ersten Mal führte Geschäftsführerin Dr. Silke Kalchofner-Mark durch das vielfältige Programm und begrüsste zu Beginn Dr. Peter Kronen von der Musculoskeletal Research Unit (MSRU) der Universität Zürich sowie von Veterinary Anaesthesia Services International in Winterthur. In seinem Übersichtsvortrag über die Richtlinien von Tierversuchen für wissenschaftliche Studien fokussierte er hauptsächlich auf das Schmerzempfinden unterschiedlicher Spezies sowie angemessenen Therapiemöglichkeiten. Prof. Regina Hofmann-Lehmann stellte im Anschluss die vielfältigen diagnostischen Leistungen des Veterinärmedizinischen Labors der UZH vor. Zusätzlich berichtete sie den Zuhörern von ihrer Forschung im Bereich der Infektionskrankheiten der Katze und dem dazugehörigen Training der Tiere, um deren Stresslevel möglichst gering zu halten. Während der nachfolgenden Kaffeepause hatten alle Teilnehmer die erste Möglichkeit, wissenschaftliche Gemeinsamkeiten zu diskutieren.

Der zweite Teil der Veranstaltung begann mit einem Vortrag von Prof. Emanuela Keller vom Universitätsspital Zürich. Sie erörterte die Notwendigkeit, während einer zerebralen Gefässverengung multiple Faktoren zu überwachen. Sie stellte ein Gerät namens „NeMo Patch" vor, mit dem viele Parameter nicht-invasiv beobachtet werden können und an dessen Entwicklung sie beteiligt war. Während der anschliessenden Präsentation berichtete Prof. Janine Reichenbach vom Universitäts-Kinderspital in Zürich über den Einsatz von Stammzelltherapien zur Behandlung verschiedener Immunkrankheiten. Trotz vielversprechender Ergebnisse ist weitere Forschung notwendig, um Spätfolgen zu minimieren. Unser Spring Seminar endete mit einem Vortrag von Dr. Karola Schlinkmann vom Wyss Translational Center Zurich. Sie stellte eine neue Methode vor, um nicht immunogene Transplantate au seiner homologen Zellpopulation mit Hilfe von Tissue Engineering herzustellen.

Nachdem die Vorsitzende des CABMM, Prof. Brigitte von Rechenberg, das Meeting beendet hatte, hatten alle Teilnehmer während eines erfrischenden Apéros die Gelegenheit zum wissenschaftlichen und auch privaten Austausch.

5th spring seminar

of the center for applied biotechnology and molecular medicine (cabmm)

On June 12th, 2015, many people connected to the CABMM network came to the animal hospital of the University of Zurich in order to participate in the 5th CABMM Spring Seminar. Beside talks given by long-time and new CABMM members, there was also one lecture about a research project performed at the newly founded Wyss Translational Center Zurich.

For the first time, the event was moderated by the managing director of our center, Dr. Silke Kalchofner-Mark, who kindly introduced the first speaker, Dr. Peter Kronen from the Musculoskeletal Research Unit (MSRU), University of Zurich, and Veterinary Anaesthesia Services International in Winterthur. He gave an overview lecture about general guidelines for animal experimentation focusing on pain and analgesia. Afterwards, Prof. Regina Hoffmann-Lehmann presented the multiple diagnostic services offered by the Clinical Laboratory of the University of Zurich. Additionally, she talked about her research in the field of infectiology using the cat as model to study feline infectious anaemia.

After the coffee break that offered the first possibility to find new collaborations, the event continued with a lecture from Prof. Emanuela Keller from the University Hospital Zurich. She reported on cerebral vasospasm and the many factors that have to be observed. Therefore, she participated in the development of the so-called "NeMo Patch" allowing for non-invasive monitoring of many parameters. During the next presentation, Prof. Janine Reichenbach from the University Children`s Hospital Zurich showed on the basis of case reports the treatment options of different primary immuno-deficiencies using gene therapy. In spite of promising results, further studies are still necessary to avoid long-term consequences. The Spring Seminar ended with a talk given by Dr. Karola Schlinkmann from the Wyss Translational Center Zurich. She presented her project "LifeMatrix" that deals with the production of novel non-immunogenic, off-the shelf tissue engineered grafts with the aim of performing a first in-man clinical study for cardiac therapy in the near future.

After the chairwomen of the CABMM, Prof. Brigitte von Rechenberg, officially closed the meeting, all participants had the possibility to join a refreshing Apéro and to discuss scientific issues and more.

6. symposium

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Ganz im Sinne des translationalen Charakters des Kompetenzzentrums für Angewandte Biotechnologie und Molekulare Medizin wurde das 6. CABMM Symposium, welches am 5. November 2015 stattfand, mit Vorträgen und anschliessender Diskussionsrunde über innovative bildgebende Technologien eröffnet.

Nach ihren einleitenden Worten begrüsste Prof. Dr. Brigitte von Rechenberg als ersten Redner der Diskussionsrunde „Innovative Imaging Technologies" Dr. Dirk Müller von Philips Healthcare. Er stellte mit dem „IQon Spectral CT" das weltweit erste CT mit Spektraldetektor vor, mit welchem unterschiedliche Gewebestrukturen dargestellt werden können. Das Gerät arbeitet mit zwei unterschiedlichen Energien und zeigt u.a. eine sehr gute Artefakt-Reduktion. Anschliessend gab Dr. Christian Brönnimann, CEO und Gründer der Firma Dectris Ltd., Baden AG, Schweiz, eine Übersicht über die verschiedenen Firmenprodukte und die zu Grunde liegende Technologie. Ziel der Firma Dectris Ltd. ist es, das schnellste und sensitivste Detektorsystem für Röntgenstrahlen sowohl für industrielle als auch wissenschaftliche Zwecke zu entwickeln. Während der folgenden Diskussionsrunde fand ein reger Austausch über die unterschiedlichen Einsatzmöglichkeiten der vorgestellten Technologien in den verschiedenen Bereichen der Forschung und der klinischen Anwendung statt.

Nach einer kurzen Kaffeepause übernahm die Geschäftsführerin des CABMM, Dr. Silke Kalchofner-Mark, die Moderation und führte durch das weitere Programm. Zunächst berichtete eines unserer neuesten Mitglieder, Prof. Dr. Dr. Farhad Hafezi vom ELZA Institut in Dietikon, über die verschiedenen Anwendungsbereiche der sogenannten Vernetzungsbehandlung (Cross-Linking, CXL). Hierbei können mittels UV-A Licht und Vitamin B2 zum Beispiel die Ausdünnung der Hornhaut oder Hornhaut-Infektionen erfolgreich behandelt werden. Im darauffolgenden Vortrag aus dem Bereich der Angewandten Biotechnologie berichtete Prof. Dr. Jeffrey Bode vom Laboratorium für Organische Chemie der ETHZ über die chemische Synthese verschiedener Proteine und Hydrogele. Mittels unterschiedlicher Verknüpfungsmöglichkeiten können in seiner Forschungsgruppe Proteine mit bis zu 200 Aminosäure-Resten sowie Membran-integrierte Proteine hergestellt werden.

Während der letzten Vortragsreihe gab es Präsentationen aus dem Bereich der Regenerativen Medizin mit dem Fokus auf Knorpel- und Bandscheibenforschung. Zuerst zeigte Prof. Dr. Gian Salzmann von der Schulthess Klinik in Zürich die derzeit angewandten Therapien von akuten und chronischen Knorpeldefekten sowie aktuelle Forschungsschwerpunkte in diesem Bereich auf. Dr. Ece Öztürk aus der Gruppe von Prof. Dr. Marcy Zenobi-Wong, EHTZ, präsentierte nachfolgend die Ergebnisse einer CABMM Start-up Grant-Studie über den Einfluss schwefelhaltiger Alginat-Hydrogele auf die zellbasierte Knorpelreparatur. Im letzten Vortrag erläuterte Prof. Dr. Karin Würtz-Kozak vom Labor für orthopädische Technologie der ETHZ die Resultate einer weiteren vom CABMM geförderten Studie über die Regulierung und Relevanz von bestimmten Matrix-abbauenden Enzymen während der Bandscheibendegeneration.

In ihren abschliessenden Worten betonte Prof. Dr. Brigitte von Rechenberg den grossen Nutzen der translationalen Veranstaltung und bedankte sich bei allen Teilnehmern für ihre interessanten Beiträge. Wie üblich wurde der abschliessende Apéro in gemütlicher Atmosphäre für wissenschaftliche Diskussionen genutzt und potentielle gemeinsame Forschungsprojekte im Sinne des translationalen Charakters unseres Zentrums debattiert.

6th symposium

of the center for applied biotechnology and molecular medicine (cabmm)

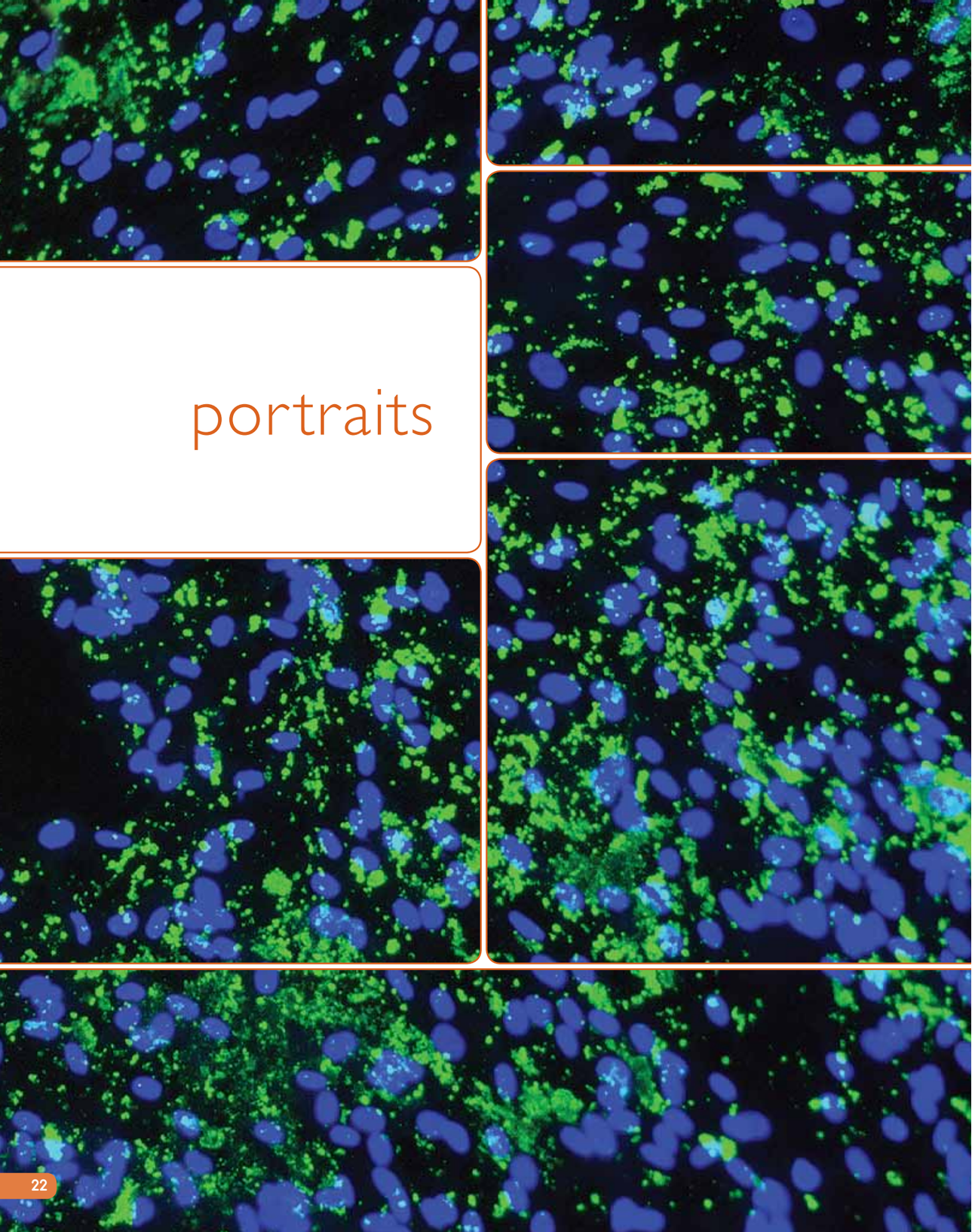
The 6th CABMM Symposium took place on November 5th, 2015. In the spirit of the translational character of the Center for Applied Biotechnology and Molecular Medicine, the event started with presentations and a round table discussion about innovative imaging technologies.

After her introducing words, Prof. Dr. Brigitte von Rechenberg welcomed the first speaker of the round table discussion "Innovative Imaging Technologies", Dr. Dirk Müller from Philips Healthcare. He presented Philips "IQon Spectral CT", the world's first spectral detector-based CT. Using two different energies, manifold structures can be displayed. Amongst other advantages, the instrument offers for example a great noise reduction. Subsequently, Dr. Christian Brönnimann, CEO and founder of Dectris Ltd., Baden AG, Switzerland, introduced the audience to the various products of his company as well as the technology used. The aim of Dectris is to develop the fastest and most sensitive X-ray detector system for scientific and industrial purposes. During the following round table discussion, a lively scientific exchange about the possible fields of application of the presented technologies in basic research as well as clinical practice took place.

After a short coffee break, Dr. Silke Kalchofner-Mark continued with the moderation of the event and introduced as first speaker one of our newest members, Prof. Dr. Dr. Farhad Hafezi from the ELZA Institute in Dietikon. He talked about the different application fields of corneal cross-linking (CXL). This method uses UV-A light and vitamin B2 and allows for example for the treatment of corneal instability and infection. During the next presentation from the field of applied biotechnology, Prof. Dr. Jeffrey Bode from the Laboratory of Organic Chemistry of the ETHZ reported about state-of-the-art chemical synthesis of proteins and hydrogels. His group successfully established methods to synthesize proteins with up to 200 amino acids as well as integral membrane proteins.

During the last session, projects from the field of regenerative medicine were presented focusing on cartilage and disc research. Prof. Dr. Gian Salzmann from the Schulthess Clinic in Zurich gave an overview talk about current treatment options of acute and chronic cartilage defects as well as current main research topics in this field, e.g., the prevention of long-term effects such as osteoarthritis. Representing the research group of Prof. Dr. Marcy Zenobi-Wong from the Cartilage Engineering and Regeneration Laboratory of the ETHZ, Dr. Ece Öztürk presented the results of a project supported by a CABMM Start-up Grant that addressed cell-based cartilage repair using sulfated alginate hydrogels. The last presentation of the symposium was given by Prof. Dr. Karin Würtz-Kozak from the Laboratory for Orthopaedic Technology, ETHZ. She also reported findings from a CABMM-funded study concerning the regulation and relevance of specific matrix degrading enzymes in intervertebral disc degeneration.

Chairwomen and co-founder of the CABMM, Prof. Dr. Brigitte von Rechenberg, closed our 6th Symposium. In her concluding remarks, she highlighted the great benefit of the translational event. She thanked all people for their interesting contributions and released the participants into an Apéro. In a relaxed atmosphere, fruitful discussions about translational research projects continued.



portraits

Behind every person there is also a personal story, but in the demanding business environment of daily work there is often not much time left to get to know each other very well on a private level. However, private and work life are always connected and one influences the other. That is why we decided to introduce some people connected to the CABMM network with a personal portrait in every CABMM Report, describing not only their scientific interests, but also some private aspects of their life.

Paula Lanfranconi, free journalist, interviewed the following three people for this CABMM Report:

Prof. Dr. Jörg Goldhahn
- Professor at the Department Health Sciences and Technology, ETH Zurich
- Basic and clinical researcher
- Member of the CABMM Scientific Advisory Board

Dr. Silke Kalchofner-Mark
- Managing Director of the CABMM
- Mother of two children
- Horse enthusiast

Prof. Dr. Marcy Zenobi-Wong
- Head of the Cartilage Engineering and Regeneration Laboratory at the ETH Zurich
- Member of a Chinese MIT-family
- Mother of 2x2 children

For those who are not yet familiar with the portrayed people, this may be a good opportunity to gain insight into their research and also to learn about their private life and personality. For those who already know these people in person, it may be still possible to learn something new about them. And for all readers, it may be interesting to recognize the parallels between their work and private life.

„tun, was einem wirklich wichtig ist“

jörg goldhahn, portrait von paula lanfranconi

Jörg Goldhahn ist Professor am Departement Health Sciences and Technology der ETH Zürich. Sein Antrieb: Forschungsresultate rasch zum Patienten bringen. Als Medical Director des neuen ETH-Studienganges Medizin-Bachelor will er etwas Nachhaltiges schaffen.

Dynamischen Schrittes eilt er den Korridor entlang. Drahtig, ein jungenhaftes Lächeln im Gesicht, die Haare leicht verstrubbelt. Jörg Goldhahn ist einer, der immer in Bewegung ist. „Nach aussen“, sagt der 47-Jährige jetzt in seinem noch nicht fertig eingerichteten Büro, „sieht meine Laufbahn nach Brüchen aus – von der Klinik in die Forschung, dann in die Industrie und zurück zur Hochschule.“

Begonnen hat seine Laufbahn an der Unfallchirurgie in Jena. Schon bald entwickelt er zusammen mit seinem Vater, einem Maschinenbauer, Prototypen für Knochenimplantate. Sein Chef ist etwas überfordert von den Exploits seines jüngsten Assistenzarztes und schickt ihn nach Davos, ans AO Forschungsinstitut. Dort ist man begeistert vom Newcomer aus der Ex-DDR. Und dort lernt Jörg Goldhahn auch Brigitte von Rechenberg kennen. Die ersten Bande zum späteren CABMM sind geknüpft.

Irgendwann jedoch muss sich der junge Mediziner entscheiden: Guter Chirurg oder guter Forschender? Seine Liebe zur Forschung ist stärker. Er macht an der ETHZ ein Nachdiplomstudium in Medizinischer Physik und Biomechanik, leitet dann die Forschungsabteilung der Oberen Extremität an der Zürcher Schulthess-Klinik und gleist Projekte an der ETH auf. 2008 wird er Dozent und Gruppenleiter an der ETH. „Ich betrieb also gleichzeitig Grundlagenforschung und klinische Forschung“, bringt er seine Aktivitäten auf den Punkt.

Dann kommt ein Angebot von Novartis. An deren Abteilung Translational Medicine könnte er beide Bereiche kombinieren. Und gleich auf globalem Level. Eine verlockende Aussicht. Aber auch ein Bruch: „Wer in Europa von der akademischen Forschung in die Industrie wechselt, schlägt sich auf die dunkle Seite“, sagt Goldhahn und schmunzelt. Auch er selber habe sein Bild von der Industrie „mächtig nachkorrigieren müssen“. Man forsche da zum Teil sehr viel ernsthafter: „Am Ende muss ein Produkt da sein, welches die rigorosen internen Testungen und die Auflagen der Gesundheitsbehörden bestanden hat.“

Er habe viel gelernt in der Pharmaindustrie, einer faszinierenden, hoch regulierten Welt, konstatiert der Forscher. Als Beispiel nennt er die Lancierung internationaler Studien, bei denen auch kulturelle Unterschiede eine Rolle spielen: Schmerz zum Beispiel wird in verschiedenen Kulturkreisen unterschiedlich intensiv beschrieben.

Doch bei aller Faszination – zum Zeitpunkt unseres Gespräches steht Jörg Goldhahn vor dem Abschied aus der Industrie. Er nennt zwei Gründe für den Wechsel. Zum einen den Druck, neue Produkte immer schneller auf den Markt zu bringen. Doch der Hauptpunkt sei die Chance, als Medical Director des neuen Studienganges Medizin-Bachelor an der ETHZ etwas Bleibendes zu schaffen: „Einen Medizinbachelor mit zusätzlicher Forschungsausbildung, wie ich ihn mir als Medizinstudent gewünscht hätte.“ Auch die technologische Infrastruktur der ETH will Goldhahn stärker für die medizinische Forschung nutzen. Und so mithelfen, das berüchtigte Valley of Death in der klinischen Forschung zu überwinden, bei dem auf der einen Talseite die Forscher sitzen und auf der anderen die Patienten, bei denen die Fortschritte nicht ankommen.

Jörg Goldhahn wird seine Funktion als Repräsentant der Industrie beim CABMM abgeben. Doch er bleibt Mitglied des wissenschaftlichen Beirates und ist dort für die Begutachtung von Projektanträgen zuständig. Mit seiner breiten Erfahrung will er darauf hinarbeiten, die Kluft zwischen Akademie und Industrie zu verringern: „Die Industrie arbeitet nach dem Motto: Underpromise, overdeliver. Wenn dann die Hochschulseite bei Kollaborationen sehr viel verspricht, es aber nicht hält, ist der Industriepartner verstimmt“, gibt er zu bedenken.

Dass er Medizin studieren würde, stand für Jörg Goldhahn früh fest. Doch die Mutter, eine Krankenschwester, sagte: Schau es dir erstmal an! Dem jungen Hilfspfleger machte es aber nichts aus, Zwölferschlafsäle zu wischen und Patienten zu waschen. Die Hürden lagen woanders: „Wer in der DDR studieren wollte, wurde regelrecht in die Nationale Volksarmee gezwungen.“ Für Jörg Goldhahn war die NVA der schlimmste Ort, wo man 1989 sein konnte, denn es gab grosse Befürchtungen, dass die Armee auf das Volk schiessen sollte.

Auch in seinem Privatleben übernahm Jörg Goldhahn früh Verantwortung. Er wurde als junger Medizinstudent Vater einer Tochter und wollte das Studium unterbrechen. Doch das funktionierte für Väter damals noch nicht. So studierte er weiter. „Den Notenknick sehe ich noch heute“, sagt er lachend. Heute habe er einen guten Draht zu seiner 23-jährigen Tochter, die Kommunikation studiert und seinem 15-jährigen Sohn, für den er dann, voll im Berufsleben, weniger Zeit gehabt habe.

Wie erholt sich der Vielbeschäftigte? Er hat Spass am Handwerklichen. Die Familie besitzt ein altes Bauernhaus in der Nähe von Basel und einen Garten. „Da pflanzen wir Gemüse. Just for fun.“ Kürzlich hat er begonnen, Saxophon zu lernen. Und mit seiner Frau teilt er – neben den beruflichen Interessen – die Freude am Skilanglauf. „Je unterschiedlicher die Freizeit, desto mehr Erholung“, stellt er fest.

Jörg Goldhahns freie Zeit bleibt knapp. Denn bis der neue Studiengang 2017 startet, wartet noch viel Arbeit auf den Medical Director. Doch Goldhahn ist es gewohnt, immer wieder ins kalte Wasser zu springen und damit zurecht zu kommen, dass von einem Tag auf den anderen neue Regeln gelten. Mit einer solchen Biographie denke man stärker darüber nach, was einem wirklich wichtig sei im Leben. „Ich bin“, bilanziert er, „immer meinen eigenen Vorstellungen gefolgt und wartete nicht ab, bis mir jemand etwas anbot.“

"Doing what's really important to me"

jörg goldhahn, portrait by paula lanfranconi

Jörg Goldhahn is a professor at the Department of Health Sciences and Technology, ETH Zurich. His motivation: to bring research results quickly to the patients. As Medical Director of the new bachelor's program in medicine at the ETHZ, he wants to create something sustainable.

He hurries along the corridor at a fast pace. Rather wiry, with a boyish smile on his face and his hair tousled. Jörg Goldhahn is a person, who is always on the move. "From the outside" the 47-year-old says in his not yet completely furnished office, "my career appears quite disjointed – from clinics to research, then to industry and back again to academia".

His career started at the trauma surgery in Jena. Already at an early age, he developed prototypes of bone implants together with his father, a mechanical engineer. His boss soon became a little overwhelmed by the exploits of his younger assistant doctor and so sent him to the AO research institute in Davos. There, everybody was very enthusiastic about the newcomer from the ex German Democratic Republic. And there, Jörg Goldhahn also met Brigitte von Rechenberg. First ties to the future CABMM are established.

However, the young physician has to decide: become a good surgeon or a good researcher? His passion for research is stronger. He accomplishes post-graduate courses in Medical Physics and Biomechanics at the ETHZ, and subsequently heads the Department of Upper Extremities at the Schulthess clinic in Zurich and establishes projects at the ETH. In 2008, he becomes lecturer and group leader at the ETH. "Thus, I did

basic research and clinical research at the same time", he puts his activities in a nutshell.

Then he receives an offer from Novartis. At their Translational Medicine department he could combine both fields. And even on a global level. These are tempting prospects. But also a break: "In Europe, changing from academia to industry means moving to the dark side", Goldhahn says, and smiles. He also "had to strongly revise" his picture of industry. Research in industry is sometimes much more serious: "In the end, there has to be a product complying with the rigorous internal tests and the regulations of the health authorities."

He learned a lot in pharmaceutical industry, a fascinating and strongly regulated world, the researcher states. As an example, he mentions the launch of international studies, where cultural differences also play a role, e.g., the perceptions of pain varies a lot in different cultural groups.

But in spite of all these fascinating aspects, at the time of this interview Jörg Goldhahn is on the way to bid his farewell to industry. He gives two reasons for this change. One reason is the pressure to bring new products faster and faster to the market. But the main reason would be the possibility to create something sustainable as Medical Director of the new bachelor's program in medicine at the ETHZ: "As a medical student, I would've liked to have undertaken a bachelor in medicine with additional training in research." He also wants to take advantage of the technical infrastructure at the ETH for medical research with an aim to bridging the gap between researchers and patients and thus help avoid the infamous Valley of Death.

Jörg Goldhahn will resign from his function as industry representative at the CABMM. However, he'll continue to be a member of the Scientific Advisory Board, where he is in charge of evaluating project proposals. With his broad experience, he will work towards reducing the gap between academia and industry: "Industry is following the slogan: Under promise, over deliver. If a collaborative partner from academia promises a lot, but doesn't deliver, then the industry partner gets annoyed" he points out.

Jörg Goldhahn knew already early on that he wanted to study medicine. But his mother, a nurse, said: Have a look at it first! The young temporary nurse didn't mind to wipe dormitories with twelve beds and to wash patients. The obstacles were different: "Whoever wanted to study in the German Democratic Republic was really forced to join the National People's Army (Nationale Volksarmee, NVA)." And in 1989, the NVA was the worst place for Jörg Goldhahn to be, as there was good reason to fear that the army was to shoot on people.

Also in his private life, Jörg Goldhahn took on responsibility at an early age. As a young medical student, he fathered a daughter and wanted to postpone his studies. But that was not possible for fathers at this time. So he continued. "Even today, I can still see the sharp drop in my grades" he says laughing. Today, he has a close relationship to his 23-year-old daughter, who studies communication, and to his 15-year-old son, for whom he had much less time, being fully occupied with his professional life.

How does the busy man relax? He enjoys craftwork. His family owns an old farmhouse close to Basel with a garden. "There we grow vegetables. Just for fun." Recently, he started playing saxophone. And with his wife he shares – in addition to their professional interests – the joy of cross-country skiing. "The more diverse the leisure time, the better the recovery", he states.

Jörg Goldhahn's free time is scarce. There is a good deal of work for the Medical Director before the new study course starts in 2017. But Goldhahn is used to jumping in at the deep end and coping with changes to rules on a daily basis. With such a biography, one thinks more about what really matters in life. "I have always followed my own ideas", he makes up the balance, "and did not wait until something was offered to me."

„managerin, mutter und pferdefan“

silke kalchofner-mark, portrait von paula lanfranconi

Dr. Silke Kalchofner-Mark ist Geschäftsführerin des CABMM. Sie arbeitet gerne mit Menschen, aber auch mit Zahlen. Als junge Mutter findet sie die zeitliche Flexibilität am CABMM toll.

Platz gibts nicht viel in ihrem Büro. Aber das findet die gross gewachsenen Frau mit den strahlenden braunen Augen nicht so wichtig: „Wichtig ist, dass wir hier, auf dem Campus der Universität Zürich-Irchel, gut erreichbar sind.“ Und der Platz reicht ja für zwei muntere Familienfotos. Und für eine Künstlerzeichnung von Kater Mäxi, dem Namensgeber der Mäxi-Stiftung, Hauptsponsorin des CABMM. Silke wirkt entspannt. Doch ihre Tage sind lang. Vor der Arbeit hat sie ihre dreijährige Tochter Jana in die Kita gebracht und den achtjährigen Jonathan in die Schule. Und Jonathan war es auch, der sie zum CABMM geführt hatte. Doch davon später.

An diesem Vormittag hat sie sich mit Finanzverwaltung befasst. Eröffnete neue Projekte und erstellte Rechtsgrundlagen für die Zahlungsabwicklung. „Nichts Dramatisches“, sagt sie auf ihre lockere Art. Die Arbeit, das spürt man rasch, macht ihr Spass. Neben der Finanzverwaltung gehört auch das Personalwesen zu ihren Aufgaben. Dazu kommt die Organisation der Forschungsplattform, die Betreuung der Mitglieder, das Organisieren von Kongressen, die Website, der Jahresbericht. Und wohl noch einiges mehr. Am meisten Freude macht ihr die Zusammenarbeit mit Menschen: „Hier, am CABMM mit seinen unterschiedlichen Forschungsgruppen und den Leuten auf der Plattform ist diese Zusammenarbeit ziemlich abwechslungsreich.“ Genau so gerne befasst sie sich mit Zahlen – ein Talent, das sie vom Vater, einem Finanzbeamten, mitbekommen hat.

Eigentlich wollte die heute 43-Jährige Chirurgin werden. Doch sie war schlau genug, vorher ein Praktikum im Krankenhaus zu machen. Dabei realisierte sie, dass die Arbeitsbedingungen im OP ein Familienleben kaum zulassen. So studierte sie Biochemie an der Universität Hannover. Ihr Ziel: die angewandte Forschung. Dass sie sich früh dem Knochenstoffwechsel zuwandte, ist Zufall. Während ihrer Doktoratszeit kam ein junger Mediziner vorbei und bat sie um Unterstützung bei der Kultivierung von Knochenzellen. „Seither“, sagt Silke lachend, „bin ich bei den Knochen hängen geblieben. Eine spannende Materie!“

Ihr Weg führte sie dann nach Lausanne, ans Ludwig Institute for Cancer Research. Doch die Immunologie war nicht so ihr Ding. So wechselte sie zu einer kleinen biomedizinischen Firma nach Zürich und damit in die Privatindustrie. Dort konnte sie ihren Forscherinnengeist mit ihrem Flair für Zahlen und Management kombinieren.

Und in Zürich lernte sie auch Brigitte von Rechenberg kennen, welche mit ihrer Gruppe Forschung für jene Biomedizinfirma betreibt. Zwei Jahre später, 2007, wurde Silke zum ersten Mal Mutter. Sie war alleinerziehend und die Grosseltern weit weg. „Es gab Probleme mit der Vereinbarkeit von Kind und Karriere. Da hab' ich gekündigt“, sagt Silke energisch. Und dann sei alles ziemlich schnell gegangen. Brigitte von Rechenberg habe gesagt: Silke, wir haben gerade ein Forschungszentrum

gegründet. Du hast Managementerfahrung: Wie wärs mit der Geschäftsführung? Zuerst, erinnert sich Silke, habe sie leer geschluckt. Doch dann sagte sie zu: „Wegen der guten Forschung und der tollen zeitlichen Flexibilität am CABMM.“

Die beiden Frauen haben etliche Gemeinsamkeiten. Beide reden nicht gerne um den heissen Brei herum. Und beide sind Pferdeliebhaberinnen. Silke verbrachte schon früh jede freie Minute im Reitstall. „Und ich hatte das Glück, dass an unserem kleinen Ort im Hessischen ein hoch professioneller Reiter den Stall übernahm und Springpferde ausbildete.“ Während des Studiums begeisterte sie sich dann auch für den Fahrsport und kaufte sich, zum Entsetzen ihrer Eltern, ein eigenes Pferd und bestritt Fahrturniere. Auch jetzt noch gerät sie ins Schwärmen über Antal, ihren dunkelbraunen Württemberger aus dem Haupt- und Landgestüt Marbach: „Antal hatte ein geniales Bewegungstalent.“

Ihre Pferdebegeisterung sprach sich in Zürich schnell herum: 2010 übernahm die passionierte Reiterin auch die Geschäftsführung der Stiftung Forschung für das Pferd. Bei den unterstützten Projekten geht es zum Beispiel um eine effektivere Behandlung von Verletzungen oder um die Bekämpfung des Pferdehustens.

Im Sattel indes trifft man die inzwischen zweifache Mutter mit ihrem 60 Prozent-Arbeitspensum kaum mehr an. Auch ihre Tauchausrüstung und das Keyboard verstauben im Keller. Ihr Ehemann, stellvertretender Rektor einer grossen Schule, unterstützt sie nach Kräften, ist aber beruflich noch mehr gefordert als Silke. So sind die Kinder stark auf die Mutter ausgerichtet: „Es ist zwar süss, wenn sie „Mama! Mama!“ rufen, aber auch schwierig, zu sagen: Nein! Heute ist Papa dran.“ Langsam lernt die Perfektionistin aber, dass die Welt nicht untergeht, wenn die Küche mal unaufgeräumt bleibt. Und sie hat entdeckt, dass Schaukeln auch für Erwachsene toll sei.

Überhaupt seien ihre Kinder das Beste, was ihr im Leben passiert sei, sagt sie und strahlt. Die beiden hätten sie gelehrt, die Welt mit anderen Augen zu sehen. Zum Beispiel die Fahrt zur Arbeit. Früher habe sie sich über jede Baustelle und jeden Stau genervt. Mit Sohn Jonathan sei das anders. Er sehe den Stau gar nicht, sondern rufe: Mama schau: Da ist ein blauer Bagger, da ein Gelber! Kinder, konstatiert die junge Mutter, begegnen der Welt unvoreingenommen: „Wenn sie, zum Beispiel, jemandem mit Behinderung begegnen, fragen sie einfach nach. Und dann ist die Person in ihre Welt aufgenommen, ohne Wenn und Aber.“

Die Zukunft? Beruflich sei sie im Moment ganz zufrieden, sagt sie. Es sei schön, am CABMM etwas zu gestalten und weiter zu entwickeln. Und privat? Da müsse sie noch stärker auf sich selber achten, meint sie selbstkritisch. Wieder mehr Sport treiben. Laufen, Tauchen. Reiten natürlich. Und Badminton. Da werde sie von Jonathan schon ganz schön herum gescheucht. „Im Moment gewinne ich beim Wettrennen noch. Aber in einem Jahr?“, fragt sie und schmunzelt.

"manager, mother and horse enthusiast"

silke kalchofner-mark, portrait by paula lanfranconi

Dr. Silke Kalchofner-Mark is Managing Director of the CABMM. She likes working with people, but also with numbers. As a young mother, she highly appreciates the flexible working hours at the CABMM.

There is not a lot of space in her office. But this is not important to the tall woman with the bright brown eyes. "It is important that our facilities at the Irchel Campus of the University of Zurich are easily reachable." And there is enough space for two cheerful photos of her family. And for an artist's drawing of Mäxi, the cat who gave his name to the Mäxi Foundation, the main sponsor of the CABMM. Silke looks relaxed. But her days are long. Before work, she took her three-year-old daughter Jana to the childcare and her eight-year-old son Jonathan to school. In the end, it was Jonathan who led her to the CABMM. But we come back to this later.

This morning she occupied herself with financial administration. Opened new projects, prepared legal bases for arranging payments. "Nothing major", she says in her easy-going way. One can feel quickly, she enjoys her work. In addition to financial management, her tasks include human resources. And furthermore, she takes care of the CABMM Research Platform, the member network, the organisation of congresses, the homepage, the yearly report. And probably even more. She most enjoys working with people: "Here at the CABMM with the different research groups of our network and the people working on our platform, this work is quite multifaceted." She enjoys working with numbers equally as much – a flair that has been passed on by her father, a taxman.

Originally, the 43-year old wanted to become a surgeon. But she was clever enough to do an internship in a hospital before her decision. In doing so, she realised that the working conditions in the operating theatre hardly permit for a normal family life. Thus, she studied biochemistry at the University of Hannover. Her goal: applied research. By coincidence, she turned her attention already early in her career to the field of bone metabolism: During her PhD work, a young physician passed by and asked for help in culturing bone cells. "Since then", Silke says laughing, "I have stayed with bone. A fascinating field!"

Her path led her to Lausanne, to the Ludwig Institute for Cancer Research. But immunology was not really her cup of tea. Thus, she moved to a small biomedical company in Zurich and thereby, to private industry. There, she was able to combine her research mind with her flair for numbers and management.

And in Zurich she met Brigitte von Rechenberg, who performed research studies for even this biomedical company. Two years later, in 2007, Silke gave birth to her first child. She was a single mother and didn't have any family close by. "Problems with the compatibility of child and career arose. So I quit", she says resolutely. And then, everything went quickly. Brigitte von Rechenberg told her: Silke, we have just founded a new research center. You have management experience: What about the position as managing director? At first, Silke remembers, she had to swallow hard. But then she accepted. "Because of the interesting research and flexible working at the CABMM."

Both women have many things in common. Both do not like to pussyfoot around. And both are horse enthusiasts. Early on, Silke spent every available minute in the riding stable. "I was very lucky, because a highly professional rider took over the riding stable in our small town in Hesse and trained jumping horses." During her studies, she became enthusiastic about horse carriage driving and bought – to the horror of her parents – her own horse and participated in horse driving competitions. She still goes into rhapsodies over Antal, her dark brown Württemberg warm blood horse from the Main and County Stud Marbach: "He showed such talented movements."

It didn't take long for her horse passion to get around in Zurich: In 2010, the enthusiastic horsewoman took over the management of the Foundation Research for Horses as well. This foundations supports projects for the well-being of horses, e.g., the development of more effective procedures for the treatment of injuries or for fighting the horse cough.

Nowadays, after giving birth to her second child, the mum of two with her 60% employment is hardly able to find time to ride herself. And also her diving equipment and the keyboard sit in the basement gathering dust. Her husband, Deputy Rector of a large school, makes his best endeavours to support her, but is even more challenged with work than Silke. Therefore, the children strongly focus on her: "Of course, it's

cute if they call 'Mummy! Mummy!', but it is also hard to say: No, today it's Daddy's turn." Slowly, the perfectionist learns that nothing happens and that it is not the end of the world if the kitchen is sometimes untidy. And she discovered that playing on the swings is also great fun for adults.

Generally, her kids are the best things that ever happened to her, she says and is all smiles. The two of them taught her to see the world in a different light. For example, on her way to work. In the past she got annoyed by every construction site and traffic jam. Together with Jonathan, this would be different. He would not realise the traffic jam, but rather get excited: Mummy look: there is a blue digger, and there is a yellow one! Children, the young mother states, are really open-minded: "If they, for example, meet a handicapped person, they simply ask about the handicap. And then, this person is accepted, without fuss or quibble."

The future? At the moment she would be quite satisfied at work, she says. It would be nice to shape and further develop things at the CABMM. And in her private life? She should still pay more attention to herself, she says self-critically. Do more sport again. Running. Scuba diving. Horse riding, of course. And Badminton. Playing Badminton, Jonathan's already keeping her rather busy. "Racing against each other, I'm still winning. But in a year's time?" she asks and smiles.

„zwei mal zwei kinder und eine volle karriere“

marcy zenobi-wong, portrait von paula lanfranconi

Marcy Zenobi-Wong ist Assistenzprofessorin am Departement Health Sciences and Technology der ETH Zürich. Sie kommt aus einer MIT-Familie, Forschung ist ihr Leben. Doch wie schafft man das mit vier Kindern?

Es ist Montagmorgen. Am Wochenende war der Geburtstag ihres Mannes. Sie hatten die jüngeren Kinder bei der Schwiegermutter abgegeben und fuhren in die Berge. „Es war“, sagt Marcy Zenobi-Wong lächelnd, „ein aussergewöhnlich ruhiges Weekend.“ Heute ist wieder volles Programm auf dem Hönggerberg. Doktorierende werden vorbei kommen. Sie hatten Publikationen eingereicht, inzwischen antwortete das Journal.

Marcy Zenobi-Wong ist die Ruhe selbst. Ihre Hauptaufgabe an der ETHZ ist, neben ihren Vorlesungen, die Forschung. Sie verbringt die Mehrheit ihrer Zeit mit der Betreuung von Doktorierenden. Da ist Marcys breite Ausbildung gefragt – und ihre besondere Fähigkeit, Informationen aus ganz unterschiedlichen Gebieten so zusammen zu bringen, wie es noch niemand versucht hatte.

Wie muss man sich ihre Zusammenarbeit mit dem CABMM vorstellen? Sie erwähnt als Erstes die Mäxi-Stiftung. Einige ihrer Projekte sind von dieser Stiftung gesponsert. „Das ist eine grosse Hilfe. Dank der Mäxi-Stiftung können wir High Risk-Projekte starten und zeigen, dass es klappt. Und dann ein Forschungsgesuch beim Schweizerischen Nationalfonds einreichen."

Auf das CABMM war Marcy 2012 an einem von diesem organisierten Symposium gestossen. Dort präsentierte Professorin Lee Laurent-Applegate vom Centre Hospitalier Universitaire Vaudois neueste Forschungsergebnisse. Seit diesem Symposium verwenden Marcy und ihre Gruppe Zellen von Professor Applegate: „Es sind spezielle und potente Zellen: Chondroprogenitors, eine Art Knorpelstammzellen.“

Auf Marcys Tisch steht das Modell eines Kniegelenks. Sie zeigt auf das Knorpelgewebe. Es ist bloss wenige Millimeter dick und wird beim Sport häufig verletzt. „Skifahren und Fussball sind schlecht für die Knie“, weiss die Forscherin. Das Problem: An der verletzten Stelle ist der Knorpel weg. Das Loch vergrössert sich mit der Zeit, und das Gewebe degeneriert, bis so starke Schmerzen entstehen, dass ein künstliches Kniegelenk nötig wird.

Ziel von Marcys Gruppe ist es, diesen Degenerationsprozess zu verlangsamen oder zu verhindern, indem sie in den frischen Defekt eine Mischung aus Zellen und Biopolymeren injizieren. *In vitro* klappt es bereits. In ein paar Wochen geht das Team *in vivo*. „Wir schauen, ob unsere Polymere und die Zellen von Frau Applegate mit der Technik von Frau von Rechenberg einen Beitrag leisten können für die Knorpelregeneration“, sagt die Forscherin. Ein Frauenpower-Projekt. Doch für Marcy macht das keinen Unterschied: „Ich arbeite einfach mit den besten Partnern.“

Marcy Zenobi-Wong kommt aus einer chinesischstämmigen MIT-Familie. Schon Vater, Onkel, Bruder und ihre zwei Schwestern studierten am MIT. Ihr Vater habe dafür Opfer gebracht: „Statt ein teures Auto zu kaufen, investierte er das Geld in unsere Ausbildungen.“ Noch heute ist ihr der Vater ein Vorbild. Er ist Materialwissenschaftler, gründete eine eigene Firma und reicht auch mit 85 noch Ideen für Patente ein. „Er liest sich in immer neue Gebiete ein. Das ist inspirierend“, sagt die Tochter.

Das MIT hat Marcy geprägt. Ihr Bachelorstudium dort sei viel härter gewesen als alles, was nachher kam: Jede Woche eine Liste mit Problemen lösen. Dann Prüfungen. Immer wieder, nonstop. „Man nennt das Drinking from a firehose“, sagt Marcy. Ihr kreatives Talent, die Freude am Suchen nach eigenen Lösungswegen, sei erst später zum Zug gekommen. Zum Beispiel in Stanford, wo Marcy ihren Doktor machte. Und wo sie ihren Mann kennen lernte: Renato Zenobi, „einen Schwiizer, das war damals selten in Stanford.“ Renato Zenobi doktorierte in analytischer Chemie.

In Europa zu leben, hatte das Paar nicht geplant. Doch dann gewann Renato Zenobi ein Stipendium an der EPFL: „Wir dachten, wir probieren es für ein paar Jahre in der Schweiz.“ Sie zogen nach Fribourg, Marcy pendelte an die Universität Bern, ihr Mann nach Lausanne. Doch dann wurde die Schweiz definitiv: Renato erhielt eine Berufung an die ETH Zürich. Und in Zürich kamen die Kinder zur Welt.

Doch wie schaffte es Marcy, Karriere zu machen und gleichzeitig vier Kinder grosszuziehen? Sie lächelt auf ihre gelassene Art und relativiert, eigentlich seien es zwei Mal zwei Kinder gewesen: „Die beiden Älteren waren schon recht selbständig, als die Jüngeren kamen. Als sie klein waren, habe ich immer Teilzeit gearbeitet.“ Noch heute ist sie ihren Chefs "dankbar für ihr Vertrauen, ihre Grosszügigkeit und Flexibilität“. Jetzt, als Professorin, arbeitet Marcy manchmal 150 Prozent. Wenn sich die Vorlesungspläne mit jenen ihres Mannes überschneiden oder die Kinder krank sind, kann sie auf die Schwiegereltern zählen. „Sie waren immer für mich da, das ist entspannend.“

Inzwischen haben die beiden älteren Söhne eine Berufslehre gemacht – einer im IT-, der andere im Versicherungsbereich. Für MIT-Absolventin Marcy war das eine ganz neue Erfahrung. Sie zeigt sich „zu 100 Prozent begeistert“ von diesem schweizerischen Weg. „Die beiden sind in dieser Zeit stark gereift“, stellt sie fest.

Zeit für Hobbies bleibt ihr im Moment nicht. Wenn die jüngeren Kinder im Bett sind, nutzt sie die Ruhe für den fachlichen Austausch mit ihrem Mann, denn Chemie ist zentral für ihre Arbeit: „Ich sage Renato: Wir möchten das und das machen. Und dann skizziert er eine Lösung von der Chemieseite her.“

Ihr nächstes grosses Ziel ist das Experiment mit der neuen Knorpeltherapie im Schaf. Ihr Hauptgefühl dabei? „Vorsicht, *in vivo* kann immer etwas passieren“, meint sie lächelnd. Und privat? „Noch besser werden im Einradfahren. Zirkusauftritte sind nicht geplant. Aber es ist auch so cool“, sagt Marcy. Und wendet sich wieder ihrer Arbeit zu.

"Two times two children and a full time career"

marcy zenobi-wong, portrait by paula lanfranconi

Marcy Zenobi-Wong is an assistant professor at the Department of Health Sciences and Technology, ETH Zurich. She was born into a technology-loving family and research is her life. But how is she able to cope with the challenges of a demanding job and four kids?

It's Monday morning. Last weekend was her husband's birthday. They brought their younger children to her mother-in-law's house and travelled alone into the mountains. "It was", Marcy Zenobi-Wong says with a smile "an exceptionally quiet weekend." Today, she has again a full program at the ETH Hönggerberg. Doctoral students will come to discuss their project results. The group submitted a publication, and in the meantime the reviewer's comments have come back and need to be answered.

Marcy Zenobi-Wong is calm by nature. Beside lecturing to Bachelor and Master students, her main job at the ETHZ is research. She spends most of her time supervising doctoral students. Here Marcy's broad research background comes in to play – in particular her ability to bring together facts from totally different fields, and to try things no one has tried before.

How has she benefited from working within the CABMM network? The first thing she mentions is the Mäxi Foundation, which has supported some of her projects. "It's so important. Thanks to the Mäxi Foundation, we can start high-risk projects and show that our ideas work. And afterwards submit a proposal to the Swiss National Science Foundation."

Marcy came across the CABMM in 2012 at one of their symposia. At this event, Prof. Lee Laurent-Applegate from the Centre Hospitalier Universitaire Vaudois presented her latest research results. And since then, Marcy and her group have been working with cells from Prof. Applegate: "These cells are very special and potent: chondroprogenitors, a kind of cartilage stem cell."

On Marcy's table is a model of a knee joint. She points to the cartilage tissue. It's only a few millimetres thick and often injured doing sports. "Skiing and soccer are the worst sports for the knee", the researcher points out. The problem: cartilage continues to degenerate in and around the injured site. With time, the lesion gets bigger and the joint degenerates until the point where the pain is so great that an artificial knee joint is required.

The goal of Marcy's group is to slow or even prevent this degenerative process by injecting a mixture of cells and biopolymers into the fresh defect. *In vitro*, it works already. In a few months, *in vivo* experiments will start. "We will investigate if our polymers together with the cells from Prof. Applegate can contribute to cartilage regeneration using the surgical techniques of Prof. von Rechenberg", the researcher says. A women power project. But for Marcy, this doesn't make any difference: "I'm simply working with the best partners."

Marcy Zenobi-Wong was born into a Chinese American MIT family. Her father, her three uncles, her brother and her two sisters all studied at the MIT. Her father sacrificed a lot for his kids: "Instead of buying an expensive car, he invested the money in our education." Her father is still one of her role models. He is a material scientist, founded his own company and is still filing patents at the age of 85. "He's continually emerging himself in new fields. That's inspiring", the daughter says.

MIT has shaped Marcy. Her bachelor studies at MIT were harder than everything else afterwards: Every week, lists of problems to be solved. Then exams. Again and again, non-stop. "They called this `drinking from a fire hose` ", Marcy says. Only later could she make use of her creative talent and her passion for solving problems. At Stanford, for example, where Marcy completed her doctorate. And where she met her husband: Renato Zenobi, "a Swiss PhD student at Stanford, that was rare at the time." Renato Zenobi did his PhD in analytical chemistry.

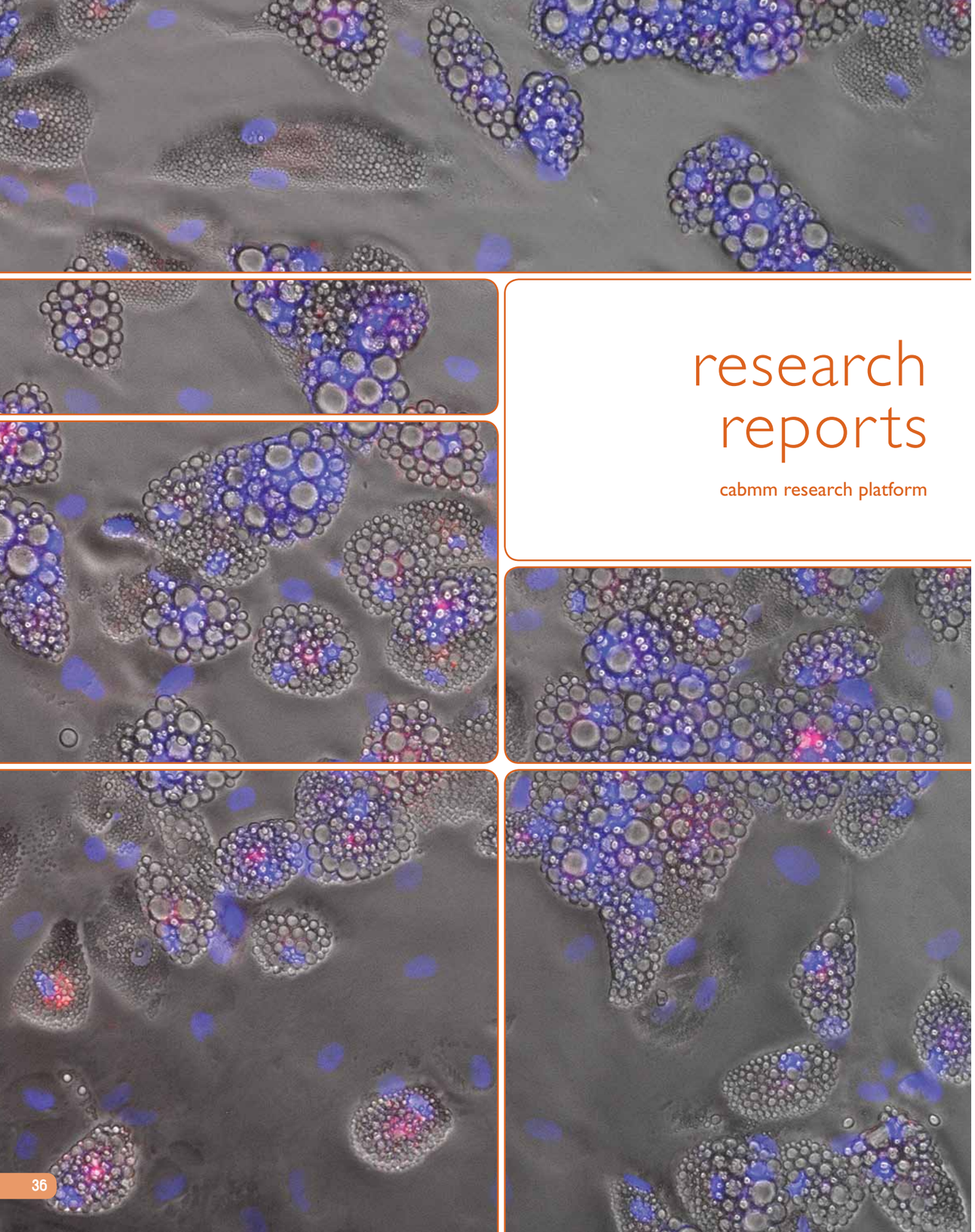
The couple didn't plan to live in Europe. But then Renato Zenobi got a fellowship at EPFL: "We thought we would try it in Switzerland for a few years." They moved to Fribourg, Marcy commuted to the University of Bern, her husband to Lausanne. But then Switzerland became more permanent: Renato was offered a professorship at the ETH. And in Zurich, their children were born.

But how was Marcy able to have a successful career and to raise four kids? She smiles, saying that it was actually `two times two` kids: "The two older ones were already rather independent, when the younger ones were born. And when the kids were young, I always worked part time." To this day she is still "grateful for the trust, generosity and flexibility" of her bosses. Now, as a professor, Marcy works sometimes 150 percent. When they both have lectures or the kids are sick, she can always count on her parents-in-law. "They are always there for me."

In the meantime, the two older sons have both finished an apprenticeship – one in IT, the other one in the insurance sector. This was a new experience for Marcy as an MIT graduate. She is "100% enthusiastic" about this Swiss career path. "Both have matured a lot during this time", she states.

She doesn't have a lot of time for hobbies at the moment. When the younger children are in bed, she often uses the quiet time to discuss science with her husband, as chemistry is essential for her work: " I tell Renato: We would like to do this and that. And then he is outlining a solution from the chemistry point of view."

Her next big goal is the sheep experiment to test the new cartilage therapy. Her overriding feelings about this? "I am cautious, *in vivo* anything can happen", she says smiling. And in her private life? To become even better at unicycling. Circus performances are not planned. "But it's cool anyway", Marcy says. And she turns back to her work.



research reports

cabmm research platform

The CABMM Research Platform is a multidisciplinary organisation embedded within the Department of Molecular Mechanisms of Disease (DMMD) at the University of Zurich. Our main objectives are to foster translational, clinically oriented research and to promote scientific collaborations between CABMM members. The CABMM Research Platform is well equipped and provides a stimulating environment, where basic scientists and clinicians 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.

During the reporting period 2014/2015, there have been a total of 5 research groups using the CABMM Research Platform, consisting of 14 people in total.

1. Bone & Stem Cell Research Group
Group leader: Peter J. Richards

2. Cranio-Maxillofacial Surgery and Implantology Group*
Group leader: Brigitte von Rechenberg

3. Equine Research Group*
Group leader: Anton Fürst

4. Musculoskeletal Research Unit
Group leader: Brigitte von Rechenberg

5. Tendon Repair Group
Group leader: Anton Fürst

A short overview of the projects conducted within these groups is given on the following pages.

Moreover, we present the research of Prof. Dr. Janine Reichenbach from the Division of Immunology at the University Childrens`s Hospital Zurich, who is also a member of the CABMM Steering Committee. The research focus of her group is on inborn errors of the immune system, spanning from the analysis of molecular pathophysiologies to the development of new therapeutic concepts, e.g., the use of gene therapy.

*until December 2014

gene therapy for inborn immuno deficiencies

Janine Reichenbach (Prof. Dr. med.)

Group members (in alphabetical order): Dr. sc. nat. Rocio Garcia de la Cruz Valencia (PostDoc), Dr. sc. nat. Elena Kuzmenko (technician), Dr. med. Virginia Meda-Spaccamela (MD-PhD student), Dr. biomed. sci. Oleksandr Pastuhkov (PostDoc), PD Dr. rer. nat. Ulrich Siler (scientific laboratory head), Dominik Wrona (PhD student)

How the human body protects itself

Humans are exposed to numerous microbes invading the body. The immune system protects humans by detecting and neutralizing these microbes. Healthy individuals have a balanced activity of the immune system: strong enough to combat invading microbes like bacteria, fungi, viruses and parasites, but balanced enough not to overreact to harmless agents (as in allergy) or not to attack own body tissue (as in autoimmunity). Numerous diseases arise from disturbed balance of immune reactions, or from absence of appropriate reaction of the immune system to microbes (as in immunodeficiency).

To date more than 250 inborn immunodeficiencies are known which result in the absence of parts of the immune system and which are caused by alterations within the genetic code (desoxyribonucleic acid, DNA). The immune system is continuously built up and renewed from a small number of cells, so called hematopoietic (blood / immune cell building) stem cells, located within the bone marrow. Defects within the genetic code of these cells result in the inability of the immune system to protect the body against microbes and the patients therefore suffer from recurrent, severe and/or long lasting infections. The latter may result in organ damage and potentially death early in life.

Cure of immunodeficiencies: hematopoietic stem cell transplantation

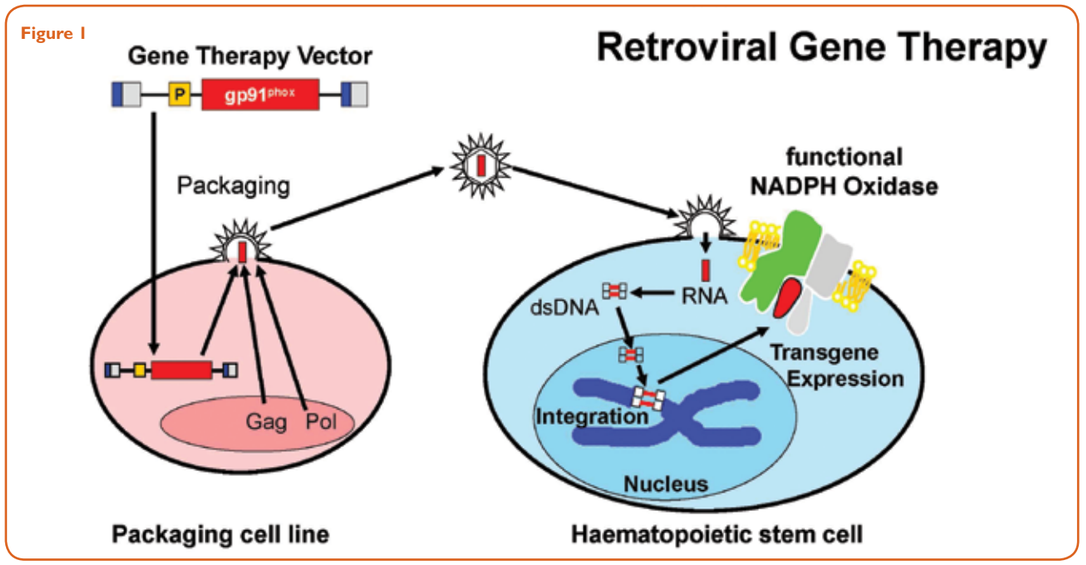
For a number of severe immunodeficiencies the exchange of defective hematopoietic stem cells (HSCs) in the bone marrow against healthy HSCs from a related or unrelated donor can cure the disease, as these healthy donor cells can build up a new immune system. This procedure is called hematopoietic stem cell transplantation (HSCT, or bone marrow transplantation). HSCT can only be conducted safely if the cells of the recipient and the cells of the donor are highly similar with regard to expression of human leukocyte antigen (HLA) surface markers and therefore do not recognize each other as foreign. For about 75 % of patients adequate HLA-compatible donors can be found. For those patients without a compatible HSC donor additional treatment options are highly desired. Gene therapy for inborn single-gene defects was developed within the last years as a treatment option for patients requiring HSCT, but lacking an appropriate HSC donor.

Cure of immunodeficiencies: stem cell gene therapy

As an alternative to exchanging the HSCs in the bone marrow by HSCs from a related or unrelated healthy donor, gene therapy for inborn immunodeficiencies relies on correction of the patient's own HSCs: a patient's HSCs are first isolated from his bone marrow, then the specific genetic defect is corrected within these cells in a highly specialized laboratory. Finally, the genetically corrected cells are given back to the patient. Gene therapy is an autologous procedure, as opposed to HSCT from a healthy donor, which is an allogeneic procedure. The gene-corrected patient's own cells do not lead to graft-versus-host disease (the newly built up immune system attacks the body of the host), which is a risk in allogeneic HSCT where foreign donor cells are involved.

The genetic code of the human body is organized in small units termed genes. Every gene comprises a regulatory unit (promoter) which determines in which cells of the body it will be active and lead to the synthesis ("expression") of a protein, and a coding unit determining the architecture of a protein to be expressed. Proteins are the structures that carry out the functions of a cell – for immune cells the protection of the body. A defect within the genetic code results most often in incorrect protein architecture and thereby in an inactive protein and missing immunological function.

Figure 1



During retroviral gene therapy, the content of a gene therapy vector encoding for a therapeutic gene, e.g., the NADPH oxidase gene for the treatment of X-linked Chronic Granulomatous Disease, is added to the genome of the patient's hematopoietic stem cells (HSCs).
First, the gene therapy vector is introduced into packaging cells *in vitro*. These packaging cells then produce retroviral particles, which are subsequently added to HSCs of the patient. The retroviral particles bind to the cell surface of the HSCs and release the corrective gene in form of ribonucleic acid (RNA) into the cells. Next, the corrective RNA is reversely transcribed into double stranded deoxyribonucleic acid (DNA) and stably integrated into the genome of the patient's HSCs, thereby compensating for the genetic defect.

Bei der retroviralen Gentherapie wird ein therapeutisches Gen mit Hilfe eines Gentherapie-Vektors in das Genom der hämatopoetischen Stammzellen (HSZ) des Patienten eingefügt. Bei der Behandlung der X-chromosomalen Form der Septischen Granulomatose handelt es sich dabei um das NADPH-Oxidase-Gen.
Zunächst wird der Gentherapie-Vektor in vitro in Verpackungszellen eingebracht. Die Verpackungszellen beginnen dann retrovirale Partikel zu bilden. Diese werden anschliessend mit den HSZ des Patienten zusammengebracht. Sie binden an die HSZ und setzen das therapeutische Gen in Form von Ribonukleinsäure (RNA) in die Zellen frei. Diese korrektive RNA wird daraufhin in doppelsträngige Desoxyribonukleinsäure (DNA) umgeschrieben und stabil in das Genom der HSZ integriert, wodurch der genetische Defekt kompensiert wird.

Present gene therapy is a gene-addition therapy, i.e. a functional gene is inserted into the genetic code of the patient's HSCs without replacing the defective gene. The activity of this newly added, corrective gene then compensates the missing function of the mutated gene. This functional corrective gene is called a transgene. To date it is inserted into the genetic code by engineered transport vehicles derived from retro-viruses. These vehicles are called gene therapy vectors. In order to utilize viruses as gene therapy vector, these have to be modified in a way that they are not able to infect a patient, i.e. they must not be able to build new viruses and spread in the body. Furthermore, the genetic code of the viruses has to be further modified to encode the new corrective transgene.

A feature of these gene therapy vectors is that they can adhere to HSCs and release the corrective gene into the cells where it is then stably integrated into the genetic code of the patient. Upon stable integration, the transgene is transmitted to all progeny cells deriving from the corrected HSCs. In these progeny cells, the activity of the transgene will result in the synthesis of functional protein and thereby correct the immunodeficiency.

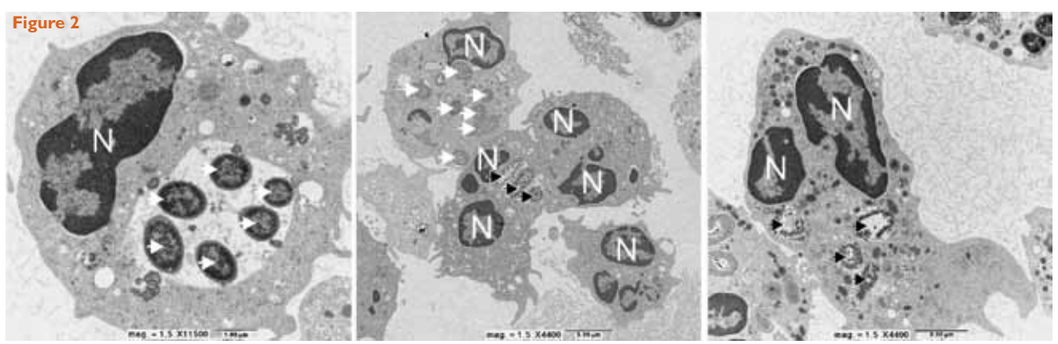
The immunodeficiency Chronic Granulomatous Disease

Chronic Granulomatous Disease (CGD) comprises a group of inborn immunodeficiencies manifesting already during childhood with recurrent and often life-threatening bacterial and fungal infections. Additionally, about half of CGD patients have severe inflammation mainly in the gastrointestinal tract (colitis). These immunodeficiencies are caused by single-gene defects in subunits of the so-called NADPH oxidase in two populations of immune cells, collectively called phagocytes as they eat and digest microbes: in granulocytes and in monocytes / macrophages.

Both cell populations play a pivotal role in the bodies' combat against invading bacteria and fungi as they normally inactivate these microbes by the production of reactive oxygen species (ROS) driven by the NADPH oxidase. ROS act similar to bleach utilized in the household for the same purpose.

In CGD, phagocytes are unable to synthesize ROS and therefore cannot kill invading bacteria and fungi with the consequence that microbes persist within the phagocytes. In addition to this intracellular killing defect, CGD phagocytes have a dysfunction of extracellular killing. Together with colleagues from the Max-Planck-Institute in Berlin (group Prof. A. Zychlinski), our laboratory has elucidated how healthy phagocytes kill fungi which are substantially larger than themselves by traps formed from DNA and antimicrobials. These web-like structures are called neutrophil extracellular traps (NETs). CGD patients cannot form NETs due to deficient ROS production, and therefore suffer from severe bacterial and fungal infections. We could show that NET formation is restored by gene therapy and lead to clearance of severe fungal infection in CGD patients (see below).

Figure 2



Electron microscopy of granulocytes from a CGD patient (left), a CGD patient after gene therapy (middle) and healthy control (right) after 2.5 h of incubation with bacteria (E. coli). Prominent dark structures are cell nuclei (N). The CGD granulocyte shows six vital bacteria (white arrows) trapped in a vacuole. The healthy control granulocyte managed to kill the engulfed bacteria (black arrows). After gene therapy, the patient possesses two populations: healthy granulocytes derived from corrected hematopoietic stem cells (HSCs) which engulfed and killed bacteria (black arrows), as well as diseased granulocytes derived from un-corrected HSCs which still show the CGD phenotype with vital bacteria inside (white arrows).

Elektronenmikroskopische Aufnahme von Granulozyten eines CGD-Patienten (links), eines CGD-Patienten nach Gentherapie (Mitte) und eines gesunden Probanden (rechts) nach 2.5-stündiger Inkubation mit Bakterien (E. coli). Die Zellkerne (N) sind als dunkle Strukturen erkennbar. Der CGD-Granulozyt zeigt sechs vitale Bakterien (weisse Pfeile) in einer Vakuole. Der Granulozyt des gesunden Probanden konnte die aufgenommenen Bakterien abtöten (schwarze Pfeile). Nach erfolgter Gentherapie weist der Patient zwei Populationen auf: Granulozyten, die von genetisch korrigierten Stammzellen abstammen und Bakterien abtöten können (schwarze Pfeile), sowie Granulozyten, welche weiterhin den CGD-Phänotyp aufweisen und Bakterien nicht abtöten können (weisse Pfeile).

In addition, CGD not only manifests in a predisposition to bacterial and fungal infections but also in a hyperactivity of the immune system leading to chronic inflammation with granuloma formation most often in the gastrointestinal tract. The mechanism of the persistence of these inflammatory reactions is only partially understood. We have shown that CGD hyperinflammation is linked to hyperactive inflammasome in monocytes and macrophages. The mechanism of granuloma formation in CGD is currently investigated in our laboratory.

In Western countries, the inability to produce ROS is caused by maternally transmitted defects within the *CYBB* gene encoding a protein called gp91phox (X-CGD) in two thirds of all CGD patients. In another 20% of CGD patients, the disease is caused by a mutation within the *NCF1* gene encoding the protein p47phox (AR-CGD). Both proteins collaborate in ROS production in phagocytes. Defects of other proteins causing CGD are less frequent in Western countries, but more frequently encountered in consanguineous populations. CGD can be cured with good results and few side-effects by HSCT if an HLA-compatible donor is available. For CGD patients without compatible donors, stem cell gene therapy might be an option to cure the disease.

Gene therapy research projects in our own laboratory

Between 2004 and 2007 our division conducted a first clinical gene therapy study aiming to cure gp91phox deficient CGD (X-CGD) patients, embedded within a collaboration network with partners in Germany. Four CGD patients were treated by gene therapy using a first-generation gamma-retroviral vector; two adult patients in Frankfurt and two children in Zurich. All four overcame their preexisting treatment refractory infections. On the one hand, this trial (see www.clinicaltrials.gov) showed that CGD can be treated by gene therapy as the killing of bacteria and fungi by phagocytes was successfully temporarily restored after gene therapy. On the other hand, like in other first-generation gene therapy studies, specific side effects related to retroviral vector mediated oncogene transactivation were observed. Therefore, a next generation lenti-viral gene therapy vector for X-CGD treatment is currently developed. This new X-CGD gene therapy vector shows an improved safety profile *in vitro* and in mice, and is presently applied in a next-generation EU FP7-funded clinical trial (www.net4cgd.eu) in study centers in Frankfurt, London, Paris and Zurich. In parallel, our laboratory developed a gene therapy vector for the second most frequent form of CGD caused by p47phox deficiency, which is currently tested pre-clinically.

Outlook gene therapy

At present, viral gene addition approaches are state of the art in clinical gene therapy, which is about to establish its potency as new treatment option in medicine. Different ongoing clinical trials are performed in few centers worldwide with the main focus on immunodeficiency, inborn errors of metabolism and cancer.

Next generation gene therapy will potentially follow a gene repair approach. In the vast majority, genetic defects causing immunodeficiency are individual in every patient. Therefore, gene repair would require the development of an individualized treatment for every patient. Methods were developed recently allowing for repair of genetic defects (Zinc-Finger nucleases, TALEN, CrispR / Cas9), but the efficiency of correction varies between different cell populations and unfortunately, is very low in HSCs, which are the target cells for gene therapy in immunodeficiencies. Our laboratory as well as others are therefore working on improvement of these gene repair systems in terms of better efficiency.

gentherapie für angeborene immun defekte

Janine Reichenbach (Prof. Dr. med.)

Gruppenmitglieder (in alphabetischer Reihenfolge): Dr. sc. nat. Rocio Garcia de la Cruz Valencia (PostDoc), Dr. sc. nat. Elena Kuzmenko (Laborantin), Dr. med. Virginia Meda-Spaccamela (MD-PhD Studentin), Dr. biomed. sci. Oleksandr Pastukhov (PostDoc), PD Dr. rer. nat. Ulrich Siler (Laborleitung), Dominik Wrona (Doktorand)

Wie sich der menschliche Körper schützt

Wir sind ständig zahlreichen Mikroorganismen ausgesetzt, welche unseren Körper infizieren. Das Immunsystem erkennt und neutralisiert diese Mikroorganismen und schützt uns dadurch. Gesunde Personen haben ein ausgeglichenes Immunsystem: stark genug, um eindringende Mikroorganismen wie Bakterien, Pilze, Viren oder Parasiten zu bekämpfen, und dennoch ausgeglichen genug, um nicht übermäßig auf harmlose Substanzen zu reagieren (wie bei Allergien) oder körpereigene Strukturen anzugreifen (wie bei Autoimmunkrankheiten). Zahlreiche Krankheiten haben ihren Ursprung in einer gestörten Ausgewogenheit der Immunreaktionen oder in einer mangelnden Reaktion des Immunsystems auf Mikroorganismen (wie bei Immundefekten).

Bislang sind mehr als 250 angeborene Immundefekte bekannt, welche zu Störungen des Immunsystems führen und deren Ursprung in Änderungen des genetischen Codes (Desoxyribonukleinsäure, DNA) liegt. Das Immunsystem wird kontinuierlich von einer kleinen, im Knochenmark lokalisierten Zellpopulation – den sogenannten hämatopoetischen Stammzellen (Blut- / Immunzell-Vorläuferzellen) aufgebaut und erneuert. Defekte im genetischen Code dieser Stammzellen führen dazu, dass das Immunsystem den Körper nicht ausreichend vor Mikroorganismen schützen kann. Betroffene Patienten leiden daher an schwerwiegenden, wiederkehrenden und / oder dauerhaften Infektionen, welche zu Organschäden und möglicherweise zu frühem Tod führen können.

Heilung von Immundefekten: Hämatopoetische Stammzelltransplantation

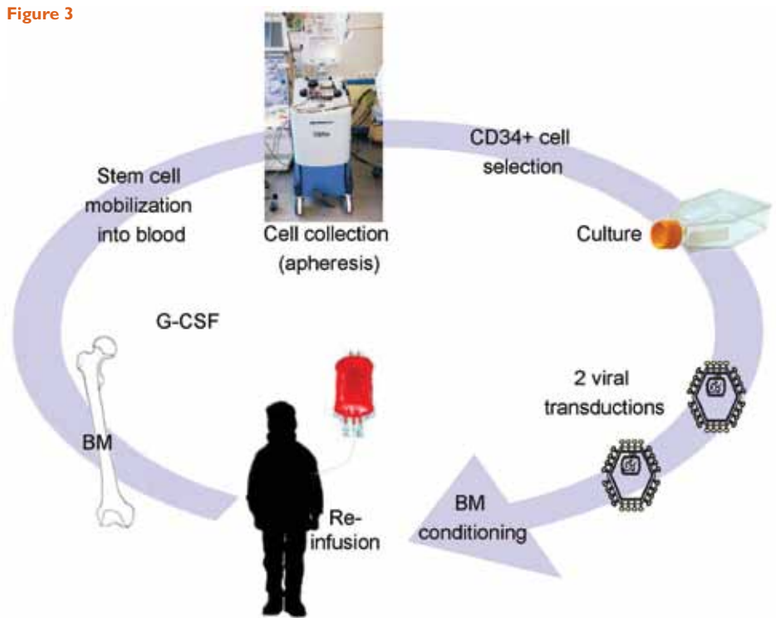
Manche dieser schwerwiegenden Immundefekte können durch den Austausch der defekten hämatopoetischen Stammzellen (HSZ) mit gesunden HSZ von einem verwandten oder nicht-verwandten Spender geheilt werden. Die gesunden Zellen des Spenders können im Knochenmark ein neues Immunsystem aufbauen. Dieses Verfahren nennt man hämatopoetische Stammzelltransplantation (HSZT) oder Knochenmarktransplantation. Die HSZT kann aber nur dann gefahrlos durchgeführt werden, wenn sich die Zellen von Empfänger und Spender in der Expression spezieller Oberflächenmarker (HLA, humane Leukozytenantigene) sehr ähnlich sind, um eine potentielle Abstoßungsreaktion zu verhindern. Für etwa 75 % aller betroffenen Patienten gibt es kompatible Spender. Für diejenigen Patienten ohne passenden HSZ-Spender werden zusätzliche Behandlungsmöglichkeiten dringend benötigt. Während der letzten Jahren wurde für solche Patienten die Gentherapie als Behandlungsmöglichkeit für Einzel-Gen Defekte entwickelt.

Heilung von Immundefekten: Stammzell-Gentherapie

Im Gegensatz zum Austausch der HSZ im Knochenmark mittels HSZT von einem verwandten oder nicht-verwandten gesunden Spender, beruht die Gentherapie für angeborene Immundefekte darauf, die körpereigenen HSZ zu korrigieren: Zunächst werden die HSZ des Patienten aus dessen Knochenmark isoliert. In hochspezialisierten Laboren wird anschließend der genetische Defekt in den Zellen korrigiert. Schließlich werden die genetisch korrigierten Zellen dem Patienten zurückgegeben. Gentherapie ist im Gegensatz zur allogenen Knochenmarktransplantation ein autologer Prozess. Die genetisch korrigierten körpereigenen Zellen führen also nicht zu einer Abstoßungsreaktion (Graft-versus-Host Disease). Diese ist bei der HSZT durch die Verwendung von körperfremden Spenderzellen ein Risikofaktor, da das neu aufgebaute Immunsystem aus Spenderzellen den Empfängerkörper angreift. Der genetische Code des menschlichen Körpers ist in kleinen Einheiten, den sogenannten Genen, organisiert. Jedes Gen besteht aus einer regulatorischen Einheit (Promotor) und einer codierenden Einheit. Der Promoter bestimmt, in welchen Zellen des Körpers das Gen aktiv ist und somit exprimiert wird (Proteinsynthese). Die codierende Einheit legt den Aufbau des exprimierten Proteins fest. Proteine sind diejenigen Strukturen, welche die Funktionen einer Zelle ausführen – im Fall von Immunzellen ist dies der Schutz des Körpers. Ein Defekt innerhalb des genetischen Codes resultiert meistens in einem fehlerhaften Protein-Aufbau und somit einem inaktiven Protein mit fehlender immunologischer Funktion.

Bei der derzeit angewandten Gentherapie wird ein funktionsfähiges Gen in die DNA der HSZ des Patienten eingefügt, ohne das defekte Gen zu ersetzen (Gen-Additions-Therapie). Die Aktivität des neu hinzugefügten, korrigierenden Gens kompensiert dann die fehlende Funktion des mutierten. Dieses funktionelle, korrigierende Gen nennt man Transgen. Es wird bislang durch spezielle Transportvehikel in den genetischen Code eingeführt, die abgeleitet von Retroviren im Labor hergestellt werden. Diese Vehikel werden Gentherapie-Vektoren genannt. Um Viren als Gentherapie-Vektoren verwenden zu können, müssen diese so verändert werden, dass sie nicht fähig sind, den Patienten zu infizieren. Das heißt,

Figure 3



Gene therapy to cure immunodeficiencies:
After treatment with granulocyte-colony stimulating factor (G-CSF), hematopoietic stem cells (HSCs) are released from the bone marrow (BM) into the blood of the patient. HSCs are then collected from the blood by apheresis, selected by surface marker CD34 and cultured *in vitro*. Next, patient HSCs are incubated twice with the gene therapy vector (transduction), by which the therapeutic gene is introduced into the genome of the patient's HSCs (see figure on page 39). In parallel, the patient is treated with chemotherapy (conditioning) to provide enough space for the genetically corrected HSCs to grow in the BM. As corrected HSCs give rise to immune cell subsets, the therapeutic gene is disseminated to these subsets upon differentiation of HSCs.

Gentherapie zur Behandlung von Immundefekten:
Durch Behandlung mit G-CSF (granulocyte-colony stimulating factor) werden hämatopoetische Stammzellen (HSZ) aus dem Knochenmark (BM) in das Blut des Patienten freigesetzt. Von dort werden die HSZ durch Apherese isoliert, mittels des Oberflächenmarkers CD34 selektiert und in vitro kultiviert. Danach werden die HSZ in vitro zweimal nacheinander mit dem Gentherapie-Vektor behandelt (Transduktion), wodurch das therapeutische Gen in die HSZ des Patienten eingebracht wird (siehe Abbildung auf Seite 39). Parallel dazu wird der Patient mit Chemotherapie behandelt (Konditionierung), so dass im BM genügend Platz für die genetisch korrigierten HSZ vorhanden ist. Da aus den korrigierten HSZ durch Differenzierung verschiedene Arten von Immunzellen gebildet werden, wird das therapeutische Gen an alle Immunzellen weitergegeben, die von diesen HSZ abstammen.

sie dürfen sich nicht vermehren oder sich im Körper ausbreiten. Zusätzlich muss der genetische Code des Virus insoweit verändert werden, dass es das neue, korrigierende Transgen in sich trägt.

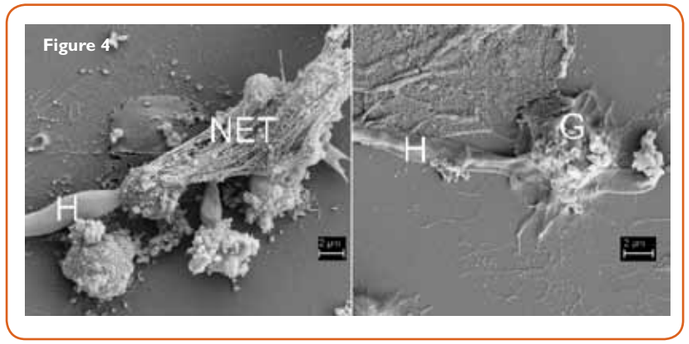
Eine Besonderheit dieser Gentherapie-Vektoren ist die Tatsache, dass sie sich an HSZ anheften können und das korrigierende Gen in die Zellen freisetzen, wo es dann stabil in den genetischen Code des Patienten integriert wird. Nach der stabilen Integration wird das Transgen an alle Nachkommen der korrigierten HSZ weitervererbt. In diesen Zellabkömmlingen resultiert die Aktivität des Transgens in der Herstellung eines funktionellen Proteins und führt somit zur Behebung des Immundefekts.

zwei Populationen der Immunzellen verursacht: Granulozyten und Monozyten / Makrophagen. Diese Immunzellen werden als Phagozyten bezeichnet, da sie Mikroben aufnehmen (phagozytieren) und verdauen. Beide Zellpopulationen spielen eine entscheidende Rolle im Kampf des Körpers gegen eindringende Bakterien und Pilze, da sie diese durch die NADPH-Oxidase-bedingte Produktion reaktiver Sauerstoffspezies (ROS) inaktivieren. ROS wirkt ähnlich wie Bleiche, welche im Haushalt für den gleichen Zweck verwendet wird.

Bei CGD-Patienten sind Phagozyten nicht fähig, ROS herzustellen. Daher können sie eindringende Bakterien und Pilze nicht töten, so dass diese Mikroben in den Phagozyten überdauern. Zusätzlich zur Unfähigkeit, Mikroben innerhalb der Zelle zu inaktivieren, haben CGD-Phagozyten ebenfalls eine Störung, welche das Inaktivieren außerhalb der Zelle beeinträchtigt. In Zusammenarbeit mit Kollegen des

Electron microscopic visualization of neutrophil extracellular traps (NETs). Upon contact with fungal hyphae (H), healthy granulocytes are able to form NETs (left), whereas CGD granulocytes (right) are unable to form NETs.

Elektronenmikroskopische Aufnahme von „neutrophil extracellular traps (NETs)". Nach Kontakt mit Pilzhyphen (H) bilden gesunde Granulozyten NETs (links), wohingegen Granulozyten eines CGD-Patienten dazu nicht in der Lage sind (rechts).



Der Immundefekt Septische Granulomatose

Septische Granulomatose (Chronic Granulomatous Disease, CGD) umfasst eine Gruppe angeborener Immundefekte, die sich bereits im Kindesalter manifestieren, mit immer wiederkehrenden und oft lebensbedrohlichen Infektionen durch Bakterien und Pilze. Etwa die Hälfte der CGD-Patienten leiden zusätzlich an schwerwiegenden Entzündungen, meistens im Bereich des Magen-Darm-Traktes (Kolitis). Diese Gruppe von Immundefekten wird durch Einzelgendefekte in den Untereinheiten der sogenannten NADPH-Oxidase in Max-Planck-Instituts in Berlin (Gruppe Prof. A. Zychlinski) konnte unser Labor aufklären, wie gesunde Phagozyten Pilze, welche erheblich grösser sind als sie selbst, mittels Fallen aus DNA und antimikrobiellen Stoffen eliminieren. Diese netzartigen Strukturen werden NETs (Neutrophil Extracellular Traps) genannt. CGD-Patienten können aufgrund mangelhafter ROS-Produktion keine NETs ausbilden und leiden daher an schweren Bakterien- oder Schimmelpilzinfektionen. Wir konnten zeigen, dass die Bildung von NETs durch Gentherapie wiederhergestellt werden kann und zur Beseitigung schwerer Pilzinfektionen bei CGD-Patienten führt (siehe unten).

Außerdem manifestiert sich CGD nicht nur in der Anfälligkeit für Bakterien- und Pilzinfektionen, sondern auch in einer Überaktivität des Immunsystems, welche zu chronischen Entzündungen mit Granulom-Bildung führt (meistens im Magen-Darm-Trakt). Der Mechanismus der Persistenz dieser Entzündungsreaktionen ist nur teilweise aufgeklärt. Wir konnten zeigen, dass CGD-assoziierte Entzündungen an ein übermäßig aktives Inflammasom in Monozyten und Makrophagen gekoppelt ist. Der Mechanismus, welcher der Granulombildung bei CGD zugrunde liegt, wird zurzeit in unserem Labor untersucht.

In den westlichen Ländern ist die Krankheitsursache bei zwei Drittel aller CGD-Patienten durch einen von der Mutter übertragenen Defekt im *CYBB*-Gen begründet. Dieses Gen codiert ein Protein namens gp91phox (X-CGD). Bei weiteren 20 % der CGD-Patienten wird die Krankheit durch eine Mutation innerhalb des *NCF1*-Gens verursacht, welches das Protein p47phox codiert (AR-CGD). Beide Proteine wirken bei der ROS-Produktion in Phagozyten zusammen. Defekte in anderen Proteinen, welche CGD verursachen, sind in westlichen Ländern weniger verbreitet, treten aber häufiger in blutsverwandten Populationen auf. Die HSZT bietet gute Heilungschancen mit geringen Nebenwirkungen für CGD, wenn ein passender Spender verfügbar ist. Für CGD-Patienten, für die kein kompatibler Spender gefunden werden kann, könnte die Stammzell-Gentherapie eine Möglichkeit zur Heilung sein.

Forschungsprojekte zur Gentherapie in unserem Labor

Zwischen 2004 und 2007 hat unsere Abteilung in Kollaboration mit verschiedenen Partnern aus Deutschland eine erste klinische Gentherapie-Studie zur Heilung von X-CGD durchgeführt. Unter Verwendung eines Gamma-retroviralen Vektors erhielten vier CGD-Patienten eine Gentherapie; zwei Erwachsene in Frankfurt und zwei Kinder in Zürich. Bei allen vier Patienten zeigte sich eine Heilung der zuvor bestehenden therapierefraktären Infektionen. Auf der einen Seite konnte diese Studie zeigen (www.clinicaltrials.gov), dass CGD mit Gentherapie behandelt werden kann, da die Fähigkeit, Bakterien und Pilze erfolgreich zu bekämpfen, zeitweise wiederhergestellt werden konnte. Andererseits wurden – wie in anderen Gentherapie-Studien mit Vektoren der ersten Generation – spezifische Nebenwirkungen beobachtet, welche in Zusammenhang mit Vektor-vermittelter Transaktivierung von Onkogenen stehen. Daher wird momentan eine neue Generation eines lentiviralen Gentherapie-Vektors zur Behandlung von X-CGD eingesetzt. Diese neuartigen X-CGD-Gentherapie-Vektoren zeigen eine verbesserte Sicherheit in Zellkultur-Versuchen und in Mäusen und werden derzeit in einer EU-geförderten, klinischen Studie (www.net4cgd.eu) in Studienzentren in Frankfurt, London, Paris und Zürich angewendet. Parallel dazu entwickelte unser Labor einen Gentherapie-Vektor für die zweithäufigste Form von CGD, welche durch einen Defekt im p47phox-Protein hervorgerufen wird. Dieser befindet sich gegenwärtig in der präklinischen Testphase.

Perspektiven der Gentherapie

Die virale Genaddition ist gegenwärtig der modernste Ansatz der klinischen Gentherapie und wird derzeit als neue Behandlungsmöglichkeit etabliert. Verschiedene klinische Studien mit Fokus auf Immundefekte, angeborene Erkrankungen des Stoffwechselsystems und Krebs werden in einigen wenigen Zentren weltweit durchgeführt.

Moderne Gentherapie der nächsten Generation wird möglicherweise den Ansatz einer Genreparatur verfolgen. Genetische Defekte, welche einen Immundefekt zur Folge haben, sind in den allermeisten Fällen in jedem Patienten individuell. Daher bedarf es der Entwicklung einer personalisierten Behandlung für jeden Patienten. Methoden, welche die Reparatur von genetischen Defekten ermöglichen (Zinkfinger Nukleasen, TALEN, CrispR / Cas9), wurden zwar kürzlich entwickelt, jedoch ist die Effizienz der Korrektur zwischen verschiedenen Zellpopulationen sehr variabel. In HSZ, welche die Zielzellen der Gentherapie bei Immundefekten sind, ist sie aktuell leider sehr gering. Sowohl unser Labor, als auch andere arbeiten daher an einer Verbesserung dieses Genreparatursystems, um eine gesteigerte Effizienz zu erlangen.

overview cabmm research platform

1. Bone and Stem Cell Research Group

Group leader: PD Dr. Peter J. Richards (PhD)
Group members: Dr. André N. Tiaden (PhD), Dr. Cristina López-Fagundo (PhD), Dr. Ali Mirsaidi (PhD), Gregor Bahrenberg (PhD student), Stephan Glanz (PhD student), Gladys Filliat (PhD student)

The main interest of the Bone and Stem Cell Research Group (BSRG) is related to musculoskeletal biology and disease (e.g., bone, cartilage, tendon, spine) with a main focus on bone research. The group is additionally specialized in multipotent stromal cell (MSC) research, and is currently involved in studies related to the regulatory mechanisms controlling osteogenic, chondrogenic and adipogenic lineage commitment. One of our main focuses has been on the functional role of the serine protease HtrA1 in regulating MSC lineage commitment. To date, we have 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.

In the reporting period, the following research projects were performed by the BSRG on the CABMM Research Platform:

Effect of bisphosphonates on the differentiation potential of mesenchymal stem cells isolated from osteoporotic patients

Dr. André N. Tiaden (PhD)
CABMM collaborators: Prof. Dr. Michael Blauth
(Dr. med. Richard Lindtner)

The primary aim of this study was to evaluate the influence of aminobisphosphonates on the osteogenesis of human bone marrow stromal cells (hBMSCs) and mineralization of differentiating bone-forming cells isolated from osteoporotic patients. The influence of aminobisphosphonate treatment on hBMSC osteogenesis was assessed by the quantitative measurement of alkaline phosphatase (ALP) activity, in addition to quantitative reverse transcription polymerase chain reaction and Western blot analysis of known osteogenic markers. Mineralized matrix formation by hBMSC-derived osteoblasts was visualized and quantified using Alizarin red staining. hBMSC cultures treated with osteogenic medium supplemented with zoledronate demonstrated a significant increase in Alizarin red staining after 3 weeks as compared to cells cultured in osteogenic medium alone. Similarly, cultures of differentiating hBMSCs isolated from patients receiving alendronate treatment also demonstrated an increased propensity for mineralization, even in the absence of further *in vitro* stimulation by zoledronate. The stimulatory effects of aminobisphosphonate treatment on hBMSC-derived osteoblast-mediated mineralization were independent of any alterations in ALP activity, although significant decreases in the expression levels of osteopontin (SPP1) were evident in hBMSCs following exposure to aminobisphosphonates. Further analysis including Western blotting and loss-of-function studies revealed osteopontin as having a negative influence on the mineralization of differentiating osteoporotic bone-forming cells. The results presented here demonstrate for the first time that aminobisphosphonate treatment of osteoporotic hBMSCs enhances their capacity for osteoblast formation and subsequent mineral deposition, thus supporting the concept of aminobisphosphonates as having an osteoanabolic effect in osteoporosis.

Therapeutic potential of adipose-derived stromal cells (ASCs) for the treatment of senile osteoporosis

Dr. Ali Mirsaidi (PhD)

Adipose-derived stromal cells (ASCs) are increasingly being used for orthopedic-based tissue engineering approaches due to their ability to readily undergo osteogenic differentiation. In the present study, we used *in vitro* and *in vivo* approaches to evaluate the use of ASCs as a treatment strategy for age-related osteoporosis. Molecular, histological and micro-computed tomography (micro-CT) based approaches confirmed that ASCs isolated from 18-week-old osteoporotic senescence-accelerated mice (SAMP6) were capable of undergoing osteogenesis when cultured in either silk fibroin (SF) scaffolds or scaffold-free microtissues (ASC-MT). A single intratibial injection of CM-DiI-labeled isogeneic ASCs or ASC-MT into SAMP6 recipients significantly improved trabecular bone quality after 6 weeks in comparison to untreated contralateral bones, as

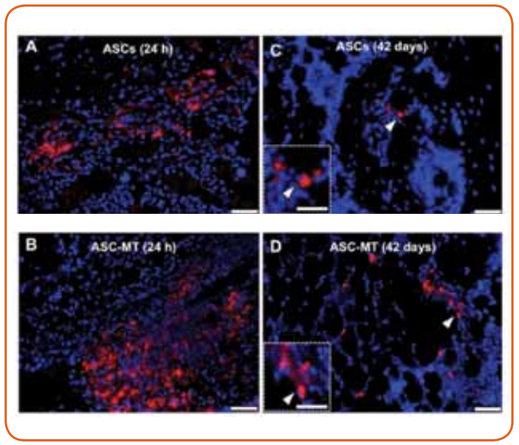


Figure 1: Representative fluorescence images of paraffin wax sections of tibia injected with undifferentiated ASCs (A, C) or ASC-MT (B, D) at 24 h (A, B) and 42 days (C, D) post treatment. Scale bar=50 µm. Inset and arrowhead, high magnification images of CM-DiI labeled cells. Scale bar=25 µm. Red, CM-DiI; blue, DAPI.

determined by micro-CT. Injected ASCs could be observed in paraffin wax bone sections at 24 h and 6 weeks post treatment (Fig. 1) and induced a significant increase in several molecular markers of bone turnover. Furthermore, a significant improvement in the osteogenic potential of osteoporotic patient-derived human bone marrow stromal cells (BMSCs) was observed when differentiated in conditioned culture media harvested from osteoporotic patient-derived human ASCs. These findings therefore support the use of ASCs as an autologous cell-based approach for the treatment of osteoporosis.

Novel function of serine protease HtrA1 in inhibiting adipogenic differentiation of human mesenchymal stem cells via MAP kinase-mediated MMP upregulation

Dr. André N. Tiaden (PhD), Gregor Bahrenberg (PhD student)

Adipogenesis is the process by which MSCs develop into lipid-laden adipocytes. Being the dominant cell type within adipose tissue, adipocytes play a central role in regulating circulating fatty acid levels, which is considered to be of critical importance in maintaining insulin sensitivity. High temperature requirement protease A1 (HtrA1) is a newly recognized regulator of MSC differentiation, although its role as a mediator of adipogenesis has not yet been defined. The aim of this work was therefore to evaluate HtrA1's influence on human MSC (hMSC) adipogenesis and to establish a potential mode of action. We report that the addition of exogenous HtrA1 to hMSCs undergoing adipogenesis suppressed their ability to develop into lipid-laden adipocytes (Fig. 2). These effects were demonstrated as being reliant on both its protease and PDZ domain, and were mediated through the actions of c-Jun N-terminal kinase and matrix metalloproteinases (MMPs). The relevance of such findings with regards to HtrA1's potential influence on adipocyte function *in vivo* is

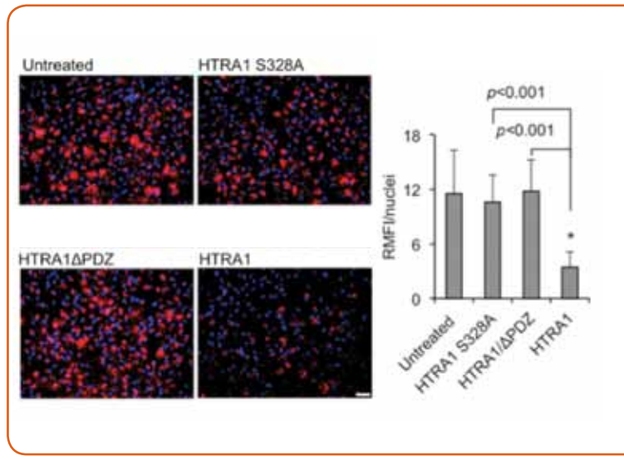


Figure 2: hMSCs were induced to undergo adipogenesis in the absence (untreated) or presence of 45 nM of recombinant wild type HtrA1 (HtrA1), proteolytic inactive HtrA1 (HtrA1 S328A) or proteolytic active HtrA1 without PDZ domain (HtrA1ΔPDZ). At day 24 post adipogenic induction, hMSCs were rinsed once with PBS and incubated for an additional 3 h with DiI-labeled VLDL and carrier protein ApoE2. VLDL-DiI (red) uptake was quantified by measuring relative linear median fluorescence intensity (RMFI) using NIH ImageJ software and normalized to cell number. Nuclei were stained with DAPI (blue). Scale bar = 75 µm. *$p < 0.001$ as compared to untreated hMSCs. Data are representative of at least 2 separate experiments performed in triplicate.

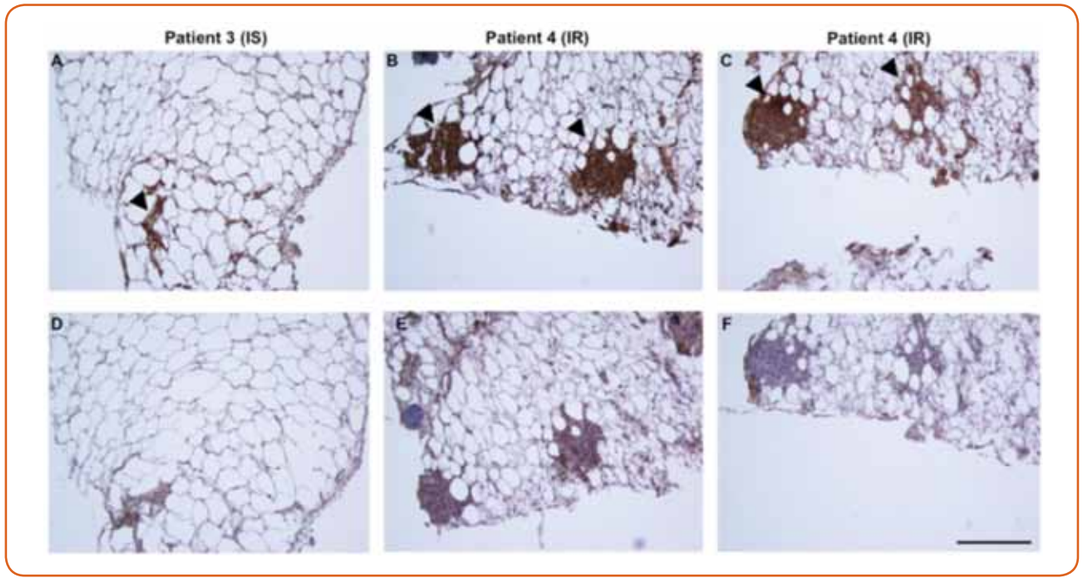


Figure 3: Identification of HtrA1 in adipose tissue. Paraffin wax sections of human visceral (omental) adipose tissue from insulin sensitive (IS) or insulin resistant (IR) obese patients were incubated with an anti-HtrA1 antibody (A, B), anti-MMP-13 antibody (C) or relevant IgG controls (D-F), and positive staining identified using an appropriate HRP-labeled polyclonal antibody with subsequent development using 3,3'-diaminobenzidine (brown). Arrow heads, HtrA1 or MMP-13 present in crown-like structures. Scale bar = 200 µm.

made evident by the fact that HtrA1 and MMP-13 were readily identifiable within crown-like structures present in visceral adipose tissue samples from insulin resistant obese human subjects (Fig. 3). These data therefore implicate HtrA1 as a negative regulator of MSC adipogenesis and are suggestive of its potential involvement in adipose tissue remodeling under pathological conditions.

Loss-of-function of HtrA1 abrogates all-trans retinoic acid-induced osteogenic differentiation of mouse adipose-derived stromal cells through deficiencies in p70S6k activation

Stephan Glanz (PhD student), Dr. Ali Mirsaidi (PhD)

All-trans retinoic acid (ATRA) is a potent inducer of osteogenic differentiation in mouse adipose-derived stromal cells (mASCs), although the underlying mechanisms responsible for its mode of action have yet to be completely elucidated. HtrA1 is a newly recognized modulator of human multipotent stromal cell (MSC) osteogenesis and as such, may play a role in regulating ATRA-dependent osteogenic differentiation of mASCs. In the current study, we assessed the influence of small interfering RNA (siRNA)-induced repression of HtrA1 production on mASC osteogenesis and examined its effects on ATRA-mediated mammalian target of rapamycin (mTOR) signaling. Inhibition of HtrA1 production in osteogenic mASCs resulted in a significant reduction of alkaline phosphatase (ALP) activity and mineralized matrix formation (Fig. 4). Western blot analyses revealed the rapid activation of Akt (Ser473) and p70S6K (Thr389) in ATRA-treated mASCs, and that levels of phosphorylated p70S6K were noticeably reduced in HtrA1-deficient mASCs. Further studies using mTOR inhibitor rapamycin and siRNA specific for the p70S6K gene Rps6kb1 confirmed ATRA-mediated mASC osteogenesis as being dependent on p70S6K activation. Finally, transfection of cells with a constitutively active rapamycin-resistant p70S6K mutant could restore the mineralizing capacity of HtrA1-deficient mASCs. These findings therefore lend further support for HtrA1 as a positive mediator of MSC osteogenesis and provide new insights into the molecular mode of action of ATRA in regulating mASC lineage commitment.

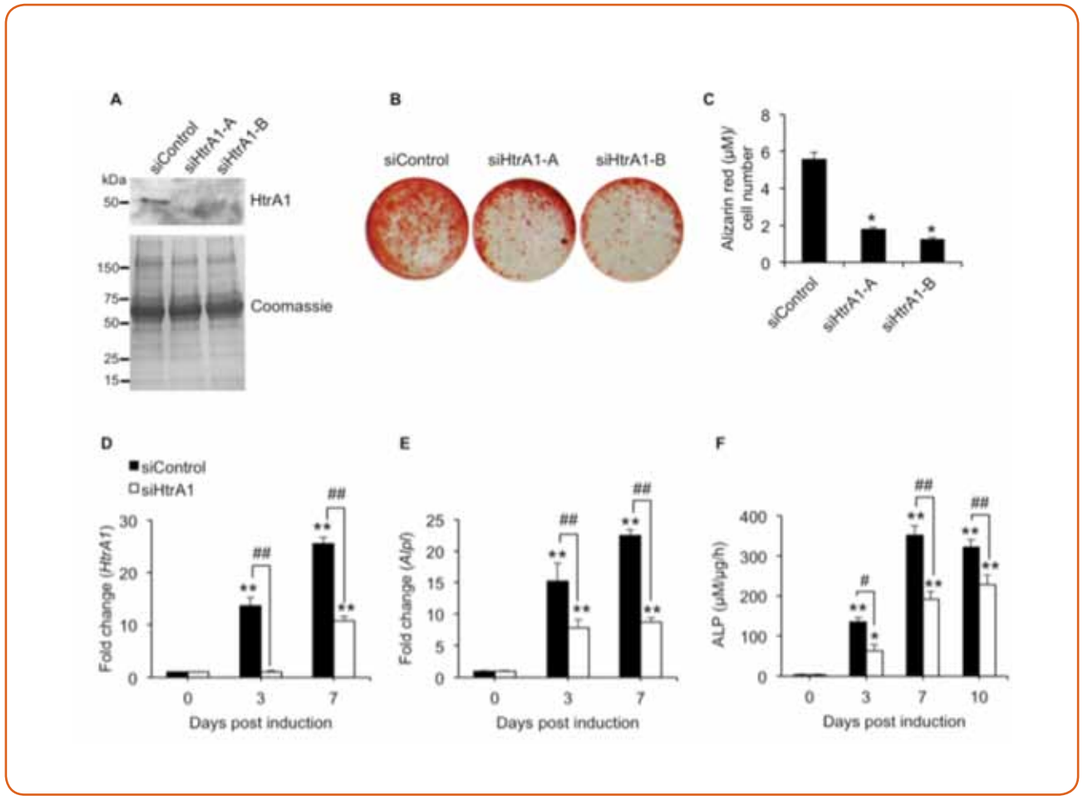


Figure 4: Effect of HtrA1 knockdown on osteogenic induction of mASCs. mASCs were pre-treated with control siRNA (siControl) or 2 selected siRNAs targeting HtrA1 (siHtrA1-A and siHtrA1-B) for 24 h and induced to undergo osteogenesis for up to 10 days. (A) Western blot analysis of HtrA1 protein in FCS-free concentrated supernatants from siRNA-treated mASCs after 4 days of osteogenic induction using an antibody specific for HtrA1. Gels were stained with Coomassie Blue to confirm equal protein loading. (B) Alizarin red staining of siRNA-treated mASCs 10 days post osteogenic induction. (C) Extracted Alizarin red stain was quantified and normalized to cell number. * $p < 0.001$ as compared to siControl using one-way ANOVA. Gene expression levels of HtrA1 (D) and Alpl (E) were determined in osteogenic mASCs at selected time points using RT-qPCR and the fold change as compared to uninduced mASCs (day 0) determined using the 2-ΔΔCT method. (F) ALP enzymatic activity levels were measured in siRNA-treated mASCs over the course of 10 days of osteogenic differentiation using a colorimetric-based ALP activity assay. All values are expressed as mean ± S.D (triplicates). * $p < 0.05$, ** $p < 0.001$ as compared to uninduced mASCs at day 0; # $p < 0.05$, ## $p < 0.001$ comparison between siControl and siHtrA1 using one-way ANOVA.

2. Cranio-Maxillofacial Surgery and Implantology Group

Group leader: Prof. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS
Group member: PD Dr. med. dent. Stefan Stübinger

Loss of bone volume in the lower jaw may compromise implant placement for dental rehabilitation of fully or partially edentulous patients. Inadequate volume of alveolar bone, the bone structure supporting the teeth, may result from physiological remodeling after tooth loss, or due to progressed periodontal disease or mechanical trauma. Horizontal augmentation using the principle of guided bone regeneration (GBR) is a well-approved technique to enhance the bone volume in case of a narrow alveolar ridge. In spite of current success rates, it would be highly beneficial if biomaterials would disclose a certain drug-releasing effect to guarantee a subsequent bone remodelling process. For this reason, it was the aim of a CTI-funded project to build up a new biomaterial for reconstruction of bone defects through local release of active components from an approved bioresorbable synthetic bone grafting material. In 12 mini pigs different biomaterial-component-systems (montelukast, simvastatin or teriparatide) were implanted in predefined, local bone alveolar ridge defects. Qualitative and quantitative histological evaluations after 6 weeks revealed that coatings with teriparatide led to a pronounced new bone formation, yet there were no statistically significant differences between coatings.

Beneath the need of adequate residual bone volumes, however, also novel implant materials play a vital role for long-term success. Beneath titanium and zirconia, recently also polyetheretherketone (PEEK) has been promoted as suitable implant material, especially in orthopedics. Although highly biocompatible, these PEEK-based materials do not show the same osteoconductive properties as conventional implant surfaces like e.g., titanium. Therefore, it was the aim of a pilot study in sheep to analyze the osseointegrative properties of coated and uncoated PEEK implant surfaces after 2 and 12 weeks. Coatings were applied by means of plasma spray equipment. After 12 weeks, coated implants demonstrated statistically significant ($p<0.001$) higher pull-out values in comparison to both reference coatings. Histologically, all groups revealed an increase of overall and cancellous BIC values from 2 to 12 weeks without any significance ($p>0.05$).

Even though biomaterials and implant surfaces have been highly improved for decades, a serious complication and risk factor for stable and sustainable integration of hard and soft tissue grafts as well as dental implants is still that of bacterial infection. An innovative new test system (funded by EU) is sensing matrix metalloproteinase regulation indicative for connective tissue degradation as present at the borderline of gingivitis / mucositis and periodontitis / peri-implantitis. The proposed test-system is designed to allow on-demand self-monitoring with the subject / patient providing surveillance of the peri-implant disease status. The system will open novel opportunities for early diagnosis and treatment modalities of peri-implant disease.

For the collection of sulcus fluid from peri-implant diseased patients, a cross-sectional study with 3 groups of patients was initiated. Each 20 patients with either a mucositis or a peri-implantitis were selected. Additionally, 20 patients with healthy peri-implant conditions were chosen as control group. Sulcus fluid was collected from the peri-implant zone using standardized MMP-8 collection strips. Data from the analysis of the stripes by the manufacturer clearly showed a characteristic conformity between the clinical findings in patients and the absolute MMP-8 results. MMP-8 concentrations were well fitting to the clinical diagnosis of mucositis, peri-implantitis or a healthy state.

Furthermore, six minipigs were used for the analysis of peri-implant hard and soft tissue structures. Clinical, radiological and histological findings of the animal experiment supported the overall applicability of the ligature-induced peri-implantitis minipig model. The animals showed a progressive inflammatory soft tissue reaction with subsequent rapid breakdown of especially buccal peri-implant hard tissues. Soft tissue structures revealed a status of severe mucositis with transition to pus formation and peri-implantitis.

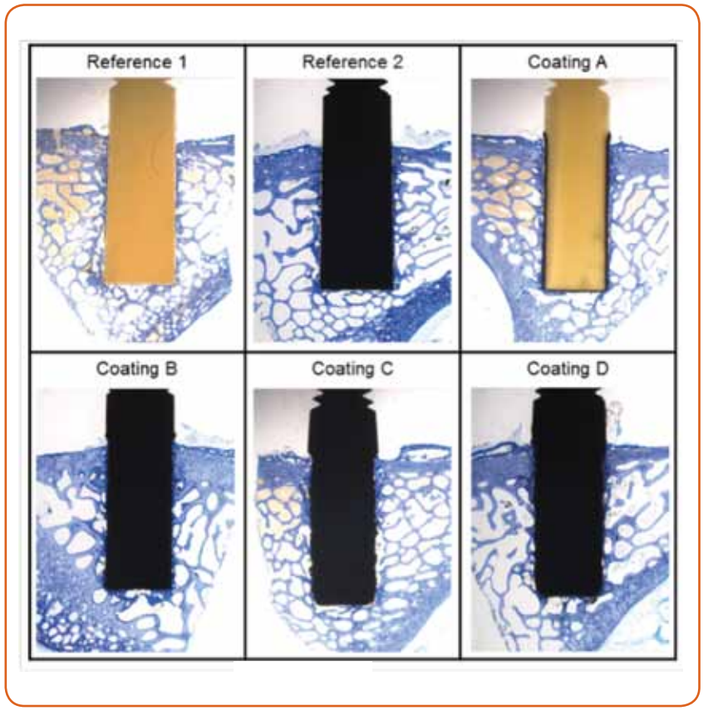


Figure 1: Toluidine-stained thick sections of the six implant groups after 12 weeks.
Reference 1 discloses scattered large pores at the cortical implant interface due to remodeling of microcracks (press-fit). Coating B and D reveal a complete bridging of the gap between implants and osteotomy sites. Sites are filled with new lamellar bone. No coronal pocket formation was found at the implants.

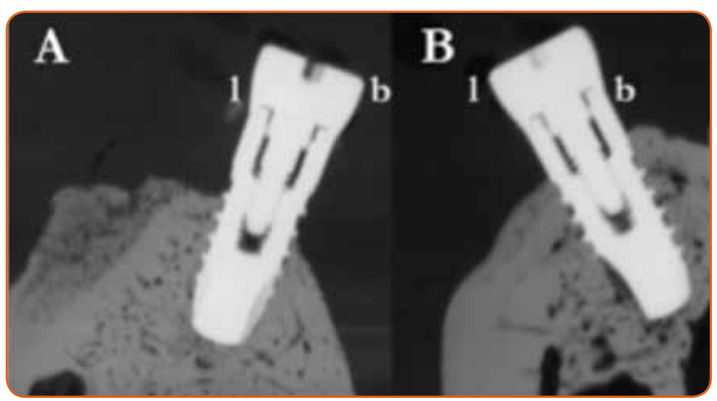


Figure 2: Microradiographic images after sacrifice (6 weeks) of experimental (A) and reference (B) implants. At the experimental implant a clear bone loss on the buccal side (b) is visible. On the lingual side (l) the resorption is less distinctive. On the buccal (b) as well as on the lingual (l) side of control implants no bone loss is detectable.

3. Equine Research Group

Group leader: Prof. Dr. med. vet. Anton Fürst, Dipl. ECVS
Group members: Dr. med. vet. Michelle Jackson (PhD student), Dr. med. vet. Jan Kümmerle (PhD student)

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 like jumping, racing, endurance or dressage competitions. The advances in equine orthopaedics and diagnostic imaging have improved our understanding of many orthopaedic injuries and, in most instances, allow for a very well defined diagnosis in terms of structural assessment of damaged musculoskeletal tissue.

However, advances in therapeutic methods are unable to keep pace with improvements in diagnostics – this is especially true in equine orthopaedics. Successful outcome 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 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 and minor-quality repair tissue within the tendon.

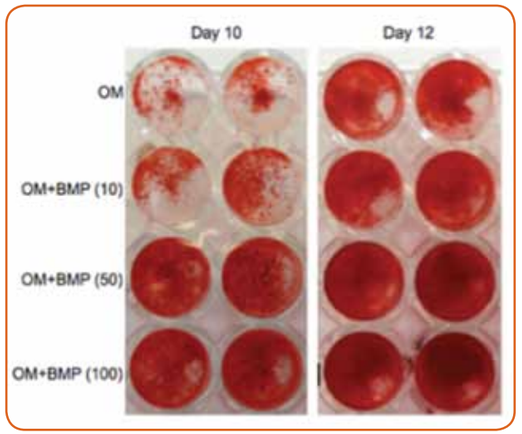


Figure 2: Equine osteoblasts undergoing osteogenesis were incubated with recombinant BMP-2 for up to 12 days and mineral deposition was visualized by Alizarin red staining.

Therefore, our group aims to study and develop regenerative methods to improve healing of injured musculoskeletal tissue in the horse.

In the field of tendon healing, this involves monitoring of the process of differentiation of mesenchymal stem cells to tenocytes (tenogenic differenation). This monitoring is currently hindered by the lack of molecular tenogenic markers. Therefore, our group is currently working on a project aiming to identify such a marker. For this purpose, gene expression analysis using RNA sequencing was performed on a variety of mesenchymal tissues relevant in orthopaedics. Furthermore, the differential expression of genes in cell cultures derived from such tissues was studied. Suitable candidate genes were validated using qPCR. This allowed us to identify 2 genes that fulfilled the criteria for use as a tendon marker. We are currently working on the publication of this study. Furthermore, we are evaluating expression of these marker genes in tenocytes cultured in a 3D tenogenic environment.

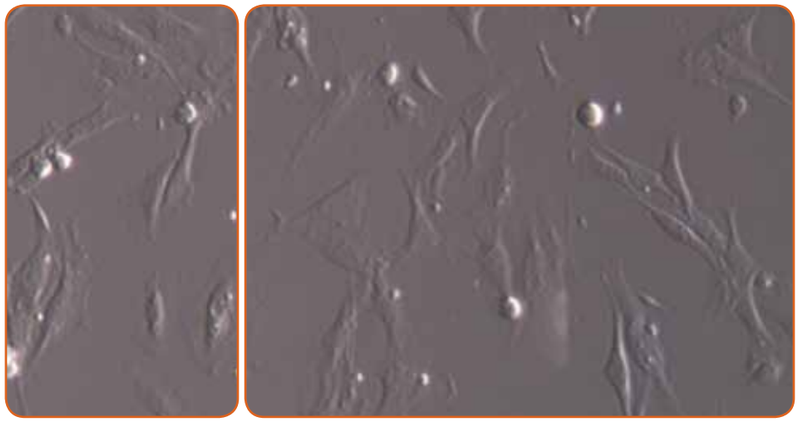


Figure 1: Phenotype of tenocytes under 2D culture conditions (passage 0).

In the field of bone regeneration, we aim to study the effect of different external sources of growth factors and cytokines on the activity of bone-forming osteoblastic cells. A suitable growth factor or cytokine combination could enhance bony regeneration, e.g., after debridement of subchondral cystic lesions, especially if delivered via a suitable matrix or carrier system. Currently, rhBMP-2 is studied in a clinical as well as in an *in vitro* study. Bone morphogenetic proteins (BMPs) are multi-functional growth factors that belong to the transforming growth factor β (TGFβ) superfamily. Preclinical and clinical studies have shown that BMPs have the potential to facilitate bone healing and augment or replace bone grafts in a variety of clinical situations in humans such as bone defects, non-union fractures, spinal fusions and osteoporosis. Our *in vitro* results show that rhBMP-2 enhances mineralization in equine osteoblasts according to the concentration of BMP-2 used (Fig. 2) and increases significantly alkaline phosphatase (ALP) activity (Fig. 3). Gene expression analysis showed that the treatment with 100 ng/ml rhBMP-2 led to a significant increase in the expression of ALP at day 2, as well as at day 5 (Fig. 4).

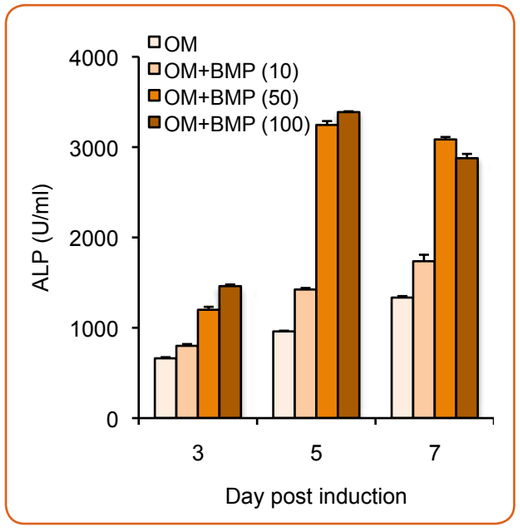


Figure 3: Analysis of ALP activity. Equine osteoblasts undergoing osteogenesis were incubated with recombinant BMP-2 for up to 10 days and ALP activity measured at selected time points. Data is expressed as mean ± S.D., and statistical significance determined by one-way ANOVA. *P < 0.01 as compared to cells treated with osteogenic medium (OM).

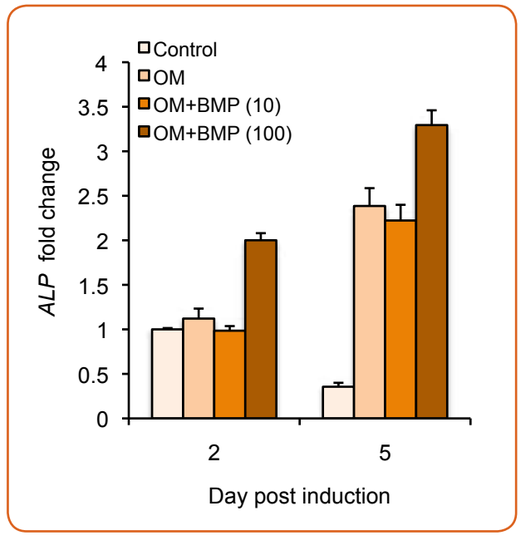


Figure 4: RT-qPCR analysis of the osteogenic marker ALP. Equine osteoblasts undergoing osteogenesis were incubated with recombinant BMP-2 for up to 5 days, RNA was isolated and the expression levels of ALP determined by RT-qPCR at selected time points. Data was normalized to GAPDH and expressed as fold change as compared to OM-treated cells (value 1) using the comparative CT method. Data is expressed as mean ± S.D., and statistical significance determined by one-way ANOVA. **P < 0.01.

In a clinical setting, 35 horses suffering from subchondral cystic lesions (SCLs) have been treated with rhBMP-2 after debridement of the cyst cavity. First results are promising, with 75 % of the patients being sound after one year.

4. Musculoskeletal Research Unit

Group leader: Prof. Dr. med. vet. Brigitte von Rechenberg, Dipl ECVS
Group members: Dr. Sabine Koch-Schneidemann (PhD), Dr. Salim E. Darwiche (PhD), Dr. med. vet. Flurina Clement Frey, PhD, Serah Naomi Saitowitz (doctoral student), Dr. med. vet. Mario Benn

The MSRU is mainly focused on studying musculoskeletal diseases (bone, cartilage, tendon, spine) with emphasis on bone and cartilage research. Soft tissue research in cardiovascular and skin systems is also carried out. The group is specialized in large animal experiments and histology including paraffin, cryo- and immunohistology as well as histology of non-decalcified bone samples. A special feature of the MSRU is its successful implementation of Good Laboratory Practice (GLP). The MSRU was confirmed to be GLP conform by Swissmedic on June 18, 2014. Thus, together with Good Manufacturing Practice (GMP) established at the Swiss Center for Regenerative Medicine, human clinical trials performed under Good Clinical Practice (GCP) at the University Hospital and the close collaboration of the involved institutions, the University of Zurich is now able to offer the complete quality chain for research and development of new therapeutics.

Cartilage remodeling and chondrocyte migration

Dr. Salim E. Darwiche (PhD), Dr. Sabine Koch-Schneidemann (PhD), Serah Naomi Saitowitz (doctoral student)

Cartilage is a flexible connective tissue found in many areas of the body like joints, the ribcage, the ear, the nose, intervertebral discs, and other parts. Due to its avascular nature, repair and regeneration of adult articular cartilage is greatly impaired. Indeed, connective tissue cells and scar formation often overtakes the repair process and produces a biomechanically and biologically inferior tissue, which inevitably leads to a degenerative state.

The project aims to investigate the mechanism of articular cartilage remodeling. To that end, the subchondral bone and inflammatory processes within bone leading to pathological bone resorption is a fundamental aspect to consider. Our histological analyses suggest that migration of chondrocytes or their precursor cells may occur even in adult tissues and may play a role in cartilage regeneration.

The main hypothesis postulates that progenitor cells, which then become chondrocytes, migrate from the subchondral bone into the cartilage. In order to investigate that theory, the cartilage and bone have to be looked at as one unit. Indeed, cells from the mesenchymal stem cell pool would respond to inflammatory factors and tissue damage indicators and migrate through the subchondral bone plate into the cartilage tissue. This process, while hypothesized to occur as a cartilage building mechanism, is presumably slower than degenerative processes. That is why understanding cartilage regeneration mechanisms is crucial in order to tackle joint pathologies in an efficient manner.

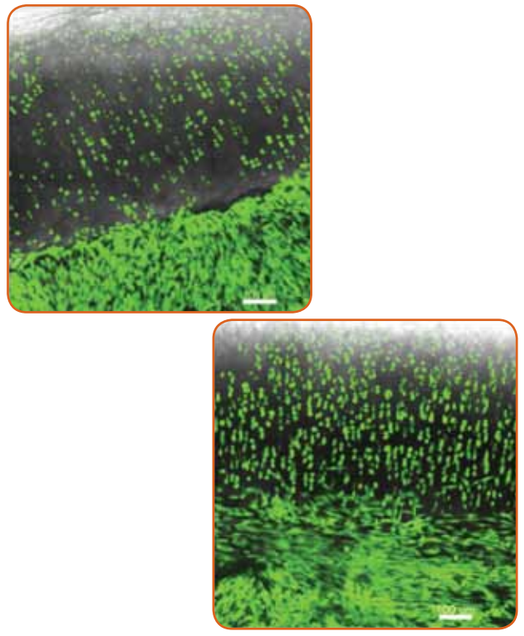


Figure 1: Osteochondral explant slices with living cells (green) within cartilage layers. Cells moving through the tidemark will be detected and tracked. Scale bar indicates 100 µm.

To date, we have successfully established an *ex vivo* explant culture model using sheep osteochondral tissue. We have also successfully maintained the viability of the explants under culture conditions (Fig. 1). In order to best visualize cells within the explant tissues, a viral transduction technology was utilized to impart fluorescent GFP expression onto cells. We are now able to visualize live cell location within the osteochondral tissue and are developing a tracking mechanism to detect cell movement within the tissue. This, combined with targeted stimulation, will help us elucidate mechanisms by which the osteochondral unit responds in simulated homeostasis and to environmental assaults.

Spying on cells: towards a new non-viral drug delivery system using superparamagnetic iron oxide nanoparticles (SPIONs)

Dr. med. vet. Flurina Clement Frey, PhD

The treatment of chronic aseptic inflammatory joint diseases like osteoarthritis and rheumatoid arthritis requires long-term application of analgesic, anti-inflammatory, immune-modulating or chondro-protective drugs. Intra-articular drug administrations often exhibit a limited efficiency due to a short persistence and an inadequate concentration of the drug within the joint cavity. Recent interest in alternative treatment methods for chronic aseptic inflammatory joint diseases afforded a novel approach of intra-articular drug applications using directed systems. Biocompatibly coated superparamagnetic iron oxide nanoparticles (SPIONs) are promising non-viral vectors for targeted drug or gene delivery since they satisfy the criteria of successful therapy: spatial placement and temporal delivery. Different from other nanoparticles, SPIONs can be directed to and maintained at a defined location using a magnetic field due to their magnetic properties. Coated with organic or inorganic materials, these particles are fully biocompatible and promise a widespread medical use for non-viral drug and gene delivery. In a method called magnetofection, SPIONs have been effectively used as transfection vectors for the introduction of nucleic acids into cells. SPIONs are, depending on the coating, easily incorporated into cells *in vitro* and *in vivo*, but the exact mechanisms of cellular uptake and their endosomal escape are unknown.

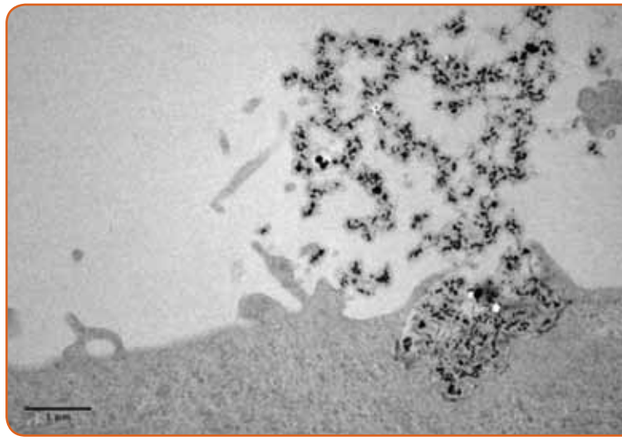


Figure 2: TEM (Transmission Electron Microscopy) image of tricalcium phosphate-coated nanoparticle phagocytosis by a HeLa cell. (L. Nufer and U. Hetzel, Institute of Veterinary Pathology).

The goal of this project was the investigation of SPION endocytosis in an established cell line (HeLa). By using plasmid DNA encoding fluorescent proteins as a model cargo, we intended to elucidate the endocytic pathway(s) involved in the uptake of SPIONs and to find out if the pathway used for particle engulfment is determined by size, charge and payload of SPIONs. With the knowledge of SPION uptake and intracellular transport, specifically functionalized SPIONs could be designed in view of medical drug targeting, gene therapy and stem cell transfection. We found that silica-coating is inappropriate due to DNA trapping on the SPION surface. With 10(7)-coated particles (a coating which is yet confidential; provided by Prof. H. Hofmann, EPFL, Lausanne), and tricalcium phosphate-coated particles (obtained from Prof. R. Grass, ETH Zurich), the model DNA cargo was successfully released and the fluorescent proteins expressed. TEM imaging (performed by U. Hetzel and L. Nufer at the Institute of Veterinary Pathology, University of Zurich) revealed that at 6 hours after particle addition to the cells, the particles are being phagocytosed (Fig. 2).

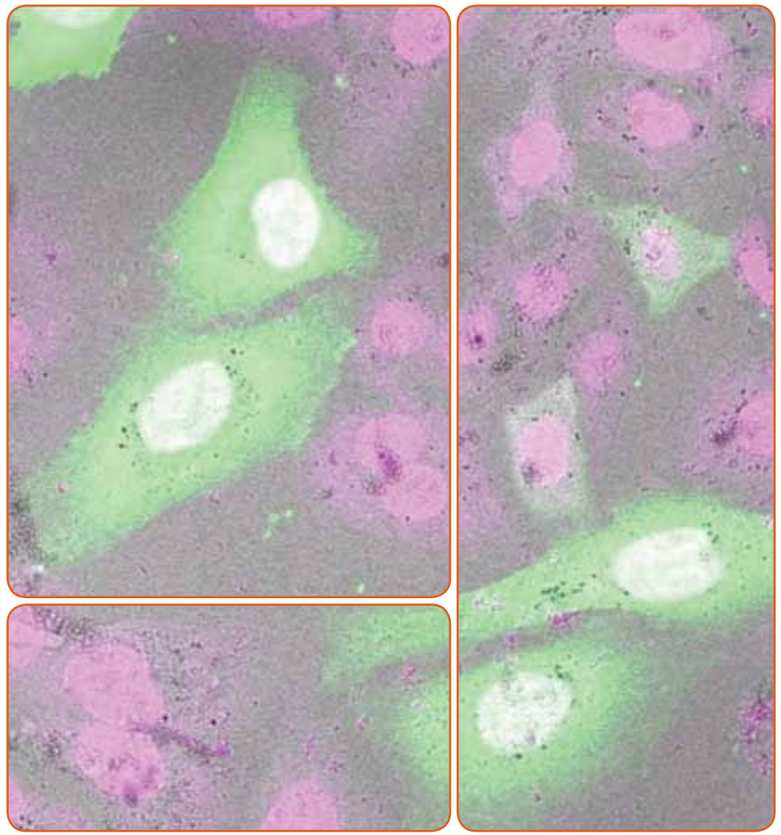


Figure 3: HeLa cells 6h after SPION addition to the medium. Purple: nuclei; black: 10(7)-coated nanoparticles.

Mesenchymal stem cells for muscle regeneration

Dr. med. vet. Mario Benn,
Dr. med. vet. Flurina Clement Frey, PhD
CABMM collaborators: Prof. Dr. med. Christian Gerber, Prof. Dr. med. Dominik Meyer

Partial or full rupture of rotator tendons occur approximately in 6 out of 10 people over 60 years of age. 60 % of these patients need therapy and 20 % need surgery. The causes of these tendon ruptures and the subsequent irreversible damages to muscle tissue are not yet completely understood. Consequently, today's therapies are still targeted at treating the symptoms rather than the cause.

In the current project, we investigate whether implantation of autologous mesenchymal stem cells (MSCs) has a positive effect on muscle regeneration. MSCs in the form of microtissues will be injected into damaged muscles of a sheep model for chronic tear and retraction of the infraspinatus muscle. We plan to determine whether MSCs have a positive stimulatory effect on muscle microarchitecture and enhance regeneration. This could lead to potential new therapeutic strategies to enhance muscle regeneration.

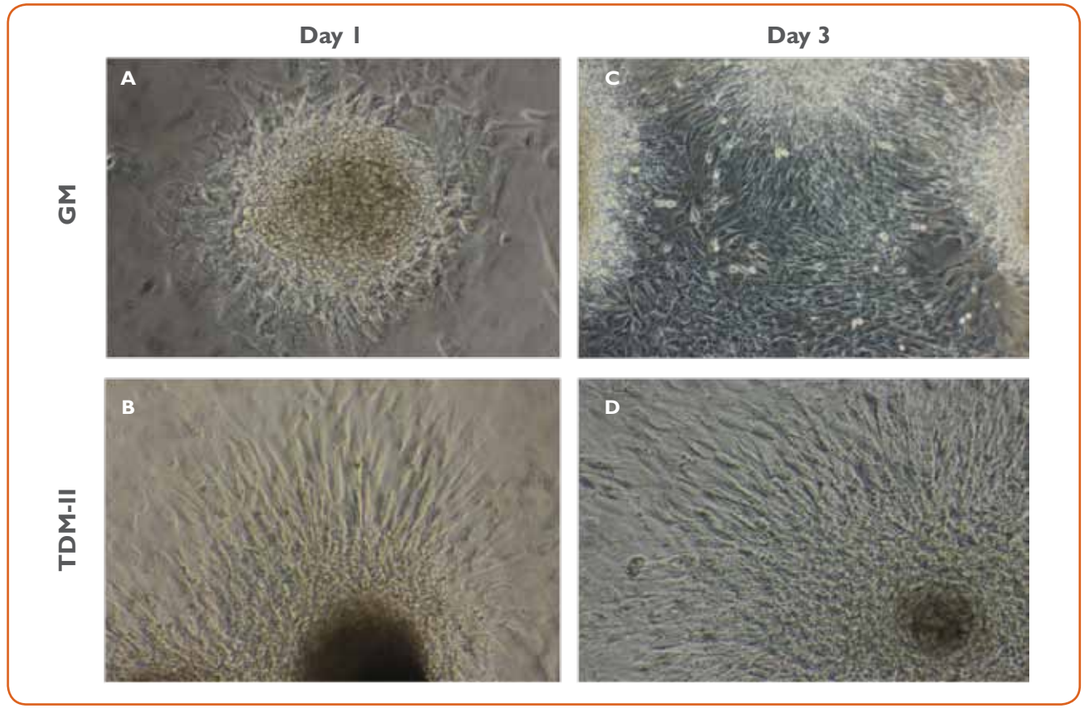
5. Tendon Repair Group

Group leader: Prof. Dr. med. vet. Anton Fürst, Dipl ECVS
Group member: Dr. med. vet. Felix Theiss, PhD, DVM, Dipl. ECVS
CABMM collaborator: PD Dr. Peter J. Richards (PhD)

Tendon injuries are a common cause of lameness and wastage in horses. The conventional and most widely spread therapy for tendon injury (tendonitis) in the horse involves administration of anti-inflammatory drugs and introduction of a controlled exercise program adjusted by regular ultrasonographic examinations. However, the healing process is very slow and results in the formation of scar tissue, which is functional 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 our 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. To evaluate this therapeutic concept, unanswered questions, like differentiation capacity of applied cells, mode of action and most suitable application format need to be addressed. In a first step, equine tenocytes are characterized in a three-dimensional culture format, including their de-differentiation and possible re-differentiation.

Figure 1: Phase contrast micrographs demonstrating outgrowth from microtissue spheroids under 2D culture conditions. Equine adult tenocytes were cultured as hanging drops for 6 days in normal growth medium (GM) or in tenogenic differentiation medium II (TDM-II).



In a second step, we aim to identify the most suitable cell source to produce tendon tissue. Therefore, mesenchymal stem cells derived from bone marrow and adipocyte tissue as well as adult and fetal tendon cells will be evaluated morphologically, histologically and histochemically regarding their potential to differentiate into tenocytes in a three-dimensional tendon model system. Beside different growth media, the influence of mechanical stimulation on cell differentiation will be investigated. Subsequently, the regenerative capacity of the best cell candidates will be investigated *in vivo* in an acute injury tendon regeneration model in mice. In the same animal model, different application forms, e.g., single cell injections and injections of micro-tissues, will be compared.

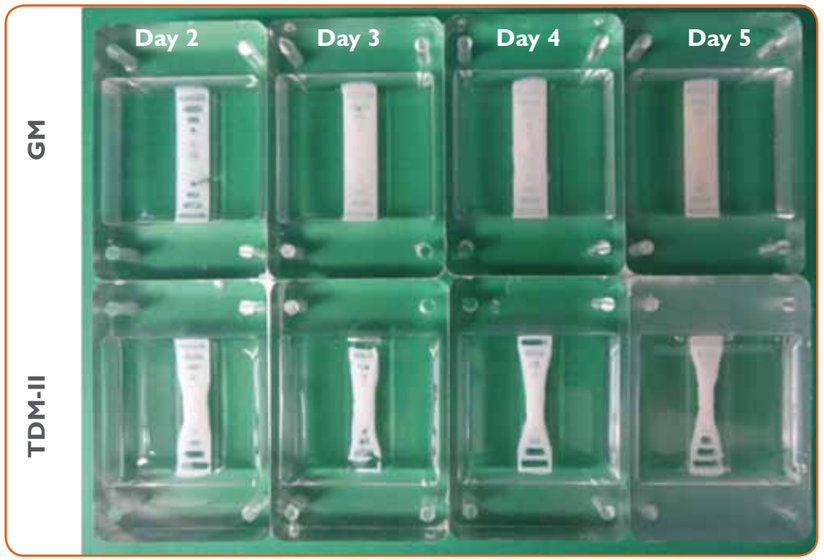


Figure 2: Macroscopic images of collagen gel constructs anchored in silicon molds at 2, 3, 4 and 5 days after tenocyte microtissue seeding of growth medium (GM) or tenogenic differentiation medium II (TDM-II) treated cultures.

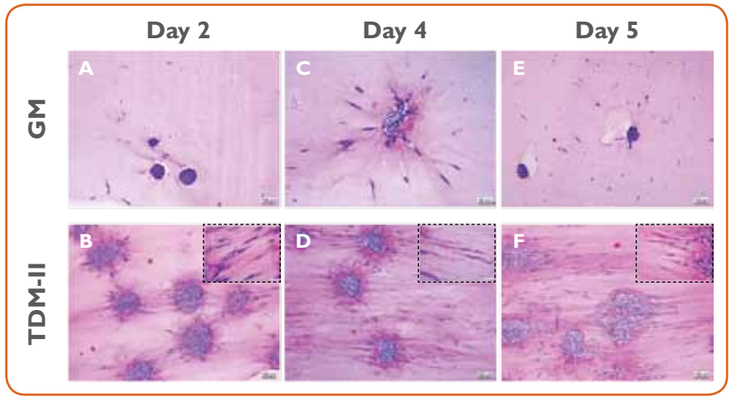
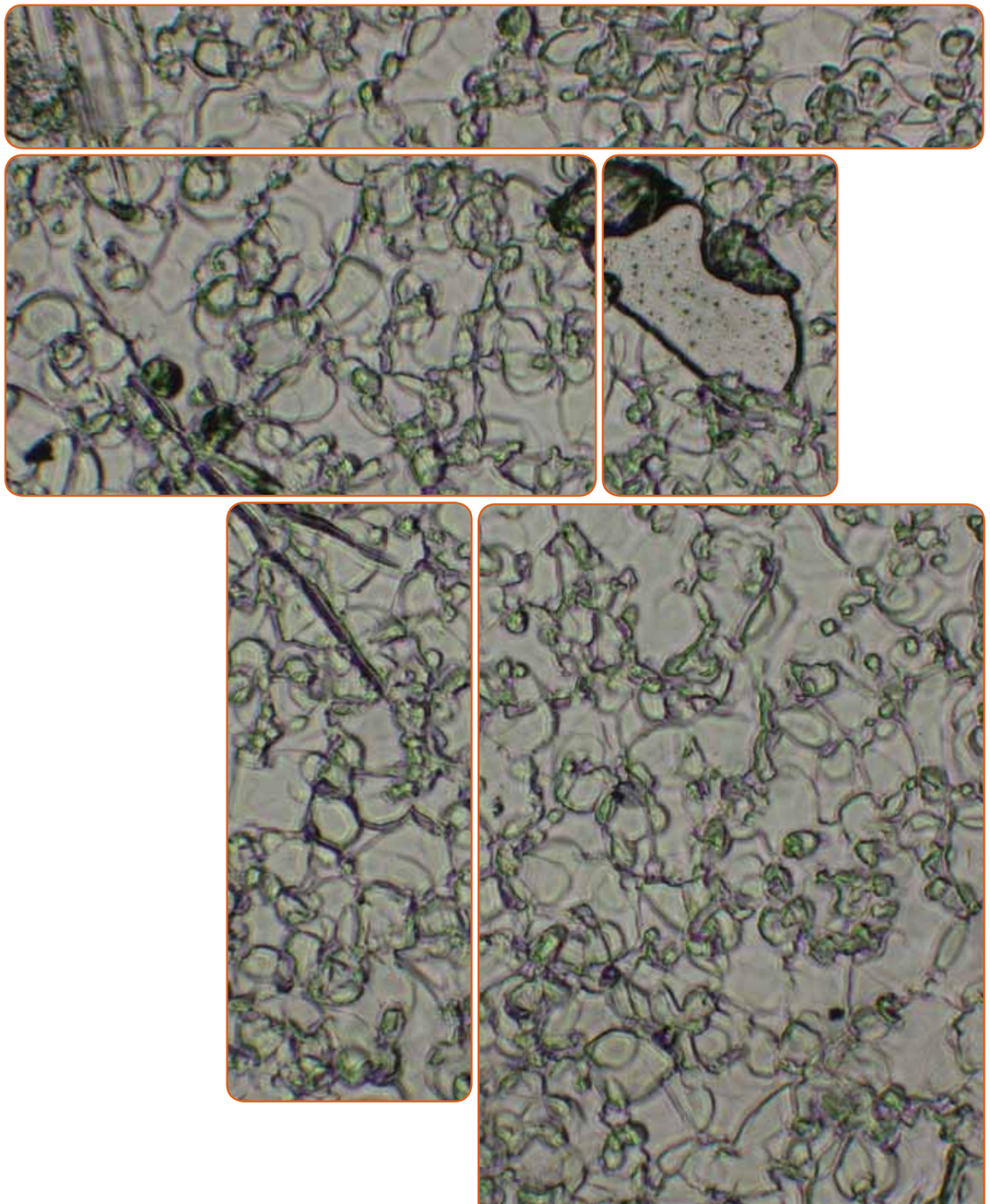
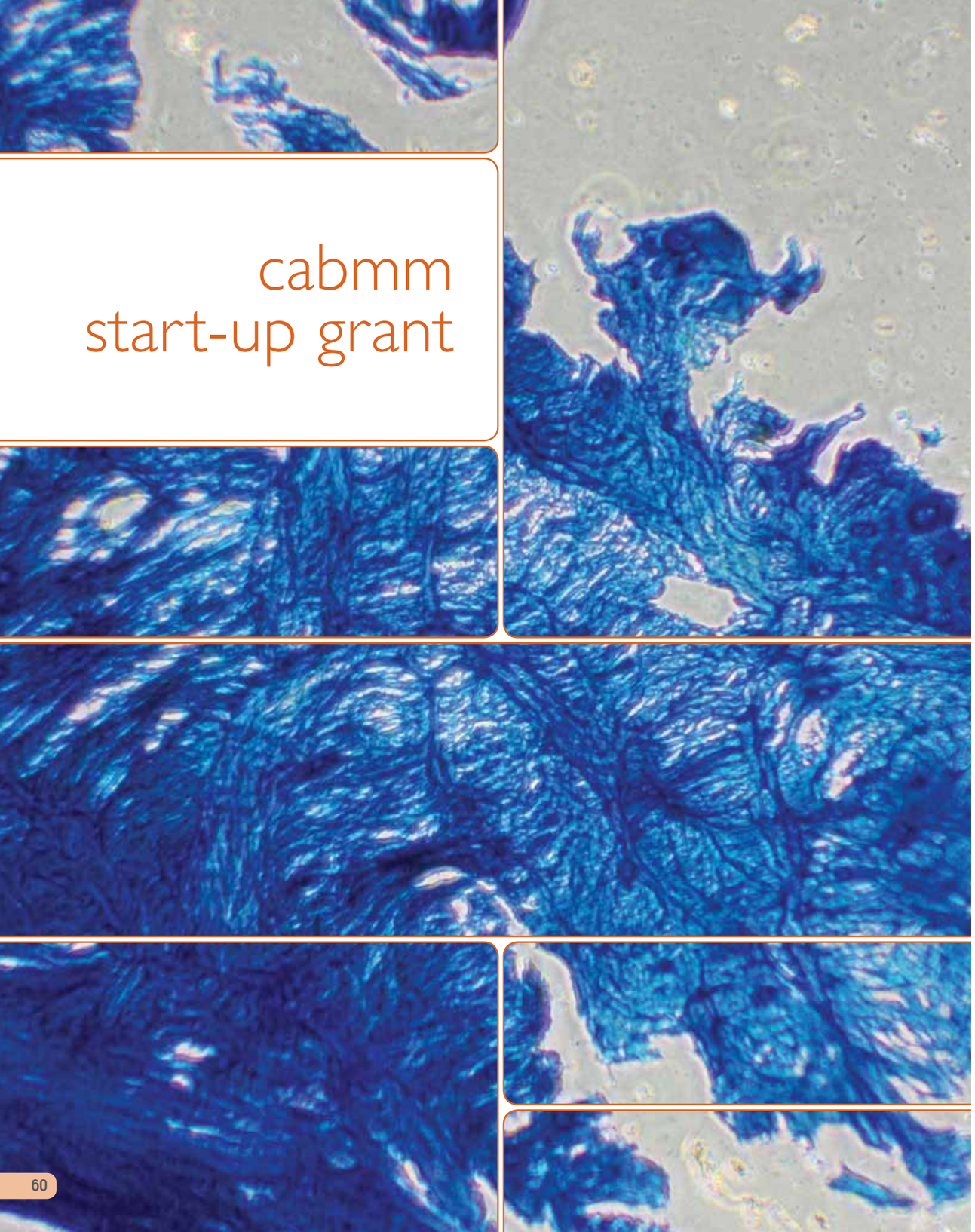


Figure 3: Micrographs of hematoxylin and eosin stained paraffin wax sections showing the outgrowth of equine tenocytes from microtissues and their alignment in static 3D collagen constructs. Microtissues were prepared in hanging drops for 6 days in either growth medium (GM) or tenogenic differentiation medium II (TDM-II) and then embedded in a 0.8% collagen matrix.



cabmm start-up grant



The CABMM Start-up Grant is a peer-reviewed funding program designed to support collaborative research projects between CABMM members and is made possible through the generous financial support of the Mäxi foundation.

The grants support 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. Application requirements include CABMM membership and an affiliation to a Swiss institution of the principal investigator. Under no circumstances can applications be considered that involve industrial partners or animal experimentation.

We offer the opportunity to apply twice a year for such preliminary studies. The applicants can receive a maximum amount of CHF 40'000.– 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 others, 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 Mäxi foundation and the CABMM, e.g., translational character of the proposal, collaborations between CABMM members and creation of additional value for our network.

At the end of the funding period, project outcome of selected projects is presented during the CABMM Symposium in autumn.

To this day, almost 30 projects were supported, from which about one-fifth has been published in peer-reviewed scientific journals, illustrating the importance of our funding program as well as the scientific excellence of the supported projects.

In this reporting period, a total of 10 projects with an overall amount of about CHF 330'000.– was funded by a CABMM Start-up Grant. A tabular summary of these projects can be found on the following pages. Additionally, short summaries of selected, already successfully completed projects are presented. If the project has been published in a scientific journal, you will also find the corresponding citation.

summary of newly approved projects in the reporting period

application rounds 1/2014 and 2/2014

Project Title	Applicants	Amount
Improvement of pedicle screw anchorage by immediate stabilization system (ISS) – a histological and biomechanical *ex vivo* study	Prof. Dr. Michael Blauth Prof. Dr. Brigitte von Rechenberg* Prof. Dr. Werner Schmoelz (Prof. Dr. Michael Blauth)**	CHF 31'750.–
Development and characterization of a pH sensitive slow release system to reduce inflammatory processes in the degenerated intervertebral disc	Prof. Dr. Jeffrey Bode Prof. Dr. Stephen Ferguson PD Dr. Oliver Hausmann Prof. Dr. Karin Würtz-Kozak*	CHF 31'300.–
Single cell analysis of NF-κB induction kinetics during innate immune response using DARPins as analytical reagents for mass cytometry	Prof. Dr. Dr. Michael O. Hottiger Vinko Tosevski***	CHF 40'000.–
Cell motility as a marker for canine and human mesenchymal stem cells multipotency	PD Dr. Frank Steffen Dr. Jivko Stoyanov*	CHF 28'964.–
The function of serine protease HTRA1 in regulating adipogenesis and bone marrow adipose tissue	PD Dr. Raffaella Santoro Dr. André N. Tiaden* (PD Dr. Peter J. Richards)**	CHF 36'500.-
	Subtotal 2014	**CHF 168'514.–**

* main applicant(s), ** corresponding CABMM member, *** no CABMM member

application rounds 1/2015 and 2/2015

Project Title	Applicants	Amount
Intraoperative tissue and fluid analysis using radiofrequency plasma spectroscopy	Prof. Dr. Christian Gerber Prof. Dr. Dominik Meyer* Sebastian Valet***	CHF 24'353.-
Establishment of the differential proteomic and biofunctional analysis of the secretome of human mesenchymal stem cell sources	Prof. Dr. Benjamin Gantenbein-Ritter PD Dr. Dr. Benedikt Weber*	CHF 38'434.-
The *in vitro* chondrogenic differentiation of human bMSCs within gel or sponge-type 3-D matrices – a comparative approach	Prof. Dr. Gian Salzmann* Prof. Dr. Marcy Zenobi-Wong	CHF 38'000.-
Prostaglandin-mediated regulation of human stem cell multipotency and its relevance to age-related bone loss	Prof. Dr. Michael Blauth PD Dr. Peter J. Richards*	CHF 20'700.-
Identification of inflammatory and pain markers in degenerative spinal disease	Dr. Luc Smolders* (PD Dr. Frank Steffen)** Prof. Dr. Karin Würtz-Kozak*	CHF 38'000.-
	Subtotal 2015	**CHF 159'487.–**
	Total amount in the reporting period:	**CHF 328'001.–**

* main applicant(s), ** corresponding CABMM member, *** no CABMM member

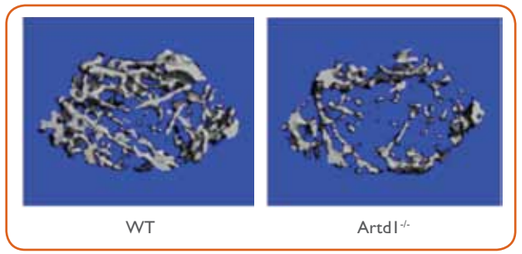
1. Identification of RANKL-activated proteins regulating poly-ADP-ribose formation

Principle Investigator: Prof. Dr. Dr. Michael O. Hottiger
Collaborator: PD Dr. Peter J. Richards
Amount funded: CHF 39'000.–
Funding period: 06/2013 – 05/2014
(application round 2/2012)

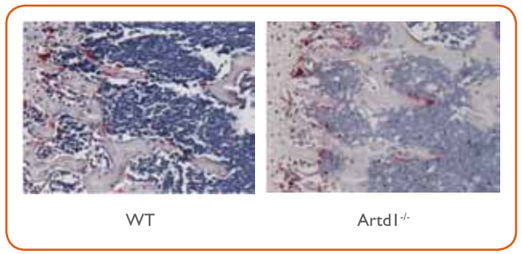
Background: Bone-related diseases affect hundreds of millions of people worldwide. The balance between continuous deposition of bone matrix by osteoblasts and bone resorption by osteoclasts assures bone homeostasis, while a shift towards bone resorption is the basis of many bone-related diseases. Osteoclastogenesis from macrophages is activated by the ligand of the receptor activator of NF-κB (RANKL) and induced by the transcription factor NF-κB. The activity of the latter is modulated by the ADP-ribosyltransferase ARTD1, which attaches poly-ADP-ribose to chromatin-associated proteins, thereby changing their function and interaction with other proteins, such as transcription co-factors. The role and mechanism of ARTD1 and its enzymatic activity in regulating osteoclastogenesis and bone homeostasis are largely unknown, however.

Aim: We therefore investigated this question in cell culture-based RANKL-induced osteoclastogenesis models and in ARTD1 knockout mice.

Results: siRNA-mediated knockdown of ARTD1 or pharmacological inhibition of its enzymatic activity enhanced RANKL-induced osteoclast differentiation and function. The recruitment of p65/RelA to the IL-1β promoter, which was associated with transcriptionally active histone marks, IL-1β expression and inflammasome-dependent secretion of IL-1β were enhanced. This led to sustained induction of the transcription factor Nfatc1/A and osteoclastogenesis in an autocrine manner via the IL-1 receptor. Artd1-deficient mice displayed significantly decreased bone mass as a consequence of increased osteoclast differentiation. Accordingly, the expression of osteoclast markers was enhanced in mutant compared to wild-type mice.



Micro computed tomography scans of femurs showing that bone volume density and bone mineral density were decreased in 8-week-old ARTD1 knockout mice (Artd1$^{-/-}$) compared to age-matched wild-type (WT) mice.



Tibial sections stained for tartrate-resistant acid phosphatase activity (red) show that the number of osteoclasts/bone surface and osteoclast surface/bone surface were increased in 8-week-old ARTD1 knockout mice (Artd1$^{-/-}$) compared to age-matched wild-type (WT) mice.

Conclusion/Significance: The results indicate that ARTD1 and ARTD1-induced poly-ADP-ribosylation controls osteoclast development and bone remodeling by modulating the epigenetic marks surrounding the IL-1β promoter and expression of Nfatc1/A. Understanding the molecular mechanisms that govern osteoclast differentiation and function will help to develop more effective therapeutic strategies against diseases such as osteoporosis and rheumatoid arthritis.

Publication

Robaszkiewicz A, Qu C, Wisnik E, Ploszaj T, Mirsaidi A, Kunze FA, Richards PJ, Cinelli P, Mbalaviele G, Hottiger MO
"ARTD1 regulates osteoclastogenesis and bone homeostasis by dampening NF-κB-dependent transcription of IL-1β"
Sci Rep. 2016 Feb 17;6:21131

2. Analysis of topographic differences in synovial fibroblasts

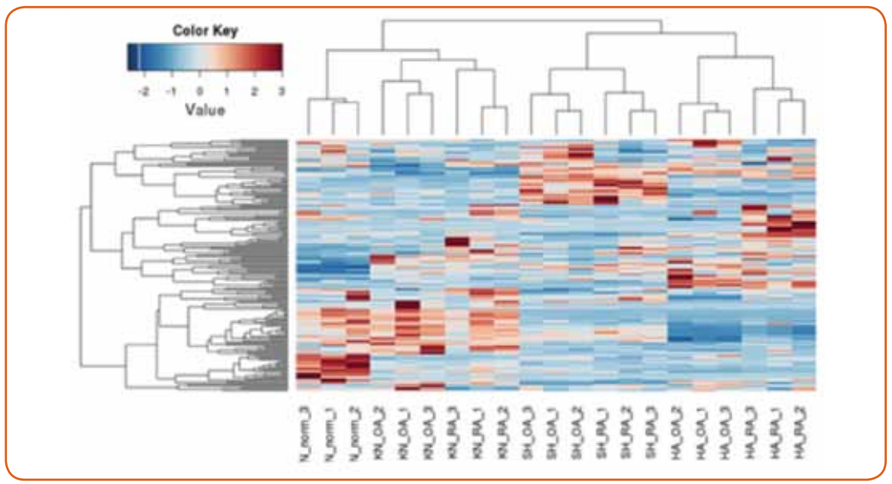
Principle Investigator: PD Dr. Dr. Caroline Ospelt
Collaborator: Prof. Dr. Dr. Michael O. Hottiger
Amount funded: CHF 38'900.–
Funding period: 02/2014 – 01/2015
(application round 2/2013)

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 (SF), 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 hypothesized that SF 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 arthritidis than others.

Results: By using RNA Sequencing we could detect significant differences in gene expression in SF cultured from knee, shoulder or hand joints. Unsupervised hierarchical cluster analysis showed clustering of human SF first according to joint location and then according to disease (Rheumatoid Arthritis, Osteoarthritis, 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 SF 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 SF from different joints. Also different expression of matrix-metalloproteinases being responsible for matrix-degradation by SF could be confirmed by real-time PCR measurements.

Conclusion: SF from joints of different anatomic sites exhibit substantial differences in gene expression, suggesting that functionally distinct subsets of SF 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.



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 diagnoses (RA, OA, norm).

3. Role of infrapatellar fat pad on the pathophysiology of the diseased cranial cruciate ligament in dogs

Principle Investigator: Dr. Simone Forterre (CABMM member Prof. Dr. David Spreng)
Collaborators: PD Dr. Peter J. Richards, Prof. Dr. David Spreng
Amount funded: CHF 24'338.–
Funding period: 10/2013 – 09/2014 (application round 1/2013)

Background: Anterior cruciate ligament tear is a common knee injury in humans and in dogs. In dogs, rupture is attributed predominantly to a degenerative process and rarely to a traumatic event, which is the main cause in humans. Dogs undergo similar treatments as humans, such as NSAID therapy, intra-articular injections and arthroscopic surgery, but no consistently effective method exists to prevent or to slow the development of knee osteoarthritis. The infrapatellar fat pad (IFP), an intracapsular and extrasynovial adipose tissue in the knee joint, has long been believed to be mostly of mechanical function with little or no metabolic responses. Since it became clear that adipose tissue also can be inflammatory or even affect immune reactions, the IFP is considered as an emerging player in knee osteoarthritis.

Aim: The objective of the study was to identify canine IFP as a potential inflammatory source and promoter of cranial cruciate ligament (CCL) disease.

Results: Compared to the subcutaneous adipose tissue or healthy tissues, the IFP from dogs with CCL rupture showed an inflammatory pattern characterized by increased T cells and macrophages, as well as higher amounts of interleukins (IL-1β, IL-6) and matrix metalloproteinases (MMP-1, MMP-13), concurrent with an increase in gene expression. Further, our results indicated a modulation of adipokine secretion in CCL diseased IFP.

Macroscopic view of a canine stifle joint after experimental transection of the cranial cruciate ligament with marked cartilage degeneration of the femur and strong vascular reaction and discoloration of the infrapatellar fat pad; framed with a white line.

Schematic illustration of the stifle joint with a rupture of the cranial cruciate ligament. The upper bones show the distal part of the femur and the patella; the lower bones represent the tibia and the fibularsity.

Conclusion / Significance: In conclusion, a higher secretory activity and cell activation discriminated IFP from its counterpart ScAT (subcutaneous Adipose Tissue) in canine CCL disease. The IFP of CCL diseased dogs seemed to drive and control local pathological processes. With this study, we open the discussion how far removal of IFP may be beneficial to delay disease progression and reduce clinical symptoms.

4. Investigation of the inflammatory processes associated with canine intervertebral disc herniation

Principle Investigators: Prof. Dr. Franck Forterre, Prof. Dr. Karin Würtz-Kozak
Amount funded: CHF 37'950.–
Funding period: 09/2013 – 08/2014 (application round 01/2013)

Background: Canine thoracolumbar intervertebral disc herniation (IVDH) results in compressive/contusive spinal cord injury and hence bears similarities to acute spinal cord injury (SCI) in humans. Although dogs are thought to serve as a useful animal model to investigate SCI or IVD disease in human medicine, the pathobiological alterations in dogs (e.g., with regard to tissue inflammation) are not investigated in sufficient detail yet.

Aim: The aim of this project was to identify key pro-inflammatory cytokines present in canine IVDH, to correlate cytokine expression with clinical parameters and to identify immune cells infiltrating the herniated IVD tissue.

Results: IVD tissue was derived from 25 canine patients with IVDH and 11 control dogs free of IVDH.

In IVDs from patients, a significantly higher gene expression of IL-1β, IL-6 and TNF-α was detected. On the protein level, high patient-patient variations were observed. Only IL-8 and TNF-α were found to be systematically significantly elevated in patients.

A patient-specific comparison between diseased and non-affected IVDs excised from an adjacent level of the same dog revealed a pronounced pathological elevation of IL-6 (Fig. 1). Furthermore, IL-6 also correlated with nociception. In contrast, mRNA levels of IL-1β, IL-8 and TNF-α were either unchanged or reduced in diseased compared to non-affected IVDs of patients.

Histological investigations demonstrated that most herniated IVDs exhibited an epidural inflammatory response, with macrophage and monocyte infiltration (Fig. 2).

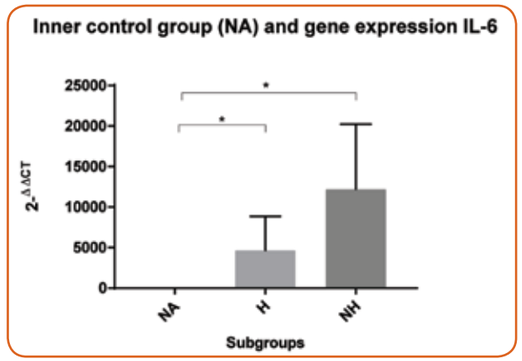


Figure 1: Elevated expression of the proinflamamtory cytokine IL-6 in diseased IVDs (herniated and non-herniated, H and NH) compared to non-affected IVDs (NA) from the same dog. Mean + StDev, n = 5, * if $p < 0.05$

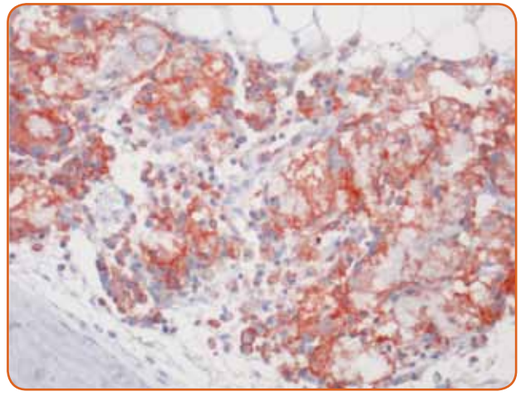


Figure 2: Immunostaining (CD18) of herniated disc material in a dog, illustrating the presence of macrophages.

Conclusion/Significance: Although expression of key cytokines found in human IVDs could also be demonstrated in canine tissue, the inflammatory mechanisms accompanying IVDH in dogs partially diverge from humans. These differences need to be taken into account when using dogs as a model for human medicine. In dogs, IL-6 seems to play an important pathological role, might influence polarization of macrophages present in the herniated disc material and may ultimately represent a potential therapeutic target for canine patients.

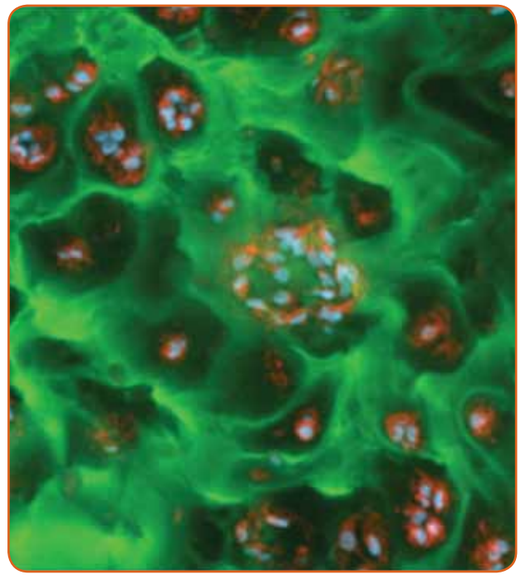
5. Evaluation of the chondrogenic potential of human epiphyseal chondroprogenitor cells in alginate sulfate hydrogels

Principle Investigator: Prof. Dr. Marcy Zenobi-Wong
Collaborator: Prof. Dr. Lee Ann Laurent-Applegate
Amount funded: CHF 35'900.–
Funding period: 01/2014 – 12/2014 (application round 2/2013)

Background: Articular cartilage is a tissue which has a low capacity to regenerate. This means that cartilage injuries due to trauma lead to progressive joint deterioration, a condition known as post-traumatic osteoarthritis. Currently, to treat such an injury, a surgeon would take a biopsy of healthy cartilage and isolate cells from it. The low cell yield from the biopsy requires one to grow the cells in plastic flasks to increase their number. Growing cells in this way however results in fibroblast-like cells with an impaired capacity to regenerate cartilage.

Aim: The goal of this study was to develop a biomaterial which would provide a more physiologic environment for the cells extracted from the biopsy to grow in. For this we developed a material based on alginate, a marine polysaccharide. The material was modified to have the same density of negatively charged sulfate groups as native cartilage, and therefore could be a good "biomimetic" material. The growth behavior of cells taken from cartilage tissue was investigated within this material.

Results: Cells isolated from cartilage showed a remarkable capacity to proliferate in the engineered matrix. In addition, they continued to secrete proteins typical for cartilage tissue. We also discovered that important signaling molecules, called growth factors, could be entrapped within the sulfated alginate. We demonstrated that the material facilitated an important interaction between the growth factors and their receptors on the cell membrane and that this interaction could be responsible for the improved cell performance.



Chondroprogenitor cells embedded in a biomimetic hydrogel produce collagen 2 matrix (green). Blue = nuclei. Red = actin.

Conclusion / Significance: This study showed the importance of one particular cue in the native cartilage environment, namely the presence of negatively charged sulfate groups. This engineered hydrogel has promise for use in treating cartilage injuries with cells, because the cells retain their original potency even upon expansion.

6. Development and characterization of a pH-sensitive slow release system to reduce inflammatory processes in the degenerated intervertebral disc

Principle Investigator: Prof. Dr. Karin Würtz-Kozak
Collaborators: Prof. Dr. Jeffrey Bode
Prof. Dr. Stephen Ferguson
Dr. Oliver Hausmann
Amount funded: CHF 31'300.–
Funding period: 01/2015 – 12/2015 (application round 1/2014)

Background: As inflammatory mediators play a crucial role in pain development during intervertebral disc (IVD) degeneration, their inhibition could be a potential treatment option for patients with discogenic pain. We have previously shown that epigallocatechin 3-gallate (EGCG) possesses strong anti-inflammatory and anti-catabolic activity in human IVD cells and prevents cells from the detrimental effects of oxidative stress. However, to restrict the need for consecutive injections and hence provide clinical practicality, sustained release of EGCG upon intradiscal injection is needed.

Aim: The aim of this study was to develop and characterize a minimally invasive slow release system for EGCG (EGCG-SRS).

Results: First, a pH-sensitive PEG hydrogel (developed by Prof. Bode, ETH Zurich) that solidifies at acidic pH levels as found in degenerating IVDs (≤ pH 6.5) was tested. Although this hydrogel showed good biocompatibility (Fig. 1A), its gelation at IVD-like pH values was too slow to be suitable for clinical application. Moreover, an unfavorable burst release of EGCG was observed (Fig. 1A/B).

Therefore, a thermo-sensitive biocompatible hyaluronic acid (HA)-pNIPAM hydrogel (developed by the AO Research Foundation Davos) was tested in a second project phase. HA-pNIPAM released EGCG over a period of 7 days. To further optimize the release characteristics, electrospraying was employed to encapsulate EGCG into gelatin microparticles. Release from this novel SRS is currently fine-tuned to achieve effective concentrations of EGCG (± 10 µM) over a sustained period. In addition, a novel IVD tissue culture system that shows sign of early degeneration was developed and is currently used to test the suitability and efficacy of this novel EGCG-SRS.

Conclusion / Significance: Minimal-invasive treatment modalities for IVD degeneration hold major promise for improving patient care. Findings indicate that the thermo-responsive HA-pNIPAM hydrogel was more suitable for EGCG encapsulation than the PEG-based pH-sensitive hydrogel due to faster gelation and better release characteristics. Additional encapsulation of EGCG into gelatin microparticles (which will be combined with the HA-pNIPAM and injected into the IVD) is used to optimize the release of EGCG and to protect it from degradation. This system will also be compatible with other therapeutics, hence offering great clinical versatility / applicability.

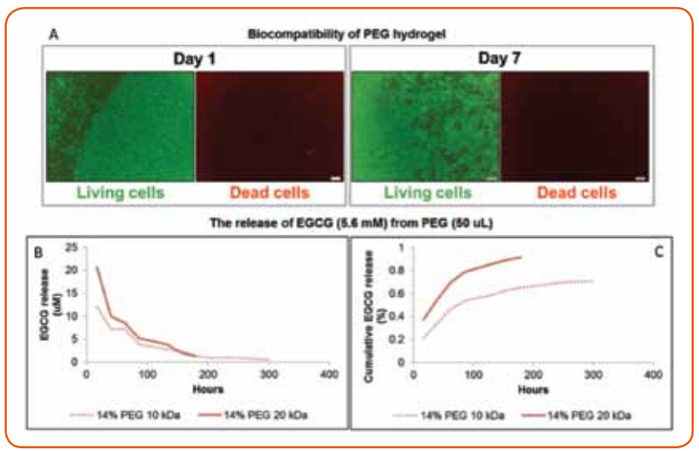


Figure 1: Living (green) and dead (red) cells in pH-sensitive PEG hydrogel on day 1 and 7 (A). EGCG release (B) and Cumulative EGCG release (C) from 14% PEG of 2 different sizes 10 kDA and 20 kDA.

facts & figures

member profiles, joint research projects and publications

The fundamental idea behind the CABMM is to perform, coordinate and promote interdisciplinary and clinically oriented, translational research. Therefore, we aim to create and continuously strengthen a network of active member groups from different fields. The number and quality of those members, as well as their collaborative research projects and scientific publications reflect not only the activity within the CABMM network, but also show the success and quality of the CABMM.

Since its foundation in 2008, the CABMM has gained acceptance and reputation in the field of interdisciplinary and translational research, which is also illustrated by a continuously growing number of CABMM members. At the end of the reporting period, our network consisted of more than 60 active members, and is still continuing to grow. Considering the number of team members behind every person, this makes for an impressive network! Although the majority of associated scientists belong to institutions in Zurich, we also have strong affiliations with other institutions located elsewhere in Switzerland as well as in other countries.

Special emphasis has to be placed on the networking within the CABMM. Basic researchers and clinicians from both human and veterinary medicine are working on numerous joint research projects, thus reflecting the multifaceted work within the CABMM. Whereas some projects are representative of long-standing collaborations between individual groups within the CABMM, some have only very recently been initiated. One of the most important instigators for starting a new collaboration is the yearly CABMM Spring Seminar and the CABMM Symposium where the presentations of new findings by scientists working within the CABMM allow for fruitful exchange of scientific knowledge and ideas. Another stimulator for scientific exchange and starting new collaborations is our own funding program, the so-called "CABMM Start-up Grant" (see pages 60-69). Taken together, this results in a very active network reflected by a continuously growing number of collaborative research projects.

Another testament to the scientific strengths and networking capabilities of our CABMM members is the fact that almost 50 peer-reviewed research articles with affiliation to the CABMM have been published in scientific journals within the reporting period, amongst others, in the highly regarded journal "Cell Stem Cell". Moreover, due to the increasing number of high impact publications, the CABMM has been recently even added as an own keyword to the list of search keywords in the online search engine "PubMed".

To summarize and illustrate the diversity and multifaceted work within the CABMM, all our members are introduced with the assistance of short profiles on the following pages. Additionally, we provide tables detailing research projects performed within the CABMM as well as CABMM-affiliated articles published in scientific journals. We conclude this chapter by providing a short list of public relation review articles about the CABMM, which we consider to be of paramount importance in promoting the uniqueness of our network and maximizing our visibility.

member profiles (in alphabetical order)

for further information on cabmm joint research projects and publications please refer to the respective numbers in the tabular summaries on pages 92-98 and 100-105

Name: **Audigé, Laurent**
PD Dr. (DMV), PhD
Institution: Research and Development Department, Upper Extremities, Schulthess Clinic, Zurich
Grants: Mäxi foundation
CABMM collaborators: Stephen Ferguson
CABMM joint projects: 12, 53

General research interest:
We are interested in a clinic-wide patient registry to monitor safety and assess cost effectiveness of orthopedic interventions. This implies the application of standardized instruments, including for documenting and reporting surgical complications. The development of a clinical decision support system based on register data is a long-term objective. We contribute in the development and evaluation of new diagnostic tools (e.g., motion analysis), as well as implants and surgical techniques (e.g., biomechanics) to improve patient care.

Name: **Beneke, Sascha***
PD Dr. rer. nat.
Institution: Ecotoxicology Group, University of Konstanz, Germany
CABMM collaborators:
Felix Althaus

General research interest:
- Poly(ADP-ribosyl)ation
- DNA repair & genomic stability
- Aging
- Parkinson's disease
- Cell death and Ca^{2+}

Name: **Blauth, Michael**
Prof. Dr. med.
Institution: Department for Trauma Surgery, Medical University of Innsbruck, Austria
Grants: CABMM, AO, DePuy-Synthes, EU, Novagenit, Novartis, Eli Lilly, Zimmer
CABMM collaborators:
Jörg Goldhahn, Ralph Müller, Brigitte von Rechenberg, Peter Richards
CABMM joint projects: 20, 37, 61
Publications with affiliation to the CABMM: 22, 17

General research interest:
We are mainly focused on elucidating the role played by mesenchymal stem cells in geriatric musculoskeletal diseases. As a clinical trauma surgery department, we have direct access to human patient material, which is processed in our cell culture lab. Experimental data are linked to data obtained from clinical tests and patient interviews and collected in a cell data base. Stem cells are analyzed by state of the art visualizing techniques, namely electron and confocal microscopy, as well as biochemical and histological methods.

* CABMM member until 2015

Name: **Bode, Jeffrey**
Prof. Dr. sc. nat.
Institution: Laboratory of Organic Chemistry, ETH Zurich
Grants: SNF, ERC, CTI, CABMM
CABMM collaborators: Stephen Ferguson, Oliver Hausmann, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 1, 15, 29

General research interest:
The Bode Group develops novel chemical reactions for the synthesis of organic molecules under physiological conditions, e.g., in water and in the presence of proteins, living cells, and tissues. Their application includes wound healing, drug delivery, cellular encapsulation, and artificial tissues.

Name: **Boos, Alois**
Prof. Dr. med. vet.
Institution: Institute of Veterinary Anatomy, Vetsuisse Faculty, University of Zurich
CABMM collaborators: Ueli Braun, Anton Fürst, Patrick Kircher Annette Liesegang, Brigitte von Rechenberg
CABMM joint projects: 2, 35
Publications with affiliation to the CABMM: 6

General research interest:
- Musculoskeletal system
- Ovary, uterus and placenta of cow and dog
- Digestive system of various species

Name: **Borel, Nicole**
Prof. Dr. med. vet.,
Dipl. ECVP, FVH pathology
Institution: Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich
Grants: SNF, Federal Food Safety and Veterinary Office (FSVO), Braun Foundation, Office International des Epizooties (OIE)
CABMM collaborators: Christian Blenn*
CABMM joint projects: 21, 75

General research interest:
Our focus is on new therapeutic strategies for intracellular bacteria such as chlamydiae. Water-filtered infrared A irradiation (wIRA) has proven its efficacy in wound healing processes in clinical settings. We could demonstrate the inhibition of chlamydial infection *in vitro* using wIRA irradiation. Ongoing work in our lab aims to demonstrate proof of concept for ocular wIRA treatment in an *in vitro* conjunctival cell culture model of chlamydial infection. Our current studies indicate that thermal as well as non-thermal effects contribute to the inhibitory effect of wIRA/VIS exposure on chlamydiae and these effects will be further characterized in the future.

* CABMM member until 2014

Name: **Cinelli, Paolo**
PD Dr. sc. nat.
Institution: Center for Clinical Research, Clinic for Trauma Surgery, University Hospital Zurich
Grants: Novartis Foundation for Medical-Biological Research, Theodor und Ida Herzog-Egli-Stiftung, Olga Mayenfisch Stiftung, CABMM, SNF
CABMM collaborators:
Martin Flück, Anton Fürst, Simon Hoerstrup, Michael Hottiger, Brigitte von Rechenberg, Peter Richards, Raffaella Santoro, Benedikt Weber, Franz Weber

CABMM joint projects: 22, 33, 64
Publications with affiliation to the CABMM: 5

General research interest:
Our laboratory is mainly interested in the analysis of the molecular mechanisms involved in the regulation of pluri/multipotency and differentiation of embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). We are especially interested in the use of these stem cells in bone regeneration.

Name: **Dip, Ramiro**
PD Dr. med. vet., PhD
Institution: Institute of Veterinary Pharmacology and Toxicology; Vetsuisse Faculty, University of Zurich; Swiss Reinsurance Company Ltd.
Grants: Stiftung Forschung für das Pferd

General research interest:
We are interested in elucidating mechanisms of inflammatory downregulation by the adenosine receptor A2A (transcriptional regulation, alteration of cytokine profiles, etc.). We currently investigate the molecular events triggered by adenosine on mast cells and how the interplay between the involved signaling pathways can be modulated in the course of an inflammatory reaction. In addition, we aim at clarifying physiopathological role of adenosine signaling in equine recurrent airway obstruction (RAO).

Name: **Ferguson, Stephen**
Prof. Dr. (PhD)
Institution: Laboratory for Orthopaedic Technology, Institute for Biomechanics, ETH Zurich
Grants: EU, SNF, CABMM, CTI, St. Josefs Hospital Fund (Iceland), ETH Foundation, Industry
CABMM collaborators: L. Audigé, J. Bode, N. Boos, F. Forterre, A. Franco-Obregón, B. Gantenbein-Ritter, S. Gay, J. Goldhahn, O. Hausmann, S. Hoerstrup, A. Liesegang, D. Meyer, R. Müller, B. von Rechenberg, J. Snedeker, F. Steffen, J. Stoyanov, A. Studart, S. Stübinger, V. Vogel, K. Würtz-Kozak, M. Zenobi-Wong

CABMM joint projects: 4, 6, 10, 12, 14, 15, 28, 43, 45, 46, 53, 66
Publications with affiliation to the CABMM: 35, 33, 23, 13, 10, 8

General research interest:
The focus of our group's research is the study of the mechanical and biological mechanisms of musculoskeletal disorders and injuries and the use of innovative technologies for their treatment. Primary challenges we address include (i) extending the life of joint prostheses, (ii) preventing or improving the treatment of fractures and (iii) eliminating disc-related back pain. Our group studies new biomaterials, molecular therapies and implant concepts and develops the technical means for their application in the clinic.

Name: **Flück, Martin**
Prof. Dr. (PhD)
Institution: Laboratory for Muscle Plasticity, University of Zurich; Balgrist Campus AG, Zurich
Grants: UZH, SNF
CABMM collaborators:
Paolo Cinelli, Christian Gerber, Peter Kronen, Dominik Meyer, Brigitte von Rechenberg, Jess Snedeker, Franz Weber, Marcy Zenobi-Wong
Publications with affiliation to the CABMM: 32

General research interest:
The research group of Prof. Flück investigates the mechanisms that are responsible for plasticity of the muscular system in response to altered use and injury, specifically muscle degeneration with unloading after tendon rupture and muscle rehabilitation subsequent to orthopedic surgery.

Name: **Forterre, Franck**
Prof. Dr. med. vet.
Institution: Department of Clinical Veterinary Medicine, Small Animal Surgery, Vetsuisse Faculty, University of Bern
Grants: Novartis Animal Health, CABMM, Heel, Marie-Louise von Muralt-Stiftung für Kleintiere
CABMM collaborators: Stephen Ferguson, Benjamin Gantenbein-Ritter, Patrick Kircher, Peter Kronen, Claudia Spadavecchia, David Spreng, Frank Steffen, Karin Würtz-Kozak
CABMM joint projects: 44

General research interest:
The main focus of the research group of Prof. Forterre is directed towards canine intervertebral disc disease and atlantoaxial instability with regard to biomechanics, inflammation, intramedullary blood flow and pressure changes. Because the dog is a recognized naturally occurring clinical model for human disc degeneration and spinal cord trauma, a translational aspect is present.

Name: **Franco-Obregón, Alfredo**
PhD
Institution: Department of Surgery, National University Hospital Singapore
Grants: Foundation Suisse de Recherche sur les Maladies Musculaires (FSRMM), European Space Agency, CABMM, Swiss Health Agency (BAG)
CABMM collaborators:
Norbert Boos, Stephen Ferguson, Annette Liesegang, Brigitte von Rechenberg, Peter Richards, Jess Snedeker, Karin Würtz-Kozak
CABMM joint projects: 4, 28, 46, 51
Publications with affiliation to the CABMM: 33, 23

General research interest:
Sarcopenia, the loss of skeletal muscle mass with advanced age, underlies many disorders inflicting the elderly such as diabetes, osteopenia, cardiovascular disease, degenerative joint disease and systemic catabolism while concomitantly reducing their resistance to infection and compromising their ability to overcome trauma. My principal research focus is the development of strategies designed at maintaining muscle mass in the elderly and those suffering from imposed immobilization. We also study the fundamental cellular mechanotransduction process that initiates the developmental programs of our major mechanosensitive tissues.

Name: **Fürst, Anton**
Prof. Dr. med. vet., Dipl. ECVS
Institution: Equine Hospital, Vetsuisse Faculty, University of Zurich
CABMM collaborators: Jörg Auer, Alois Boos, Paolo Cinelli, Anja Kipar, Patrick Kircher, Peter Kronen, Lee Ann Laurent-Applegate, Annette Liesegang, Brigitte von Rechenberg, Peter Richards, Jess Snedeker
CABMM joint projects: 25, 33, 62
Publications with affiliation to the CABMM: 7

General research interest:
Our technical expertise and interests cover all fields of equine surgery. Currently, our research focuses mainly on equine orthopaedics, e.g., the treatment of arthritis, subchondral cystic lesions (SCLs) and tendon injuries in the horse. After successful development of new treatment options *in vitro*, the clinical caseload offers direct future opportunities for their clinical application.

Name: **Gantenbein-Ritter, Benjamin**
Prof. Dr. (PhD)
Institution: Institute of Surgical Technology and Biomechanics, University of Bern
Grants: Gebert Rüf Foundation, CABMM, International Scientific Research Network, Private donation Prof. Dr. Paul Heini, Lindenhof Foundation, SNF
CABMM collaborators: Stephen Ferguson, Franck Forterre, Brigitte von Rechenberg, Peter Richards, David Spreng, Jivko Stoyanov, Benedikt Weber, Karin Würtz-Kozak
CABMM joint projects: 10, 24, 27, 47
Publications with affiliation to the CABMM: 3

General research interest:
The Tissue & Organ Mechanobiology (TOM) Group of the Institute for Surgical Technology and Biomechanics (ISTB), University of Bern, is performing basic research in the area of tissue engineering using a cross-disciplinary approach of biology and mechanics. Our primary aim is to understand the cellular response to biomechanical stimuli and how cellular communities are affected *in situ* using 3D tissue and organ culture models. Our focus is on the regeneration or repair of the intervertebral disc and on the anterior cruciate ligament.

Name: **Gay, Steffen**
Prof. Dr. med.
Institution: Center of Experimental Rheumatology, University Hospital Zurich
Grants: EU FP7 Masterswitsch, EU FP7 PEOPLE-2011-ITN Marie Curie Training Network, EU FP7-TEAM HEALTH.2012.2.4.5-2, EU IMI BTCure, CABMM, Industry
CABMM collaborators: Norbert Boos, Stephen Ferguson, Christian Gerber, Oliver Hausmann, Simon Hoerstrup, Michael Hottiger, Caroline Ospelt, Karin Würtz-Kozak
CABMM joint projects: 3, 43, 45
Publications with affiliation to the CABMM: 13

Home: www.zkf.uzh.ch/de/ResearchGroups/Gay.html
General research interest:
The Center of Experimental Rheumatology Zurich is performing molecular research in the field of rheumatoid arthritis (RA) and related autoimmune diseases. Thereby, we investigate key molecular and cellular events in RA, ankylosing spondylitis and scleroderma. In particular, our research focuses on the activation of the innate immune system in RA and on epigenetic changes leading to the stably activated phenotype of RA synovial fibroblasts such as DNA and histone methylation, histone and non-histone acetylation, and the expression of non-coding RNAs, including miRs, lncRNAs, PIWIL.

Name: **Gerber, Christian**
Prof. Dr. med.
Institution: Department of Orthopaedics, University Hospital Balgrist, Zurich
Grants: SNF, CABMM
CABMM collaborators: Jörg Auer, Norbert Boos, Martin Flück, Steffen Gay, Simon Hoerstrup, Dominik Meyer, Ralph Müller, Brigitte von Rechenberg, Jess Snedeker, Wendelin Stark
CABMM joint projects: 19, 36, 42, 72
Publications with affiliation to the CABMM: 43, 32

General research interest:
Our research focus is primarily on surgical reconstructive procedures on the shoulder. In a series of research projects on a sheep shoulder model, our group investigated over the last seventeen years the etiology, pathophysiology and novel treatment options for rotator cuff tears. Particular interest lies in the degeneration and retraction of the musculotendinous unit in chronic tendon tears. Novel treatment approaches include chemical anabolic stimulation, mechanical expansion of the musculotendinous unit and optimization of the surgical techniques.

Name: **Hafezi, Farhad**
Prof. Dr. med., PhD
Institution: ELZA Institute AG, Dietikon; Department of Ophthalmology, University of Southern California, Los Angeles, California, USA
Grants: SNF, AURIS Foundation, Velux Foundation, Gelbert Foundation, Trust Frantheral
CABMM collaborators: Brigitte von Rechenberg
Publications with affiliation to the CABMM: 31, 27, 26

General research interest:
Farhad Hafezi's main research interests are corneal wound healing, corneal infection, ocular biomechanics, and progressive myopia. The common link among these interests is a treatment modality that is now used in clinical ophthalmology for corneal diseases and dystrophies. This modality is called corneal cross-linking (CXL). CXL combines UV light and riboflavin (Vitamin B2) to modify collagen structure and biomechanics. The newest clinical application is using CXL to treat bacterial and fungal corneal infections.

Name: **Hämmerle, Christoph**
Prof. Dr. med. dent.
Institution: Center of Dental Medicine, Clinic of Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich
Grants: Osteology Foundation, International Team for Implantology, Swiss Society of Odontology, Swiss Society of Reconstructive Dentistry
CABMM collaborators: Wendelin Stark, Franz Weber

General research interest:
Our focus is to develop and teach clinical concepts for the treatment of patients in need of hard and soft tissue regeneration and the placement of oral implants for rehabilitation with fixed dental reconstructions. Research areas include regeneration of bone and oral soft tissues (pre-clinical animal models as well as clinical trial in patients). We aim for the development of barrier membranes for guided bone regeneration, the application of growth factors and carriers for bone formation and the application of biomaterials for augmentation of soft and hard tissues.

Name: **Hausmann, Oliver**
PD Dr. med.
Institution: Neurozentrum Zentralschweiz, Hirslanden Hospital St. Anna, Lucerne
Grants: CABMM
CABMM collaborators: Jeffrey Bode, Norbert Boos, Stephen Ferguson, Steffen Gay, Daniel Rüfenacht, Isabel Wanke, Karin Würtz-Kozak
CABMM joint projects: 6, 15, 43, 45
Publications with affiliation to the CABMM: 13, 8

General research interest:
I am working as a neurosurgeon at the Hirslanden Hospital St. Anna in Lucerne. The research is focused on degeneration of the spine as well as on spinal cord injury. I am collaborating with Prof. Dr. Würtz-Kozak in the most recent past. After obtaining ethical approval for the collection of disc biopsies in 2010, I currently provide the Laboratory of Orthopaedic Technology with surgical material, which will be used for investigations.

Name: **Hirsch, Sven**
PhD
Institution: Institute of Applied Simulation, Zürcher Hochschule für Angewandte Wissenschaften (ZHAW), Wädenswil
Grants: SystemX.ch – AneuX, University Hospital Essen
CABMM collaborators: Patrick Kircher, Peter Kronen, Niels Kuster, Serge Marbacher, Brigitte von Rechenberg, Daniel Rüfenacht, Isabel Wanke
CABMM joint projects: 5

General research interest:
Dr. Hirsch applies computational techniques to model selected aspects in complex physiological systems, which are subsequently validated using image data of real biological experiments. A strong focus is on vessel wall pathologies and their lifecycle, e.g., cerebral aneurysms.

Name: **Hoerstrup, Simon P.**
Prof. Dr. med. Dr. rer. nat.
Institution: Institute for Regenerative Medicine, University of Zurich; Wyss Translational Center Zurich, ETH and University of Zurich
Grants: EU FP7, SNF, HSM, Schweizerische Herzstiftung, CTI, EMDO-Stiftung, CABMM, Olga Mayenfisch Stiftung, Mäxi foundation, Zurich Heart, SwissTransMed, 3R, Wyss Translational Center Zurich
CABMM collaborators: F. Althaus, J. Auer, P. Cinelli, S. Ferguson, S. Gay, C. Gerber, M. Hottiger, E. Keller, P. Kircher, P. Kronen, L. Laurent-Applegate, D. Meyer, R. Müller, B. von Rechenberg, J. Reichenbach, D. Rüfenacht, C. Schwarzwald, J. Snedeker, W. Stark, V. Vogel, I. Wanke, B. Weber, M. Zenobi-Wong
CABMM joint projects: 23, 34, 48, 49, 50, 55, 56, 59, 68
Publications with affiliation to the CABMM: 21

General research interest:
The research expertise of Prof. 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 as well as (3) disease modeling, e.g., studying inflammatory processes that occur in the early development of arteriosclerosis.

Name: **Hofmann-Lehmann, Regina**
Prof. Dr. med. vet.
Institution: Clinical Laboratory, Vetsuisse Faculty, University of Zurich
Grants: SNF, Forschungskredit UZH, EGMASA, Bundesprogramm Chancengleichheit, Industry, CABMM
CABMM collaborators: Peter Kronen, Annette Liesegang, Brigitte von Rechenberg, Raffaella Santoro
CABMM joint projects: 52

General research interest:
Our interest is in clinical research, mainly clinical infectiology and clinical pathology. We apply animal models in experimental studies to investigate host-pathogen interactions and immunoprophylaxis. Our group has developed molecular and serological diagnostic tools for a variety of infectious diseases. We are particularly interested in retroviral infections, haemotropic mycoplasmas and vector-borne diseases of domestic and wild animals. Together with the clinics of small animal medicine, we established the clinical infectiology in 2011.

Name: **Hottiger, Michael O.**
Prof. Dr. med. vet. Dr. phil. II
Institution: Departement of Molecular Mechanisms of Disease, University of Zurich
Grants: SNF, SystemsX, Krebsliga Zürich, Gottfried und Julia Bangerter-Rhyner Foundation, Kurt & Senta Hermann-Foundation, URPP, CABMM, Forschungskredit UZH
CABMM collaborators: Paolo Cinelli, Steffen Gay, Simon Hoerstrup, Caroline Ospelt, Brigitte von Rechenberg, Janine Reichenbach, Peter Richards, Daniel Rüfenacht, Raffaela Santoro, Viola Vogel, Isabel Wanke, Benedikt Weber
CABMM joint projects: 3, 31, 64, 67, 69

Publications with affiliation to the CABMM: 46, 38

General research interest:
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 posttranslational modifications of proteins. Our current work focuses on the activation and function of the enzymes that catalyze these protein modifications and the identification of their target proteins.

Name: **Keller, Emanuela**
Prof. Dr. med.
Institution: Neurocritical Care Unit, Department of Neurosurgery, University Hospital Zurich
Grants: Gebert Rüf Stiftung, Hasler Foundation, SNF, Helmut Horten Foundation
CABMM collaborators: Simon Hoerstrup, Serge Marbacher, Daniel Rüfenacht, Isabel Wanke

General research interest:
- Development of new methods to estimate cerebral hemodynamics and oxygenation
- Optical spectroscopy: Theoretical examinations, *in vitro* examinations, development of new medical devices for clinical applications
- Examination of the cerebral and systemic inflammatory response; development of new treatment strategies against delayed ischemic deficits after subarachnoid hemorrhage
- Development of predictive views and treatment recommendations based on data mining in intensive care medicine (project "ICUCockpit")

Name: **Kipar, Anja**
Prof. Dr. med. vet.
Institution: Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich
Grants: Stiftung für Wissenschaftliche Forschung an der UZH, Medical Research Council UK, Ministry of Higher Education Malaysia, Biotechnology and Biological Sciences Research Council UK (BBSRC), WINN Foundation
CABMM collaborators: Ueli Braun, Anton Fürst, Patrick Kircher, Peter Kronen, Annette Liesegang, Brigitte von Rechenberg, Colin Schwarzwald, Viola Vogel

General research interest:
The main interest of my group is the pathogenesis of infectious diseases with a main focus on virus infections, like Boid Inclusion Body Disease (BIBD) of boid snakes or Feline Infectious Peritonitis (FIP) in cats. Our animal work covers a wide range of viral and bacterial diseases and expands to toxicopathology. To accommodate the specific requirements for morphological studies in different animal models, we have established the Laboratory for Animal Model Pathology (LAMP) that provides technical service and expert pathologist input to a wide range of collaborative studies.

Name: **Kircher, Patrick R.**
Prof. Dr. med. vet., PhD, Dipl. ECVDI
Institution: Division of Diagnostic Imaging, Vetsuisse Faculty, University of Zurich
Grants: Nano-Tera.ch, CABMM
CABMM collaborators:
Alois Boos, Ueli Braun, Franck Forterre, Anton Fürst, Sven Hirsch, Simon Hoerstrup, Anja Kipar, Peter Kronen, Niels Kuster, Brigitte von Rechenberg, Daniel Rüfenacht, Frank Steffen, Isabel Wanke
CABMM joint projects: 11, 17, 30, 35, 41, 59, 60, 70
Publications with affiliation to the CABMM: 7

General research interest:
We are interested in the development of Functional Magnetic Resonance Imaging (fMRI) and MR Spectroscopy, as well as cardiac MRI (cMRI) in animal patients and animal models. In general, the cross-sectional angiographic techniques are being optimized and utilized in the group. The Division shall serve as centre of expertise in animal imaging for all affiliates of the CABMM.

Name: **Kronen, Peter**
Dr. med. vet., DVM, Dipl. ECVAA
Institution: Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich; Veterinary Anaesthesia Services International, Winterthur
Grants: CTI, 3R, Industry, EU
CABMM collaborators: Martin Flück, Franck Forterre, Anton Fürst, Sven Hirsch, Simon Hoerstrup, Regina Hofmann-Lehmann, Anja Kipar, Patrick Kircher, Serge Marbacher, Dominik Meyer, Brgitte von Rechenberg, Daniel Rüfenacht, Jess Snedeker, Claudia Spadavecchia, David Spreng, Stefan Stübinger, Isabel Wanke, Franz Weber

CABMM joint projects:
8, 9, 17, 18, 38, 39, 41, 59, 60, 63, 71
Publications with affiliation to the CABMM:
36, 24, 4

General research interest:
- Improvement of anaesthetic techniques and methods in large experimental animals (rabbits, sheep, pigs, goats)
- Pain diagnosis in behavioral schemes (pain scales), their comparison with neurophysiological parameters and clinical relevance

Name: **Kuster, Niels**
Prof. Dr. (PhD)
Institution: IT'IS Foundation for Research on Information Technologies in Society, Zurich
Grants: SNF, CTI, INERIS, ANSES, EU FP7, BAFU, Boston Scientific, COST
CABMM collaborators: Sven Hirsch, Patrick Kircher, Brigitte von Rechenberg, Daniel Rüfenacht, Isabel Wanke
CABMM joint projects: 5

General research interest:
The IT'IS Foundation is a leading developer of tools for *in silico* investigations of specific tissue models and electromagnetic (EM) interactions with complex anatomies, e.g., tissue heating and cooling, bio-mechanics, -acoustics, and -fluid dynamics. Additional competencies include the production of systems for experimental *in vitro*, *in vivo* and human exposure to EM radiation and for evaluations of radiofrequency transmitters implanted in or operating near the human body, and the development of state-of-the-art computational human models.

Name: **Laurent-Applegate, Lee Ann**
Prof. Dr. med.
Institution: Department of Musculoskeletal Medicine, Service of Plastic and Reconstructive Surgery, Unit of Regenerative Therapy, University Hospital Lausanne
Grants: FRNS, SwissTransMed, CABMM, SCIEX, EU FP7
CABMM collaborators: Felix Althaus, Anton Fürst, Simon Hoerstrup, Peter Kronen, Brigitte von Rechenberg, Gian Salzmann, Jess Snedeker, Stefan Stübinger, Marcy Zenobi-Wong
CABMM joint projects: 7, 26, 40, 57, 62

General research interest:
We are interested in addressing clinical problems relating to tissue repair based on the concept that unlike adult tissue, fetal tissue undergoes rapid healing with little inflammation and no scar tissue. As such, our laboratory has now established cell banks of progenitor cells harvested from a variety of tissue sources including human bone, cartilage, disc, muscle, tendon and skin, and these are being used to successfully develop cellular therapies and associated delivery systems for severely burned patients, acute and chronic wounds and musculoskeletal tissues.

Name: **Liesegang, Annette**
Prof. Dr. med. vet., Dipl. ECVCN, IVAS
Institution: Institute of Animal Nutrition, Vetsuisse Faculty, University of Zurich
Grants: SNF, Forschungskredit UZH, Albert-Heim-Stiftung, CABMM
CABMM collaborators: A. Boos, U. Braun, S. Ferguson, A. Franco-Obregón, A. Fürst, R. Hofmann-Lehmann, A. Kipar, D. Meyer, B. von Rechenberg, R. Santoro, J. Snedeker, K. Würtz-Kozak
CABMM joint projects: 2, 16, 46, 52
Publications with affiliation to the CABMM: 28, 15, 6

General research interest: Bone and mineral research
- Importance of physiological and nutritional influences on bone resorption and formation
- Measurement of bone and cartilage markers and bone mineral density (quantitative peripheral computertomography) in many species, also during gestation and lactation under different influences
- Ca resorption in the intestine with Immunhistochemistry and Western blot
- Mechanisms of longitudinal growth regulation within growth plates in foals and lambs
- Hormones of Ca metabolism
- Osteoporosis
- Vitamin D metabolism in the skin

Name: **Marbacher, Serge**
PD Dr. med., PhD
Institution:
Cerebrovascular Research Group,
Department of Neurosurgery,
Kantonsspital Aarau
Grants: Research Council
Kantonsspital Aarau
CABMM collaborators: Sven Hirsch,
Emanuela Keller, Peter Kronen,
Brigitte von Rechenberg, Daniel Rüfenacht, Isabel Wanke

General research interest:
The cerebrovascular research group focuses on cerebral aneurysms, e.g., endovascular treatment options to prevent aneurysm rupture and sequels of subarachnoid hemorrhage after their rupture. We currently implement a novel sidewall rat aneurysm model using decellularized arterial grafts to investigate inflammatory processes eventually leading to aneurysm growth and rupture. It is our ultimate goal to find novel endovascular treatment modalities that completely exclude the aneurysm from the circulation and reconstruct the diseased arterial segment.

Name: **Meyer, Dominik C.**
Prof. Dr. med.
Institution: Department of Orthopedics,
University Hospital Balgrist, Zurich
Grants: SNF, ResOrtho Foundation,
EMPA, CABMM, Karl Storz GmbH
CABMM collaborators:
Jörg Auer, Norbert Boos, Stephen Ferguson,
Martin Flück, Christian Gerber,
Jörg Goldhahn, Simon Hoerstrup,
Peter Kronen, Annette Liesegang, Brigitte von Rechenberg,
Jess Snedeker
CABMM joint projects: 19, 36, 38, 42, 72
Publications with affiliation to the CABMM: 43, 32

General research interest:
Our research focuses on surgical reconstructive procedures on soft tissues such as muscles, tendons, ligaments and menisci in the shoulder and the knee. In a sheep shoulder model, our group has investigated for seventeen years the etiology, pathophysiology and novel treatment options for rotator cuff tears. On the knee, we primarily investigate novel treatment approaches for the reconstruction and repair of the cruciate ligament *in vivo* and *in vitro*.

Name: **Müller, Ralph**
Prof. Dr. sc.
Institution: Laboratory for Bone
Biomechanics, Institute for Biomechanics,
ETH Zurich
Grants: COST, EU, SNF
CABMM collaborators:
Michael Blauth, Stephen Ferguson,
Christian Gerber, Jörg Goldhahn,
Simon Hoerstrup, Brigitte von Rechenberg,
Peter Richards, Jess Snedeker, Wendelin Stark, André Studart,
Viola Vogel, Marcy Zenobi-Wong
Publications with affiliation to the CABMM: 9, 17

General research interest:
The research the Müller group has completed and is currently pursuing employs state-of-the-art biomechanical testing and simulation techniques as well as novel bioimaging and visualization strategies for musculoskeletal tissues. Today, these techniques are successfully employed for the quantitative assessment and monitoring of structure function relationships in tissue regeneration, growth and adaptation. The approaches are now often used for precise phenotypic characterization of tissue response in mammalian genetics, mechanobiology as well as tissue engineering and regenerative medicine.

Name: **Ospelt, Caroline**
PD Dr. med., PhD
Institution: Center of Experimental
Rheumatology, University Hospital Zurich
Grants: EU IMI BTCure, EU FP7
EuroTEAM, CABMM, EMDO Foundation,
Theodor und Ida Herzog-Egli-Stiftung,
Hartmann Müller-Stiftung,
Novartis Foundation, Promedica Stiftung
CABMM collaborators:
Steffen Gay, Michael Hottiger, Karin Würtz-Kozak
CABMM joint projects: 3
Publications with affiliation to the CABMM: 13

General research interest:
In one of the leading centers worldwide for the analysis of synovial fibroblasts in rheumatoid arthritis, Dr. Ospelt`s track record is the analysis of innate immune mechanisms and epigenetic changes within this complex field. Furthermore, the group analyses the role of non-coding RNAs, histone acetylation and DNA methylation.

Name: **von Rechenberg, Brigitte**
Prof. Dr. med. vet., Dipl. ECVS
Institution: Musculoskeletal Research
Unit (MSRU), Vetsuisse Faculty,
University of Zurich
Grants: EU FP7, SwissTransMed,
Nano-Tera.ch, SystemsX, CTI, CABMM,
Mäxi foundation
CABMM collaborators:
Michael Blauth, Alois Boos, Paolo Cinelli,
Stephen Ferguson, Martin Flück, Anton Fürst,
Alfredo Franco-Obregón, Benjamin Gantenbein-Ritter,
Christian Gerber, Jörg Goldhahn, Farhad Hafezi, Sven Hirsch,
Simon Hoerstrup, Regina Hofmann-Lehmann,
Michael Hottiger, Anja Kipar, Patrick Kircher, Peter Kronen,
Niels Kuster, Lee Ann Laurent-Applegate, Annette Liesegang,
Serge Marbacher, Dominik Meyer, Ralph Müller,
Janine Reichenbach, Daniel Rüfenacht, Gian Salzmann,
Raffaella Santoro, Jess Snedeker, David Spreng,
Wendelin Stark, Frank Steffen, Stefan Stübinger, Viola Vogel,
Isabel Wanke, Benedikt Weber, Karin Würtz-Kozak,
Marcy Zenobi-Wong

CABMM joint projects:
4, 5, 7, 8, 9, 11, 16, 23, 25, 30, 34, 35, 36, 37, 38, 39, 40, 41, 48, 49,
50, 52, 57, 58, 63, 66, 68, 69, 71, 72
Publications with affiliation to the CABMM:
44, 43, 42, 36, 35, 32, 24, 22, 18, 17, 10, 9, 4, 1

General research interest:
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 as well as the importance of physiological remodeling of subchondral bone and cartilage. At the same time, we have embarked in wound healing of deep and infected skin wounds. Furthermore, as experimental animal facility we have received GLP accreditation by the Swiss Medic in June 2014 and in this capacity we have broadened our scope to other fields of experimental medicine as well.

Name: **Reichenbach, Janine**
Prof. Dr. med.
Institution: Division of Immunology, University Children`s Hospital Zurich
Grants: EU FP7, Gebert Rüf Stiftung, Gottfried und Julia Bangerter-Rhyner-Stiftung, Fondazione Ettore e Valeria Rossi, ZHIP
CABMM collaborators: Simon Hoerstrup, Michael Hottiger, Brigitte von Rechenberg
Publications with affiliation to the CABMM: 29, 25

General research interest:
The research group of Prof. Reichenbach is focused on inborn errors of the immune system, spanning from analysis of molecular pathophysiology to development of new therapeutic concepts and therapeutic correction by clinical gene therapy. Furthermore, the focus lies on the analysis of hyper-inflammatory pathophysiology observed in Chronic Granulomatous Disease.

Name: **Richards, Peter J.**
PD Dr. (PhD)
Institution: Bone and Stem Cell Research Group, CABMM, University of Zurich
Grants: SNF, Uniscientia Stiftung, CABMM, Swiss Life, Stiftung für wissenschaftliche Forschung an der UZH
CABMM collaborators:
Michael Blauth, Paolo Cinelli, Alfredo Franco-Obregón, Anton Fürst, Benjamin Gantenbein-Ritter, Michael Hottiger, Ralph Müller, Raffaella Santoro, David Spreng, Franz Weber
CABMM joint projects: 20, 33, 51, 61, 64, 65, 73

Publications with affiliation to the CABMM:
46, 38, 30, 22, 17, 2

General research interest:
We are primarily interested in elucidating the processes governing multipotent stromal cell (MSC) lineage commitment, and in understanding how dysregulation of such processes can contribute to the development of various human pathologies.

Name: **Rüfenacht, Daniel A.**
Prof. Dr. med.
Institution: Neuroradiology, SwissNeuro-Institute, Klinik Hirslanden, Zurich; InterventionalWorkResearch (IWR), SwissNeuro-Foundation; Department of Cardiovascular Science, University of Sheffield, UK
Grants: SNF, CTI, EU FP7, University of Essen, SwissNeuroFoundation, Industry
CABMM collaborators: Oliver Hausmann, Sven Hirsch, Simon Hoerstrup, Michael Hottiger, Emanuela Keller, Patrick Kircher, Peter Kronen, Nils Kuster, Serge Marbacher, Brigitte von Rechenberg, Isabel Wanke
CABMM joint projects: 5, 48, 59, 70

Publications with affiliation to the CABMM: 24

General research interest:
The IWR group is interested in understanding, imaging and visualization of neurovascular diseases and minimally invasive treatment options (imaging methods, devices and implants). Our research focuses on vessel wall pathologies, in particular on intracranial aneurysms. By replicating the biological findings on a computer model, we intend to understand the life cycle of aneurysms, to understand the impact of endovascular flow correction on blood and vessel wall and to improve methods of imaging and endovascular treatment options.

Name: **Salzmann, Gian**
Prof. Dr. med.
Institution: Orthopaedics, Lower extremities, Schulthess Klinik, Zurich
Grants: SNF, GOTS, Mäxi foundation, Lindenhofgruppe Bern, Alwin Jäger Stiftung, CABMM
CABMM collaborators:
Lee Ann Laurent-Applegate, Brigitte von Rechenberg, Marcy Zenobi-Wong
CABMM joint projects: 74

General research interest:
As a clinician-scientist, Prof. Salzmann is optimally positioned to observe first-hand the limitations of current cartilage repair procedures and will help towards translation from bench-to-bedside. Experimental research includes the application of gene therapy and mechanical loading on articular chondrocytes in small animal models and the use of chondrocytes and stem cells in clinical applications.

Name: **Santoro, Raffaella**
PD Dr. (PhD)
Institution: Department of Molecular Mechanisms of Disease, University of Zurich
Grants: SNF, Krebsliga Schweiz, Krebsliga Zurich, CABMM, Stiftung für wissenschaftliche Forschung an der UZH, Theodor und Ida Herzog-Egli-Stiftung, Sassella-Stiftung, Julius-Müller-Stiftung, Olga Mayenfisch Stiftung
CABMM collaborators: Paolo Cinelli, Regina Hofmann-Lehmann, Michael Hottiger, Annette Liesegang, Brigitte von Rechenberg, Peter Richards
CABMM joint projects: 22, 31, 52, 73
Publications with affiliation to the CABMM: 5

General research interest:
Every cell contains the same genetic information, yet they differentiate into distinct tissues and organs. This property is mainly interpreted at the level of epigenetics and chromatin structure via non-coding RNAs and modifications at histones and DNA. We aim to elucidate how epigenetic mechanisms establish and maintain cell identity. Our mission is to identify chromatin and epigenetic regulators and to define the pathways contributing to pluripotency, neoplastic transformation and metastasis.

Name: **Schwarzwald, Colin C.**
Prof. Dr. med. vet., PhD, Dipl. ACVIM, ECEIM
Institution: Clinic for Equine Internal Medicine, Equine Department, Vetuisse Faculty, University of Zurich
Grants: Forschungskredit UZH, Stiftung für Wissenschaftliche Forschung an der UZH
CABMM collaborators:
Ueli Braun, Simon Hoerstrup, Anja Kipar, Benedikt Weber
CABMM joint projects: 55, 56
Publications with affiliation to the CABMM: 34

General research interest:
Large animal and comparative cardiology, with emphasis on echocardiography, cardiac electrophysiology, hemodynamic monitoring, cardiovascular pharmacology, and cardiac biomarkers. Rodent echocardiography service.

Name: **Snedeker, Jess G.**
Prof. Dr. (PhD)
Institution: Department of Orthopedic Biomechanics, University of Zurich; Institute for Biomechanics, ETH Zurich
Grants: SNF, CTI, Vontobel Foundation, ETH VPR Grants, Balgrist Foundation, Kurt und Senta Hermann Foundation
CABMM collaborators: Stephen Ferguson, Martin Flück, Alfredo Franco-Obregón, Anton Fürst, Christian Gerber, Simon Hoerstrup, Peter Kronen, Lee Ann Laurent-Applegate, Annette Liesegang, Dominik Meyer, Ralph Müller, Brigitte von Rechenberg, Viola Vogel, Franz Weber, Karin Würtz-Kozak

CABMM joint projects: 19, 38, 46, 62

General research interest:
The Snedeker Laboratory expertise is in the development and application of novel functional imaging platforms to quantify and characterize cell-matrix mechanical interactions. The laboratory specifically targets hypotheses related to the influence that extracellular matrix composition (collagen type, proteoglycan content) and mechanics have on tendon cell and stem cell behaviour (proliferation, differentiation).

Name: **Spadavecchia, Claudia**
Prof. Dr. med. vet., PhD, Dipl. ECVAA
Institution: Institute of Veterinary Anaesthesiology and Pain Therapy, Department of Clinical Veterinary Medicine, Vetsuisse Faculty, University of Bern
Grants: Fondation Sur-La-Croix / Agroscope
CABMM collaborators: Franck Forterre, Peter Kronen, David Spreng

General research interest:
Our main research interest is pain in animals. We aim at developing objective, valid and reliable tools to evaluate species-specific nociceptive physio-pathological processes and pain behaviour and at refining procedures and techniques to improve pain treatment in domestic and laboratory animals. Our major areas of interest are 1) neurophysiological characterization of acute and persistent pain to provide evidence in the context of animal welfare, 2) development of perioperative pain treatment strategies in clinical and experimental settings and 3) optimization of methods to treat acute perioperative pain.

Name: **Spreng, David**
Prof. Dr. med. vet., Dipl. ECVS, Dipl. ACVECC
Institution: Section of Small Animal Surgery, Vetsuisse Faculty, University of Bern
Grants: CABMM
CABMM collaborators: Franck Forterre, Benjamin Gantenbein-Ritter, Peter Kronen, Brigitte von Rechenberg, Peter Richards, Claudia Spadavecchia, Karin Würtz-Kozak
CABMM joint projects: 44, 65

General research interest:
Our group is interested in the pathophysiology of partial cranial (anterior) cruciate ligament rupture in the dog. We are currently working on understanding the pathomechanism of NO induced apoptotic cell death and its consequences on potential healing capacities of the ligament.

Name: **Stark, Wendelin J.**
Prof. Dr. (PhD)
Institution: Functional Materials Laboratory, Institute for Chemical and Bioengineering, ETH Zurich
Grants: SNF, CTI
CABMM collaborators: Christian Gerber, Christoph Hämmerle, Simon Hoerstrup, Ralph Müller, Brigitte von Rechenberg, André Studart, Viola Vogel, Franz Weber, Marcy Zenobi-Wong

General research interest:
We are interested in the development of bioresorbable materials for reconstructive bone surgery, based on calcium phosphates (TCP) and their composites with degradable biocompatible polymers like PLGA. Such PLGA / TCP / collagen membranes are designed to induce bone regeneration and prevent scar tissue formation on the other side. The research is also focused on the development of soft machines and pumps and its use as possible next generation heart replacements.

Name: **Steffen, Frank**
PD Dr. med. vet., Dipl. ECVN
Institution: Section of Neurology / Neurosurgery, Small Animal Department, Vetsuisse Faculty, University of Zurich
Grants: SNF, CABMM
CABMM collaborators: Stephen Ferguson, Franck Forterre, Patrick Kircher, Brigitte von Rechenberg, Jivko Stoyanov, Karin Würtz-Kozak
CABMM joint projects: 13, 14, 32

General research interest:
There is a broad interest focused on clinical and surgical aspects of intervertebral disc degeneration including regeneration strategies, clinical assessment of outcome, diagnostic imaging follow-up and translational studies. Currently, we are treating dogs with degenerated discs using autologous mesenchymal stem cells and follow those dogs clinically and with MRI in order to study the clinical efficacy of this novel therapy.

Name: **Stoyanov, Jivko**
PD Dr. (PhD)
Institution: Biomedical Laboratories, Swiss Paraplegic Research, Nottwill
Grants: SNF, Swiss Paraplegic Foundation, CABMM
CABMM collaborators: Stephen Ferguson, Benjamin Gantenbein-Ritter, Frank Steffen
CABMM joint projects: 13, 14

General research interest:
We are interested in optimizing cell interaction with tissue engineering matrices for the purpose of regeneration and to modulate inflammation in intervertebral discs (IVD). We isolate and culture human and canine IVD cells and mesenchymal stem cells (MSCs) and have knowledge in hypoxic cell culture, molecular and biochemical methods and live cell imaging. We have a substantial collection of matched (from same donor) cell sets – IVD cells, MSCs and PBMCs. Other focus areas are the aging of MSCs, development of a biobank for SCI samples and immunosenescence in persons with spinal cord injury (SCI).

Name: **Studart, André R.**
Prof. Dr. (PhD)
Institution: Complex Materials, Department of Materials, ETH Zurich
Grants: SNF, Industry
CABMM collaborators:
Stephen Ferguson, Ralph Müller, Wendelin Stark, Marcy Zenobi-Wong

General research interest:
Our research is focused on the design and assembly of new porous materials and functional capsules of potential use as scaffolds and drug release agents in regenerative medicine. In the area of porous materials, we are interested in studying hierarchical porous architectures that can provide physical and chemical cues to accelerate regeneration in soft and hard tissues. In the area of functional capsules, we use microfluidic devices to develop smart, responsive capsules that could potentially be used for the controlled release of drugs and growth factors in the body upon different types of external stimuli.

Name: **Stübinger, Stefan**
PD Dr. med. dent.
Institution: Hightech Research Center of Cranio-Maxillofacial Surgery, Department Biomedical Engineering, Medical Faculty, University of Basel
Grants: CTI, Industry
CABMM collaborators:
Stephen Ferguson, Peter Kronen, Lee Ann Laurent-Applegate, Brigitte von Rechenberg, Franz Weber
CABMM joint projects: 8, 9, 18, 39, 58, 63, 71
Publications with affiliation to the CABMM:
44, 41, 40, 36, 35, 20, 19, 18, 16, 12, 11, 10

General research interest:
The Department Biomedical Engineering at the Medical Faculty of the University of Basel was recently awarded a Flagship Project from the Werner Siemens Foundation (Zug / Switzerland). Aim of this interdisciplinary project called Minimally Invasive Robot-guided Computer-assisted Laser OsteotomE (MIRACLE) is the development of an endoscopic system for cutting bone with laser light. The project deals with three main topics: A) Laser technology and robotics, B) navigation and augmented reality and C) smart implants and clinical transfer.

Name: **Vogel, Viola**
Prof. Dr. (PhD)
Institution: Laboratory of Applied Mechanobiology, ETH Zurich
Grants: SNF, TransMed, NCCR
CABMM collaborators:
Stephen Ferguson, Simon Hoerstrup, Michael Hottiger, Anja Kipar, Ralph Müller, Brigitte von Rechenberg, Jess Snedeker, Wendelin Stark, Benedikt Weber, Marcy Zenobi-Wong

General research interest:
The focus of Prof. Vogel's laboratory is to learn how mechanical forces are sensed by bacteria, cells and tissues, how the stretching of proteins can switch their structure-function relationship and thus cell signaling, and how such insights can be exploited for biomedical applications and in regenerative medicine. This includes asking how the mechanobiology of extracellular matrix directs stem cell differentiation and (micro)tissue functions.

Name: **Wanke, Isabel**
Prof. Dr. med.
Institution: Neuroradiology, SwissNeuroInstitute, Klinik Hirslanden, Zurich; InterventionalWorkResearch (IWR), SwissNeuroFoundation; Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Germany
Grants: SNF, CTI, EU FP7 (VDHDARE, VPHSHARE), University of Essen, SwissNeuroFoundation, Industry
CABMM collaborators: Oliver Hausmann, Sven Hirsch, Simon Hoerstrup, Michael Hottiger, Emanuela Keller, Patrick Kircher, Peter Kronen, Niels Kuster, Serge Marbacher, Brigitte von Rechenberg, Daniel Rüfenacht

CABMM joint projects: 5
Publications with affiliation to the CABMM: 24

General research interest:
The IWR group is interested in understanding, imaging and visualization of neurovascular diseases and minimally invasive treatment options (imaging methods, devices and implants). Our research focuses on vessel wall pathologies, in particular on intracranial aneurysms. We are preparing for further contributions concerning mechanisms of destructive and reverse remodeling of the aneurysm wall, both processes, where mechanisms of inflammation are increasingly suspected to exhibit the key role when it comes aneurysm stability and healing.

Name: **Weber, Benedikt**
PD Dr. med., PhD
Institution: Regenerative Medicine and Organoid Technology Research Program, Department of Surgical Research, University and University Hospital Zurich
Grants: CABMM, Forschungskredit UZH, Stiftung für Wissenschaftliche Forschung, HMZ Seed Grant, 3R Foundation, Fonds Medizinische Forschung, Olga Mayenfisch Stiftung, ETH Research Grant
CABMM collaborators:
Paolo Cinelli, Benjamin Gantenbein-Ritter, Simon Hoerstrup, Michael Hottiger, Brigitte von Rechenberg, Colin Schwarzwald, Viola Vogel

CABMM joint projects: 24
Publications with affiliation to the CABMM: 21

General research interest:
The research focus of Dr. Weber is to investigate the use of different cell and stem cell sources for vascular bioengineering and for *in vitro* modeling of (cardio)vascular diseases. The group has demonstrated the successful *in vitro* manufacture and *in vivo* implantation of different vascular bioengineered structures, including heart valves, venous vales and blood vessels. A major focus lies on the underlying remodeling mechanisms *in vivo* with regards to guiding *in situ* cellularization, scaffold (bio)degradation and neotissue formation.

Name: **Weber, Franz E.**
Prof. Dr. rer. nat.
Institution: Oral Biotechnology & Bioengineering, Center of Dentistry / MKG, University of Zurich
Grants: SNF, EU FP7, SSO, AO CMF Grant
CABMM collaborators:
Paolo Cinelli, Martin Flück, Christoph Hämmerle, Peter Kronen, Peter Richards, Jess Snedeker, Wendelin Stark, Stefan Stübinger, Marcy Zenobi-Wong
CABMM joint projects: 18
Publications with affiliation to the CABMM: 45, 39, 37, 14

General research interest:
The main interest of our research laboratory is the healing of large bone defects of the mandible and the cranium. At present we mainly focus on the microstructure of bone substitutes to optimize osteoconduction and realize this topic by additive manufacturing of calcium phosphates and with partners for titanium and magnesium. Epigenetics and bone regeneration are another subject of research. On the field of osteoinduction, we produce and design growth factors to promote bone formation.

Name: **Würtz-Kozak, Karin**
Prof. Dr. (PhD)
Institution: Laboratory for Orthopaedic Technology, Institute for Biomechanics, ETH Zurich; University of Potsdam, Germany
Grants: Spine Society of Europe, AO, Sciex, ETH Foundation, OPO Stiftung, Theodor und Ida Herzog-Egli-Foundation, CABMM
CABMM collaborators: Jeffrey Bode, Norbert Boos, Stephen Ferguson, Franck Forterre, Alfredo Franco-Obregón, Benjamin Gantenbein-Ritter, Steffen Gay, Oliver Hausmann, Annette Liesegang, Caroline Ospelt, Brigitte von Rechenberg, Jess Snedeker, David Spreng, Frank Steffen, Marcy Zenobi-Wong

CABMM joint projects:
4, 6, 10, 15, 27, 28, 32, 43, 44, 45, 46, 47, 54
Publications with affiliation to the CABMM: 33, 23, 13, 8, 3

General research interest:
The human musculoskeletal system adapts to external cues not only during development, but also throughout the entire life. External cues hence play an important role in tissue remodeling, repair and degeneration. We aim to analyze how mechanical and chemical cues (e.g., inflammatory signals) and the physical environment of cells can regulate cellular behavior and ultimately tissue functionality. This information is subsequently used for the development of novel, targeted treatments of musculoskeletal disorders.

Name: **Zenobi-Wong, Marcy**
Prof. Dr. (PhD)
Institution: Cartilage Engineering and Regeneration, Institute for Biomechanics, ETH Zurich
Grants: SNF, CABMM, ETH Foundation
CABMM collaborators: Jeffrey Bode, Stephen Ferguson, Martin Flück, Simon Hoerstrup, Lee Ann Laurent-Applegate, Ralph Müller, Brigitte von Rechenberg, Gian Salzmann, Wendelin Stark, André Studart, Viola Vogel, Franz Weber, Karin Würtz-Kozak
CABMM joint projects: 1, 26, 29, 40, 54, 74

Publications with affiliation to the CABMM: 37

General research interest:
We use biomaterials and biofabrication techniques to create 3D cellular systems for cartilage regeneration. Biomimetic hydrogels are designed to control stem cell and chondrocyte fate, having engineered adhesion and growth factor binding properties. We are using bioprinting and electrospinning to create complex function mimics of the cartilage matrix and geometry. Finally, we are developing ways to engineer cell-cell and cell-tissue interactions for use in organotypic microtissue formation and regenerative medicine.

honorary members:

Name: **Auer, Jörg A.**
Prof. em. Dr. med. vet. Dr. h. c., Dipl. ECVS, Dipl. ACVS
Institution: Equine Hospital, Vetsuisse Faculty, University of Zurich

Name: **Hübscher, Ulrich**
Prof. em. Dr. med. vet.
Institution: Institute of Veterinary Biochemistry and Molecular Biology, University of Zurich

alumni members:

Name: **Althaus, Felix R.**
Prof. em. Dr. med. vet.
Institution: Institute of Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich

Name: **Boos, Norbert**
Prof. Dr. med.
Institution: Prodorso, Centre for Spinal Medicine, Zurich

Name: **Braun, Ueli**
Prof. Dr. med. vet. Dr. h. c.
Institution: Department of Farm Animals, Vetsuisse Faculty, University of Zurich

Name: **Bürki, Kurt**
Prof. em. Dr. sc. nat.
Institution: Institute of Laboratory Animal Science, Vetsuisse Faculty, University of Zurich

Name: **Goldhahn, Jörg**
Prof. Dr. med.
Institution: Novartis Institutes for Biomedical Research, Basel (until 2016), Department Health Sciences and Technology, ETH Zurich

joint research projects 2014/2015 (in alphabetical order)

Number	Title	Collaborator (CABMM members)
1	**3D Patterning of Proteins on Hydrogels**	Jeffrey Bode Marcy Zenobi-Wong*
2	**Absorption mechanisms in the intestines of goat and sheep**	Alois Boos Annette Liesegang*
3	**Analysis of topographic differences in synovial fibroblasts**	Steffen Gay Michael Hottiger Caroline Ospelt *
4	**Analyzing the benefit of PEMF treatment in stem-cell based, equine cartilage regeneration**	Stephen Ferguson Alfredo Franco-Obregón Brigitte von Rechenberg Karin Würtz-Kozak*
5	**AneuX project – Modeling Shape as a Biomarker for Instability of Intracranial Aneurysms**	Philippe Bijlenga*/** Sven Hirsch Niels Kuster Brigitte von Rechenberg Daniel Rüfenacht Isabel Wanke
6	**Annulus fibrosus rupture**	Stephen Ferguson* Oliver Hausmann Karin Würtz-Kozak
7	**B5 SwissTransMed: biological, biodegradable and anti-bacterial burn-wound bandages**	Lee Ann Laurent-Applegate* Brigitte von Rechenberg
8	**Biocompatibility testing of coated titanium and ceramic implants in the pelvic model in sheep**	Peter Kronen Brigitte von Rechenberg Stefan Stübinger*
9	**Biocompatibility testing of PEEK implants in the pelvic model in sheep**	Peter Kronen Brigitte von Rechenberg Stefan Stübinger*
10	**Biological response of the intervertebral disc to repetitive short-term cyclic torsion**	Stephen Ferguson Benjamin Gantenbein-Ritter* Karin Würtz-Kozak*
11	**Biomechanical characterization of the Luque Trolley System to avoid adjacent segment disease**	Patrick Kircher Brigitte von Rechenberg*

* Principal Investigator, ** no CABMM member

Number	Title	Collaborator (CABMM members)
12	**Biomechanical comparison of shoulder arthroplasty design variation**	Laurent Audigé* Stephen Ferguson
13	**Cell motility as a marker for canine and human mesenchymal stem cells multipotency**	Frank Steffen Jivko Stoyanov*
14	**Cell therapy for degenerative disc disease using injectable microcarriers**	Stephen Ferguson Frank Steffen Jivko Stoyanov*
15	**Development and characterization of a pH sensitive slow release system to reduce inflammatory processes in the degenerated intervertebral disc**	Jeffrey Bode Stephen Ferguson Oliver Hausmann Karin Würtz-Kozak*
16	**Development, implementation and validation of an osteopenic sheep model for use in evaluating novel implant fixation techniques in low density bone applications**	Annette Liesegang* Brigitte von Rechenberg
17	**Development of a transvascular bypass operation technique in pigs**	Patrick Kircher Peter Kronen*
18	**Development of an animal model to study the osteonecrosis of the jaw**	Peter Kronen Stefan Stübinger* Franz Weber
19	**Diagnosis and minimally invasive treatment of rotator cuff tendon tear**	Christian Gerber* Dominik Meyer Jess Snedeker
20	**Effect of bisphosphonates on the differentiation potential of mesenchymal stem cells isolated from osteoporotic patients**	Michael Blauth Peter Richards*
21	**Effect of water-filtered infrared A (wIRA) on chlamydial infections**	Christian Blenn Nicole Borel*
22	**Epigenetic rRNA gene silencing during ESC differentiation**	Paolo Cinelli Raffaella Santoro*
23	**Establishment of a cell- and tissue biobank**	Simon Hoerstrup* Brigitte von Rechenberg

* Principal Investigator, ** no CABMM member

Number	Title	Collaborator (CABMM members)
24	**Establishment of the differential proteomic and biofunctional analysis of the secretome of human mesenchymal stem cell sources**	Benjamin Gantenbein-Ritter Benedikt Weber*
25	**Evaluation of recombinant human bone morphogenetic proteins (rhBMP-2) on equine osteoblasts and bone marrow-derived mesenchymal stem cells *in vitro* for a future clinical application in subchondral cystic lesions (SCLs) in horses**	Anton Fürst* Brigitte von Rechenberg
26	**Evaluation of the chondrogenic potential of human epiphyseal chondroprogenitor cells in alginate**	Lee Ann Laurent-Applegate Marcy Zenobi-Wong*
27	**Expression, regulation and relevance of hyaluronidases in the intervertebral disc**	Benjamin Gantenbein-Ritter Karin Würtz-Kozak*
28	**Expression, regulation and role of the TRP channel family in disc and muscle**	Norbert Boos Stephen Ferguson Alfredo Franco-Obregón* Karin Würtz-Kozak
29	**Formation of Hydrogels by KAT Amide Forming Ligations**	Jeffrey Bode* Marcy Zenobi-Wong
30	**From superparamagnetic nano-particles to tools for the detection and treatment of cancer**	Patrick Kircher Brigitte von Rechenberg Heinrich Hofmann*/**
31	**Functional analysis of non-coding RNA in osteoclastogenesis**	Michael Hottiger Raffaella Santoro*
32	**Identification of inflammatory and pain markers in degenerative spinal disease**	Luc Smolders (Frank Steffen***) Frank Steffen Karin Würtz-Kozak*
33	**Identification of tenocytic specific markers in the horse**	Paolo Cinelli* Anton Fürst Peter Richards
34	**ImaValve**	Simon Hoerstrup* Brigitte von Rechenberg
35	**Impingement syndrome in hip joints**	Alois Boos* Patrick Kircher Brigitte von Rechenberg

* Principal Investigator, ** no CABMM member, *** corresponding CABMM member

Number	Title	Collaborator (CABMM members)
36	**Improved cruciate ligament reconstruction through enhanced graft incorporation at the bone-graft interface – An experimental study in rabbits**	Christian Gerber* Dominik Meyer Brigitte von Rechenberg
37	**Improvement of pedicle screw anchorage by immediate stabilization system (ISS) – a histological and biomechanical *ex vivo* study**	Michael Blauth Brigitte von Rechenberg*
38	**Improved soft tissue anchorage for anterior cruciate reconstruction**	Peter Kronen Dominik Meyer Brigitte von Rechenberg Jess Snedeker*
39	**Influence of a new polymer dowel on primary stability and osseointegration of dental implants**	Peter Kronen Brigitte von Rechenberg Stefan Stübinger*
40	**Injectable hyaluronan based adhesive technology for cartilage regeneration using human epiphyseal chondroprogenitor cells – an experimental study in sheep**	Lee Ann Laurent-Applegate Brigitte von Rechenberg Marcy Zenobi-Wong*
41	**Intracranial tissue perfusion, pressure and temperature**	Patrick Kircher Peter Kronen* Brigitte von Rechenberg
42	**Intraoperative tissue and fluid analysis using radio-frequency plasma spectroscopy**	Christian Gerber Dominik Meyer*
43	**Investigating the role of Toll-like receptor 2 in intervertebral disc degeneration and inflammation**	Norbert Boos Stephen Ferguson Steffen Gay Oliver Hausmann Karin Würtz-Kozak*
44	**Investigation of the inflammatory processes associated with canine intervertebral disc herniation**	Franck Forterre* David Spreng Karin Würtz-Kozak*
45	**Investigation the anti-inflammatory, anti-catabolic, anti-apoptotic and anti senescence properties of Epigallo-catechin gallate (EGCG) in human disc cells**	Norbert Boos Stephen Ferguson Steffen Gay Oliver Hausmann Karin Würtz-Kozak*

* Principal Investigator, ** no CABMM member

Number	Title	Collaborator (CABMM members)
46	**Investigation the effects of PEMF in a murine *in vivo* model**	Stephen Ferguson Alfredo Franco-Obregón* Annette Liesegang Jess Snedeker Karin Würtz-Kozak
47	**Investigation of the Regenerative Effects of porcine Notochordal Cells onto bovine Intervertebral Disc Cells under Co-Culture**	Benjamin Gantenbein-Ritter* Karin Würtz-Kozak
48	***In vitro* point-of care blood clot profiling by thromboelastography**	Simon Hoerstrup Brigitte von Rechenberg Daniel Rüfenacht*
49	**iValve**	Simon Hoerstrup* Brigitte von Rechenberg
50	**LifeValve**	Simon Hoerstrup* Brigitte von Rechenberg
51	**Molecular regulation of myogenesis: role of serine protease HTRA1**	Alfredo Franco-Obregón Peter Richards*
52	**Monitoring osteomyelitis by biomarkers following systemic inflammation parameters**	Regina Hofmann-Lehmann Annette Liesegang* Brigitte von Rechenberg Raffaella Santoro
53	**Motion analysis of the proximal interphalangeal joint in healthy hands, as well as in osteoarthritis hands following implantation with the new CapFlexPIP implant compared with silicone implants**	Laurent Audigé* Stephen Ferguson
54	**NEMO and IKKβ: Identifying potential targets for the treatment of early osteoarthritis using shRNA technology**	Karin Würtz-Kozak Marcy Zenobi-Wong*
55	**Novel heterotopic working heart transplantation in rodents as a model for orthotopic *in vivo* investigation of tissue engineered heart valves**	Simon Hoerstrup* Colin Schwarzwald
56	**Novel "stretched" PGA/PCL dip coated copolymer stented scaffold: biomaterial *in vivo* evaluation in a rodent animal model**	Simon Hoerstrup* Colin Schwarzwald

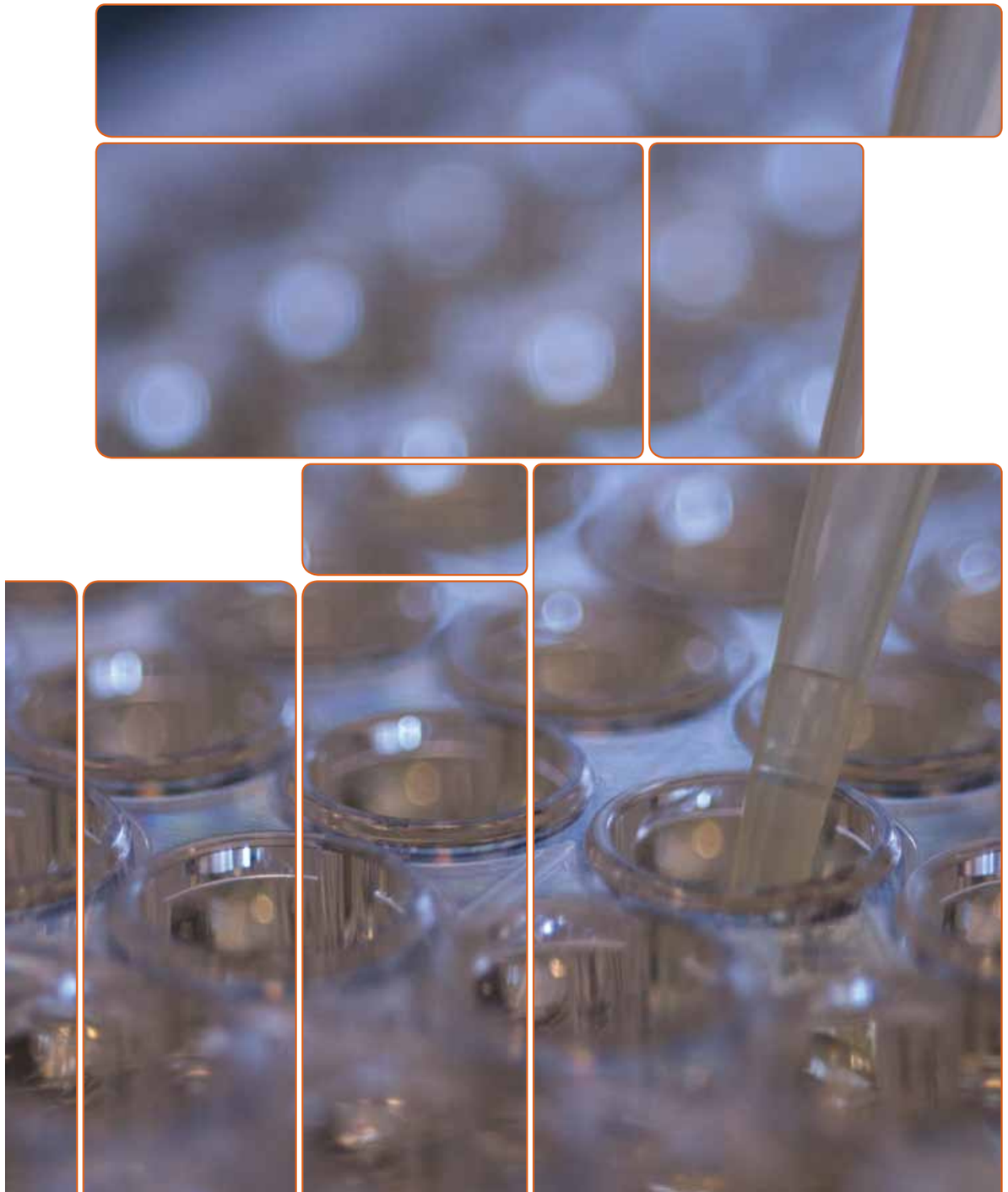
* Principal Investigator, ** no CABMM member

Number	Title	Collaborator (CABMM members)
57	**Osteochondral bone stimulation with fetal progenitor cells**	Lee Ann Laurent-Applegate* Brigitte von Rechenberg
58	**Photodynamic laser application for bisphosphonate-induced avascular bone necrosis**	Brigitte von Rechenberg Stefan Stübinger*
59	**Performance and safety of a new embolizing device in a pig model**	Simon Hoerstrup Patrick Kircher Peter Kronen* Daniel Rüfenacht
60	**Preliminary investigation into Radio-opacity of intravascular stents**	Patrick Kircher Peter Kronen*
61	**Prostaglandin-mediated regulation of human stem cell multipotency and its relevance to age-related bone loss**	Michael Blauth Peter Richards*
62	**Regeneration of equine weight bearing tendons**	Anton Fürst* Lee Ann Laurent-Applegate Jess Snedeker
63	**Rekonstruktion von Knochendefekten durch lokale Wirkstofffreisetzung aus dem bioabbaubaren synthetischen Knochenersatzmaterial easy-graft®**	Peter Kronen Brigitte von Rechenberg Stefan Stübinger*
64	**Role of ARTD1 in osteoclastogenesis and bone homeostasis**	Paolo Cinelli Michael Hottiger* Peter Richards
65	**Role of the infrapatellar fat pad on the pathophysiology of the diseased cranial cruciate ligament in dogs**	Peter Richards David Spreng*
66	**Silicon Nitride Coatings for Improved Implant Function (LifeLongJoint)**	Stephen Ferguson Richard Hall*/** Brigitte von Rechenberg
67	**Single cell analysis of NF-kB induction kinetics during innate immune response using DARPins as analytical reagents for mass cytometry**	Bernd Bodenmiller** Michael Hottiger* Andreas Plückthun**
68	**Skin regeneration using MSC**	Salim Darwiche* (Brigitte von Rechenberg***) Simon Hoerstrup

* Principal Investigator, ** no CABMM member, *** corresponding CABMM member

Number	Title	Collaborator (CABMM members)
69	**Spying on cells: towards the establishment of a new non-viral drug delivery system using silica-coated superparamagnetic iron oxide nanoparticles (SPIONs)**	Flurina Clement Frey* (Brigitte von Rechenberg***) Michael Hottiger
70	**Steam device in transrectal interventional MRI usage on canine prostates**	Patrick Kircher* Daniel Rüfenacht
71	**STEP – Sensing peri-implant disease**	Peter Kronen Brigitte von Rechenberg Stefan Stübinger*
72	**The effect of pharmacological and mechanical stimulation on the chronically retracted torn rotator cuff muscle – An experimental study in sheep**	Christian Gerber* Dominik Meyer Brigitte von Rechenberg
73	**The function of serine protease HTRA1 in regulating adipogenesis and bone marrow adipose tissue**	Peter Richards* Raffaella Santoro
74	**The *in vitro* chondrogenic differentiation of human bMSCs within gel or sponge-type 3-D matrices – a comparative approach**	Gian Salzmann* Marcy Zenobi-Wong
75	**Water-filtered infrared A (wIRA): new therapeutic strategies for treatment of chlamydial infections in humans and animals**	Christian Blenn Nicole Borel*

* Principal Investigator, ** no CABMM member, *** corresponding CABMM member



summary publications 2015 (order date of publication)

Number	
46	Lehmann M, Pirinen E, Mirsaidi A, Kunze FA, Richards PJ, Auwerx J, Hottiger MO **ARTD1-induced poly-ADP-ribose formation enhances PPARγ ligand binding and co-factor exchange** *Nucleic Acids Research, 2015 Jan 9, 43(1):129-42*
45	Hänseler P, Ehrbar M, Kruse K, Fischer E, Schibli R, Ghayor C, Weber FE **Delivery of BMP-2 by two clinically available apatite materials: *In vitro* and *in vivo* comparison** *J Biomed Mater Res A, 2015 Feb, 103(2):628-38*
44	Stübinger S, Nuss K, Bürki A, Mosch I, Sidler M, Meikle ST, von Rechenberg B, Santim M **Osseointegration of titanium implants functionalised with phosphoserine-tethered poly(epsilon-lysin) dendrons: a comparative study with traditional surface treatments in sheep** *J Mater Sci Mater Med, 2015 Feb, 26(2):87*
43	Wieser K, Farshad M, Meyer DC, Conze P, von Rechenberg B, Gerber C **Tendon response to pharmaco-mechanical stimulation of the chronically retracted rotator cuff in sheep** *Knee Surg Sports Traumatol Arthrosc, 2015 Feb, 23(2):577-84*
42	Ouellet JA, Ferland CE, Racloz G, Klein K, Richter H, Steffen T, Rechenberg BV **Evaluation of the Modern Luque Trolley Construct for Treatment of Early Onset Scoliosis Using a Gliding Implant in an Immature Animal Model** *J Spinal Disord Tech, 2015 Feb 25, [Epub ahead of print]*
41	Stricker A, Fleiner J, Stübinger S, Fleiner H, Buser D, Bosshardt DD **Ridge preservation after ridge expansion with simultaneous guided bone regeneration: a preclinical study** *Clin Oral Implants Res, 2015 Mar 9, [Epub ahead of print]*
40	Cai WX, Ma L, Zheng LW, Kruse-Gujer A, Stübinger S, Lang NP, Zwalen R **Influence of non-steroidal anti-inflammatory drugs (NSAIDs) on osseointegration of dental implants in rabbit calvaria** *A Clin Oral Implants Res, 2015 Apr, 26(4):478-83*
39	Karfeld-Sulzer LS, Ghayor C, Siegenthaler B, de Wild M, Leroux JC, Weber FE **N-methyl pyrrolidone/bone morphogenetic protein-2 double delivery with *in situ* forming implants** *J Control Release, 2015 Apr 10, 203:181-188*
38	Müller-Edenborn K, Léger K, Glaus Garzon JF, Oertli C, Mirsaidi A, Richards PJ, Rehrauer H, Spielmann P, Hoogewijs D, Borsig L, Hottiger MO, Wenger RH **Hypoxia attenuates the proinflammatory response in colon cancer cells by regulating IκB** *Oncotarget, 2015 Apr 21, 6(24):20288-301*

Number	
37	Gjoksi B, Ghayor C, Siegenthaler B, Ruangsawasdi N, Zenobi-Wong M, Weber FE **The epigenetically active small chemical N-methyl pyrrolidone (NMP) prevents estrogen depletion induced osteoporosis** *Bone, 2015 May 7, 78:114-121*
36	Stübinger S, Drechsel A, Bürki A, Klein K, Kronen P, von Rechenberg B **Titanium and hydroxyapatite coating of polyetheretherketone and carbon fiber-reinforced polyetheretherketone: A pilot study in sheep** *J Biomed Mater Res B Appl Biomater, 2015 Jun 11, [Epub ahead of print]*
35	Ernst S, Stübinger S, Schüpbach P, Sidler M, Klein K, Ferguson SJ, von Rechenberg B **Comparison of two dental implant surface modifications on implants with same macrodesign: an experimental study in the pelvic sheep model** *Clin Oral Implants Res, 2015 Aug, 26(8):898-908*
34	Trachsel DS, Grenacher B, Schwarzwald CC **Plasma atrial/A-type natriuretic peptide (ANP) concentration in horses with various heart diseases** *J Vet Cardiol, 2015 Sep, 17(3):216-28*
33	Spaas JH, Broeckx SY, Chiers K, Ferguson SJ, Casarosa M, Van Bruaene N, Forsyth R, Duchateau L, Franco-Obregón A, Wuertz-Kozak K **Chondrogenic Priming at Reduced Cell Density Enhances Cartilage Adhesion of Equine Allogenic MSCs – a Loading Sensitive Phenomenon in an Organ Culture Study with 180 Explants** *Cell Physiol Biochem, 2015 Sep 8, 37(2):651-665*
32	Gerber C, Meyer DC, Flück M, Benn MC, von Rechenberg B, Wieser K **Anabolic Steroids Reduce Muscle Degeneration Associated With Rotator Cuff Tendon Release in Sheep** *Am J Sports Med, 2015 Oct, 43(10):2393-400*
31	Hammer A, Kling S, Boldi MO, Richoz O, Tabibian D, Randleman JB, Hafezi F **Establishing Corneal Cross-Linking With Riboflavin and UV-A in the Mouse Cornea *In Vivo*: Biomechanical Analysis** *Invest Ophthalmol Vis Sci, 2015 Oct 1, 56(11):6581-90*
30	Theiss F, Mirsaidi A, Mhanna R, Kümmerle J, Glanz S, Bahrenberg G, Tiaden AN, Richards PJ **Use of biomimetic microtissue spheroids and specific growth factor supplementation to improve tenocyte differentiation and adaptation to a collagen-based scaffold *in vitro*** *Biomaterials, 2015 Nov, 69:99-109*

Number	
29	Dreyer AK, Hoffmann D, Lachmann N, Ackermann M, Steinemann D, Timm B, Siler U, Reichenbach J, Grez M, Moritz T, Schambach A, Cathomen T **TALEN-mediated functional correction of X-linked chronic granulomatous disease in patient-derived induced pluripotent stem cells** *Biomaterials, 2015 Nov, 69:191-200*
28	Elfers K, Liesegang A, Wilkens MR, Breves G, Muscher-Banse AS **Dietary nitrogen and calcium modulate bone metabolism in young goats** *J Steroid Biochem Mol Biol, 2015 Nov 14, [Epub ahead of print]*
27	Randleman JB, Khandewal SS, Hafezi F **Corneal cross-linking** *Surv Ophthalmol, 2015 Nov-Dec, 60(6):509-23*
26	Hashemi H, Miraftab M, Seyedian MA, Hafezi F, Bahrmandy H, Heidarian S, Amanzadeh K, Nikbin H, Fotouhi A, Agari S **Long-term Results of an Accelerated Corneal Cross-linking Protocol (18 mW/cm2) for the Treatment of Progressive Keratoconus** *Am J Ophtalmol, 2015 Dec, 160(6):1164-1170*
25	Harbort CJ, Soeiro-Pereira PV, von Bernuth H, Kaindl AM, Costa-Carvalho BT, Condino-Neto A, Reichenbach J, Roesler J, Zychlinsky A, Amulic B **Neutrophil oxidative burst activates ATM to regulate cytokine production and apoptosis** *Blood, 2015 Dec 24, 126(26):2842-51*

summary publications 2014 (order date of publication)

Number	
24	Mallik AS, Nuss K, Kronen PW, Klein K, Karol A, von Rechenberg B, Rüfenacht DA, Wanke I, Kulcsár Z **A new-generation, low-permeability flow diverting device for treatment of saccular aneurysms** *Eur Radiol, 2014 Jan, 24(1):12-8*
23	Broeckx S, Zimmermann M, Crocetti S, Suls M, Marien T, Ferguson SJ, Chiers K, Duchateau L, Franco-Obregón A, Wuertz K, Spaas JH **Regenerative therapies for equine degenerative joint disease: a preliminary study** *PLoS One, 2014 Jan 20, 9(1):e85917*
22	Lindtner RA, Tiaden AN, Genelin K, Ebner HL, Manzl C, Klawitter M, Sitte I, von Rechenberg B, Blauth M, Richards PJ **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*
21	Driessen-Mol A, Emmert MY, Dijkman PE, Frese L, Sanders B, Weber B, Cesarovic N, Sidler M, Leenders J, Jenni R, Grünenfelder J, Falk V, Baaijens FP, Hoerstrup SP **Transcatheter implantation of homologous "off-the-shelf" tissue-engineered heart valves with self-repair capacity: long-term functionality and rapid *in vivo* remodeling in sheep** *J Am Coll Cardiol, 2014 Apr 8, 63(13):1320-9*
20	Stricker A, Fleiner J, Stübinger S, Schmelzeisen R, Dard M, Bosshardt DD. **Bone loss after ridge expansion with or without reflection of the periosteum** *Clin Oral Implants Res, 2014 Jun 26, doi: 10.1111/clr.12437. [Epub ahead of print]*
19	Hauser-Gerspach I, Mauth C, Waltimo T, Meyer J, Stübinger S **Effects of Er:YAG laser on bacteria associated with titanium surfaces and cellular response *in vitro*** *Lasers Med Sci, 2014 Jul, 29(4):1329-37*
18	Stübinger S, Waser J, Hefti T, Drechsler A, Sidler M, Klein K, von Rechenberg B, Schlottig F. **Evaluation of local cancellous bone amelioration by poly-l-dl-lactide copolymers to improve primary stability of dental implants: a biomechanical study in sheep** *Clin Oral Implants Res, 2014 Jul 2, doi: 10.1111/clr.12445. [Epub ahead of print]*
17	Mirsaidi A, Genelin K, Vetsch J, Stanger S, Theiss F, Lindtner R, von Rechenberg B, Blauth M, Kuhn GA, Müller R, Hofmann Boss S, Ebner HL, Richards PJ **Therapeutic potential of adipose-derived stromal cells in age-related osteoporosis** *Biomaterials, 2014 Aug, 35(26):7326-35*

Number	
16	Stübinger S, Buitrago-Tellez C, Cantelmi G **Deviations between placed and planned implant positions: an accuracy pilot study of skeletally supported stereolithographic surgical templates** *Clin Implant Dent Relat Res, 2014 Aug, 16(4), 540-51*
15	Wilkens MR, Liesegang A, Richter J, Fraser DR, Breves G, Schröder B **Differences in peripartal plasma parameters related to calcium homeostasis of dairy sheep and goats in comparison with cows** *J Dairy Res, 2014 Aug, 81(3):325-32*
14	Thoma DS, Kruse A, Ghayor C, Jung RE, Weber FE **Bone augmentation using a synthetic hydroxyapatite/silica oxide-based and a xenogenic hydroxyapatite-based bone substitute materials with and without recombinant human bone morphogenetic protein-2** *Clin Oral Implants Res, 2014 Aug 19, doi: 10.1111/clr.12469. [Epub ahead of print]*
13	Klawitter M, Hakozaki M, Kobayashi H, Krupkova O, Quero L, Ospelt C, Gay S, Hausmann O, Liebscher T, Meier U, Sekiguchi M, Konno SI, Boos N, Ferguson SJ, Wuertz K. **Expression and regulation of toll-like receptors (TLRs) in human intervertebral disc cells** *Eur Spine J, 2014 Sep, 23(9):1878-91*
12	Wennerberg A, Jimbo R, Stübinger S, Obrecht M, Dard M, Berner S **Nanostructures and hydrophilicity influence osseointegration: a biomechanical study in the rabbit tibia** *Clin Oral Implants Res, 2014 Sep, 25(9):1041-50*
11	Stricker A, Stübinger S, Voss P, Duttenhoefer F, Fleiner J **The bone splitting stabilisation technique – a modified approach to prevent bone resorption of the buccal wall** *Oral Health Dent Manag, 2014 Sep, 13(3):870-6*
10	von Salis-Soglio M, Stübinger S, Sidler M, Klein K, Ferguson SJ, Kämpf K, Zlinszky K, Buchini S, Curno R, Péchy P, Aronsson BO, von Rechenberg B **A novel multi-phosphonate surface treatment of titanium dental implants: a study in sheep** *J Funct Biomater, 2014 Sep 11, 5(3):135-57*
9	Lapczyna H, Galea L, Wüst S, Bohner M, Jerban S, Sweedy A, Doebelin N, van Garderen N, Hofmann S, Baroud G, Müller R, von Rechenberg B **Effect of grain size and microporosity on the *in vivo* behavior of β-tricalcium phosphate scaffolds** *Eur Cell Mater, 2014 Oct 23; 28:299-319*

Number	
8	Krupkova O, Sekiguchi M, Klasen J, Hausmann O, Konno S, Ferguson SJ, Würtz-Kozak K **Epigallocatechin 3-gallate suppresses interleukin-1β-induced inflammatory responses in intervertebral disc cells *in vitro* and reduces radiculopathic pain in rats** *Eur Cell Mater, 2014 Nov 25; 28:372-86*
7	Trump M, Siegenthaler E, Kircher PR, Fürst A, Theiss F **Comparison of radiographic changes of the proximal third metacarpal and metatarsal bones in horses with and without proximal suspensory dermitis** *Pferdeheilkunde, November/Dezember, 30(2014) 6, 671-676*
6	Haxhiu D, Hoby S, Wenker C, Boos A, Kowalewski MP, Lewis F, Liesegang A **Influence of feeding and UVB exposition on the absorption mechanisms of calcium in the gastrointestinal tract of veiled chameleons (Chamaeleo calyptratus)** *J Anim Physiol Anim Nutr (Berl), 2014 Dec, 98(6):1021-30*
5	Savić N, Bär D, Leone S, Frommel SC, Weber FA, Vollenweider E, Ferrari E, Ziegler U, Kaech A, Shakhova O, Cinelli P, Santoro R **lncRNA maturation to initiate heterochromatin formation in the nucleolus is required for exit from pluripotency in ESCs** *Cell Stem Cell, 2014 Dec 4; 15(6):720-34*
4	Sidler M, Fouché N, Meth I, von Hahn F, von Rechenberg B, Kronen PW **Preliminary study on carprofen concentration measurements after transcutaneous treatment with Vetdrop® in a microfracture joint defect model in sheep** *BMC Vet Res, 2014 Dec 9; 10(1):268 [Epub ahead of print]*
3	Gantenbein B, Calandriello E, Wuertz-Kozak K, Benneker LM, Keel MJ, Chan SC **Activation of intervertebral disc cells by co-culture with notochordal cells, conditioned medium and hypoxia** *BMC Musculoskelet Disord, 2014 Dec 11; 15:422*
2	*Richards PJ* **Impact of senescence on bone quality: lessons from animal models of aging** *Drug Discov Today Dis Models, 2014 Autumn; 13:17-22*
1	*von Rechenberg B* **Animal models in bone repair** *Drug Discov Today Dis Models, 2014 Autumn; 13:23-27*

Public relation articles about the CABMM 2014/ 2015

Pan European Networks

Simon Pot, Farhad Hafezi
"Using light to save sight"
Science and Technology, Issue 17: 216-217, December 2015
Government, Issue 16: 48-49, November 2015

Brigitta Wichert, Annette Liesegang, Brigitte von Rechenberg
"The path to understanding"
Science and Technology, Issue 17: 216-217, December 2015
Government, Issue 16: 48-49, November 2015

Brigitte von Rechenberg, Karina Klein,
Katja Nuss, Joerg Mayer
"BoneWelding® Technology"
Science and Technology, Issue 15: 98-99, June 2015

Peter Kronen
"Requirements of anaesthesia and analgesia"
Science and Technology, Issue 15: 96-97, June 2015
Government, Issue 14: 48-49, May 2015

Brigitte von Rechenberg, Simon P. Hoerstrup,
Michael O. Hottiger
"Translational Research"
Science and Technology, Issue 14: 112-113, January 2015

David Spreng, Simone Forterre
"Cranial cruciate ligament rupture"
Science and Technology, Issue 13: 186-189, December 2014
Government, Issue 13: 140-143, February 2015

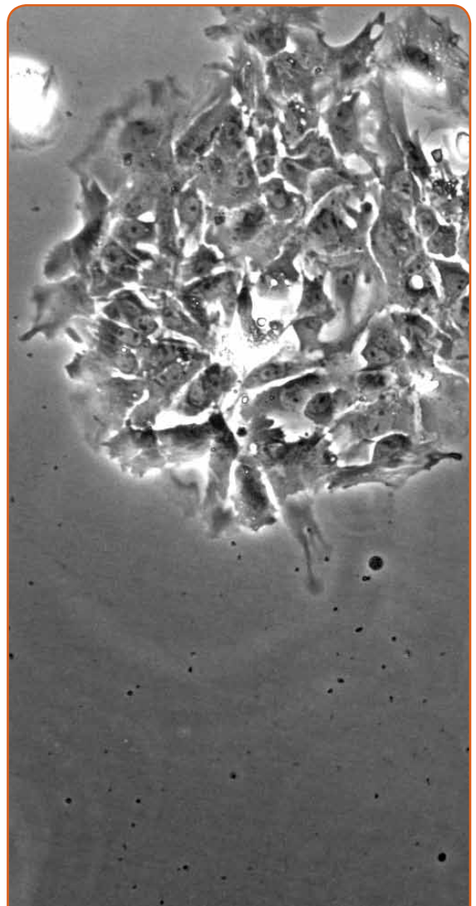
Brigitte von Rechenberg, Michael Plecko
"Dynamisation of fracture healing"
Science and Technology, Issue 12: 108-111, Sept 2014
Government, Issue 12: 208-211, November 2014

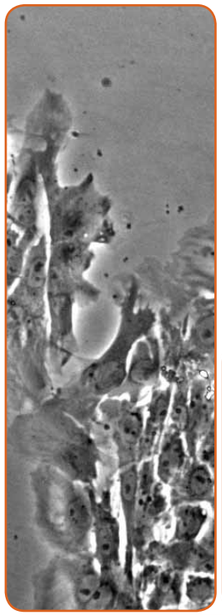
Daniel Rüfenacht
"The shape of things to come"
Science and Technology, Issue 11: 212-213, June 2014
Government, Issue 11: 170-171, August 2014

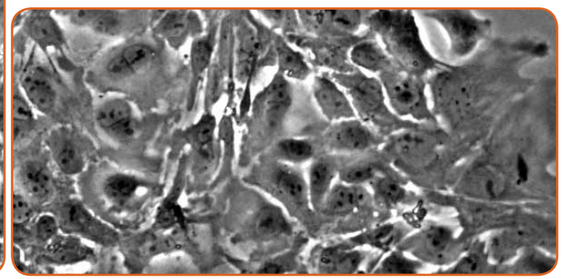
Brigitte von Rechenberg
"Not lost in translation"
Science and Technology, Issue 10: 224-225
Government, Issue 10: 206-207, May 2014

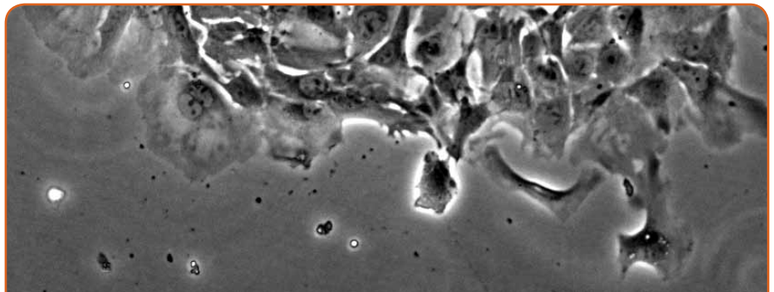
Marcy Zenobi-Wong, Lee Ann Laurent-Applegate
"Lessons from the womb"
Government, Issue 10: 242-245, May 2014

Brigitte von Rechenberg
"From bench to bedside and back"
Government, Issue 10: 240-241, May 2014









Horizon 2020 Projects: Portal

Brigitte von Rechenberg, Michèle Sidler, Nathalie Fouché,
Peter Kronen, Katja Nuss, Claudio Venzin, Friedrich von Hahn
"Transcutaneous drug delivery"
Issue 08: 114-117, October 2015

Ines Carrera, Henning Richter, Patrick Kircher
"More than just imaging"
Issue 07: 104-107, July 2015

Brigitte von Rechenberg
"Everyday ethical considerations"
Issue 07: 166-167, July 2015

Nicole Borel, Cory Ann Leonard, Hanna Marti
"More than meets the eye"
Issue 06: 40-43, April 2015

Katharyn J. Mitchell, Colin C. Schwarzwald
"The heart in motion"
Issue 05: 36-39, January 2015

Serge Marbacher, Javier Fandino
"From rupture to haemorrhage"
Issue 05: 44-45, January 2015

Annette Liesegang
"Bone to bone marker"
Issue 04: 126-127, October 2014

Martin Flück
"From sports bench to bedside"
Issue 04: 132-135, October 2014

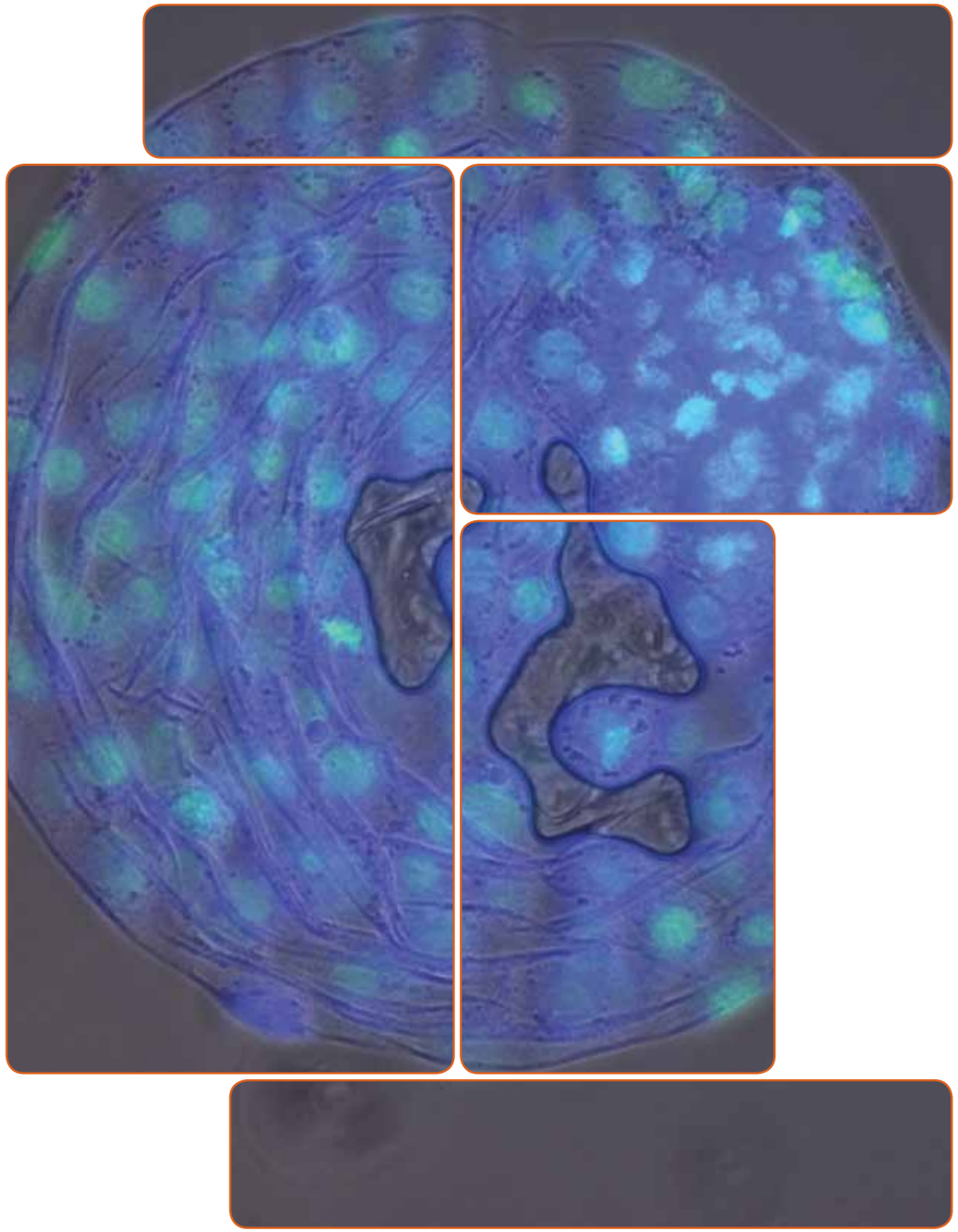
Michael O. Hottiger
"Inflammation / metaflammation"
Issue 03: 48-51, July 2014

Benjamin Gantenbein
"TOMorrow people"
Issue 03: 56- 59, July 2014

Simon P. Hoerstrup
"Regenerative medicine for the heart"
Issue 02: 106-107, April 2014

Brigitte von Rechenberg
"From bench to bedside and back again"
Issue 01: 96-97, January 2014

Brigitte von Rechenberg
"The Competence Center for Applied Biotechnology and Molecular Medicine"
Issue 01: 167-174, January 2014



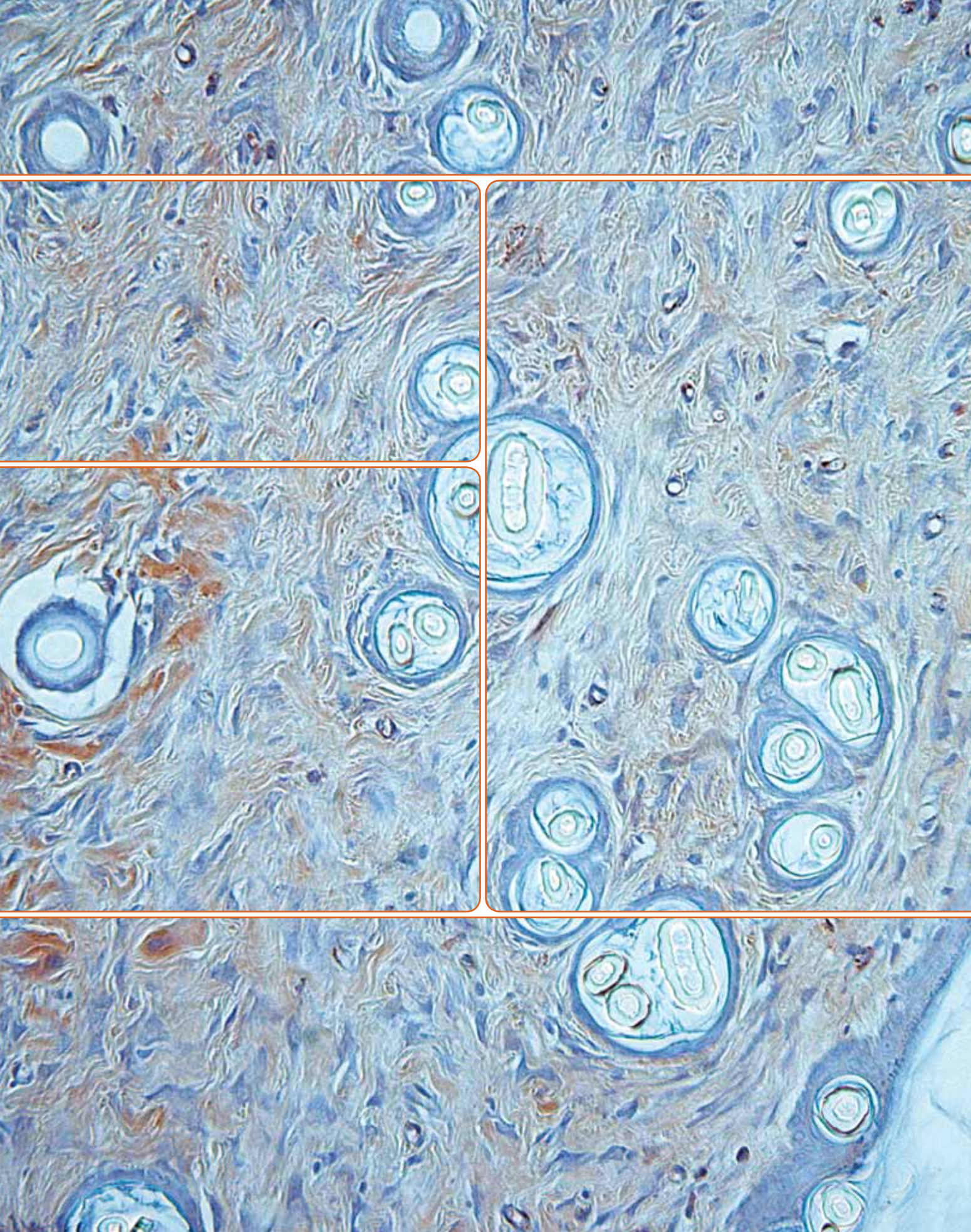
Report 2014 / 2015

Impressum
Herausgegeben vom Center for Applied Biotechnology and Molecular Medicine (CABMM),

© alle Rechte vorbehalten

Verantwortlich für den Inhalt:
S. Kalchofner-Mark, M. Klawitter, B. von Rechenberg

Gestaltung:
Jule Puppato-Krüger, Grafik Design, 8032 Zürich, www.designhexe.com

Druck:
werk zwei Print + Medien Konstanz GmbH, D - 78467 Konstanz

Korrespondenzadresse:
Center for Applied Biotechnology and Molecular Medicine (CABMM)
Universität Zürich
Frau Dr. Silke Kalchofner-Mark
Winterthurerstrasse 190
8057 Zürich