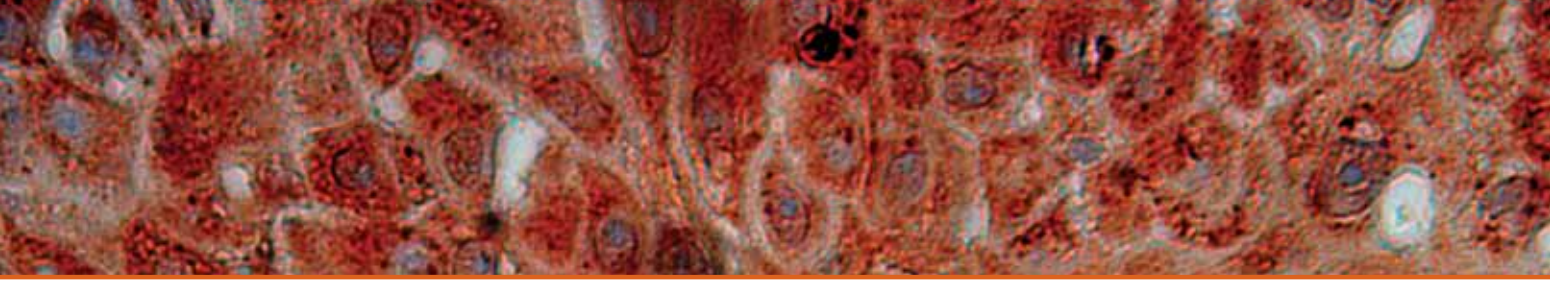
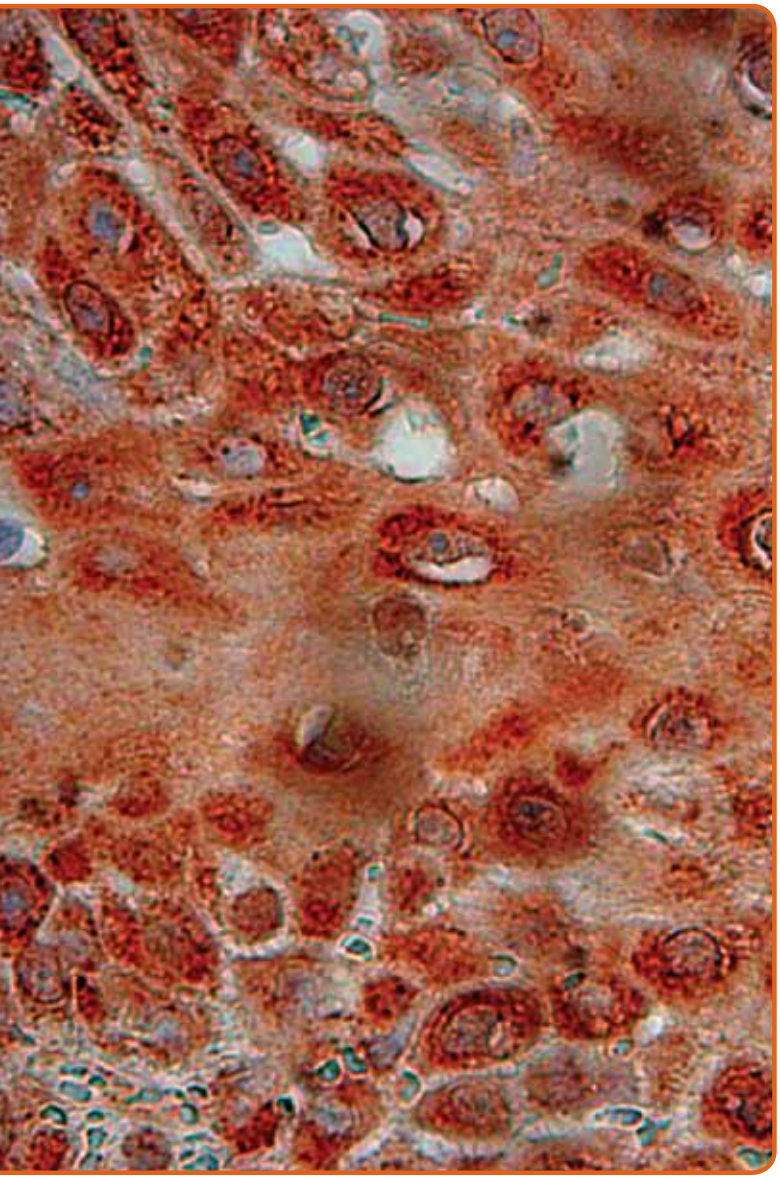
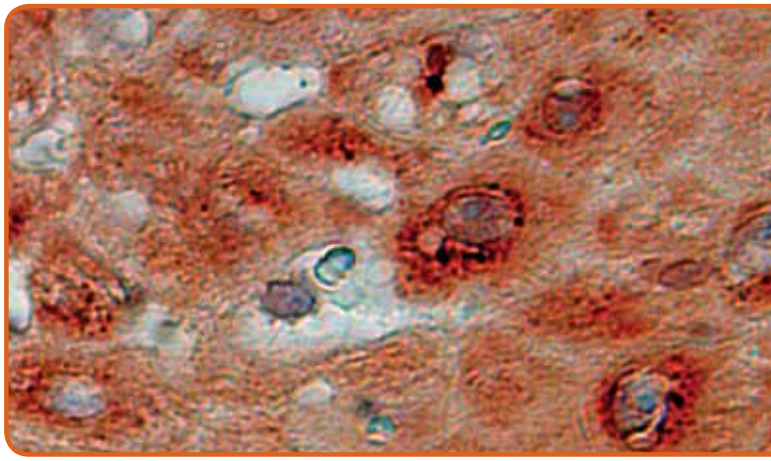
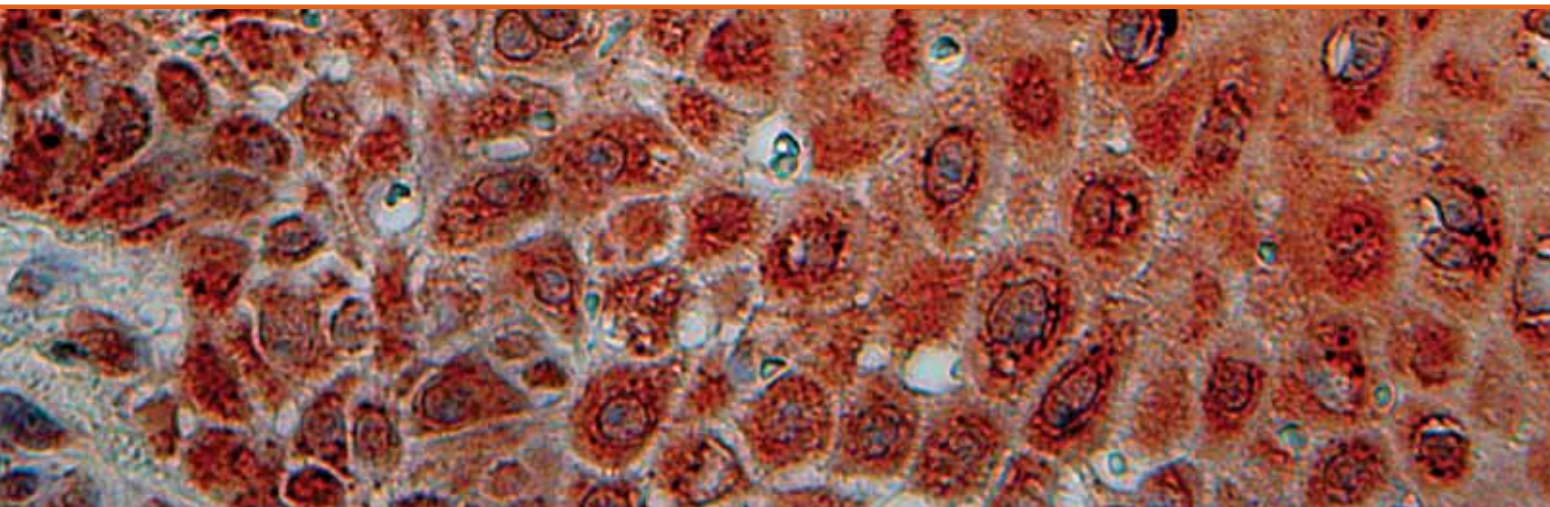




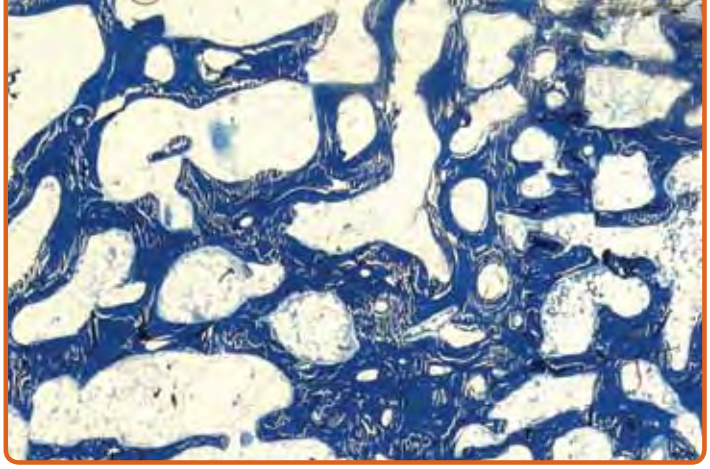


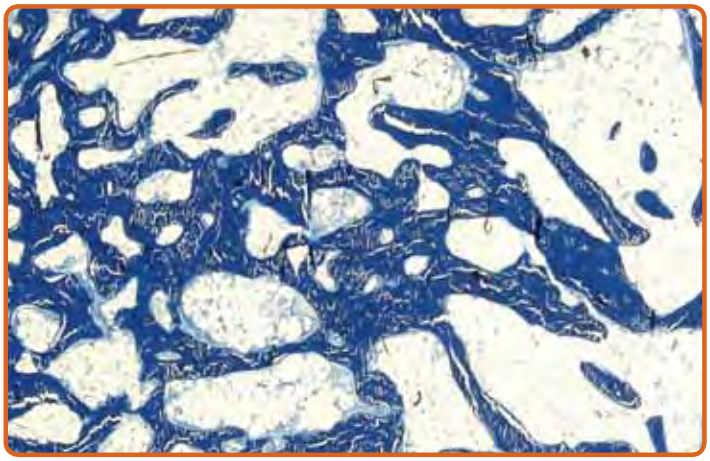
cabmm
center for applied biotechnology and molecular medicine

report 2012/2013



cabmm report
2012/2013





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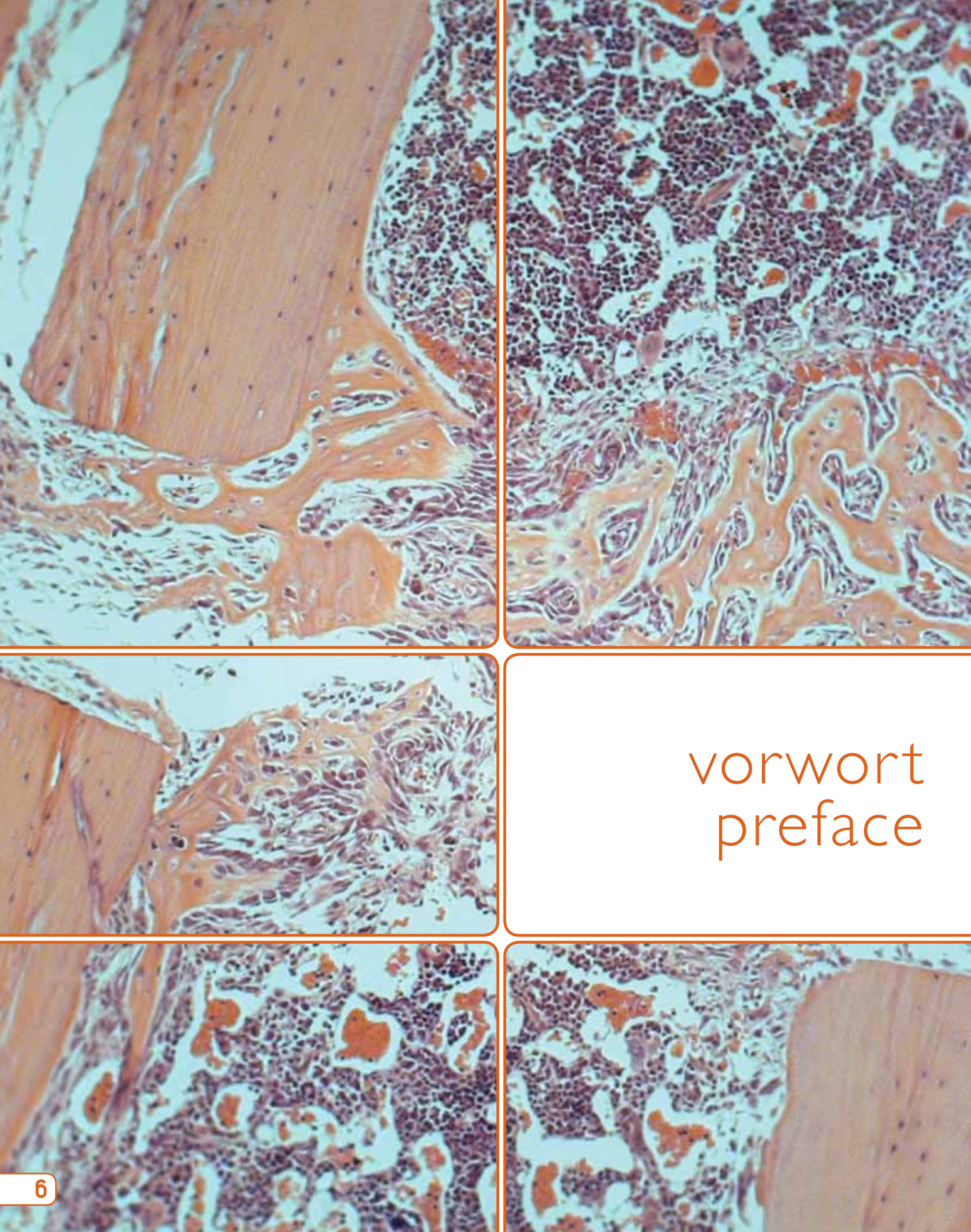


vorwort
preface

Liebe Leserin, lieber Leser

Als Nestor externus des CABMM darf ich Ihnen dessen Jahresbericht 2012/2013 zur Lektüre ans Herz legen. Aber wer liest schon Jahresberichte ...? Und doch sind sie nützlich. Sie geben die Möglichkeit zum Innehalten und zur Rückschau auf das eigene Schaffen, und gerade bei einem so heterogenen Verein wie dem CABMM helfen sie bei der Identitätsstiftung und stärken das Gruppenbewusstsein, denn schliesslich soll ja die Institution nach dem Ausscheiden der Gründergeneration weiterbestehen. Und nicht zuletzt dienen sie der Rechtfertigung gegenüber Kanton, Universität und den übrigen Geldgebern.

Neben der wissenschaftlichen Arbeit und erfolgreichem Ausbildungsengagement waren die Jahre geprägt durch turbulente, aber elegant genommene administrative Hürden. Würdig ist das erlangte Zertifikat für Good Laboratory Practice (GLP). Das wird sich zusammen mit dem mit aller Kraft vorangetriebenen Bau des Vetsuisse Laborgebäudes als Segen erweisen. Enorm wichtig war auch der Kampf gegen eine grössere räumliche Zersplitterung. Mit Pressionen, Konzentration der Kräfte, Beziehungen und nicht zuletzt dank geschicktem Verhandeln von Brigitte von Rechenberg konnte schliesslich eine vernünftige Lösung gefunden werden.

Mit einem aufmunternden Gruss an die Schar der Leserinnen und Leser bin ich Euer

Bruno Bonin
Mäxi Stiftung

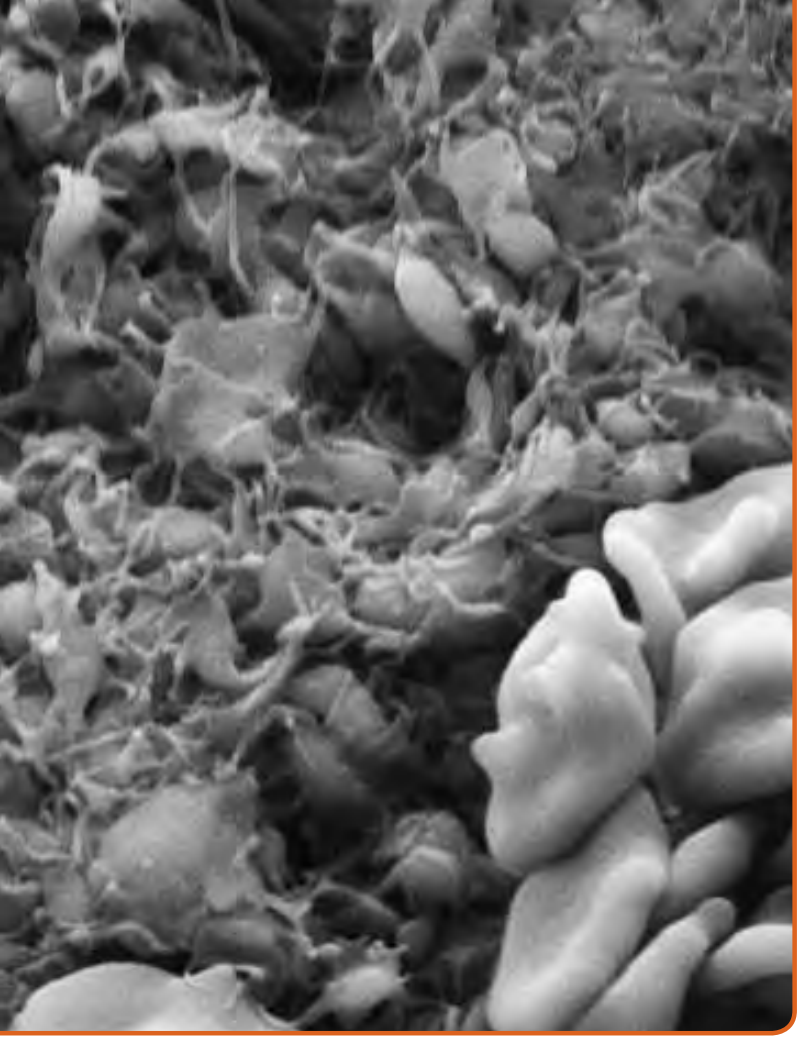
Dear reader,

As Nestor externus of the CABMM, I warmly recommend you to read the CABMM Report 2012/2013. But who is reading yearly reports ...? And yet, they are valuable. They offer the possibility for backpedaling and reviewing your own work and – especially in such an heterogeneous union like the CABMM – they help to build a sense of identity and strengthen the team feeling, which will be required to keep the institution running after the resignation of the founding generation. And last but not least, they serve as a justification towards the Canton, the University and all other sponsors.

Besides the scientific work and the successful teaching engagement, the last years were affected by turbulent, but elegantly overcome administrative obstacles. Worthy is the acquired certificate for Good Laboratory Practice (GLP), which will prove to be a blessing together with the construction of the Vetsuisse Laboratory building that is actively being promoted. Of major importance was also the fight against a huge areal splintering. Thanks to pressure, concentration of forces, connections and not least to the negotiating skills of Brigitte von Rechenberg, a reasonable solution was finally found.

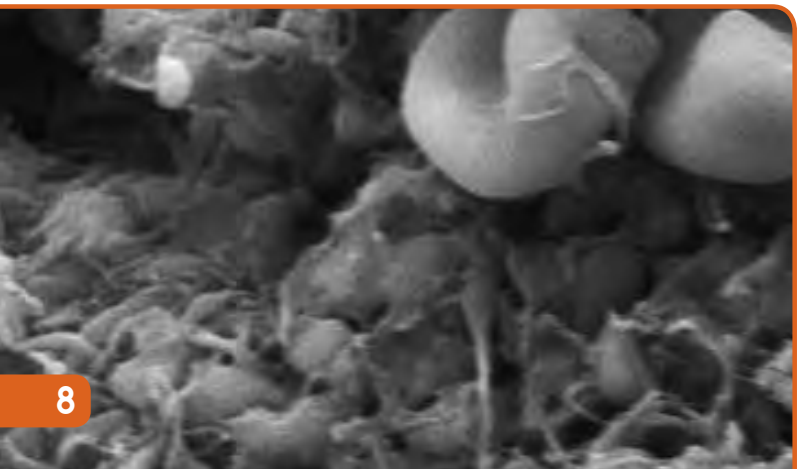
With encouraging regards to all readers
Yours,

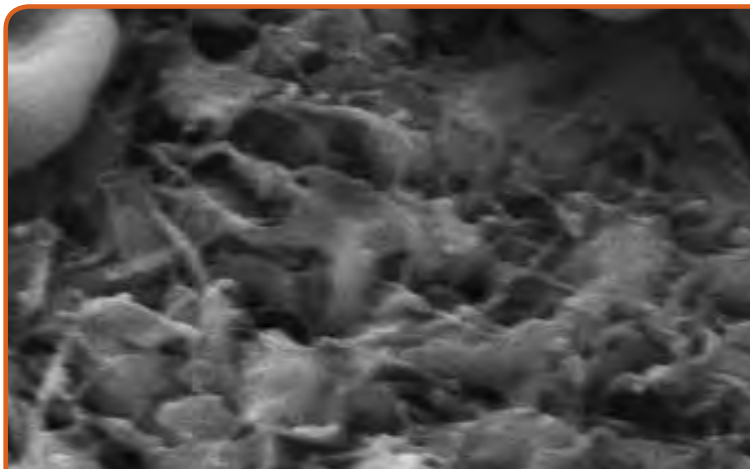
Bruno Bonin
Mäxi Foundation



about us

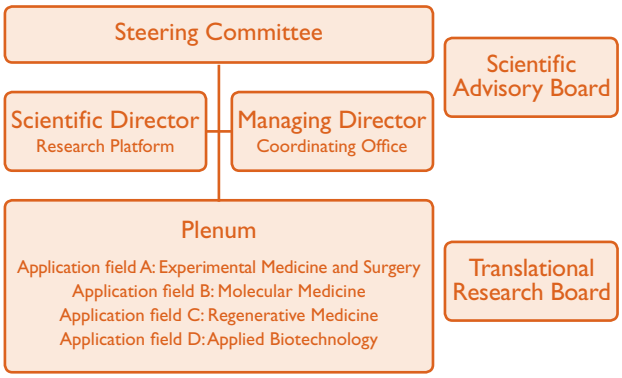
cabmm bodies and events





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 the highest decision-making body, the Steering Committee as operating body, the Scientific Director as head of the CABMM Research Platform and the Managing Director running the Coordinating Office as the central contact and coordination point. Additionally, a Scientific Advisory Board was established as controlling body and a Translational Research Board is currently being set up, with the aim to facilitate the translation of basic scientific research results into clinically relevant therapies.



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 tissue.

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.

Moreover, through efforts within the CABMM, the University of Zurich is now one of the first European universities combining all regulatory requirements for the development, production and first clinical trials of new drugs and therapies under one roof. Whereas Good Clinical Practice (GCP) has already been running at the University Hospital for several years, Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) have recently been established at the Swiss Center 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. We now hope that all our members will profit from our regulatory expertise.

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 are considered to play essential roles in strengthening the CABMM network and enhancing collaborations between CABMM members from a variety of research disciplines.

In this chapter, the chairwoman of the CABMM Steering Committee, Prof. Dr. Brigitte von Rechenberg, and the CABMM Scientific Advisory Board are looking back on the achievements and changes within the reporting period. Additionally, brief articles about our main events during the last two years can be found.

from the cabmm steering

CABMM network

During the last two years, the CABMM further established itself as a translational research platform and Competence Center of the University of Zurich. This is well reflected by our growing network and steadily increasing number of CABMM members. At the moment, we have a total number of 56 CABMM members, consisting of 50 active, four alumni and two honorary members, representing basic researchers, veterinarians and clinicians from various fields. When taking into account the number of students and scientists in each of their groups, this builds up to an impressive network!

But what holds particular relevance for the CABMM is all the active collaborations amongst its members. It's also especially noteworthy that since the formation of the CABMM, many competitive grants from the SNF, CTI and EU commission, as well as from internal funding of the UZH and ETHZ, were granted to its members. Furthermore, the translational expertise of the CABMM platform was considered to be one of the outstanding characteristics of the consortium. So our network is already "paying out", also for the never-ending task of raising funds and finding soft money to conduct our research.

CABMM events

The platform to meet and – in equine language – to graze over the fence and look into other professional fields, was again our CABMM Seminars and Symposia in spring and autumn. Our speakers are always encouraged to present not only their individual research projects, but also the expertise and technology available at their institutions. And it works! As our grant records show, our meetings are the platform where initial contacts are made, new partners are found and connections built. Our meetings demonstrate how exciting translational medicine can be. From "bench to bedside – and back" is our motive. Bringing basic researchers and clinicians together so they can start talking in the same language will undoubtedly lead to more opportunities in basic and clinical research alike.

Regulatory affairs

A very big step was taken concerning regulatory affairs. Official regulations of *Good Manufacturing Practice* (GMP) for the production of drugs and active compounds, *Good Laboratory Practice* (GLP) for all preclinical safety studies and *Good Clinical Practice* (GCP) for clinical trials in humans are gaining more and more importance, also already at an early stage of development. While the University Hospital Zurich (USZ) has successfully established GCP for several years, GMP and GLP are now newly established through members of the CABMM. Prof. Hoerstrup's group received GMP accreditation at the Swiss Center for Regenerative Medicine in 2012, and the Musculoskeletal Research Unit (MSRU) under my own leadership has officially submitted the documents for GLP accreditation in June 2013. The subsequent inspection went well and only a few amendments had to be made such that final accreditation was already confirmed during the inspection and will come within a couple of weeks. This means that the University of Zurich (UZH) is the only university in Europe, which fulfills all the regulatory requirements of GMP, GLP and GCP under one roof. This should prove attractive for research and development in academia and industry alike. We also hope that this will assist CABMM members in their efforts to raise external funding.

Public relations

The Steering Committee also decided that it would be important to increase the visibility of the CABMM. Thus, in addition to this second official CABMM Report, the first CABMM Newsletter was published in autumn 2013. As the feedback was positive throughout, our newsletter will now be published twice a year.

committee

Additionally, the CABMM has been made visible to the European science community in conjunction with the Pan European Networks in Brussels. Partnership was launched until the year 2020 in the context of the new call "Horizon 2020" of the European commission. Our network will be advertised on partner lists for research projects throughout Europe and articles about the uniqueness of our network have been, and will be, published on a regular basis. As this activity is rather costly, we would like to thank the Mäxi Foundation at this point, who generously supported us for this activity. We hope that this will help many CABMM members in finding new partners and to get their research funded by participating in European consortiums.

from left to right:
Prof. Dr. Dr. Simon P. Hoerstrup,
Prof. Dr. Brigitte von Rechenberg,
Prof. Dr. Annette Liesegang

from left to right:
PD Dr. Peter J. Richards,
Dr. Silke Kalchofner-Mark,
Prof. Dr. Dr. Michael O. Hottiger

CABMM research platform

Furthermore, the Steering Committee was successful in keeping the CABMM research platform in conjunction with the Institute for Veterinary Biochemistry and Molecular Biology (IVBMB) at the Irchel Campus. Although the initially planned relocation to Schlieren could be avoided, the labs will have to move within the Irchel Campus in 2014, as the ETHZ requires the laboratory space for their own scientists. But the arguments to keep our translational platform within the heart of preclinical studies and basic science were strong enough to convince our University leaders that a move to Schlieren would have been detrimental to our development. We are grateful for this decision and will notify you in time, where the new platform will be established.

CABMM bodies

Fortunately, no personal changes were noted in the **CABMM Steering Committee.** During the election in 2012, all members of the Steering Committee ran for office again and were reelected without a dissent vote. Our managing director, Dr. Silke Kalchofner-Mark, was on maternity leave after giving birth to her second child, but is already back again on a reduced workload of 60%. We would also like to thank Marina Klawitter at this point, who did a wonderful job to replace her during her absence.

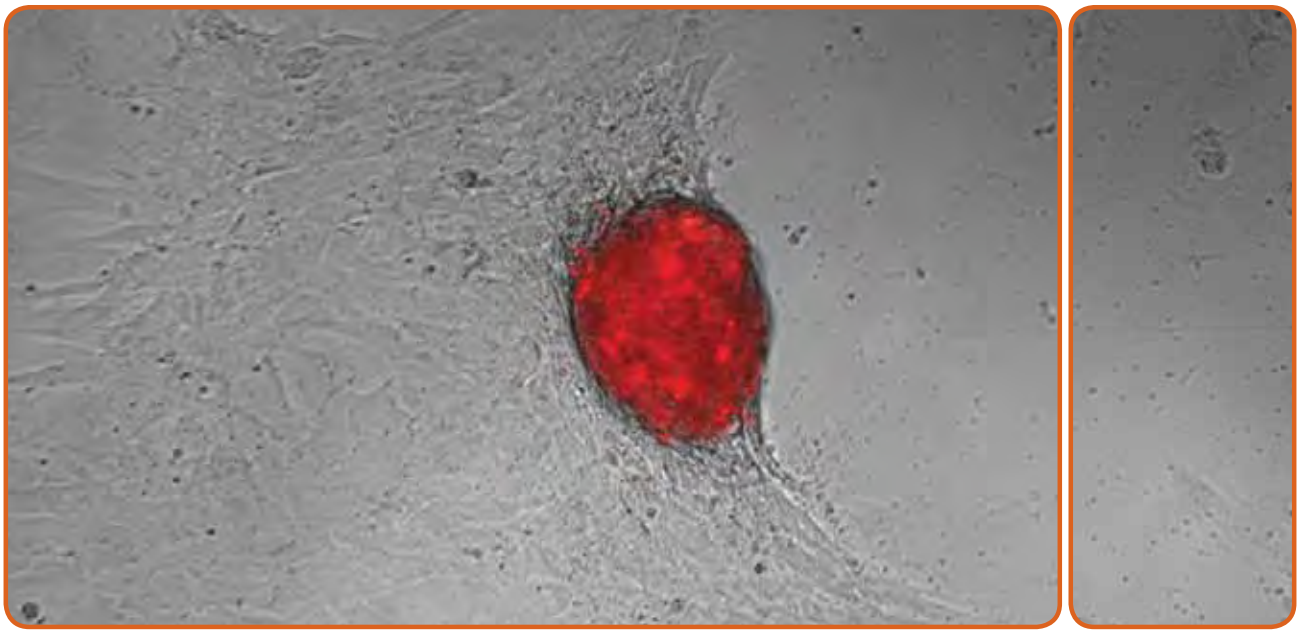
However, changes took place in our **Scientific Advisory Board (SAB).** After the resignation of Dr. Pedro Bittmann in spring 2012, two further valuable and dedicated members decided to retire at the end of 2013, namely Dr. Margarethe Hofmann and Prof. em. Dr. Peter Sonderegger. Their work was officially acknowledged during our CABMM events, but still we would like to take this opportunity to thank them and the SAB in general for their motivation and support. Their very valuable comments, ideas and visions were instrumental in the development and success of the CABMM. Despite the great loss we feel with the departure of these members, we are also extremely pleased to welcome both Prof. Dr. Jörg Goldhahn and Prof. Dr. Walter Schaffner as their replacements. Prof. Dr. Goldhahn will also be the official liaison member in the soon to be established **Translational Research Board.** He is the ideal person for this, since he knows the "coin" from both sides, from academia and industry and will advice the Steering Committee in its establishment and interactions with industrial partner. We are very pleased that he will dedicate his time to us and join us on this new journey.

Zurich, June 2014

Prof. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS,
Chairwoman of the CABMM Steering Committee

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, 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
PD Dr. Peter J. Richards (PhD), Vetsuisse Faculty, University of Zurich	C – Regenerative Medicine
Dr. rer. nat. Silke Kalchofner-Mark, Vetsuisse Faculty, University of Zurich	Managing Director



the scientific advisory board of

The Scientific Advisory Board (SAB) of the CABMM continues to provide advice and guidance on CABMM operations. This involves reviewing proposed internally-funded research activities and outcomes, meeting with members and trainees and providing recommendations to the Steering Committee (SC) to help the CABMM in achieving its mandate. Our meetings are twice a year, in spring and autumn, coinciding with the receipt of new and revised funding applications from CABMM members submitted to the SC. At this time, we also attend the scientific symposia of the CABMM and contribute to the discussions and presentations. We report to the SC verbally at the end of each meeting. Subsequently, we supply, in writing, our advice and recommendations regarding all activities that we have reviewed and discussed at the meeting.

We review and critique the CABMM differently from most review boards in that we are there to work with CABMM members and the SC to help in their research. We want to ensure that the research is feasible, focused and the study is appropriately designed; that the necessary human resources are available and are being utilized, both within and outside the CABMM; that the funding is available for the internal programs and is spent according to the rules of CABMM and the Mäxi Foundation. So we work in partnership to help and guide CABMM research and also its translation. We are therefore pleased that the Steering Committee is acting on our recommendation to create a Translational Research Board to help advance the application of new discoveries towards helping patients.

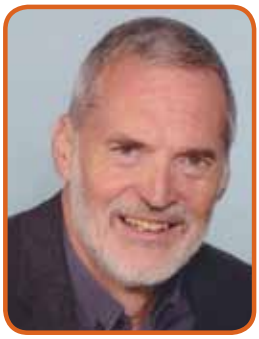
Professor Emeritus Peter Sonderegger (biochemical and molecular sciences), Dr. Margarethe Hofmann (material sciences, industry and research management) and Dr. Pedro Bittmann (regenerative medicine and industry; retired 2012) have worked closely with Professor Emeritus Robin Poole (chair; musculoskeletal sciences and multidisciplinary research programs), Professor Frank Baaijens (biomaterials and multidisciplinary tissue engineering) and Dr. Bruno Bonin (Mäxi Foundation) to bring a wealth of experience to the SAB. At the end of 2013, both Peter Sonderegger and Margarethe Hofmann stepped down from the SAB. Their input and wisdom will be greatly missed. We thank them, as friends and colleagues, for their many contributions.
We are fortunate, however, to welcome Prof. Dr. Jörg Goldhahn and Prof. Dr. Walter Schaffner, with collective scientific, medical and industry expertise to replace who we have lost.

Discussions with CABMM members, both those who have submitted research proposals to the SC and others in their laboratory settings, play an important role in helping us review funding applications and evaluate ongoing projects. It is this close contact and discussion that enables us to achieve a better understanding of the research and more fully appreciate all the different types of research that come together under the CABMM umbrella.

We are delighted to see that the CABMM continues to grow in expertise and research networking and that collaborative research, both within and outside the CABMM, continues to grow, utilizing the CABMM's considerable human and technical resources. And that the start-up funding program is acting as a real springboard for new research directions.

the cabmm




The recent creation within the CABMM of Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) at the University of Zurich is a great strength for future European Commission funded research programs such as Horizon 2020 in 2014 that require such facilities. As few universities have such opportunities to promote translation research and development, this places CABMM researchers in an advantageous position with regards to future Swiss and European collaborations and funding opportunities to put research findings into practice. Here, the new Translational Research Board can play a key role in helping identify industrial partners.

We are privileged to be a part of the CABMM in helping ensure creativity and excellence in research, training and development that the CABMM represents.

cabmm scientific advisory board

Name and affiliation	Representing
Prof. em. Dr. A. Robin Poole (PhD) (Chairman), McGill University, Montréal, Canada	Application field A – Experimental Medicine and Surgery
Prof. Dr. ir. Frank P. T. Baaijens, Eindhoven University of Technology, The Netherlands	Application field C – Regenerative Medicine
Prof. Dr. med. Jörg Goldhahn, Novartis Institutes for Biomedical Research, Basel, Switzerland	Industry
Prof. em. Dr. Walter Schaffner (PhD), University of Zurich, Switzerland	Application field B – Molecular Medicine
Dr. med. Bruno Bonin, Meilen, Switzerland	Mäxi Foundation
Prof. Dr. med. vet. Felix R. Althaus, Dean of the Vetsuisse Faculty, University of Zurich, Switzerland	(ex officio)
Prof. Dr. med. Dr. med. dent. Klaus Grätz, Dean of the Medical Faculty, University of Zurich, Switzerland	(ex officio)

2. spring seminar

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Als eine der beiden jährlichen Hauptveranstaltungen fand am 07. Juni 2012 das zweite Spring Seminar des CABMM an der Universität Zürich statt. Im Anschluss an die jährliche Vollversammlung des Zentrums hatten erneut Mitglieder – vor allem aus dem Bereich der Experimentellen Medizin und Chirurgie – die Möglichkeit, ihre Arbeit zu präsentieren.

PD Dr. Peter J. Richards, der wissenschaftliche Direktor des CABMM, führte die etwa 50 Zuhörer durch ein abwechslungsreiches Programm. Er begrüsste als ersten Redner Dr. Alfredo Franco-Obregón von der ETH Zürich, der über die Effekte von Pulsierenden Elektromagnetischen Feldern (PEMF) auf Muskelzellen und die Rolle von Ionenkanälen in diesem System berichtete. Prof. Dr. Dominik Meyer von der Universitätsklinik Balgrist, Zürich, verdeutlichte anschliessend anschaulich, wie experimentelle Ergebnisse das Studiendesign und die Behandlung von chronischen Sehnendefekten verbessern können. Im Anschluss gab es von Prof. Dr. Lee Ann Laurent-Applegate von der Universitätsklinik in Lausanne eine Art Zeitreise durch die Stammzellforschung der vergangenen 30 Jahre. Sie referierte über die wichtige Definition von Stammzellen, Schwierigkeiten durch verschiedene Gesetzesänderungen und die vielfältige Anwendung von Zelltherapien.

Nach einer kurzen Kaffeepause eröffnete PD Dr. Raffaella Santoro von der Universität Zürich den zweiten Teil des Seminars. Als einzige Rednerin aus dem Bereich der Molekularen Medizin gab sie einen eindrucksvollen Übersichtsvortrag über die Rolle von nicht-kodierenden Nukleinsäuren während der epigenetischen Kontrolle der Zellidentität. Danach stellte sich Prof. Dr. Claudia Spadavecchia von der Universität Bern als neues Mitglied mit einen Übersichtsvortrag über die aktuellen Möglichkeiten in der Schmerzforschung bei Tieren vor. PD Dr. Stefan Stübinger von der Universität Zürich beendete die Vortragsreihe dieses Seminars mit einer Präsentation über verschiedene Eigenschaften von Zahnimplantaten und deren Rolle bei der Integration in den Knochen.

Am Ende der Veranstaltung verabschiedete Prof. Dr. Brigitte von Rechenberg, die Vorsitzende unseres Leitungsausschusses, Dr. Pedro Bittmann als Mitglied des Wissenschaftlichen Beirates des CABMM und wünschte ihm für die Zukunft nur das Beste.

Nachdem auch der Dank an alle Redner und Organisatoren des Seminars ausgesprochen war, hatten alle Teilnehmer während eines Apéro bei strahlendem Sonnenschein die Möglichkeit, weitere wissenschaftliche Kontakte zu knüpfen.

2nd spring seminar

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

One of the two major yearly events of the CABMM took place on June 7th, 2012 at the University of Zurich – namely our 2nd Spring Seminar. Subsequent to the plenary meeting, several CABMM members took the opportunity to introduce themselves and presented their research to the CABMM network.

The scientific director of the CABMM, PD Dr. Peter J. Richards chaired the sessions and welcomed more than 50 participants to a very diverse program. He first introduced Dr. Alfredo Franco-Obregón from the ETH Zurich who talked about the influence of Pulsed Electromagnetic Fields (PEMF) on ion channels in the context of muscle cell function. Afterwards, Prof. Dr. Dominik Meyer from the Balgrist University Hospital in Zurich presented data relating to chronic tendon repair and demonstrated how experimental results from yesteryear clearly influence the study design of today. The last talk of the session was by Prof. Dr. Lee Ann Laurent-Applegate from the University Hospital of Lausanne. She took the audience through a kind of time travel with respect to stem cell research over the last three decades, illustrating problems concerning the definition of stem cells, difficulties regarding revisions of statutes and the multifaceted possibilities of stem cell therapies.

The intervening short coffee break gave time enough for the first scientific discussions.

Representing the field of Molecular Medicine, PD Dr. Raffaella Santoro from the University of Zurich opened the second session of the seminar. She gave an impressive overview with respect to the role of noncoding nucleic acids in the epigenetic control of cell identity. Afterwards, one of our new members, Prof. Dr. Claudia Spadavecchia from the University of Bern, took the opportunity to introduce herself and talked about veterinary pain research. Last but not least, PD Dr. Stefan Stübinger finished the series of lectures by presenting aspects of different characteristics of dental implants and their strong influence on integration into the bone.

At the end of the Seminar, Prof. Dr. Brigitte von Rechenberg, chairwomen of the CABMM Steering Committee, announced the departure of Dr. Pedro Bittmann as a member of the Scientific Advisory Board of the CABMM and wished him all the best for the future.

Shortly after the speakers and organizers had been congratulated for their contribution to our successful 2nd Spring Seminar, all participants had the opportunity to meet, to socialize and to discuss scientific topics during an Apéro in glorious sunshine.

3. symposium

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Die grösste Veranstaltung unseres Zentrums, das CABMM Symposium, fand am 22. November 2012 zum dritten Mal an der Universität Zürich statt. Das interessante Programm, welches zum ersten Mal eine Vortragsreihe über Projekte enthielt, die durch einen CABMM Start-up Grant finanziert wurden, lockte mehr als 65 Teilnehmer.

Der erste Hauptredner war Prof. Dr. Stephen J. Ferguson vom Institut für Biomechanik der ETH Zürich. Er schilderte, wie sich seine Forschung im Bereich der Behandlung von Wirbelsäulen-Frakturen über die letzten Jahre neben der Biomechanik auf andere Bereiche der Naturwissenschaften wie Biomaterialien und Biologie ausgedehnt hat. Die zweite Hauptrede wurde im Anschluss von Prof. Dr. Franz E. Weber von der Klinik für Mund-, Kiefer- und Gesichtschirurgie des Zürcher Unispitals gehalten. Er gab eine detaillierte Übersicht über verschiedene Faktoren, welche zur Knochenbildung beitragen.

Nach einer erfrischenden Kaffeepause wurde die Sitzung „CABMM Start-up Grants" von Prof. em. Dr. A. Robin Poole moderiert, der aufgrund seiner Funktion als Vorsitzender des Wissenschaftlichen Beirates Hintergrundinformationen zu den Projekten und Projektleitern geben konnte. Im ersten Vortrag beschrieb PD Dr. Peter J. Richards neueste Erkenntnisse über die Serinprotease HTRA1 und deren mögliche Rolle in Knochenkrankheiten. Dr. Karin Würtz von der ETH Zürich, Institut für Biomechanik, referierte anschliessend über die Beteiligung von verschiedenen Oberflächen-Rezeptoren an Bandscheibendegeneration und -entzündung.

Die dritte Session unseres Symposiums eröffnete Prof. Dr. Patrick R. Kircher von der Universität Zürich. Er gab eine Übersicht über derzeit angewendete bild-gebende Technologien in der Tiermedizin. Als nächster Redner schilderte Dr. Zsolt Kulcsár als Vertreter der Gruppe von Prof. Daniel Rüfenacht von der Hirslanden Klinik in Zürich, wie sich Erkenntnisse des Labors auf die Behandlung von Aneurysmen in der Klinik auswirken. Den letzten Vortrag gab Dr. Gisela Kuhn aus der Forschungsgruppe von Prof. Dr. Ralph Müller vom Institut für Biomechanik der ETH Zürich. Sie referierte über die Kombination von pharmakologischen Substanzen und mechanischer Stimulierung in einem Mausmodell der Osteoporose.

Prof. Dr. Brigitte von Rechenberg beendete unser Event und erwähnte, dass erneut aufgezeigt werden konnte, wie wichtig die Förderung der interdisziplinären Zusammenarbeit ist, um wissenschaftliche Erfolge zu erzielen. Und hierfür bietet das CABMM die beste Grundlage. Ein abschliessender Apéro bot für alle Beteiligten die Möglichkeit des wissenschaftlichen Austauschs, sei es für Diskussionen über die gehörten Projekte oder für den Beginn künftiger Kollaborationen.

3rd symposium

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

The most important annual meeting of the CABMM – the CABMM symposium – took place for the third time on November 22th, 2012 at the University of Zurich. Over 65 participants attended the meeting, with oral presentations being given in different fields. For the first time during the existence of our centre there was one session dealing with studies funded by the CABMM Start-up Grant.

Prof. Dr. Stephen J. Ferguson from the Institute of Biomechanics, ETH Zurich, gave the first keynote lecture. He elegantly described the problems associated with treating spinal fractures from a biomechanical point of view, and gave important insights into how biomaterial- and biological-based approaches are helping to improve both our understanding and also the treatment of such injuries. Subsequently, the second keynote speaker Prof. Dr. Franz E. Weber from the department of Cranio-Maxillofacial Surgery, University Hospital Zurich, presented an in-depth overview of the many contributory factors, such as the bone morphogenetic proteins (BMPs), which have been described over the past years as being centrally involved in governing bone formation.

After a refreshing coffee break, the second session began with Prof. em. Dr. A. Robin Poole introducing presentations based around projects funded by CABMM Start-up Grants. In the first presentation, PD Dr. Peter J. Richards described recent work concerning the serine protease HTRA1 and its potential role in bone disease. Dr. Karin Würtz from the Institute for Biomechanics, ETH, Zurich then gave an overview of some of her recent findings relating to the involvement of Toll-like receptors (TLRs) in disc degeneration.

The last session was opened with a presentation given by Prof. Dr. Patrick R. Kircher from the division of Diagnostic Imaging, University of Zurich. He gave an insightful overview of some of the current imaging technologies in the field of veterinary medicine and discussed their scientific applications. Following this talk, Dr. Zsolt Kulcsár from the Hirslanden Hospital in Zurich – representing the group of Prof. Dr. Daniel Rüfenacht – gave an interesting account of the research currently being undertaken to help better our understanding of how to treat aneurysms. Dr. Gisela Kuhn from the group of Prof. Dr. Ralph Müller, Institute of Biomechanics, ETH Zurich, delivered the final presentation and talked about the combinatory effects of pharmacological substances and mechanical loading in a mouse model of osteoporosis.

Prof. Dr. Brigitte von Rechenberg closed the event by delivering the take home message that the CABMM offers an ideal platform for the promotion of interdisciplinary collaborations, and that this was re-confirmed yet again by the overwhelming success of the symposium. The following Apéro offered the opportunity to exchange scientific ideas – not only discussing the presented projects, but also finding people for the beginning of new collaborations.

3. spring seminar

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Am 23. Mai 2013 fand am Tierspital Zürich das 3. Spring Seminar unseres Zentrums statt. Mit Vorträgen aus all unseren Forschungsbereichen wurde den mehr als 50 Zuhörern ein interessantes Programm geboten. Mehrere neue Mitglieder nutzten dabei die Gelegenheit, um sich und ihre Forschung vorzustellen.

Prof. Dr. Brigitte von Rechenberg eröffnete das Seminar und begrüsste als ersten Redner Dr. Sven Hirsch von der ETH Zürich. Er gab eine Übersicht über verschiedene computer-basierte Modelle des Gefässsystems und betonte, dass die Analyse solcher Modelle einen Einfluss auf die spätere Behandlung des Patienten haben kann. So kann zum Beispiel die optimale Positionierung einer Gefässprothese im Vorfeld ermittelt werden. Im Anschluss referierte Prof. Dr. Annette Liesegang von der Universität Zürich über den Auf- und Abbau von Knochen und Knorpelgewebe in verschiedenen Spezies. Sie erläuterte, dass die Analyse von Marker-Proteinen für eine Vielzahl klinischer Anwendungen und Krankheiten relevant und daher weitere Forschung nötig sei. Dr. Jivko Stoyanov von der Schweizer Paraplegiker Forschung in Nottwil beendete den ersten Teil des Seminars mit einem Vortrag über die Fitness von Stammzellen. Er erklärte, dass die Untersuchung eines Sets bestimmter Proteine Aufschluss über das Differenzierungspotential dieser Zellen gibt.

Nach einer kurzen Kaffeepause, die bereits für erste wissenschaftliche Diskussionen genutzt wurde, begann die zweite Hälfte des Seminares mit einem Vortrag über die Behandlung von Handarthrosen mit einer neuartigen Prothese (CapFlex PIP). PD Dr. Laurent Audigé von der Schulthess Klinik in Zürich stellte die Ergebnisse einer Pilotstudie vor und verwies auf die positiven Resultate hinsichtlich Schmerzlinderung und Funktionalität. Prof. Dr. Nicole Borel von der Universität Zürich sprach im Anschluss über die antibakterielle Wirkung von wasser-gefiltertem Infrarot A (wIRA) auf Chlamydien-infizierte Zellen. Sie erwähnte vor allem die gute Verträglichkeit dieser nicht-chemischen Behandlung sowie die hohe Wirksamkeit. Im letzten Vortrag erörterte Prof. Dr. Jörg Goldhahn von Novartis Institutes for Biomedical Research in Basel den Begriff der translationalen Medizin. Er betonte, wie wichtig es ist, Resultate aus der Grundlagenforschung in die klinische Forschung zu übergeben, und welche Fragestellungen hierbei hilfreich sind.

Auch Prof. Dr. Brigitte von Rechenberg verwies in ihren abschliessenden Worten auf die Notwendigkeit zum Austausch zwischen den unterschiedlichen Forschungsbereichen.

Am Ende dieser Veranstaltung gab es bei einem Apéro die Gelegenheit, sich kennenzulernen, auszutauschen und neue Kooperationen auf den Weg zu bringen.

3rd spring seminar

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

The third Spring Seminar of our center took place on May 23th, 2013 at the animal hospital in Zurich, with presentations from all of our application fields as well as from new CABMM members.

The chairwoman of the CABMM, Prof. Dr. Brigitte von Rechenberg, opened the meeting and PD Dr. Peter J. Richards subsequently introduced the first speaker of the session, Dr. Sven Hirsch from the ETH Zurich. He presented an overview of various virtual representations of the vasculature and mentioned the enormous influence of such models, e.g. precise positioning of vascular implants in patients. Afterwards, Prof. Dr. Annette Liesegang from the University of Zurich discussed the options available for analyzing different marker proteins and evaluating their influence on bone disease. Dr. Jivko Stoyanov from the Swiss Paraplegic Research in Nottwil gave the next presentation. He talked about the fitness of stem cells and presented a score system in order to determine the differentiation potential of these cells.

After a short coffee break, the second session of the meeting opened with a talk about the treatment of hand osteoarthritis using a new prosthesis device (CapFlex PIP). PD Dr. Laurent Audigé from the Schulthess clinic in Zurich presented the results of a pilot study and mentioned the positive results concerning pain relief and functionality. Subsequently, Prof. Dr. Nicole Borel from the University of Zurich gave a lecture on the antibacterial potential of water-filtered infrared A irradiation (wIRA) on chlamydial infected cells. She highlighted the efficacy and good tolerability associated with this non-chemical intervention. During the last presentation of our seminar, Prof. Dr. Jörg Goldhahn from Novartis Institutes for Biomedical Research in Basel talked about the definition of the term Translational Medicine. He mentioned the importance of transferring results from basic research into medical routine and tried to figure out which questions should be addressed.

In her concluding remarks, Prof. Dr. Brigitte von Rechenberg referred the audience to the importance of collaborations within the different research fields.

At the end of the meeting, all participants had the opportunity to meet during an Apéro. This allowed not only for scientific discussions to be conducted in a relaxed atmosphere, but also represented an ideal platform for new collaborations to be initiated.

4. symposium

des zentrums für angewandte biotechnologie und molekulare medizin (cabmm)

Als grösstes CABMM Event des Jahres fand am 5. Dezember 2013 bereits das 4. Symposium unseres Zentrums an der Universität Zürich statt. Das abwechslungsreiche Programm beinhaltete unter anderem Vorträge von Mitgliedern unseres Leitungsausschusses und Wissenschaftlichen Beirates.




Das Meeting wurde traditionsgemäss von der Vorsitzenden des CABMM Leitungsausschusses, Prof. Dr. Brigitte von Rechenberg, eröffnet. Im Anschluss leitete sie die erste Vortragsreihe mit einem Bericht über die Qualitätsakkreditierung medizinischer Forschung an Universitäten ein. Dabei verwies sie auf die wachsende Bedeutung der translationalen Medizin und die damit verbundenen Fragen der Qualitätssicherung wie zum Beispiel GLP, GCP und GMP – Richtlinien, welche an der Universität Zürich als eine der ersten Universitäten in Europa gemeinsam angeboten werden. Anschliessend sprach PD Dr. Paolo Cinelli vom Universitätsspital in Zürich über die Identifizierung und Isolierung von verschiedenen Stammzellen und deren Verwendung bei der Regeneration von Knochengewebe. PD Dr. Frank Steffen von der Universität Zürich hielt den nächsten Vortrag. Er präsentierte Ergebnisse einer Pilotstudie, welche die Effekte von Stammzellen aus dem Knochenmark zur Reparatur von Bandscheiben im Hund untersuchte.

Der zweite Teil des Symposiums begann mit einem Hauptvortrag von Dr. Esra Neufeld über das Tätigkeitsfeld der IT`IS Foundation in Zürich. Er verwies auf die wachsende Bedeutung von computer-basierten Modellen für verschiedene physiologische Prozesse. Ein Mitglied unseres Wissenschaftlichen Beirates, Prof. Dr. Frank P. T. Baaijens von der Eindhoven Universität für Technologie in den Niederlanden hielt die zweite Hauptrede. Er berichtete von neuen Möglichkeiten in der Herzklappenersatz-Forschung mit dem Ziel, lebende Herzklappen innerhalb des menschlichen Körpers zu züchten, welche ein Menschenleben lang halten.

Im dritten und letzten Teil des Symposiums wurden Projekte vorgestellt, welche durch einen CABMM Start-up Grant gefördert wurden. PD Dr. Benjamin Gantenbein-Ritter von der Universität in Bern stellte Ergebnisse einer Studie über die regenerativen Effekte von notochordalen Zellen dar. Mit einem Vortrag über die Effekte von Bisphosphonaten auf das Differenzierungspotential von Stammzellen aus osteoporotischen Patienten beendete PD Dr. Peter J. Richards von der Universität Zürich die Vortragsreihe. Seine Ergebnisse zeigten, dass verschiedene Bisphosphonate einen positiven Effekt auf die Knochenbildung ausüben.

Am Ende der Veranstaltung richtete Brigitte von Rechenberg einige abschliessenden Worte an die Zuhörer und verabschiedete Dr. Margarethe Hofmann-Amtenbrink und Prof. em. Dr. Peter Sonderegger als Mitglieder des Wissenschaftlichen Beirates. Sie bedankte sich für ihre Unterstützung in den letzten Jahren und wünschte ihnen für die Zukunft alles erdenklich Gute. Während des abschliessenden Apéro gab es für alle Teilnehmer die Gelegenheit, in entspannter Atmosphäre über Gehörtes zu diskutieren und Netzwerke weiter auszubauen.

The 4th CABMM Symposium was kindly supported by

4th symposium

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



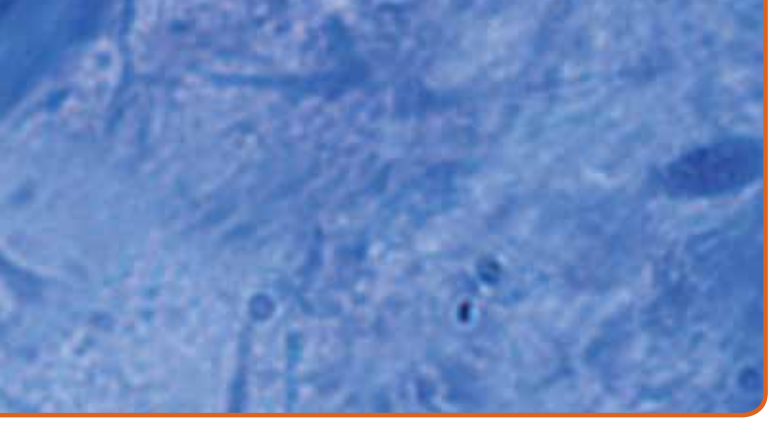
On December 5th, 2013, the main yearly event of the CABMM took place – the 4th Symposium. All participants had the opportunity to follow an interesting program and to hear – amongst others – presentations from both members of the CABMM Steering Committee and members of our Scientific Advisory Board.

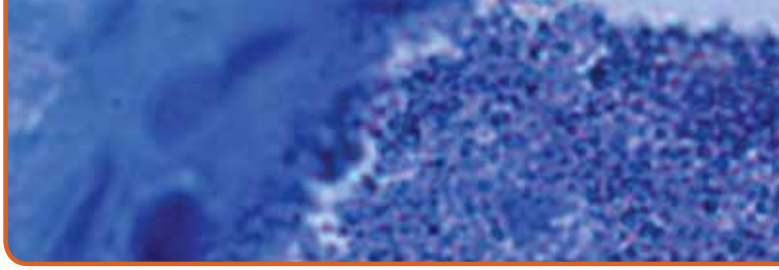
As is customary, the meeting was opened by the chairwoman of the CABMM, Prof. Dr. Brigitte von Rechenberg who also started the presentations with a talk about quality accreditation for medical research. She highlighted the growing need for translational medicine at universities and the associated regulatory issues that come with it. She confirmed that the University of Zurich is one of the first European universities that offers GMP, GLP and GCP at the same institution. Afterwards, PD Dr. Paolo Cinelli from the University Hospital in Zurich talked about the methods to identify and isolate different stem cell populations for subsequent use in the regeneration of bone tissue. The last speaker of this session was PD Dr. Frank Steffen from the University of Zurich who discussed work related to a clinical pilot study evaluating the use of stem cells for spinal disc repair in dogs.

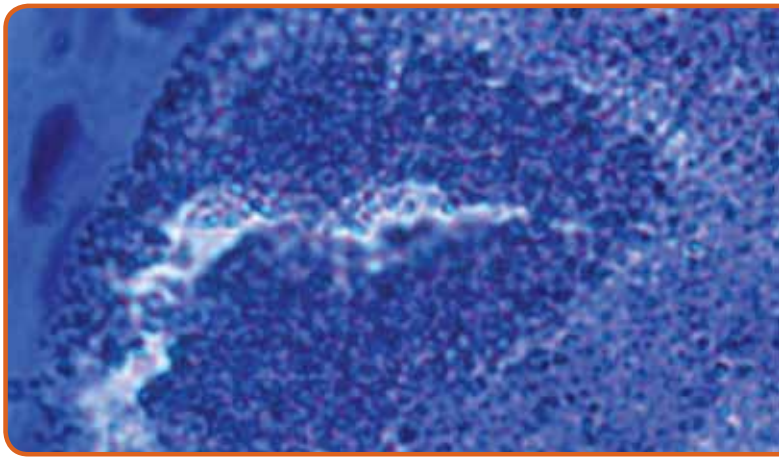
The second session started with a keynote lecture given by Dr. Esra Neufeld who introduced everyone to the field of activity of the IT`IS foundation in Zurich. He mentioned the importance of image-based models of physical and physiological processes. The second keynote lecture was given by one of the members of the CABMM Scientific Advisory Board, namely Prof. Dr. Frank P.T. Baaijens from the Eindhoven University of Technology, the Netherlands. He gave an overview of the current situation in the field of heart valve prostheses and the problems concerning re-intervention or reduced life expectancy. He mentioned that *in situ* cardiovascular tissue engineering is a promising technology for improving heart valve transplantation.

The third session included reports of projects that were funded by CABMM Start-up Grants. PD Dr. Benjamin Gantenbein-Ritter from the University of Bern started with a talk about the regenerative effects of notochordal cells. Last but not least, PD Dr. Peter J. Richards from the University of Zurich talked about the effects of different bisphosphonates on the osteogenesis of mesenchymal stem cells from osteoporotic patients. He demonstrated that both zoledronate and alendronate have a positive effect on osteoblast formation and mineralization.

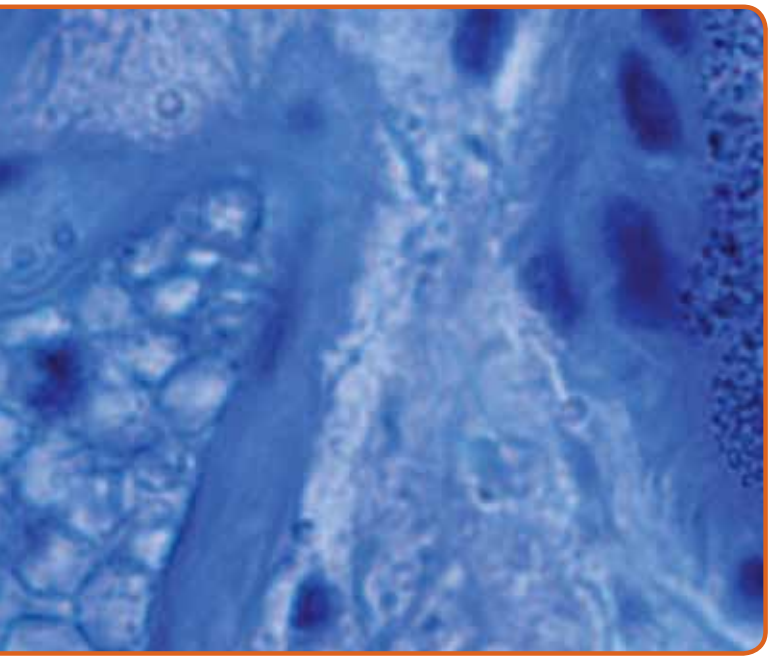
In her concluding remarks, Brigitte von Rechenberg thanked all speakers and organizers for their contribution. Additionally, she said good-bye to Dr. Margarethe Hofmann-Amtenbrink and Prof. em. Dr. Peter Sonderegger as members of our Scientific Advisory Board and thanked both of them for their support over the last years. There upon, another successful meeting ended with an Apéro for all participants offering a relaxed platform to discuss scientific themes and to strengthen collaborations within the CABMM.

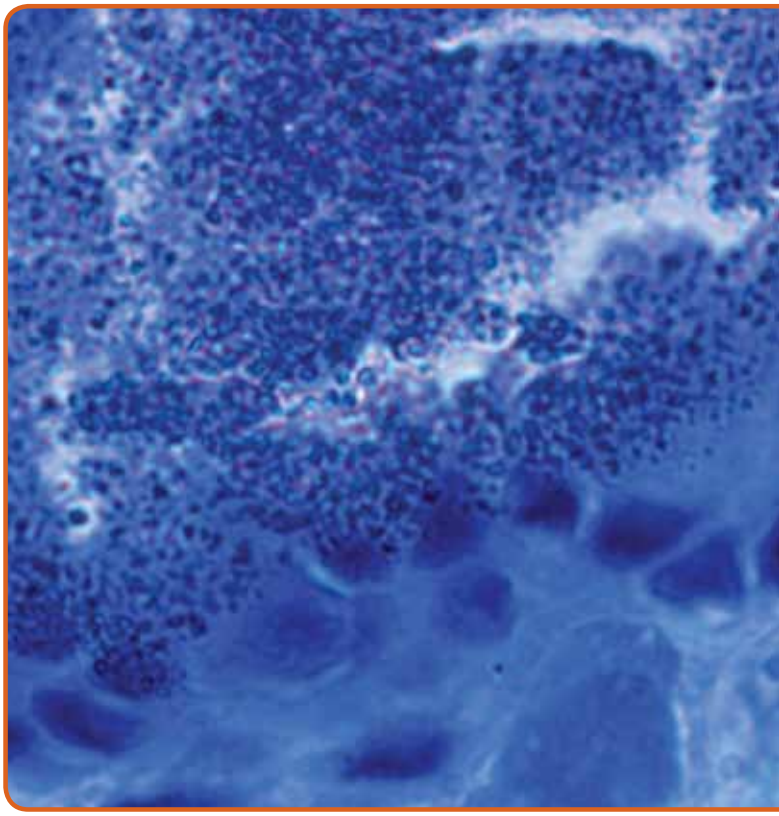


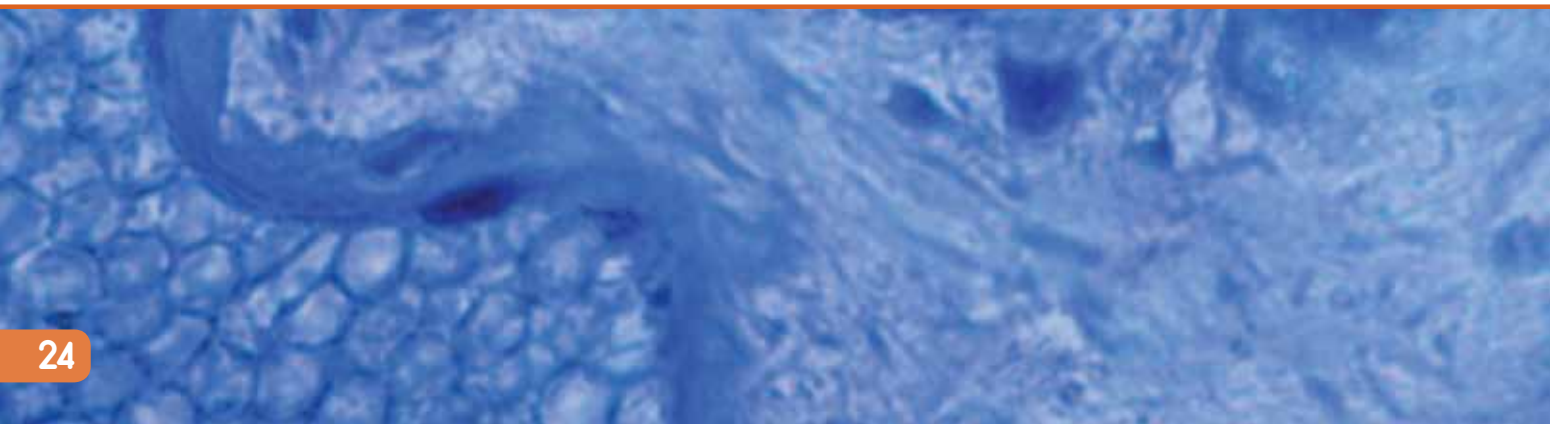




portraits







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, freelance journalist, interviewed the following four people for this CABMM Report:

Prof. Dr. Stephen J. Ferguson

- Associated CABMM member
- Professor at the Institute for Biomechanics at the ETH Zurich
- Athletic Canadian with a good sense of humour

Prof. Dr. Dr. Michael O. Hottiger

- Co-founder of the CABMM
- Member of the CABMM Steering Committee
- Head of the Institute of Veterinary Biochemistry and Molecular Medicine

Prof. Dr. Daniel A. Rüfenacht

- Head of the Interventional Work Research Group at the CABMM
- Medical specialist for neuroradiology and radiology at the Klinik Hirslanden, Zurich
- Connoisseur and aesthete

Dr. Irem Gül Sancak

- Turkish scholarship holder at the CABMM
- Veterinarian and researcher
- Mother of two daughters

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.

„ich bin fast immer gut gelaunt“

stephen j. ferguson, portrait von paula lanfranconi

Stephen Ferguson ist Professor für Biomechanik an der ETH Zürich. Am CABMM reizen den studierten Maschinenbauer vor allem molekularmedizinische Aspekte. Aber auch die beteiligten Menschen.

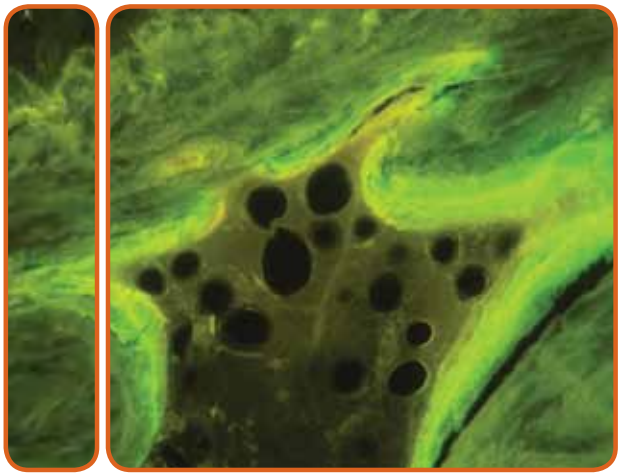
Sein Rollkoffer steht schon bereit. Doch bevor Stephen Ferguson an den nächsten Kongress reist, wollen alle noch etwas von ihm. Der feingliedrige 45-Jährige lässt sich keinen Stress anmerken. „Eigentlich bin ich fast immer gut gelaunt“, sagt er und lächelt. Später wird er erwähnen, er sei mit Monty Python aufgewachsen und habe so auch eine Ader für Satire entwickelt.

Seinen Sinn für Humor und skurrile Ideen belegt auch eine farbige Zeichnung an seiner Bürowand. Sie ist das Geschenk eines ehemaligen Mitarbeiters und zeigt eine Katze mit einem Butterbrot auf dem Rücken. Katzen, erklärt Ferguson lachend, landen immer auf den Pfoten, ein Butterbrot scheinbar immer auf der Butterseite. „Für mich“, sagt der Forscher, „stellt das Bild die Ungewissheit, gleichzeitig aber auch den Reiz dar, in der Wissenschaft mit widersprechenden ‚Fakten‘ konfrontiert zu sein.“

Stephen Fergusons Forschungsfeld gilt den Erkrankungen des Bewegungsapparates, ein Gebiet, welches angesichts der alternden Bevölkerung immer wichtiger wird. Er und seine Gruppe forschen nach neuen Biomaterialien als Ersatz für Gewebe, und sie entwickeln neue chirurgische Verfahren. Dabei arbeitet die Gruppe mit der Zürcher Schulthess-Klink zusammen. „Diese enge Kooperation mit den Klinikern“, sagt Ferguson, „ist für mich der grösste Anreiz für meine Arbeit.“ Seitdem er vor zwei Jahren an die ETH kam, habe er auch etwas mehr Zeit für Grundlagenforschung. Seine Gruppe schafft neue Erkenntnisse über die biologische und biomechanische Funktion von Zellen und Geweben und über die Antwort von Zellen auf mechanische und chemische Belastungen.

Am CABMM interessieren Stephen Ferguson einerseits die Menschen, welche dort arbeiten. Und inhaltlich „vor allem der MM-Teil“, die molekularmedizinischen Aspekte. Ferguson ist Maschinenbauer und hat an der University of Toronto studiert. In den ersten zehn Jahren seiner Tätigkeit, sagt er, habe es gereicht, mit technischen Materialien und mechanischen Systemen zu arbeiten. Doch heute sei klar: zwischen Implantat und Körper gibt es immer Wechselwirkungen. Ferguson findet es spannend, mit lebenden Zellen zu arbeiten und zu sehen, dass sich die Körpergewebe anpassen können. Aber auch umgekehrt: „Manchmal beschädigen die Körperzellen die implantierten Biomaterialien.“ Mit drastischen Folgen.

Ursprünglich wollte der Kanadier bloss für einen einjährigen Forschungsaufenthalt in die Schweiz kommen, an das AO Forschungsinstitut in Davos. „Schneesportfaktoren“ hätten dabei eine Rolle gespielt, sagt er. Auch er selber sei damals so ungefähr jeden snowboardtauglichen Berg heruntergefahren. Das war in den Neunzigerjahren. In dieser Zeit lernte er auch Ladina Ettinger kennen, seine heutige Frau. Sie machte damals in Davos ihre Lehre als Biologielaborantin. Später folgte sie ihrem Mann an die Universität Bern, wo Stephen Ferguson 2006 die Lehrbefugnis für muskuloskeletale Biomechanik erhielt. Acht Jahre arbeitete das Paar dort zusammen. Inzwischen hat seine Frau ans CABMM gewechselt, in die Gruppe von Brigitte von Rechenberg.



Stephen Ferguson bereut es nicht, in der Schweiz geblieben zu sein. Im Gegenteil: „In Europa ein Projekt zu lancieren, ist viel einfacher als in Nordamerika, sowohl finanziell wie technisch". Inzwischen hat er sich ein exzellentes Netzwerk aufgebaut. Und er ist ein Meister in Sachen Understatement. Mit keinem Wort erwähnt er seine über hundert wissenschaftlichen Papers, drei Patentanmeldungen und weitere Verdienste. Lieber spricht er über künftige Vorhaben.

Vor allem die Lehre liegt ihm am Herzen. Im Moment sei das Teaching indes recht stressvoll: Das ETH-Departement Health Sciences and Technology (HEST) gibt es erst seit kurzem. Auch das Bachelor-Studium war neu zu konzipieren, bei Klassengrössen von über 200 Studierenden. Wie schafft man es, mit so vielen Leuten in Kontakt zu sein? „Da", sagt Ferguson, „hilft mir meine lockere Art." Er plant auch neue Kurse, zum Beispiel Simulationsverfahren in der Biomedizinischen Technik für die Analyse und Vorhersage der Belastbarkeit des Körpers oder den Wechselwirkungen zwischen Körper und Biowerkstoffen.

Auch das Gespräch mit seinen Mitarbeitenden ist ihm ein Anliegen. Er möchte nicht bloss Projektmanager sein: „Einer, der eine tolle Gruppe von 20 Leuten hat, aber eigentlich keine Ahnung, was dort passiert." Seine Bürotüre ist immer offen. Am liebsten würde er, wie früher, während den Kaffeepausen über die Arbeit und auch mal über private Dinge diskutieren. Doch an der ETH, bedauert er, seien die räumlichen Distanzen dafür zu lang.

In seiner Forschung befasst sich Stephen Ferguson täglich mit altersbedingten Erkrankungen des Bewegungsapparates. Angst vor dem eigenen Altern? „Überhaupt nicht", antwortet er. Um seine Gelenke zu schonen, hat er indes entschieden, nicht mehr täglich zu joggen, sondern abwechslungsweise Velo zu fahren. Diesen Sommer habe er auch angefangen zu rudern. „Es muss einfach eine Balance sein", bringt er seine Strategie auf den Punkt. Private Projekte? „Gesund bleiben!" Er hat auch ein paar Ideen für längere Mountainbike- und Skitouren. Am liebsten in der Schweiz, da gebe es so viele Möglichkeiten.

Wie lang seine Arbeitswochen sind, weiss der Forscher nicht so genau, Arbeit und Freizeit gehen für ihn ineinander über. Manchmal denke er allerdings, das Leben ticke sehr schnell, und es sei zu viel Administratives zu erledigen. „Aber", fügt er bei, „ich muss dieses Stressniveau in Kauf nehmen, um diese tolle Arbeit machen zu dürfen." Dem Stress begegnet er mit ausgedehnten Waldläufen. Dann sinke die Anspannung, und er könne neue Ideen entwickeln. Musik, sagt er, höre er beim Sporttreiben nicht: „Ich brauche keinen Soundtrack für mein Leben!"

Morgen gehts auf zum nächsten Kongress. Nach Leuven, Belgien. Und danach? Er überlegt einen Moment. „Nach Graz, glaube ich."

"i am almost always in a good

Stephen Ferguson is a Professor for biomechanics at the ETH Zurich. At the CABMM, the mechanical engineer is particularly attracted by the aspects of molecular medicine, and also by the people involved.

His suitcase is already packed, but before Stephen Ferguson can leave for the next congress, everybody wants something from him. The slender 45-year-old does not give a stressed impression. "Actually, I am almost always in a good mood", he says and smiles. He will mention later on that he grew up watching Monty Python and developed a sense for satire.

A colourful drawing on his office wall also reflects his sense of humour and bizarre ideas. It is a gift from a former co-worker showing a cat with bread and butter on its back. Cats, Ferguson explains laughing, are always landing on their paws, a bread with butter seems to fall always on the buttered side. "For me", the researcher says, "this picture represents this uncertainty, but additionally the attraction of science to be confronted with paradoxical 'facts'".

His research addresses musculoskeletal diseases, a field gaining more and more importance in view of the aging society. He and his group investigate, among other topics, new biomaterials that can be used as tissue replacements and new surgical techniques for their application. His group is working together with the Schulthess clinic in Zurich. "This close collaboration with the clinicians", Ferguson says, "provides the biggest incentive for my work." Since his move to the ETH two years ago, he's also had a bit more time for basic research. His group investigates the biological and biomechanical function of cells and tissues as well as the cellular response to mechanical and chemical stimuli.

Regarding the CABMM, Stephen Ferguson is on the one hand interested in the people working at the CABMM, and on the other, with its focus "mainly in the MM-part", in the aspects of molecular medicine. Ferguson is a mechanical engineer, who studied at the University of Toronto. During the first ten years of his professional work, he says, it was sufficient to work just on technical materials and mechanical systems. However, nowadays it's clear that there are always interactions between an implant and the human body. Ferguson finds it exciting to work with living cells and to see how tissues can adapt, but the reverse situation is equally important. "Sometimes the cells in the body can degrade the implanted biomaterials, often with drastic consequences".

Originally, the Canadian wanted to come to Switzerland for only one year, for a research stay at the AO Research Institute in Davos. "Winter sport factors certainly played a contributing role", he says. At that time, in the mid-90s, he used his free time to descend almost every mountain suitable for snowboarding. At that time, he also met his wife, Ladina Ettinger, who was training as a laboratory technician in Davos. Later on, she followed her husband to the University of Bern, where Ferguson was promoted to the position of lecturer in musculoskeletal biomechanics in 2006. There, the couple worked together for eight years. In the meantime, his wife has changed to a position at the CABMM, in the group of Brigitte von Rechenberg.

Stephen Ferguson doesn't regret that he stayed in Switzerland. On the contrary: "It is much easier to launch a project in Europe than in North America, financially as well as technically." Over the years, he has created an excellent network. And he is a master of understatement. There is not even a single word about his more than one hundred scientific papers, three patent applications and additional awards. He prefers to talk about future plans.

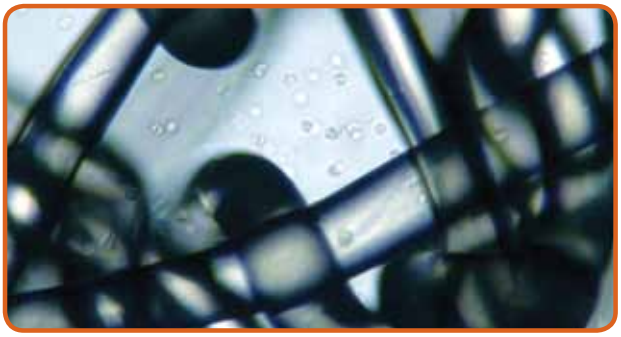
mood''

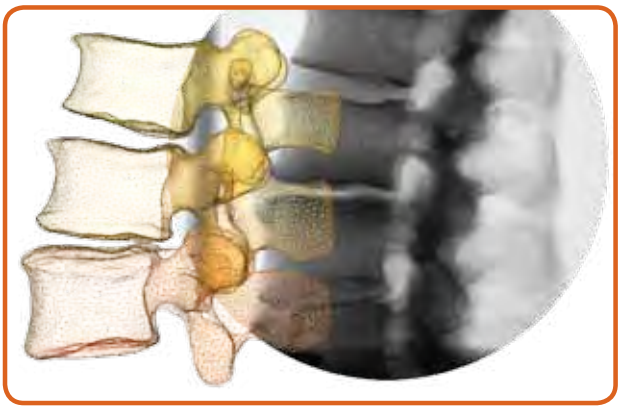
stephen j. ferguson, portrait by paula lanfranconi

Teaching is particularly close to his heart, although it is quite stressful at the moment. The ETH department Health Sciences and Technology (HEST) has existed for only a short time. The bachelor studies needed to be newly designed, with class sizes of over 200 students. How is it possible to be in contact with such a lot of people? "In that", Ferguson says, "my easy-going way helps." He also plans new courses, for example about computer simulation methods in biomedical engineering, for analysing and predicting the loading capacity of the human body or evaluating the interactions between the human body and biomaterials.

The conversation with his team members is also of great importance to him. He doesn't want to be a simple project manager, "Someone with a large group of people, who has no clue what's going on in the lab." His office door is always open. He would prefer if he would also be able to discuss work matters during the informal coffee breaks, as before, but on the Hönggerberg campus, he regrets, the spatial distance is often too great.

In his research, Stephen Ferguson is dealing every day with age-related diseases of the musculoskeletal system. Is he concerned about his own aging? "Not at all", he says. However, in order to treat his joints with care, he decided to no longer go jogging every day, but rather to alternate with cycling. Last summer, he also started rowing for a change. "Life has to be balanced", he brings his strategy to the point. Private projects? "Simply to keep well and fit!" He has also a few longer mountain bike or ski tours in mind, preferably in Switzerland, as there are so many possibilities.





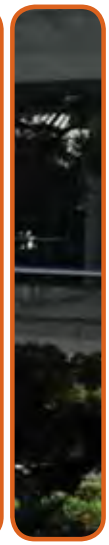
The researcher doesn't know exactly how long his working weeks are; for him, work and spare time routinely cross over. However, sometimes he feels that life is moving too quickly and that there is too much administrative work. "But", he adds, "I accept this level of stress, otherwise I wouldn't have the possibility to do this great job." He combats the stress with runs in the Hönggerberg forest, where he can also develop new ideas. He doesn't listen to music when doing sports, he says: "I do not need a soundtrack for my life."

Tomorrow is the next congress, in Leuven, Belgium. And afterwards? He has to think for a short moment. "Graz, I think."

„ich lasse mich bewusst auf etwas

Professor Michael O. Hottiger ist Mitgründer des CABMM und gehört dessen Leitungsausschuss an. Der Molekularbiologe und ausgebildete Tierarzt versteht sich auch als eine Art Diamantschleifer.

An der Pinnwand seines Büros an der Universität Zürich-Irchel hängen geschätzte zwei Dutzend Portraitfotos – lachende, ernste oder neutral blickende Gesichter junger Menschen. Es sind Doktoranden und Postdocs, welche Professor Michael O. Hottiger in den letzten Jahren begleitet hat.



An diesem Nachmittag wirkt der 47-jährige Molekularbiologe so entspannt, als hätte er alle Zeit der Welt. Ab und zu blitzt in seinen Augen etwas Verschmitztes auf; es kontrastiert mit seiner präzisen, fast druckreifen Ausdrucksweise. In Hottigers Labor geht es, verkürzt gesagt, um das Verständnis jener molekularen Mechanismen, welche Entzündungsprozesse regulieren. Hottiger schaut dabei gerne über den Rand seines grundlagenorientierten Forschergartens hinaus. Er hat ein offenes Ohr für Kliniker, die sagen: „An diesen konkreten Problemen leiden unsere Patienten, hier brauchen wir Lösungen." Ein solcher Beitrag könne, zum Beispiel, eine Art Dimmschalter sein, mit dem sich chronische Entzündungsprozesse regulieren lassen, zumal eine Entzündung nicht immer etwas Negatives sei.

An der passionierten Art, wie Hottiger über seine Arbeit spricht, spürt man: Da sitzt einem ein Forscher gegenüber, den komplexe Problemstellungen geradezu befeuern. Hottigers Interesse an Translationalität und Interdisziplinarität motivierte ihn zur Mitgründung des CABMM. „Ich lasse mich", sagt er, „bewusst auf etwas Fremdes ein und versuche, mit anderen Forschenden Synergien zu finden." Die fachliche Distanz, relativiert er, dürfe allerdings nicht zu gross sein. Mit Brigitte von Rechenberg und Simon Hoerstrup, den anderen Mitgründern des CABMM, verbindet ihn vor allem das Interesse an der Regeneration von beschädigten Gefässen und Geweben, zum Beispiel Knochen und Muskeln.

Sein Faible für die Klinik hat auch mit Hottigers Erstausbildung zu tun. Er studierte Veterinärmedizin, wusste aber immer, dass er in die biomedizinische Forschung wollte. Am Zürcher Tierspital, erinnert er sich, sei er dann ein bisschen das schwarze Schaf gewesen: „Es hiess: Du steckst so viel Zeit in deine Ausbildung, bist aber dann nicht kurativ tätig."

Nein, ein James Herriot sei er nicht geworden, sagt Hottiger und schmunzelt. Gemeint ist jener leidenschaftliche very britische TV-Tierdoktor, welcher in den 1970er-Jahren viele junge Leute zum Veterinärstudium motivierte. Als Tierarzt, meint Hottiger lachend, hätte er es wohl nicht weit gebracht: „Wer dem Besitzer einer übergewichtigen Katze mit Diabetes gerade heraus sagt, er trage auch ‚Schuld' am Übergewicht seines Haustieres, ist seine Kundschaft rasch los."

Hottigers Arbeitstage dauern zwölf Stunden, er verbringt mehr Zeit mit seinen Doktoranden als mit seiner Frau. Doch die Zeit zuhause sei „Quality time, ein etwas abgedroschener Begriff", wie er einräumt. Seine Frau ist Musiklehrerin, das Paar hat vier Kinder. Letztes Jahr feierten sie den zwanzigsten

fremdes ein“

michael o. hottiger, portrait von paula lanfranconi

Hochzeitstag. Das Erfolgsgeheimnis ihrer Ehe, sagt Hottiger, hänge wohl damit zusammen, dass seine Partnerin und er „zwei sehr unterschiedliche Farben“ mitgebracht und von Anfang an versucht hätten, einen Konsens beim Zusammenleben und in Erziehungsdingen zu finden. Ohne die Kompromissbereitschaft seiner Frau hätte seine Karriere indes nicht funktioniert: „Als es galt, akademisch Gas zu geben, steckte sie zurück und folgte mir in die USA.“

Die Familienplanung, stellt der Professor fest, sei auch heute noch ein grösseres Karrierehindernis, als man wahrhaben wolle. Denn immer noch verabschiedeten sich die meisten Forscherinnen, wenn Betreuungsaufgaben anstehen, sagt Hottiger und verweist auf die gängigen Rollenerwartungen: „Gibt es im Kinderhort ein Problem, ruft man noch immer die Mutter an, nicht den Vater.“ Und bei Assessments für Führungspositionen gäben nach wie vor männliche Eigenschaften den Ausschlag. Hottiger ist durchaus für Frauenförderung, nicht aber für Gleichmacherei. Es sei ein biologischer Fakt, dass es ausschliesslich die Frau sei, welche gebären könne. „Solange wir nicht unterschiedliche Rahmenbedingungen schaffen, können wir die beiden Geschlechter nicht auf die gleiche Stufe stellen“, ist er überzeugt.

Inzwischen sind Hottigers Kinder aus dem Gröbsten heraus. Druck, eine akademische Karriere machen zu müssen, gebe es von seiner Seite nicht. Im Gegenteil. Manchen Studierenden, konstatiert der Professor, wäre besser gedient, wenn sie eine Berufslehre oder eine Ausbildung an einer Fachhochschule gemacht hätten, statt sich „mit Hängen und Würgen“ durchs Universitätsstudium zu schlängeln. Und trotzdem nicht glücklich zu werden.

Hottiger betrachtet es als eine seiner wichtigsten universitären Aufgaben, möglichst viele talentierte Nachwuchsleute auszubilden. Auf der Doktoratsstufe bleibt ihm dafür ein Zeitfenster von drei bis vier Jahren. Viele Doktoranden, stellt er fest, wüssten gar nicht, was alles in ihnen stecke: „Sie sind wie Rohdiamanten, die noch geschliffen werden müssen.“

In seinem Portfolio gebe es indes auch junge Menschen, die es kaum an die schmale akademische Spitze schaffen würden. Zu seinem Job gehöre es, sie so zu begleiten, dass sie sich rechtzeitig für eine andere, ihren Fähigkeiten entsprechende Laufbahn entscheiden können. „Die Gesellschaft“, wünscht sich Hochschullehrer Hottiger, „sollte auch jenen Menschen viel mehr Respekt und Wertschätzung entgegen bringen, die keine akademische Ausbildung haben.“

“i deliberately get into something

Professor Michael O. Hottiger is one of the co-founders of the CABMM and a member of its Steering Committee. The molecular biologist and veterinarian by training also describes himself as a kind of diamond cutter.

About two-dozen portraits of laughing, serious or neutral looking faces of young people are hanging up on the pin board in his office at the University of Zurich. These photos belong to doctoral students and postdocs, who Professor Michael O. Hottiger supervised during the last years.

This afternoon, the 47 years old molecular biologist appears to be completely relaxed, as if he would have all the time in the world. From time to time something impishing is flashing up in his eyes, which is in contrast to his precise, well-worded phrasing. In short, the Hottiger lab investigates the molecular mechanisms regulating inflammatory processes. In doing so, Hottiger likes to look beyond his own basic research-oriented scientific back yard. He has an open ear for clinicians saying, “Our patients suffer from these defined problems, here we need a solution.” Such a contribution could be for instance a kind of dimmer switch regulating chronic inflammatory processes, especially as inflammation is not always negative.

In the enthusiastic way Hottiger is talking about his work, one can feel: This researcher is really urged by complex problems. Hottiger’s interest in translational and interdisciplinary research motivated him to co-found the CABMM. “I deliberately get into something new”, he says, “and try to find synergies with other researchers.” However, the professional difference, he relativizes, must not be too wide. The connection to Brigitte von Rechenberg and Simon Hoerstrup, the other co-founders of the CABMM, consists mainly in their common interest in the regeneration of damaged vessels and tissues, such as bones and muscles.

His passion for clinical work is also connected with his initial training. He studied veterinary medicine, although he always knew that he would like to go into biomedical research. He remembers that he was always a little bit the black sheep at the veterinary clinic: “They said: You are putting such a lot of time in your training, but you will never work in a curative way.”

No, he didn’t become a James Herriot, Hottiger says and smiles. Referring to that passionate and very British animal doctor on TV, who motivated a lot of young people to study veterinary medicine in the seventies. As an animal doctor, guesses Hottiger laughing, he wouldn’t have got anywhere: “Who ever would tell the owner of an overweight cat suffering from diabetes that the excess weight of his pet was also his or her own fault, would loose his costumers very quickly.”

Hottiger’s working days are twelve hours long, he spends more time with his doctoral students than with his wife. But the time at home would be “quality time, a somewhat hackneyed saying”, he admits. His wife is a music teacher, and

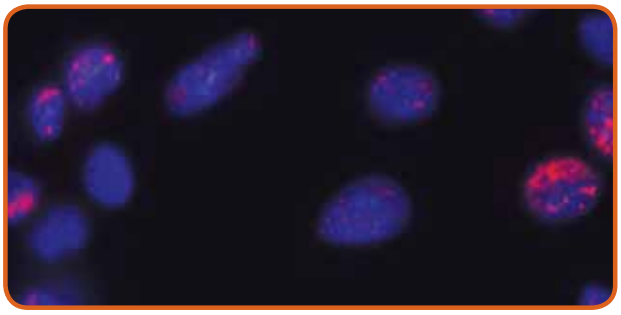
new"

michael o. hottiger, portrait by paula lanfranconi

together they have four children. Last year they celebrated their 20th wedding anniversary. The secret to their marriage success, Hottiger says, may be connected to the fact that despite he and his wife having "two very different views", they have tried from the beginning to find a consensus for living together, as well as for educating their children. Without the willingness of his wife to compromise, his career never would have worked out. "As it was the time to push the academic gas pedal, she cut back her own interests and followed me to the USA."

Even today, the professor states, family planning would be a bigger barrier to a career than one would like to believe. Because most of the female researchers would still take leave to take care of the children, Hottiger says and refers to the established role expectations: "If there is a problem at the day nursery, they still call the mother, not the father." And during assessments for leadership positions, male characteristics would still turn the balance. Hottiger is absolutely in favour of women's advancement, but not for enforced conformity. It would be a biological fact that only women could give birth. He is convinced "As long as we are not able to create different environments, we cannot place both genders on the same level".

By now, Hottiger's kids are out of the woods. There would be no pressure to make an academic career from his side.



Rather the contrary. For some of the students, the professor states, it would have been better to make a vocational training or an education at a technical college instead of writhing through the university studies by the skin of their teeth and not being happy by doing so.

Hottiger considers the training of as many talented young academics as possible as one of his most important tasks at the University. On the doctoral level, he has a time frame of three to four years for it. A lot of doctoral students, he mentions, would not know what they would be capable of: "They are like rough diamonds that still need to be cut."

There are also youngsters existing in his portfolio, who would not be able to reach the narrow academic summit. Then it's also part of his job to advise them, so that they can decide in time on a different career more suitable for their capability. It is the wish of the university lecturer Hottiger that, "Society should show much more respect and appreciation to people without university education."

„das wichtigste ist, den patienten

Professor Daniel A. Rüfenacht ist Facharzt für Radiologie, diagnostische und interventionelle Neuroradiologie sowie assoziiertes Mitglied des CABMM. Seine Faszination gilt dem menschlichen Gehirn. Er ist ein Querdenker mit weitem Horizont.

Den Tisch aus Massivholz in seinem Büro an der Zürcher Privatklinik Hirslanden hat er extra etwas breiter anfertigen lassen. „Das Wichtigste", sagt der Mann mit dem Lockenkopf, „ist, den Patienten Komfort zu geben." Damit meint Daniel Rüfenacht Komfort im englischen Wortsinn: Trost geben und Vertrauen. Denn oft sitzen an seinem Tisch Menschen mit einem Aneurysma, und sie haben grosse Angst, das gefährdete Gefäss in ihrem Gehirn könnte reissen.

Rüfenacht nimmt sich Zeit für seine Patienten. Er versucht, ihnen die Diagnose und ihre möglichen Folgen so zu erläutern, dass es ihrer Denkweise entspricht: „Das Schwierige ist, den Patienten einerseits die Panik zu nehmen, anderseits aber auch keine unerfüllbaren Erwartungen zu wecken." Oft kommt die Diagnose aus heiterem Himmel, denn die moderne Bildgebung findet auch symptomlose Aneurysmen. Dann gibt es Erklärungsbedarf, denn gemessen an den Operationsrisiken wäre ein sofortiger Eingriff oft nicht notwendig. „Meine Aufgabe", sagt der Neuroradiologe, „ist, herauszufinden, ob es sich um ein gefährliches Aneurysma handelt oder nicht."

Daniel Rüfenacht, das merkt man rasch, geht es um sein Fachgebiet, die interventionelle Neuroradiologie. Eine administrative Karriere hingegen habe er nie gewollt. Konflikte und Grabenkämpfe hält er für reine Energieverschwendung. Der gebürtige Berner war 2008, nach 16 Jahren als Professor für Neuroradiologie an der Universität Genf, nach Zürich gekommen. Hier, an der Privatklinik Hirslanden, wollte er sich zusammen mit seinen Partnern Isabel Wanke und Zsolt Kulcsár auf die interventionelle Neuroradiologie konzentrieren und neue Forschungsansätze nutzen.

Ein wichtiger Grund für seinen Wechsel nach Zürich war das damals neu gegründete CABMM. Die Idee einer interdisziplinären Forschungsplattform zur Entwicklung biologischer Implantate entspricht Rüfenachts integrativem Wesen. Am CABMM kann er Verbindungen schaffen zwischen den Denkweisen von Medizinern, Biologen, Informatikern, Ingenieuren. Die Nähe des Tierspitals erlaubt zudem Experimente im Tiermodell. Seine eigene Arbeit vergleicht Rüfenacht mit jener eines Klempners: „Wir untersuchen Schwachstellen an Gefässen und setzen dann Implantate ein, welche den Blutfluss korrigieren, so dass sich die Gefässwand selber heilen kann."

Wenn Daniel Rüfenacht über sein Metier spricht, wird Passion spürbar. Da ist kein Routinier am Werk, sondern jemand, der noch immer über unser Gehirn staunen kann. Einer mit weitem Horizont, ein Schöngeist auch, der mühelos Medizin mit Informatik und Kunst in Verbindung bringt. Ursprünglich hatte er sich der Kunst zuwenden wollen, entschied sich dann aber für die Radiologie. Bilder, sagt er, hätten ihn schon immer interessiert: „In der Radiologie sah ich dann, wie elegant man dank bildgesteuerten Technologien Chirurgie machen kann."

Schon früh faszinierte ihn die Informatik und ihre Möglichkeiten, mit enormen Datenmengen umzugehen. Oder die 3D-Technik, welche es erlaubt, Aneurysmen zu modellieren und so verlässlicher zu entscheiden, ob, wie und wann ein Eingriff gemacht werden solle. Nach Gründung der Swiss-NeuroFoundation, einer Stiftung zur Förderung der klinischen Neurowisssenschaften, beschäftigt er sich zur Zeit vorwiegend mit der Entwicklung einer Aneurysmendatenbank. Zudem engagiert er sich bei einem neuen, IT-gestützten europäischen

komfort zu geben“

daniel a. rüfenacht, portrait von paula lanfranconi

Forschungsvorhaben, bei dem es um vaskuläre Aspekte der Demenz geht. Projektname: VPHDARE@IT.

Daniel Rüfenacht denkt assoziativ. Von der Informationstechnologie schweift das Gespräch zurück zum menschlichen Gehirn. Und da hat Rüfenacht auch nach über 30 Jahren das Staunen nicht verlernt. „Das Gehirn“, sagt er, „macht unsere Welt.“ Er liest viel über visuelle Wahrnehmung, schätzt die Bücher des türkischstämmigen Neurobiologen Semir Zeki, welcher sich mit den neurobiologischen Grundlagen von Kunst und Ästhetik befasst, der so genannten Neuroästhetik. Und schon ist die Brücke zur Kunst geschlagen. Denn viel früher als die Neurobiologen, sagt Rüfenacht, hätten sich Künstler des 20. Jahrhunderts mit dem modularen Aufbau unserer visuellen Verarbeitung befasst und sie nach aussen gespiegelt.

Der Privatmensch Daniel Rüfenacht? Der sei ein Geniesser, sagt er ohne Umschweife. „Ich lese gerne, sitze im Garten, rauche eine Zigarre, trinke ein Glas Wein, meine Frau kocht gut, wir hören gerne klassische Musik.“ In den Ferien aquarelliere er, benütze dazu japanische Materialien, die er während seiner dortigen Aufenthalte schätzen gelernt habe. Vor ein paar Jahren erwarb die Familie am Neuenburgersee ein kleines Häuschen. Er halte sich gerne am und auf dem Wasser auf. „Da“, sagt er und schlägt erneut den Bogen zu seinem Metier, „geht es auch ums Fliessen.“

Der 59-Jährige hat noch viel vor. Er möchte die Data Base Research im Bereich der Aneurysmen vorantreiben. Bis in fünf Jahren, so hofft er, werde es eine internationale Bibliothek für Aneurysmen geben, geordnet nach Formen. Sein Beitrag sei, für die nötige Finanzierung zu sorgen. Auch die Entwicklung neuer Implantate liegt ihm am Herzen. Hier sieht er sich als Mutmacher und Vernetzer: „Ich möchte Industrie und Sponsoren motivieren, in innovative Projekte zu investieren, damit begabte Leute nicht ins Ausland abwandern.“

Das Gespräch hätte noch lange so weiter gehen können. Doch Daniel Rüfenacht blickt auf die Uhr. Nun ist er wieder ganz Arzt. Draussen wartet ein Patient. Er hat einen grossen Hirntumor, es geht um die Vorbereitungen für eine Operation. Er könne sich gut einfühlen in die Gefühle der Patienten, sagt Rüfenacht. Als Vierzehnjähriger sei er selber dem Tod nahe gewesen. Nach einem schweren Schlittelunfall war seine Milz gerissen. Die Frage lautete: Operieren oder nicht? „Damals realisierte ich, dass sich das Leben plötzlich fundamental verändern kann.“

Heute, als Arzt, sieht er seine Aufgabe darin, die Patienten so zu leiten, dass sie nicht unnötig Angst vor einem Eingriff haben. „Ich glaube“, fügt er in seinem gemütlichen Berndeutsch bei, „das schaffe ich gut.“

“it is most important to give the

Professor Daniel A. Rüfenacht is a medical specialist for radiology, diagnostic and interventional neuroradiology as well as an associated CABMM member. He is fascinated by the human brain and a lateral thinker with a wide horizon.

The desk in his office in the private clinic Hirslanden in Zurich is made out of solid wood and is a custom product specially made to be a little larger. “It is most important”, the man with the head of curly hair and an appearance of brilliance says, “to give the patients comfort.” And he refers to the English meaning of the word: to give hope and confidence. Because the people sitting at his table have often an aneurysm and are terrified by the thought that the vulnerable vessel in their brain could rupture.



Rüfenacht takes time for his patients. He tries to explain to them the diagnosis and the possible consequences in a way matching with their way of thinking: “The most difficult part is to take their panic away, but on the other hand not to raise unrealizable expectations.” Often, the diagnosis is coming out of the blue, as modern imaging technologies are also able to detect aneurysms causing no symptoms. Then there is a need for clarification, as an immediate intervention often doesn’t make much sense as measured by the surgical risk. “It is my function”, the neuroradiologist says, “to find out if the aneurysm is a so-called poisonous aneurysm or not.”

Daniel A. Rüfenacht – one notices very fast – is referring to his speciality: interventional neuroradiology. He never wanted an administrative career. He thinks that conflicts and trench warfare are simply a waste of energy. After working for 16 years as a Professor of neuroradiology at the University of Geneva, the native Bernese moved to Zurich in 2008. Here, at the private clinic Hirslanden, he and his colleagues Isabel Wanke and Zsolt Kulcsár wanted to focus on interventional neuroradiology and to use new research approaches.

One important reason for his relocation to Zurich at this time was also the newly founded CABMM. The idea of an interdisciplinary research platform for the development of biological implants corresponds exactly to the integrative personality of Rüfenacht. At the CABMM, he can connect the way of thinking of physicians, biologists, computational scientists, and engineers. Furthermore, the proximity to the animal hospital enables experiments in animal models. Rüfenacht compares his own work to the one of a dentist: “We are investigating cavities on vessels, inserting implants to correct the blood flow, and thus enabling the vessel wall to heal by itself.”

When Daniel A. Rüfenacht talks about his profession, one can feel his passion. There is no veteran at work here, but rather someone who is still amazed by the brain. A person with a wide horizon, also an aesthete, who can easily put medicine, informatics and arts in the same context. Originally, he wanted to turn towards arts, but then he decided on radiology. He was always interested in pictures, he says: “In radiology I discovered the elegant way of doing surgery thanks to imaging-based technologies.”

Very early on, he was fascinated by informatics and the possibility to treat an enormous data volume. Or by 3D-techonolgy, allowing the modelling of aneurysms and thus, helping with the decision, if, how and when a surgical intervention should be made. Rüfenacht is setting up an aneurysm database structure within the recently founded SwissNeuroFoundation together with other inernational capacities in the field. Furthermore, he is engaged in a new, IT-supported European research project investigating the vascular aspects of dementia. Project name: VPHDARE@IT.

patients comfort''

daniel a. rüfenacht, portrait by paula lanfranconi

Daniel Rüfenacht is thinking associatively. From information technology, the conversation is wandering back to the human brain. And even after working for 30 years in this field, Rüfenacht is still being amazed by the human brain. "The brain", he says, "creates our world". He is reading much about visual cognition, and appreciates the books of the Turkish neurobiologist Semir Zeki, who addresses the neurobiological basic principles of arts and aesthetics, the so-called neuroaesthetics. Because much earlier than the neurobiologists, Rüfenacht says, the artists of the 20th century gave attention to the visual processing and reflected them outwards.



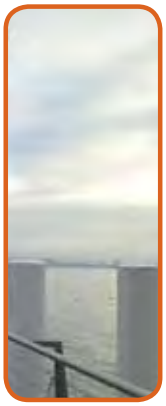
And the private person Daniel A. Rüfenacht? He would be a connoisseur, he says direct and straightforward. "I like to read, to sit in the garden, to smoke a cigarette, to drink a glass of wine. My wife is cooking very well, we like to listen to classical music." In his holidays, he paints in watercolours using Japanese materials that he has come to appreciate during his local stays in Japan. A few years ago, the family bought a little house at the lake of Neuchâtel. He likes to be close to and on water. "There", he says by building again a bridge to his profession, "it is also all about flow."

The 59-year-old has still many plans in the pipeline. He would like to promote database research in the field of aneurysms. He hopes that an international library for aneurysms will be created within five years, ordered by types of aneurysms. His contribution would be to provide the necessary funding. Furthermore, the development of new implants is important for him. He sees himself as a motivator and linking

person: "I would like to motivate industry and banks to invest in innovative projects, so that talented people will not go abroad."

The conversation could have continued for a long time in the same way. But Daniel A. Rüfenacht looks at his watch. Now, he is a physician again. There is a patient waiting. He has a big tumour in his brain; the surgery needs to be prepared. He could easily empathize with the feelings of the patient, Rüfenacht says. When being 14-year-old, he barely escaped death. After a serious accident with a sledge, his spleen was ruptured. The question was: Surgery or not? "At that time, I realized that life could suddenly change fundamentally."

Nowadays, as a medical doctor, he sees his duty in accompanying his patients in such a way that they are not being unnecessarily scared of the surgery. "I think", he adds in his relaxed Bernese German, "I am doing well".



„ich wollte unbedingt in die

Irem Gül Sancak gehört zu den ersten Stipendiaten des CABMM. Der Aufenthalt in Zürich hat ihren Blick auf ihre Karriere und das Leben überhaupt verändert.

An diesem Morgen hat sie, wie immer, ihre siebenjährige Tochter Meriç in den Schulhort gebracht und danach die zweijährige Defne in die Kinderkrippe des Tierspitals. Dieses Morgenprozedere, sagt die schmale Frau mit den ausdrucksstarken grauen Augen, brauche viel Zeit, weil ihre jüngere Tochter immer genau nachahme, was ihr die Ältere vormache. „Schaffe ich es, die Grosse rechtzeitig bereit zu kriegen, ist das Problem gelöst", sagt sie und lächelt.

Inzwischen ist es Viertel nach acht. Irem Gül Sancak trinkt in der Mensa des Tierspitals ihren Kaffee und setzt sich dann an den Zellkulturplatz des CABMM. Die 38-jährige ist Forschungsassistentin in der Gruppe der Musculoskeletal Research Unit (MSRU). Sie arbeitet an einem Projekt zur Gewinnung von Knorpelersatz aus Stammzellen. Im Moment, erläutert sie, teste sie die Zellen *in vitro*: „Es sieht gut aus."

Irem Gül Sancak hat einen weiten Weg zurück gelegt. Sie studierte in Ankara Veterinärmedizin und führte danach vier Jahre lang eine Kleintierpraxis im Stadtzentrum. Sie mag Tiere und möchte, dass sie weniger leiden müssen. Doch die Kleintierpraxis sei Routinearbeit gewesen. Langweilig. „Ich wollte unbedingt in die Forschung." Nach ihrem PhD an der Universität Ankara zum Thema Stammzellen in der Augenheilkunde bewarb sich Irem für einen Kurzaufenthalt am Departement für Ophthalmologie an der Vetsuisse Fakultät der Universität Zürich. Die modernen Labors, besonders aber das Teamwork und die gute Vernetzung der Forschenden hätten sie beeindruckt.

Nach ihrer Rückkehr nach Ankara sei „Zürich in ihrem Blut gewesen", sagt Irem in ihrer blumigen Sprache. Ihr Mann, ebenfalls Veterinärmediziner, habe ihre Pläne unterstützt. Ein seltenes Glück. So bewarb sie sich um ein Forschungsstipendium beim Schweizer Staatssekretariat für Bildung, Forschung und Innovation. Und wurde angenommen. „Eine Frau, aus der Türkei? Willkommen!", sagte ihre künftige Chefin, CABMM-Mitgründerin Brigitte von Rechenberg.

Doch bevor Irem nach Zürich aufbrechen konnte, galt es, ein paar unvorhergesehene Hürden zu bewältigen. Nachdem sie das Stipendium beantragt hatte, realisierte die junge Frau nämlich, dass sie schwanger sei: Defne, ihre zweite Tochter, kam ein paar Wochen vor der Abreise in die Schweiz zur Welt. Eine Stipendiatin mit Kindern, das war von den Schweizer Behörden nicht vorgesehen. Mit klopfendem Herzen habe sie nach Zürich telefoniert, erinnert sich Irem. Doch Brigitte von Rechenberg habe kurzerhand das Migrationsamt kontaktiert, und das Kinderproblem sei gelöst gewesen. Eine derartige Unterstützung, sagt die junge Mutter, habe sie noch nie erlebt: „Es war so emotional und ein Wendepunkt in meiner Karriere."

Auch von ihrer Forschungsgruppe habe sie tatkräftige Unterstützung bekommen. Als Newcomerin, sagt sie nachdenklich, könne man in einer Gruppe unsichtbar bleiben oder gar untergehen. Doch diese Gruppe habe sich um sie gekümmert. Und sie habe viel profitiert. Nicht nur als Forscherin, sondern

forschung“

irem gül sancak, portrait von paula lanfranconi

auch als Mensch: „Ich habe gelernt, Grenzen zu setzen, ohne andere zu verletzen.“

Das Schwierigste in ihrem Zürcher Alltag? Irems Antwort kommt rasch: „Die Trennung von der Familie.“ Plötzlich allein zu sein mit zwei kleinen Kindern, in einer unbekannten Stadt, einer fremden Kultur. Dazu das Gefühl, sich wie eine Rabentochter zu verhalten. Doch schon bald, sagt Irem, habe sich etwas in ihr verändert: „Ich merkte, dass mich das Leben ohne Verpflichtungen gegenüber der Grossfamilie freier macht.“ Auch ihr Blick auf ihre Karriere, ihr Leben und ihre Töchter sei heute anders. Während sie sich früher nicht habe vorstellen können, ihre Kinder im Ausland studieren zu lassen, wisse sie jetzt: „Ich muss ihnen Flügel geben. Sie sollen die Chance haben, überall auf der Welt zu leben.“

Doch wie bringt sie in Zürich Kinder und Arbeit unter einen Hut? Kein Problem, meint Irem. Wenn sie am Abend nach Hause komme, vergesse sie den beruflichen Stress: „Wir spielen zusammen, und die Kinder laden meine Batterien wieder auf.“ Sie hat die Mädchen so erzogen, dass sie um acht Uhr schlafen gehen. Danach kommt Irems Zeit. Bis Mitternacht liest sie Publikationen und schreibt Arbeiten. „Ohne diese Disziplin könnte ich unseren Alltag nicht meistern“, sagt sie.

Eigentlich wäre ihr Stipendium nach neun Monaten zu Ende gewesen. Doch ihre Mentorin, Brigitte von Rechenberg, beschaffte die nötigen Finanzen, und so konnte Irem zwei Jahre bleiben. Doch nun geht ihre Zürcher Zeit zu Ende. Während Irems Gefühle gemischt sind, freuen sich ihre Töchter darauf, wieder mit ihrem Vater zusammen zu sein. Meriç, die Ältere, spricht schon gut Deutsch. Und das soll so bleiben. Zuhause werden beide Mädchen eine deutschsprachige Schule besuchen, deren Matura international anerkannt ist.

Irem fühlt sich verpflichtet, das in Zürich Gelernte in Ankara weiter zugeben. Sie will sich neben ihrer Arbeit als Veterinärchirurgin auf einem Spezialgebiet qualifizieren und dann Studierende ausbilden. Eine Spezialisierung wie bei einem Europäischen College existiert indes an türkischen Universitäten noch nicht. Im Sinne der Nachhaltigkeit werden deshalb die MSRU und die Fakultät der Universität Ankara versuchen, ein Programm zu erarbeiten, welches es Irem erlaubt, in vier Jahren solch ein international anerkanntes Diplom zu erwerben.

Was wird Irem nach ihrer Rückkehr am meisten vermissen? „Alles!“, antwortet sie, fast ein wenig überschwänglich. Natur und Berge, die saubere Luft, das freie Atmen. Ihre Gruppe. Und Brigitte natürlich, ihre Chefin, die ihr zum Vorbild geworden sei. Mit ihr habe sie „tief durchgeatmet“. Und gelernt, gelassener zu werden, als Frau und als Forscherin, denn der Weg sei wichtiger als das Ziel. „Das Wasser“, sagt Irem beim Abschied, „wird seinen Weg finden. Immer.“

"i have been desperate to do

Irem Gül Sancak belongs to the first scholarship holders at the CABMM. Her residence in Zurich changed her view of her career as well as of her life in general.

This morning, as always, she took her seven-year-old daughter Meriç to the school day-care and afterwards her two-year-old daughter Defne to the animal hospital nursery. This type of morning procedure, the slim woman with the expressive, grey eyes says, needs a lot of time, as her younger daughter tends to copy exactly what the older one does. "If I succeed to get the older one ready in time, the problem is solved" she says and smiles.

In the meantime, it is a quarter past eight. Irem Gül Sancak takes a cup of coffee in the cafeteria of the animal hospital and proceeds afterwards to the cell culture of the CABMM. The 38-year-old woman works as a research assistant in the Musculoskeletal Research Unit (MSRU). She is trying to produce a replacement for cartilage using stem cells. At the moment, she explains, she is investigating the cells *in vitro*: "It looks good."

Irem Gül Sancak has come a long way. She studied veterinary medicine in Ankara and subsequently, worked for four years in a veterinary practice for small animals in the city centre. She cares about animals and wants them to suffer as little as possible. But the work in the small animal practice was simple routine. Boring. "I have been desperate do to research." After doing her PhD at the University of Ankara working on the use of stem cells in ophthalmology, she applied for a short-term stay at the Department of Ophthalmology at the Vetsuisse Faculty of the University of Zurich. She was impressed by the modern labs and particularly by the teamwork and the good networking of the researchers.

After her return to Ankara, "Zurich would have run in her blood", Irem says in her flowery language. Her husband, also a veterinarian, supported her plans. A very rare, lucky situation. Thus, she applied for a research scholarship at the Swiss State Secretariat for Education, Research and Innovation. And was accepted. "A woman, from Turkey? Welcome!", her future boss and co-founder of the CABMM, Brigitte von Rechenberg, said.

But before Irem could take off for Zurich, a few unexpected obstacles had to be overcome. After she applied for the scholarship, the young woman realised that she was pregnant: Defne, her second daughter, was born a few weeks before her departure to Switzerland. A scholarship holder with children, that wasn't programmed for by the Swiss authorities. Her heart pounding, Irem remembers, she made a phone call to Zurich. But Brigitte von Rechenberg contacted the migration office without further ado and the problem was solved. She would have never experienced such support before, the young mother says: "It was so emotional and a turning point in my career."

She was also actively supported by her research group. As a newcomer, she says thoughtfully, one could stay invisible in a group, or even disappear. But this group has really taken care of her. And she has benefited a lot. Not only as a researcher, but also as a human being: "I learned to set boundaries without hurting anybody."

What is the most difficult part of her daily life in Zurich? Irem answers very quickly: "The separation from my family." Suddenly to be alone with two little children in an unfamiliar city, with a different culture. Additionally, the feeling of acting as a bad daughter. But very soon, Irem says, something changed

research"

irem gül sancak, portrait by paula lanfranconi

within her: "I realized that the life without the duties of an extended family sets me free." Today, she has a different view on her career, her life and her daughters. While she could not have imagined before that her children may study abroad, she knows now: "I have to give them wings. They should have the chance to live anywhere in the world".

But how does she manage to juggle kids and career in Zurich? No problem, Irem answers. When she goes home in the evening, she forgets all the job-related stress: "We are playing together, and the kids are charging my batteries." The girls are educated in the way that they go to bed at eight o'clock. Then Irem has time for herself. Until midnight she is reading papers and writing reports. "I couldn't cope with our daily life without this discipline", she says.

Actually, her scholarship would have been finished after nine months. But due to the support of her mentor, Brigitte von Rechenberg, Irem was allowed to stay for two years. But now, her time in Zurich is coming close to an end. While Irem has mixed feelings, her daughters are looking forward to staying with their father again. Meriç, the older one, speaks quite well German, which she will continue. Back home, both girls will attend a German-language school, with an internationally accepted high school diploma.

Irem feels responsible to pass on all the things that she has learned in Zurich to the people back in Ankara. Besides her work as a veterinary surgeon, she wants to become a qualified specialist and subsequently, to train students. However, a specialization like the ones of a European College does not yet exist at Turkish universities. That is why, also in terms of sustainability, the MSRU and the respective faculty of the University of Ankara will try to set up a program allowing Irem to obtain such an internationally acknowledged diploma within four years.

What will Irem miss the most when being back in Turkey? "Everything", she answers almost a little exuberantly. The nature, the mountains, the fresh air, the free breathing. Her group. And of course her boss Brigitte, who has become her idol. With her, she learned to be more relaxed, as a woman and as a researcher, because the journey would be more important than the destination. "The water will find its own way", Irem says when leaving. "Always."

research reports

cabmm research platform

The CABMM Research Platform is a multidisciplinary organisation embedded within the Institute of Veterinary Biochemistry and Molecular Biology (IVBMB) 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 years 2012/2013, there have been a total of 7 research groups using the CABMM Research Platform:

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

2. **Cranio-Maxillofacial Surgery and Implantology Group**
   Group Leader: Brigitte v. Rechenberg

3. **Equine Research Group**
   Group Leader: Anton Fürst

4. **Interventional Work Research Group**
   Group Leaders: Daniel A. Rüfenacht, Brigitte v. Rechenberg

5. **Musculoskeletal Research Unit**
   Group Leader: Brigitte v. Rechenberg

6. **Spine Research Group***
   Group Leader: Karin Würtz-Kozak

7. **Tendon Repair Group**
   Group Leader: Anton Fürst

In this chapter, a short overview of the projects conducted within these groups is given. Moreover, we present the research of Prof. Dr. Dr. Michael O. Hottiger, CABMM co-founder, member of its Steering Committee and director of our host institute, namely the IVBMB. He gives some important insights into the molecular mechanisms governing inflammatory processes and describes his own research within this complex field.

*until April 2013

molecular tuning of inflammation

Michael O. Hottiger (Prof. Dr. med. vet. Dr. phil. II)

Group Members: Jeannette Abplanalp (PhD student), Anneli Andersson (PhD student), Giody Bartolomei (PhD student), Vera Bilan (PhD student), Monika Fey (research assistant), Florian Freimoser (research administrator), Mareike Hesse (PhD student), Friedrich Kunze (PhD student), Karolin Leger, (postdoc), Bin Ma (postdoc), Agnieszka Robaszkiewicz (postdoc), Florian Rosenthal (postdoc), Alan Valperti (postdoc)

Inflammation is a complex reaction of cells and tissues in response to pathogens, cell damage or harmful molecules

Inflammation is a general cell and tissue response elicited by the recognition of pathogen- or danger-associated molecular patterns (PAMPs and DAMPs, respectively), and whose intended function is to repair or regenerate cell and tissue damage. Innate immunity is the defensive frontline that coordinates an organism's response to injury and infection to initiate the transition to adaptive immunity, eradicate pathogens, and to facilitate healing. As such, the innate immune response plays a crucial role in the inflammatory response and for immunity in general. The molecular patterns recognized are generic structures of the cell surface of pathogens or other microorganisms, as well as intracellular molecules that are only released if cells are damaged or destroyed in an uncontrolled manner. In contrast to the innate immune response, adaptive immunity is a delayed, pathogen-specific reaction. Importantly, controlled or programmed cell death (apoptosis) does not lead to the release of intracellular molecules and therefore does not elicit an inflammatory response.

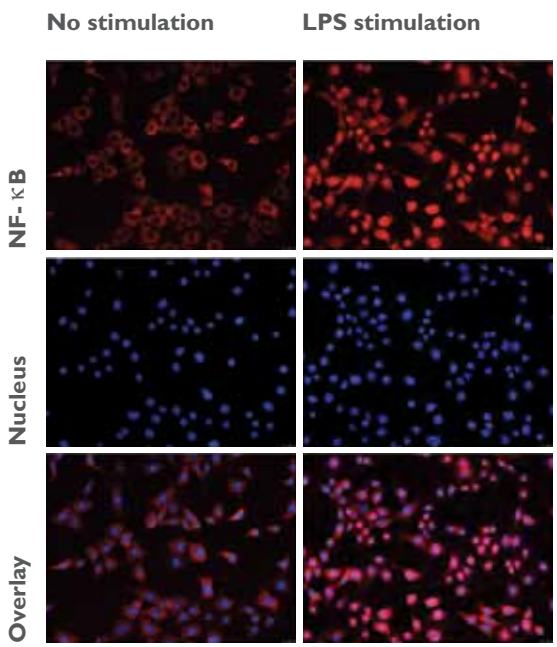
The regulation of inflammatory responses is crucial for the maintenance of cell integrity

Recently, it has been discovered that not only DAMPs or PAMPs, but also an excess of nutrients (e.g., in obesity or during excessive muscle training) can result in an inflammatory response in metabolic tissues and cells. Reactive oxygen species (ROS), formed by the redox reactions of aerobic metabolism in mitochondria, are involved in the pathogenesis of many diseases such as Alzheimer's disease, cardiovascular diseases, diabetes and neurodegenerative disorders and have been implicated in inflammation and aging. This type of non-infectious, sterile, chronic, low-grade inflammatory response has been termed metaflammation. Furthermore, dysregulation of the inflammatory response results in chronic inflammation, which too is involved in a plethora of medical conditions such as chronic infections, cardiovascular diseases, inflammatory neuropathies, neurodegenerative diseases or the development of cancer. While inflammatory responses promote and protect the integrity and healthy state of cells or tissues on the one hand, they can also lead to serious diseases on the other hand, if not properly controlled.

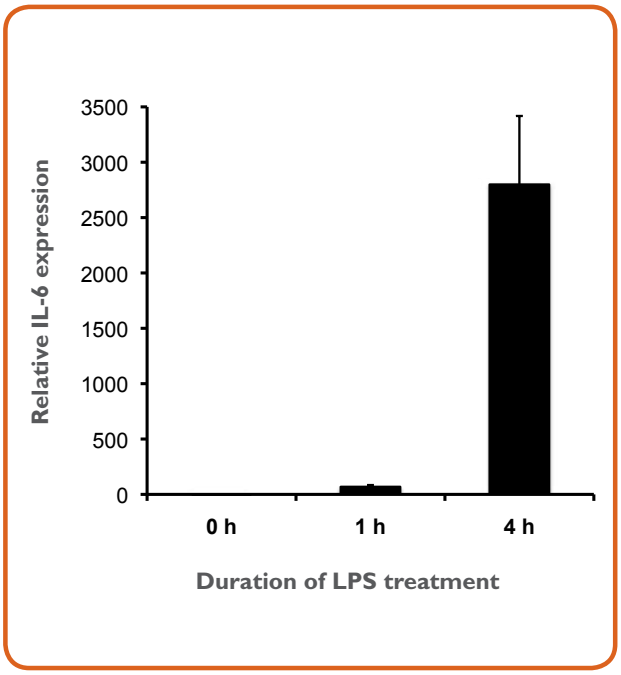
Inflammatory responses cause changes in the chromatin structure, and in gene expression and cellular function

Mounting of an inflammatory response alters gene expression and therefore drastically changes the amounts and nature of the proteins synthesized and thus present in a cell. An external inflammatory stimulus is translated into a response in the cell nucleus. One of the most important regulators of this response is the transcription factor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). In response to an inflammatory stimulus, NF-κB translocates from the cytoplasm to the nucleus, where it binds to the regulatory sequences of target genes and activates the transcription of these genes, which encode specific signalling molecules, so-called cytokines (or adipokines in obesity). Important cytokines are for example tumour necrosis factor alpha (TNF-α), interleukin 1 (IL-1) or interleukin 6 (IL-6). Remarkably, NF-κB is further stimulated by cytokines, resulting in a positive feedback loop that, when not tightly controlled, leads to a deleterious inflammatory response. Understanding the regulatory mechanism of NF-κB-dependent gene expression is thus biologically as well a medically highly relevant. It is becoming clear that NF-κB-mediated transcriptional activation is coordinated by the synergistic interaction of various cofactors and signaling

networks and by the regulation of the chromatin structure to allow the transcriptional regulation of specific genes. This is mainly achieved by modifying the proteins that interact with DNA and thereby establish the complex three-dimensional structure of chromatin. The most important DNA-interacting proteins of this kind are histones. DNA is wrapped around histone complexes and is thereby condensed and protected. In general, DNA stretches that are highly condensed are not transcribed, while genes in loosely condensed DNA segments are actively transcribed. Interestingly, inflammatory stimuli induce changes in the histone modifications, thereby altering the chromatin structure, which consequently leads to changes in gene expression. Histone modifications are therefore critical players in the orchestration of NF-κB function.



Stimulation of mouse (tumor) cells with the inflammatory bacterial cell wall component lipopolysaccharide (LPS) leads to translocation of NF-κB (in red, visualized by an antibody) from the cytoplasm to the nucleus. Nuclei (in blue) were visualized by staining with DAPI.
Die Stimulierung von Mäuse(Tumor)-Zellen mit dem entzündlichen bakteriellen Zellwandbestandteil Lipopolysaccharid (LPS) führt zu einer Verschiebung von NF-κB (in rot, mittels eines spezifischen Antikörpers gefärbt) vom Zytoplasma in den Zellkern. Zellkerne (in blau) wurden durch eine Färbung mit DAPI sichtbar gemacht.



LPS strongly induces the expression of the gene encoding for the cytokine interleukin 6 (IL-6) in mouse (tumor) cells. (0 h value = 1)
LPS induziert in Mäuse(Tumor)-Zellen eine starke Expression des Gens, welches für das Zytokin Interleukin 6 (IL-6) kodiert. (0 h Wert = 1)

ADP-ribosylation regulates innate immunity

An important modification of histones, but also of other proteins, is ADP-ribosylation, which is intensely studied in our group. The enzymes that perform this reaction are the ADP-ribosyltransferases (ARTs). They use nicotinamide dinucleotide (NAD^+) as a substrate to mark specific sites on various proteins by attaching an ADP-ribose group (i.e., writer function). ADP-ribose consists of an adenine group (a nucleotide) that is linked via two phosphate groups to a particular sugar molecule (a ribose). Some ARTs are also able to extend existing ADP-ribose modifications and thereby generate poly-ADP-ribose chains comprised of several dozen units attached to target

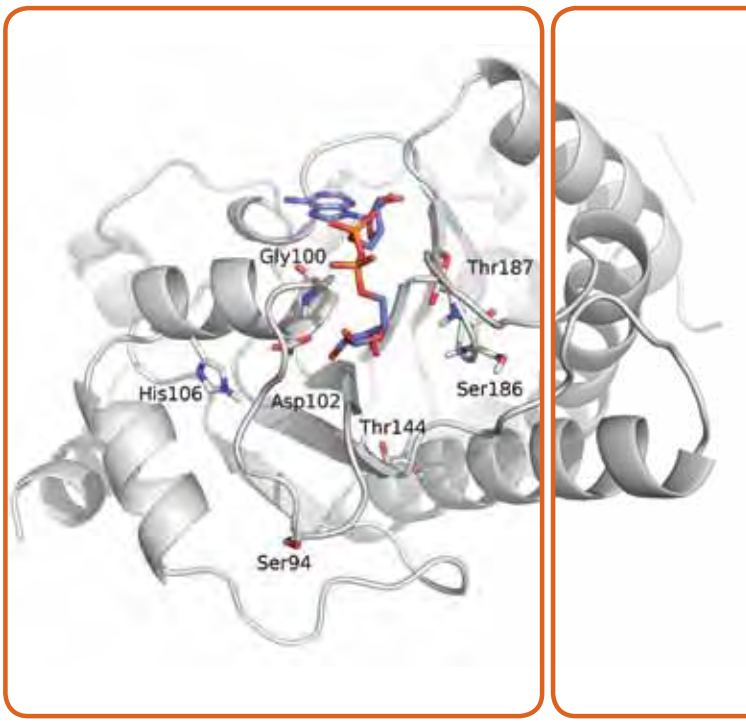
proteins. We distinguish two broad groups of ARTs in mammalian cells. Extracellular enzymes that resemble the mammalian C2/C3 toxins are called ARTCs. In contrast, ARTDs are intracellular ARTs with similarity to *diphtheria* toxins and play important functions during inflammation, stress responses as well as in many diseases. Of particular interest to our research, stimulation of cells with an inflammatory mediator leads to a strong increase in intracellular ADP-ribosylation. During the last 12 years, our research has revealed many new functions of ADP-ribosylation, in particular that mediated by ARTD1 (also known as PARP1) in NF-κB-dependent gene expression.

Interestingly, NAD^+ fulfils essential functions as an acceptor of electrons in primary energy metabolism (ATP generation in mitochondria) that are carried out by every cell. Due to this shared dependence on NAD^+, ADP-ribosylation is indirectly linked to the metabolic state of a cell.

The ADP-ribose modification alters the physicochemical properties of the acceptor proteins and thereby changes their functions, stability and interactions. For ADP-ribosylation to act as a regulator, the modification not only has to be synthesized in response to a specific stimulus, but also must be removed once the signalling function has been fulfilled. The proteins that remove ADP-ribose from modified proteins are not well characterized, but recent research from our group, as well as from other laboratories, has identified new important players with this function. The best-studied ADP-ribosylhydrolase activity has been ascribed to the enzyme poly-ADP-ribosylglycohydrolase (PARG). As the name implies, PARG degrades poly-ADP-ribose modifications, but it is not able to release the initial ADP-ribose unit attached to the modified protein. Depending on the modified amino acid, this activity is carried out by ADP-ribosylhydrolase (e. g. ARH1 for arginines) and the more recently described macrodomain-containing proteins (e.g., MacroD1 and MacroD2 for aspartic and glutamic acid). Interestingly, ARH1 or macrodomain-containing proteins are not able to release ADP-ribose from all modified proteins, suggesting that these enzymes are specific for particular modification types and that possibly other erasers, for example for modified lysine residues, exist.

Exact molecular details of ADP-ribosylation are still unknown

The important finding that ADP-ribosylhydrolases (e.g., PARG, ARHs, MacroD proteins) can only remove a fraction of all ADP-ribose modifications highlights the importance of the nature of the modified protein and the specific ADP-ribose acceptor groups. The identification of all ADP-ribosylated proteins of the cell and, most importantly, of the specific amino acid that is modified is therefore essential for the understanding the molecular details of the turnover, function and signalling of cellular ADP-ribosylation during inflammation. Unfortunately, specific antibodies that recognize mono-ADP-ribose modifications do not exist and the localization of an ADP-ribosylated amino acid has been challenging. This specific field of research has therefore been dominated by the development of new affinity purification protocols and mass spectrometry approaches. Our research group is at the



Structural model of MacroD2 with mutated residues.
Strukturmodel von MacroD2 mit Aminosäuremutationen.

forefront of these developments and has succeeded, for the first time, to identify specific ADP-ribosylated lysine residues in histone proteins in cells. However, many other amino acids have also been suggested as ADP-ribose acceptor sites and it is completely unknown which ARTD is responsible for generating which modification. One of our main goals is to resolve these questions and to establish reliable protocols to isolate, enrich and identify the entity of all ADP-ribosylated proteins in cells and tissues during inflammation.

Research projects in our laboratory

Based on our work carried out so far, we hypothesize that ADP-ribosylation affects NF-κB-dependent gene expression either directly by modifying histones or indirectly by altering histone-modifying enzymes. Following this hypothesis, the identification of nuclear protein ADP-ribosylation after inflammatory, metaflammatory, or oxidative stress signalling is one of our main areas of research. We aim to identify all ADP-ribosylated proteins in cells exposed to inflammatory stimuli and characterize the already identified histones and histone-modifying enzymes in regard to their involvement in NF-κB-dependent gene expression. To correlate distinct ARTD proteins with specific ADP-ribose modifications, we are performing extensive analyses with cells lacking a particular ARTD member, as well as with purified ARTD proteins *in vitro*. Furthermore, we include clinically well-tolerated PARP inhibitors in our studies, which have been developed as anticancer drugs and inhibit cellular ADP-ribosylation. Interestingly, these inhibitors have been shown to significantly reduce *Helicobacter*-induced neoplasia, heart and brain stroke areas, or the generation of atherosclerotic plaques. However, at the molecular level the action of PARP inhibitors is not well understood. Our research therefore aims to correlate the presence and absence of specific ADP-ribose modifications to the activity of different PARP inhibitors.

An important aspect of our work is the development of new tools for analysing ADP-ribosylated proteins and the identification of genes regulated by ADP-ribosylation. In particular, we plan to use our technological innovations to define ADP-ribosyl modifications as specific biomarkers for stress conditions and employ our analytical tools to study the sensitivity of inflammatory and cancer cells to clinically used PARP inhibitors. The goal of these projects is to employ our newly developed tools to identify all ADP-ribosylated proteins in PARP inhibitor-sensitive and -insensitive cell lines and to identify important target proteins. This will help to further develop PARP inhibitors for cancer therapy.

Conclusions

Innate immunity-related health care costs are estimated to exceed 10 billion USD annually in the United States. The global pain management market was worth 46.4 billion USD in 2007 and is expected to reach 57.2 billion USD by 2014. Understanding the global innate immunity signalling network is thus of large economic and medical importance.

As described above, the transcription factor NF-κB is an important regulator of the innate immune response. It is becoming clear that NF-κB-mediated transcriptional activation is coordinated by the synergistic interaction of various cofactors and signalling networks. Histone modifications are being recognised as critical players in the orchestration of NF-κB functions. Therefore, an important goal of our research is to analyse the intricate, reciprocal regulation of histone modification and the NF-κB pathway. The long-term goal of these studies is to understand the effect of nuclear ADP-ribosylation on the NF-κB enhanceosome network involved in acute or chronic inflammation and the subsequent progression to disease (e.g., cancer). These results will also consolidate the importance of NF-κB during inflammatory, metaflammatory and oxidative stress signalling and may thereby generate new insights concerning the onset and development of diseases and disorders which will allow the development of better diagnostic, prognostic and therapeutic tools.

molekulare regulation der entzündung

Michael O. Hottiger (Prof. Dr. med. vet. Dr. phil. II)

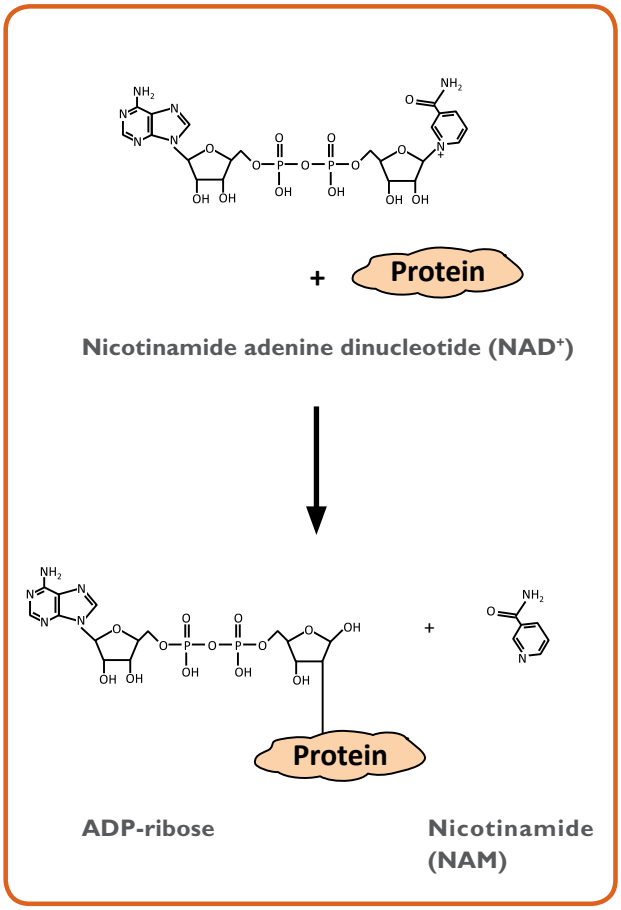
Gruppenmitglieder: Jeannette Abplanalp (PhD student), Anneli Andersson (PhD student), Giody Bartolomei (PhD student), Vera Bilan (PhD student), Monika Fey (research assistant), Florian Freimoser (research administrator), Mareike Hesse (PhD student), Friedrich Kunze (PhD student), Karolin Leger, (postdoc), Bin Ma (postdoc), Agnieszka Robaszkiewicz (postdoc), Florian Rosenthal (postdoc), Alan Valperti (postdoc)

Entzündungen sind komplexe Reaktionen von Zellen und Geweben, die durch Pathogene, Zellschäden und schädliche Moleküle ausgelöst werden

Entzündungen sind eine generelle Zell- und Gewebsantwort, die durch den Kontakt mit Pathogen- oder Gefahr-assoziierten molekularen Mustern (PAMPs und DAMPs) ausgelöst werden und schlussendlich zur Reparatur und Regenerierung von Zell- und Gewebsschäden führen. Die angeborene Immunabwehr ist die erste Verteidigungslinie, welche die Antwort eines Organismus koordiniert, so dass die adaptive Immunabwehr eingeleitet wird, Pathogene zerstört werden und die Heilung erleichtert wird. Die angeborene Immunantwort ist somit ein entscheidendes Element der Entzündungsantwort. Die molekularen Muster, die erkannt werden, sind Oberflächenproteine von Pathogenen oder Mikroorganismen sowie auch intrazelluläre Moleküle, die freigesetzt werden, wenn Zellen geschädigt oder unkontrolliert zerstört werden. Im Gegensatz zur angeborenen Immunabwehr stellt die adaptive Immunabwehr eine pathogen-spezifische Reaktion dar. Wichtig ist auch, dass der kontrollierte Zelltod (Apoptose) nicht zur Freisetzung intrazellulärer Moleküle und damit nicht zu einer Entzündungsreaktion führt.

Die Regulation der Entzündungsantwort ist für den Erhalt der Zellintegrität entscheidend

Kürzlich hat man festgestellt, dass nicht nur DAMPs und PAMPs, sondern auch ein Überschuss an Nährstoffen (z. B. bei Fettleibigkeit [Adipositas] oder übermässigem Muskeltraining) zu Entzündungsreaktionen in metabolischen Geweben und Zellen führen können. Reaktive Sauerstoffspezies (ROS), die während Redox-Reaktionen des aeroben Metabolismus in Mitochondrien gebildet werden, sind in der Pathogenese vieler Krankheiten wie z. B. Alzheimer, Herzerkrankungen, Diabetes oder neurodegenerativen Erkrankungen involviert und spielen auch bei Entzündungen und dem Alterungsprozess eine Rolle. Diese Art nicht-infektiöser, steriler, chronischer, niedergradiger Entzündungsantworten wird als Meta-Entzündung (metaflammation) bezeichnet. Auch eine Fehlregulation der Entzündungsantwort, welche chronische



ADP-ribosyltransferases attach the ADP-ribose moiety of NAD⁺ to acceptor proteins and thereby release nicotinamide.
ADP-Ribosyltransferasen übertragen die ADP-Ribose-Gruppe von NAD⁺ auf Akzeptorproteine und setzen dabei Nicotinamid frei.

Entzündungserscheinungen zur Folge hat, ist bei einer Vielzahl von Erkrankungen oder bei der Entstehung von Krebs von Bedeutung. Entzündungsreaktionen schützen daher nicht nur die Integrität und den gesunden Zustand von Zellen und Geweben, sondern führen auch zu schwerwiegenden Krankheitsformen, wenn sie nicht richtig reguliert werden.

Entzündungsantworten bewirken Änderungen der Chromatin-Struktur, Genexpression und Zellfunktion

Das Auslösen einer Entzündungsantwort beeinflusst die Genexpression und führt zu drastischen Veränderungen der Anzahl und Art der Proteine, die in einer Zelle hergestellt werden und somit vorhanden sind. Der externe Auslöser der Entzündungsreaktion wird somit in eine Antwort im Zellkern übersetzt. Einer der wichtigsten Regulatoren dieser Antwort ist der Transkriptionsfaktor NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Als Antwort auf einen entzündungsauslösenden Reiz wird NF-κB vom Zytoplasma in den Nukleus transportiert und bindet dort regulatorische Sequenzen von Zielgenen, wodurch die Transkription dieser Gene, welche für spezifische Signalmoleküle, sogenannte Zytokine (oder Adipokine in Adipositas), kodieren, aktiviert wird. Wichtige Zytokine sind beispielsweise der Tumornekrose-Faktor alpha (TNF-α), Interleukin 1 (IL-1) oder Interleukin 6 (IL-6). Erstaunlicherweise wird NF-κB durch Zytokine selbst wieder stimuliert, was zu einer positiven Rückkopplung und bei fehlender Regulation zu einer unkontrollierten Immunantwort führen kann. Das Verständnis der Regulationsmechanismen NF-κB-abhängiger Genexpression ist somit sowohl biologisch als auch medizinisch höchst relevant. Es zeigt sich, dass die NF-κB-abhängige Aktivierung der Transkription durch synergistische Interaktionen verschiedener Kofaktoren und Signalnetzwerke koordiniert wird und dabei durch die Regulation der Chromatin-Struktur die transkriptionelle Regulation spezifischer Gene ermöglicht. Dies wird in erster Linie durch Proteine erreicht, die mit DNS interagieren und dadurch deren komplexe dreidimensionale Chromatin-Struktur etablieren. Die wichtigsten derartigen Proteine sind Histone. Die DNS ist um Histonkomplexe gewickelt und wird dadurch stark komprimiert und geschützt. Generell werden DNS-Abschnitte, die sehr stark kondensiert sind, nicht transkribiert, wohingegen weniger stark komprimierte Segmente aktiv transkribiert werden. Interessanterweise induzieren Entzündungsauslöser Veränderungen in den Modifikationen von Histonen, wodurch die Chromatin-Struktur und schlussendlich die Genexpression verändert wird. Histonmodifikationen sind deshalb Schlüsselelemente für die Etablierung und Integration der verschiedenen NF-κB Funktionen.

Separation of poly-ADP-ribose polymers
Auftrennung von Poly-ADP-Ribose-Polymeren

ADP-Ribosylierung reguliert die angeborene Immunantwort

Eine wichtige Modifikation von Histonen, aber auch von anderen Proteinen, ist die ADP-Ribosylierung, welche in unserer Arbeitsgruppe intensiv und seit langem untersucht wird. Die Enzyme, welche diese Reaktion durchführen, sind ADP-Ribosyltransferasen (ARTs). Diese Eiweisse benutzen Nicotinamidadenindinukleotid (NAD^+) als Substrat um spezifische Stellen verschiedener Proteine durch das Anheften einer ADP-Ribose-Gruppe zu modifizieren („Schreibfunktion"). ADP-Ribose besteht aus einer Adenin-Gruppe (einem Nukleotid), welche durch zwei Phosphat-Gruppen mit einem bestimmten Zuckermolekül (einer Ribose) verknüpft ist. Manche ARTs sind auch in der Lage, existierende ADP-Ribose-Modifikationen zu verlängern und dadurch poly-ADP-Riboseketten zu bilden, die aus einigen Dutzend Einheiten bestehen können und auch an Zielproteine angeheftet sind. In Säugetieren unterscheiden wir zwei Hauptgruppen von ARTs. Extrazelluläre Enzyme, die C2/C3 Toxinen gleichen, werden als ARTCs bezeichnet. Im Gegensatz hierzu sind ARTDs intrazelluläre ARTs, die dem Diphtherietoxin ähnlich sind und wichtige

Rollen während der Entzündungsreaktion, Stressantwort und in vielen Krankheiten spielen. Die Stimulierung von Zellen mit einem Entzündungsauslöser führt zu einer stark erhöhten intrazellulären ADP-Ribosylierung. Während der letzten 12 Jahre haben wir durch unsere Forschung viele neue Funktionen der ADP-Ribosylierung aufgedeckt und besonders die Aktivität von ARTD1 (ehemals PARP1) für die NF-κB-abhängige Genexpression genauestens untersucht.

Neben seiner Funktion als Substrat für die ADP-Ribosylierung, ist NAD^+ ein essentieller Elektronenakzeptor im primären Energiehaushalt jeder Zelle (ATP Herstellung in Mitochondrien). Aufgrund dieser Abhängigkeit von NAD^+ ist die ADP-Ribosylierung somit indirekt mit dem metabolischen Zustand der Zellen verknüpft.

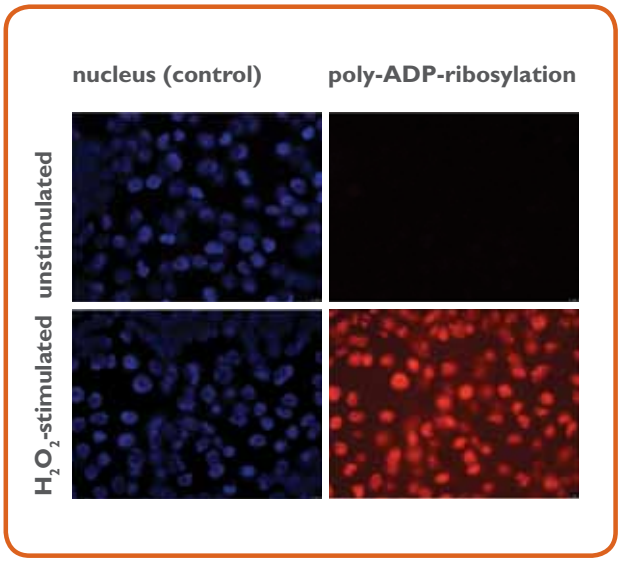
Das Anheften der ADP-Ribose-Moleküle verändert die physikalisch-chemischen Eigenschaften der modifizierten Proteine und beeinflusst dadurch deren Funktionen, Stabilität und Interaktionen. Damit ADP-Ribosylierung als Regulator wirken kann, ist es aber nicht nur nötig, die Modifikation aufgrund spezifischer Reize zu synthetisieren, sondern sie muss auch wieder entfernt werden, nachdem die Signalfunktion erfüllt ist. Proteine, die ADP-Ribose von modifizierten Proteinen entfernen, waren bisher praktisch unbekannt, aber neueste Arbeiten in unserer Gruppe und in anderen Laboratorien haben neue, wichtige Proteine mit dieser Funktion entdeckt. Die am besten beschriebene ADP-Ribosylhydrolase-Aktivität wird dem Enzym poly-ADP-Ribosylglycohydrolase (PARG) zugeschrieben. Wie der Name impliziert, baut PARG Poly-ADP-Ribosemodifikationen ab, ist aber nicht in der Lage die erste ADP-Riboseeinheit, welche am Protein angeknüpft ist, zu entfernen. Je nach modifizierter Aminosäure wird diese Reaktion durch die ADP-Ribosylhydrolase 1 (ARH1) oder die kürzlich beschriebenen Makrodomänen-Proteine (z. B. MacroD1 oder MacroD2) ausgeführt. Interessanterweise können diese Proteine nicht alle ADP-Ribosemodifikationen entfernen, was impliziert, dass diese Enzyme für bestimmte Modifikationen spezifisch sind und dass möglicherweise weitere Hydrolasen existieren, welche die Modifikationen von Aminosäuren, wie z. B. von Lysinen, entfernen können.

Die molekularen Mechanismen der ADP-Ribosylierung sind noch unbekannt

Die wichtige Entdeckung, dass ADP-Ribosylhydrolasen (z. B. PARG, ARHs, MacroD Proteine) nur einen Teil aller ADP-Ribose-Modifikationen entfernen können, illustriert die Wichtigkeit der Identität des modifizierten Proteins und des spezifischen ADP-Ribose-Akzeptors. Das Identifizieren aller ADP-ribosylierter Proteine einer Zelle, und vor allem der modifizierten Aminosäure, ist somit unabdingbar, um den Metabolismus und die Signalfunktion der zellulären ADP-Ribosylierung während der Entzündungsantwort auf molekularer Ebene zu verstehen. Leider gibt es keine spezifischen Antikörper, die mono-ADP-Ribose-Modifikationen detektieren könnten und das Lokalisieren ADP-ribosylierter Aminosäuren war bis anhin eine grosse Herausforderung. Dieses Forschungsgebiet wurde und wird immer noch sehr stark von der Entwicklung neuer Anreicherungsmethoden und Massenspektrometrieverfahren dominiert. Unsere Forschungsgruppe hat es dabei als Erste geschafft, spezifische, ADP-ribosylierte Lysine in Histonen aus Zellextrakten zu identifizieren. Es wurden bisher allerdings auch andere Aminosäuren als ADP-Ribose Akzeptoren bestimmt und es ist nach wie vor unbekannt, welche dieser Modifikationen durch welches ARTD Enzym synthetisiert wird. Eines unserer wichtigsten Ziele ist es, diese Fragen zu beantworten und verlässliche Protokolle für die Isolierung und Identifizierung aller ADP-ribosylierter Proteine in Zellen und Geweben während der Entzündungsreaktion zu etablieren.

Forschungsprojekte in unserer Arbeitsgruppe

Aufgrund unserer früheren Arbeiten erwarten wir, dass ADP-Ribosylierung die Expression von NF-κB-Genen entweder direkt durch Histonmodifikationen oder indirekt durch histonmodifizierende Proteine beeinflusst. Entsprechend dieser Hypothese ist die Identifikation ADP-ribosylierter Proteine nach Entzündungstress sowie metaflammatorischen oder oxidativen Stimuli eines unserer Hauptprojekte. Wir sind daran, alle ADP-ribosylierten Proteine in Zellen zu identifizieren, welche Entzündungsstimuli ausgesetzt waren, und charakterisieren die dabei neu entdeckten Histone und



Stimulation of human cells with the stress factor hydrogen peroxide leads to massive induction of poly-ADP-ribosylation (in red, visualized by staining with a specific antibody). Nuclei (in blue) were visualized by staining with DAPI.

Die Stimulierung von menschlichen Zellen mit dem Stressfaktor Wasserstoffperoxid führt zu einer massiv erhöhten Bildung von poly-ADP-Ribose (in rot, mittels eines spezifischen Antikörpers gefärbt). Zellkerne (in blau) wurden durch eine Färbung mit DAPI sichtbar gemacht.

histonmodifizierenden Enzyme bezüglich ihrer Rolle für die NF-κB-abhängige Genexpression. Um spezifischen Modifikationen bestimmte ARTD-Proteine zuzuordnen, analysieren wir Zellen, denen jeweils ein ARTD-Protein fehlt. Diese Experimente werden durch biochemische *in vitro* Studien ergänzt. Weiter verwenden wir klinisch gut tolerierte PARP-Inhibitoren in unseren Studien, weil diese Stoffe als Tumor-Medikamente entwickelt worden sind, welche die zelluläre ADP-Ribosylierung hemmen. Interessanterweise reduzieren diese Inhibitoren auch durch *Helicobacter*-induzierte Neoplasien und zeigen bei Herz- oder Hirn-Infarkten sowie arteriosklerotischen Ablagerungen eine positive Wirkung. Allerdings ist die Wirkung von PARP-Inhibitoren auf molekularer Ebene nur sehr schlecht verstanden. Unsere Forschung hat deshalb auch zum Ziel, die An- oder Abwesenheit spezifischer ADP-Ribosemodifikationen mit der Aktivität verschiedener PARP-Inhibitoren in Verbindung zu setzen. Ein wichtiger Aspekt unserer Arbeit ist das Entwickeln neuer Werkzeuge für die Analyse ADP-ribosylierter Proteine und die Identifizierung derjenigen Gene, die durch ADP-Ribosylierung reguliert werden. Insbesondere möchten wir unsere technologischen Innovationen dazu verwenden, um ADP-Ribosylmodifiationen als spezifische Marker für Stressbedingungen zu definieren und um die Sensitivität von Krebs- und Entzündungszellen gegenüber PARP-Inhibitoren zu prüfen. Das Ziel dieser Projekte ist es, die Gesamtheit der ADP-ribosylierten Proteine in PARP-Inhibitor-sensitiven und nicht-sensitiven Zelllinien mit den neuentwickelten Methoden zu bestimmen, um dadurch Proteine zu identifizieren, welche den individualisierten Einsatz von PARP-Inhibitoren in der Krebs-Therapien ermöglichen sollen.

Schlussfolgerungen

Laut Schätzungen übersteigen in den USA die Gesundheitskosten, die mit der angeborenen Immunantwort in Verbindung stehen, 10 Mrd. USD. Der globale Markt für Schmerzmittel umfasste im Jahr 2007 etwa 46.4 Mrd. USD und wird im Jahr 2014 auf über 57 Mrd. USD steigen. Es ist deshalb von grösster ökonomischer wie auch medizinischer Wichtigkeit, die globalen Signalnetzwerke der zellulären, angeborenen Immunantwort zu verstehen.

Wie oben beschrieben stellt der Transkriptionsfaktor NF-κB einen wichtigen Regulator der angeborenen Immunantwort dar. Es hat sich klar gezeigt, dass die NF-κB-abhängige Aktivierung der Transkription durch die synergistische Interaktion verschiedener Kofaktoren und Signalnetzwerke koordiniert wird. Histonmodifikationen werden als besonders kritische Elemente für diese integrative Regulation der NF-κB Funktionen betrachtet. Es ist deshalb ein wichtiges Ziel unserer Forschung, die komplexe und gegenseitige Regulierung von Histonmodifikationen und des NF-κB-Signalwegs zu analysieren. Das langfristige Ziel dieser Studien ist es, den Effekt nukleärer ADP-Ribosylierung auf das NF-κB-Kofaktor-Netzwerk, welches zu akuten oder chronischen Entzündungserkrankungen führt und als Auslöser für Erkrankungen (z. B. Krebs) gilt, zu verstehen. Diese Resultate können somit auch neue Erkenntnisse bezüglich des Ausbruchs und der Entwicklung von Krankheiten geben und werden es ermöglichen, bessere diagnostische, prognostische und therapeutische Anwendungen zu finden.

overview cabmm research platform

1. Bone and Stem Cell Research Group

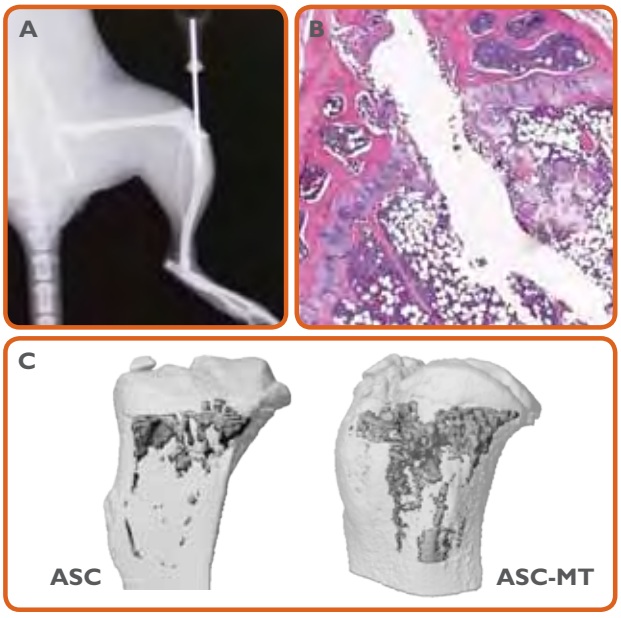
Group leader: PD Dr. Peter J. Richards (PhD)
Group members: Dr. Cristina López-Fagundo (PhD), Dr. A. Nicki Tiaden (PhD), Gregor Bahrenberg (PhD student), Stephan Glanz (PhD student), Ali Mirsaidi (PhD student), Marina Klawitter (research assistant)

The main interest of the Bone and Stem Cell Research Group (BSRG) is related to musculoskeletal biology and disease (e.g., bone, cartilage, tendon, and 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 aims therefore is to characterize the functional role played by MSCs in the development of age-related bone loss through the use of molecular, biochemical and histological techniques. We are currently utilizing stem cells isolated from both human patients and experimental models and have developed the necessary techniques with which to successfully harvest and differentiate stem cells from various tissue sources.

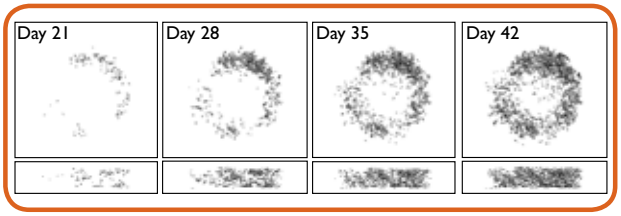
In the reporting period, the following research projects were performed by the BSRG on the CABMM research platform:

Therapeutic potential of adipose-derived stromal cells (ASCs) for the treatment of senile osteoporosis
Ali Mirsaidi (PhD student)
CABMM collaborators: Prof. Dr. med. Michael Blauth, Prof. Dr. sc. Ralph Müller (Dr. med. vet. Gisela Kuhn)

The application of ASCs as a cell-based therapy for the purpose of enhancing orthopaedic tissue repair and regeneration is at an early stage of research and as such, no studies have yet been carried out to evaluate the possible therapeutic benefits of treating osteoporotic bone with autologous ASCs. In pilot experiments we have demonstrated that ASCs isolated from senile osteoporotic mice retain their capacity for osteogenic differentiation as compared to age-matched non-osteoporotic control mice. This was in direct contrast to the impaired osteogenic status of MSCs isolated from the bone marrow of the same osteoporotic animal. This study therefore sets out to determine whether transplanted ASCs have the capacity to promote new bone formation and restore trabecular structure in an osteoporotic mouse model. Nascent and pre-differentiated ASCs and ASC-microtissues will be injected directly into the bone marrow of SAMP6 mice and their effects on bone formation and quality evaluated based on molecular and radiological analyses.



(A) Digital radiograph illustrating an intratibial injection into the left proximal tibia of a SAMP6 mouse. **(B)** Representative hematoxylin & eosin stained paraffin wax section of decalcified tibia 1 day after injection. **(C)** Representative 3-D micro-CT images of control tibia (ASC) and adipose-derived stromal cell microtissue (ASC-MT)-treated tibia.



Representative micro-CT images of silk fibron scaffolds seeded with ASCs (1×10^6) at selected time points following incubation in osteogenic induction medium. Top panel: transverse cross section; bottom panel: longitudinal cross section.

Role of serine protease HtrA1 in the regulation of multipotent stromal cell (MSC) differentiation and its implications for bone disease

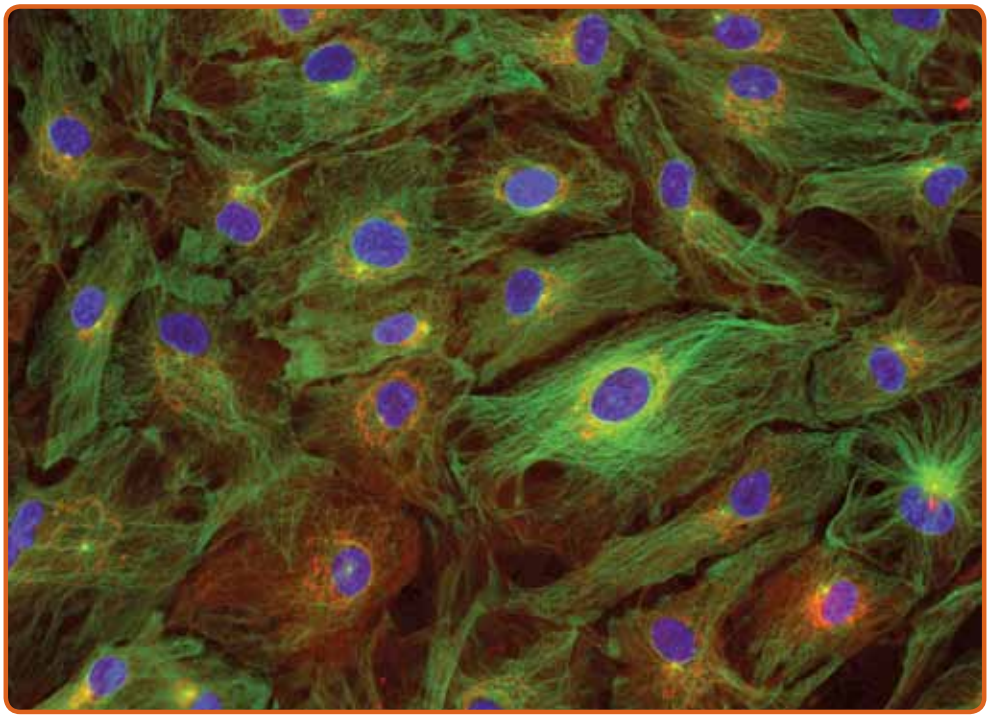
Dr. A. Nicki Tiaden (PhD), Gregor Bahrenberg (PhD student), Stephan Glanz (PhD student)

Our recent studies have demonstrated that HtrA1 (High Temperature Requirement protease A1) is expressed and secreted by human bone marrow stromal cells (hBMSCs) and mouse adipose-derived stromal cells (mASCs) undergoing osteogenic differentiation. Furthermore, HtrA1 was shown to impart a positive influence on both the early and late phases of osteogenic differentiation in these cells. This is in direct contrast to earlier studies using mouse 2T3 osteoblasts where HtrA1 was actually identified as having a negative role on osteogenic differentiation. Clearly therefore, a more intensive investigation into the mechanisms governing the effects of HtrA1 on osteogenic progenitor cells are needed. The overall aim of this project is therefore to discern a role for HtrA1 in the regulation of MSC differentiation and development of bone disease.

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

Dr. A. Nicki Tiaden (PhD)
CABMM collaborator: Prof. Dr. med. Michael Blauth
(Dr. med. Richard A. Lindtner)

Bisphosphonates are a class of synthetic compounds structurally related to pyrophosphate, and are endogenous regulators of calcium metabolism. They are extensively used in the treatment of osteoporosis, where their primary mode of action is considered to be inhibition of bone resorption through alterations in osteoclast activity. However, no studies have yet sought to determine whether bisphosphonates also have the capacity to alter differentiation profiles in BMSCs isolated from osteoporotic patients. Certainly, a more in-depth analysis of the effects of bisphosphonates on diseased stem cells would help to better define their exact mechanism of action in osteoporosis and related bone disorders. The main aims of this study are therefore to characterize the differentiation potential of human BMSCs from non-osteoporotic patients and osteoporotic patients either receiving or not receiving bisphosphonate therapy, and to evaluate the effects of bisphosphonates on the differentiation potential of BMSCs isolated from osteoporotic patients.



Cell morphology of multipotent stromal cells (MSCs) during adipogenesis. Immunofluorescent staining of cytoskeleton protein α-Tubulin (green), DAPI-staining of nuclei (blue) and HtrA1 (red).

Role of serine protease HtrA1 in spinal disc degeneration

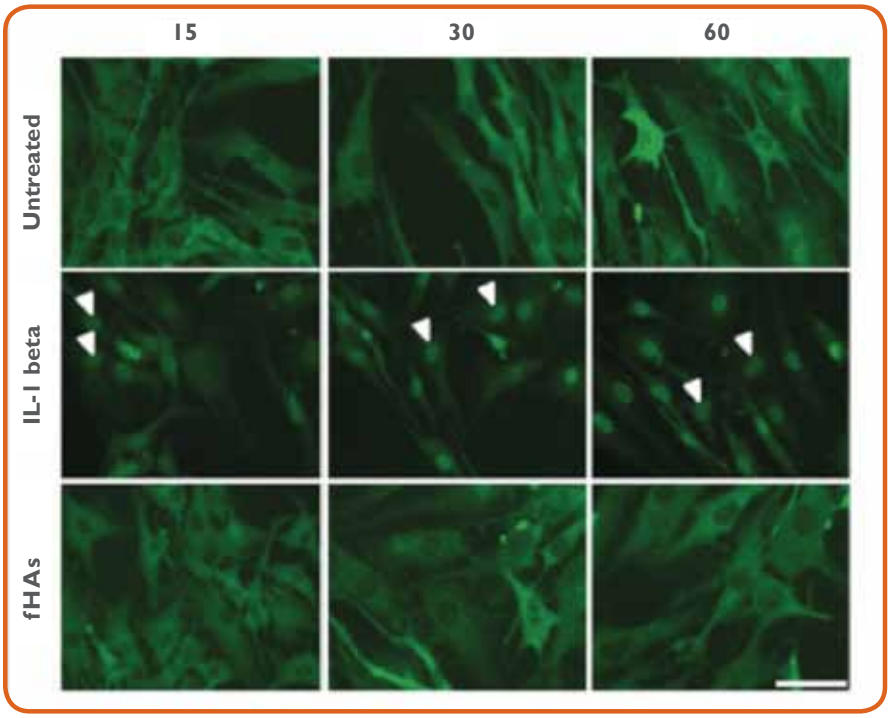
Dr. A. Nicki Tiaden (PhD), Marina Klawitter (research assitant) (in collaboration with the Spine Research Group)

There is now a growing body of evidence to suggest that HtrA1 plays a destructive role in musculoskeletal disease through its capacity to degrade a variety of extracellular matrix (ECM) proteins. Moreover, fibronectin fragments generated following ECM digestion by HtrA1 have been shown to upregulate matrix metalloproteinase (MMP) expression in synovial fibroblasts, thus contributing further to ECM breakdown. A recent report has linked a polymorphism within the HtrA1 promoter region to disc space narrowing in human patients. However, the impact of such a finding on disease pathogenesis has not yet been elucidated. Preliminary findings from our own research have shown that HtrA1 protein is present within human intervertebral disc (IVD) tissue and that levels were enhanced in tissue samples taken from patients with severe disc degeneration. Considering the fact that both MMPs and fibronectin fragments are potent instigators of disc degeneration, we hypothesize that involved in spinal disc degeneration in its expression and secretion have on disease pathology.

Accumulation of N-(carboxymethyl)-lysine and hyaluronic acid fragments in the ageing intervertebral disc – a potential trigger of discogenic back pain

Lilian Quero (PhD student; in collaboration with the Spine Research Group)

IVD degeneration is characterized by extracellular matrix breakdown and is considered to be a primary cause of discogenic back pain. Although increases in proinflammatory cytokine levels within degenerating discs are associated with discogenic back pain, the mechanisms leading to their overproduction have not yet been elucidated. As fragmentation of matrix components occurs during IVD degeneration, we assessed the potential involvement of hyaluronic acid fragments (fHAs) in the induction of inflammatory and catabolic mediators.



Immunofluorescence staining of intervertebral disc cells for NF-κB (p65, green) following treatment with either hyaluronic acid fragments (fHAs) (20 µg/ml) or interleukin (IL)-1β (5 ng/ml) at selected time points. Nuclear NF-κB (p65) is indicated by arrowheads.

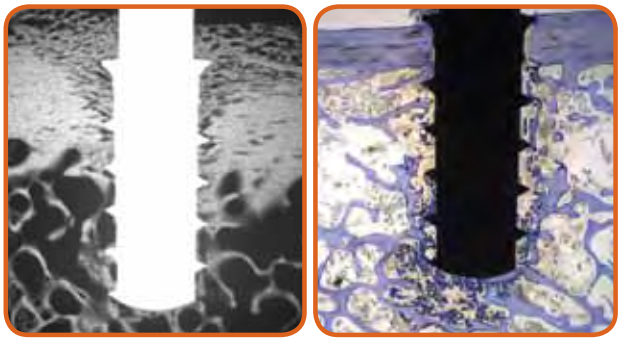
2. Cranio-Maxillofacial Surgery and Implantology Group

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

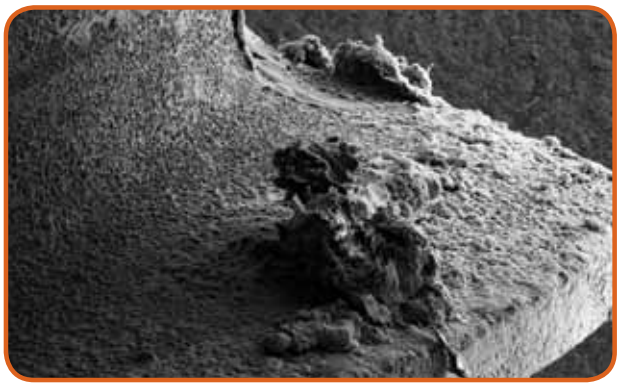
For the integration, stability and preservation of a dental implant, the structures of the surrounding hard and soft tissues – namely the jawbone and the oral mucosa – are very important and their significance on the successful fixation of dental implants has been clinically and scientifically assessed in several pre-clinical and clinical situations. Yet, the subsequent loss of hard and soft tissue structures by e.g. local infection, adverse biomechanical loading, trauma or physiological bone resorption, still poses a critical clinical problem. Restoration of lost tissue volume using own bone and mucosa transplants is well established in daily clinical practice being used to extend the width of the jawbone and adjacent soft tissue.

However, surgical difficulties like the bone cutting technique and an increased patient morbidity represent major disadvantages. Another serious complication and risk factor for stable and sustainable integration of bone and soft tissue transplants as well as dental implants is that of bacterial infection.

The high affinity and adhesion of microorganisms to implant surfaces impede normal physiologic or mechanical cleaning by means of saliva or oral hygiene. Subsequent bacterial colonization and biofilm formation can lead to a tremendous loss of dental hard and soft tissue structures. Following this, the onset of severe inflammatory reactions is often inevitable. In addition, bone loss following osteoporosis or cancer treatment with bisphosphonates causes severe problems in oral and maxillofacial surgery. Despite modern and state-of-the art technologies, there are currently still no convincing and successful treatment options available for bisphosphonate induced bone loss.



Microradiographic *(left)* and histological *(right)* analysis of a titanium implant in ovine pelvic bone.



Scanning electron microscope (SEM) image of a titanium dental implant with bone remnants.

Our own clinical research could demonstrate that antimicrobial soft tissue treatment by lasers can have a beneficial impact on the healing tendency of adjacent infected hard tissue. Laser light can help to control or even prevent the deleterious effect of oral bacteria on teeth or dental implants on their surface.

Therefore, our research is aimed at the analysis of the mutual interaction mechanisms at the surface of dental implants, biomaterials and vital tissues. This will help us to better understand normal, undisturbed or compromised healing and integration of biomaterials into the living human body. Focus is placed on the analysis of principle biological reactions that have a vital influence on early inflammatory soft tissue reactions on adjacent bone. A second main topic deals with the development and evaluation of innovative treatment strategies to foster a tight and stable bone integration of implants (osseointegration). This will finally help to define optimal surface structures for implants as well as to have suitable diagnosis and treatment tools to assess peri-implant tissues.

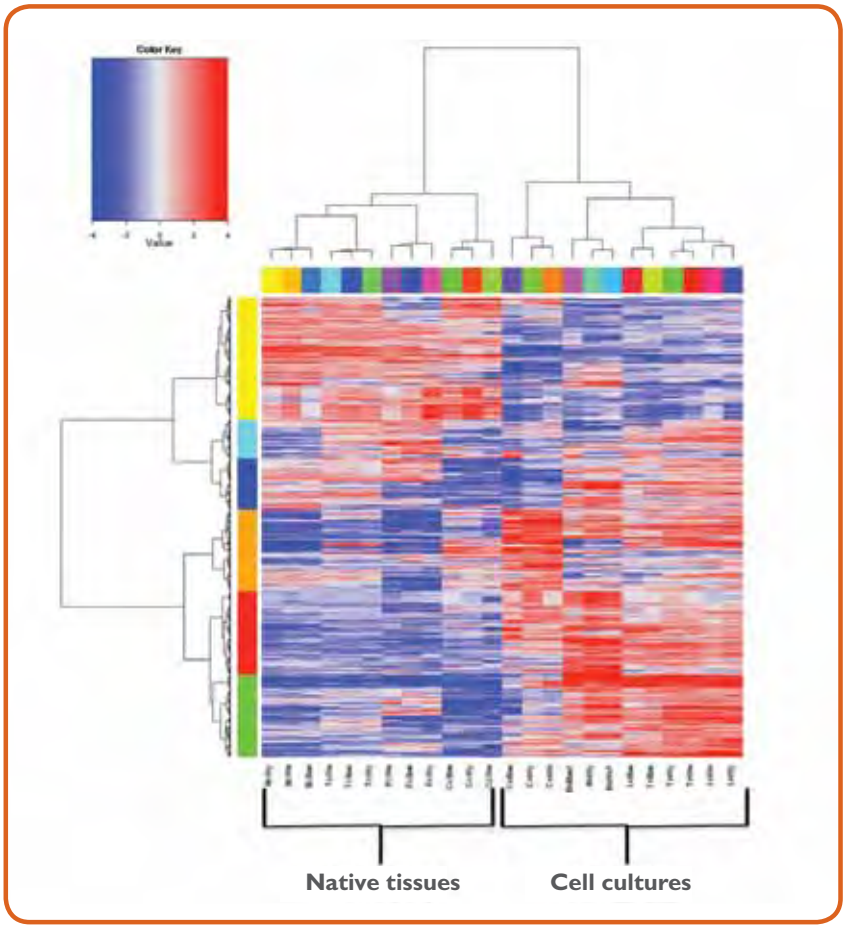
3. Equine Research Group

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)
CABMM collaborators: PD Dr. sc. nat. Paolo Cinelli, PD Dr. Peter J. Richards (PhD)

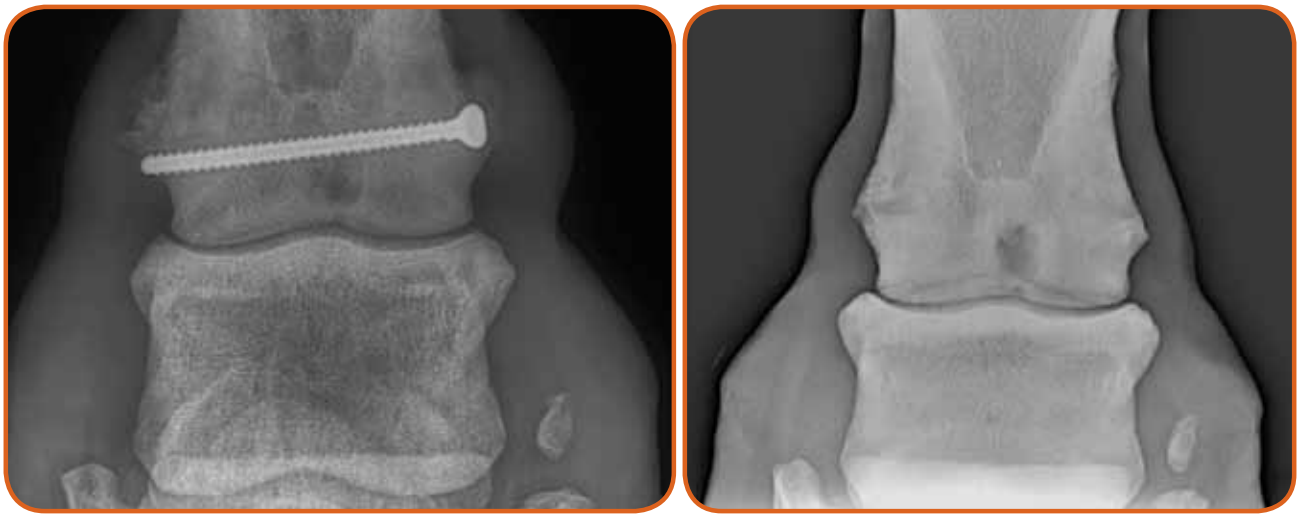
Orthopaedic injuries account for the majority of career-limiting diseases in horses used for athletic purposes ranging from pleasure riding to high-performance sport endeavours like jumping, racing, endurance or dressage competitions. The advances in equine orthopaedics and diagnostic imaging have improved 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. 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 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 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 are currently validated using qPCR. Once a suitable molecular marker of tenogenic differentiation is identified, we aim to improve the conditions of the stem cell environment to



Gene expression analysis of equine mesenchymal tissues and cell cultures.

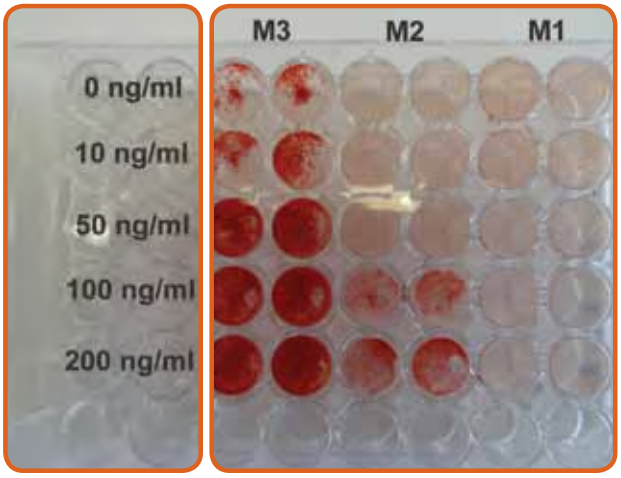


Radiography of a subchondral cystic lesion in the distal aspect of the fetlock joint directly after surgery *(left)* and three months thereafter *(right)*. The bone cyst was debrided, filled with rhBMP-2 and stabilized with a screw.

achieve regeneration of tendon tissue after stem cell treatment of a tendon lesion.

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 being examined 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 preliminary results show that rhBMP-2 increases alkaline phosphatase (ALP) activity as well as osteocalcin production and enhances mineralization in equine osteoblasts. In a clinical setting, 21 horses suffering from subchondral cystic lesions (SCLs) have been treated with rhBMP-2 after debridement of the cyst cavity. First results are promising.



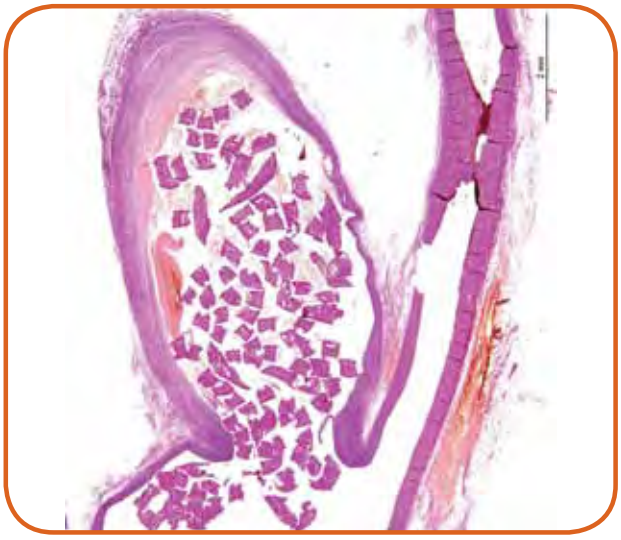
Alizarin Red Staining showing mineralization (red) of equine osteoblasts cultured with different concentrations of rhBMP-2 and in different culture media (M1, M2 and M3).

4. Interventional Work Research Group

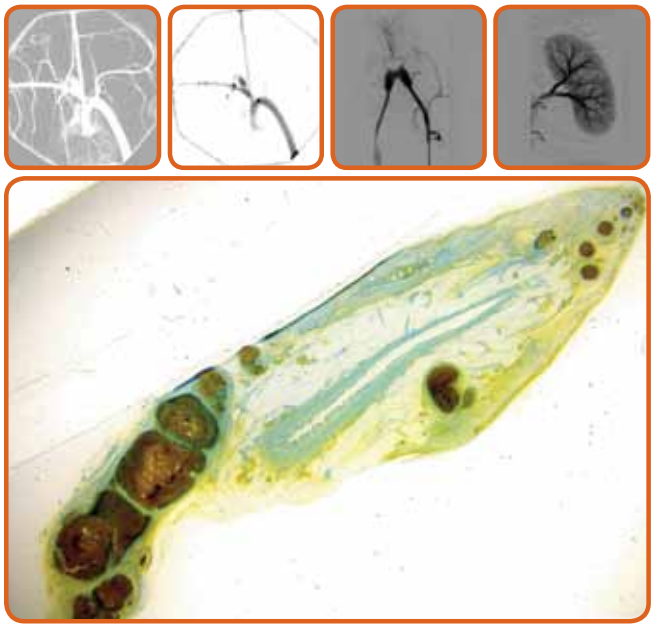
Group leaders: Prof. Dr. med. Daniel A. Rüfenacht,
Prof. Dr. med. vet. Brigitte v. Rechenberg, Dipl. ECVS
Group members: PD Dr. med. Zsolt Kulcsár,
Dr. med. vet. Katja Nuss, Dr. med. vet. Agnieszka Karol

The IWR (Interventional Work Research) Group is generally interested in understanding diseases and minimally invasive treatment options using medical devices and implants in the field of clinical neurosciences. The work currently focuses on neurovascular defects such as wall pathologies (e.g., aneurysm) and structural anomalies (e.g., arteriovenous malformation [AVM]).

A cerebral aneurysm is a bulge or ballooning of a blood vessel in the brain, and its formation represents the second major pathology affecting the arterial system after atherosclerosis. When harboring a cerebral aneurysm, the major risk is its rupture, which causes bleeding within the brain or more precisely, subarachnoid and eventually intra-cerebral hemorrhage. One third of patients suffering from subarachnoid hemorrhage will die within 24 hours before receiving adequate therapy, and an other third will be severely disabled because of bleeding consequences.



Histological image of a treated aneurym (H&E staining).



Upper panel: Digital subtraction angiographies of treated organs.
Lower panel: Histological section of an embolized kidney (tumor model; Giemsa staining).

Arteriovenous malformation is an abnormal connection between arteries and veins, bypassing the capillary system. This vascular anomaly may appear in any location of the body, but the most common occurrence involves the central nervous system, where it may lead to severe pain, hemorrhage and neurological impairment.

Both neurovascular defects are usually treated with minimally invasive, endovascular surgery, in which a catheter is inserted directly into the blood vessel.

The endovascular treatment of brain aneurysms has evolved from balloons through detachable micro-coils and intracranial stents to arrive to the use of potentially more promising blood flow modulating endovascular prostheses.

The treatment of the vessel malformations includes injection of an embolization material through the catheter, in order to permanently occlude the redundant vessel in an affected area. Additionally, this technique can be applied to discontinue or minimalize blood supply to the tumor-altered tissue, causing their involution and shrinkage.

5. Musculoskeletal Research Unit

Group leader: Prof. Dr. med. vet. Brigitte v. Rechenberg, Dipl ECVS
Group members: Dr. med. vet. Flurina Clement Frey, PhD, Dr. Sabine Koch-Schneidemann (PhD), Mario Benn (doctoral student), Lena Sara Müller (doctoral student)

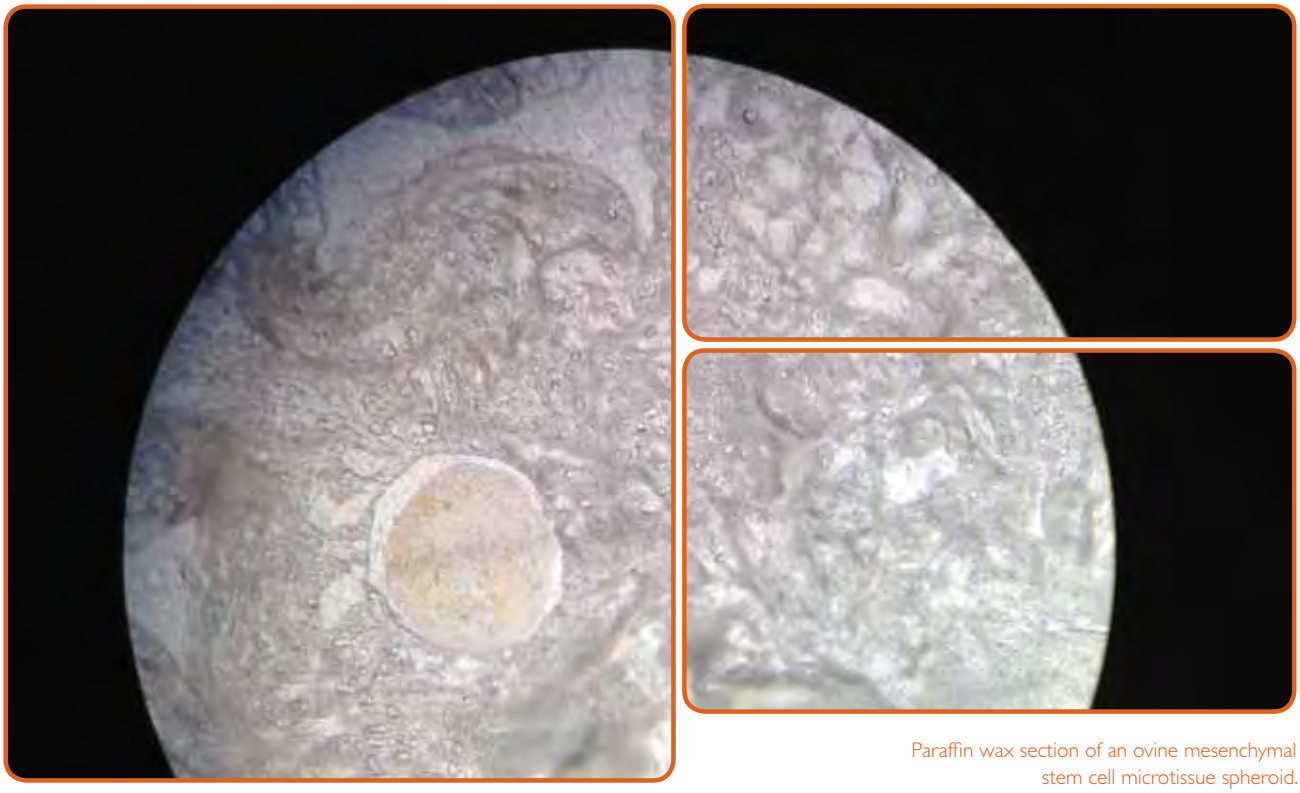
The main interest of the MSRU is related to musculoskeletal diseases (bone, cartilage, tendon, spine) with focus on bone and cartilage research. Additionally, soft tissue research (cardiovascular, wound and tendon healing) is carried out. The group is specialized on large animal experiments and histology 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). In June 2013, the application for GLP inspection and certification by Swissmedic was filed. After the subsequent inspection in April, 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 and 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.

In the reporting period, the following research projects were performed by the MSRU on the CABMM research platform:

Chondrocyte migration in cartilage

Dr. Sabine Koch-Schneidemann (PhD)

Cartilage is a flexible connective tissue found in many areas in the body like joints, the ribcage, the ear, the nose, intervertebral



Paraffin wax section of an ovine mesenchymal stem cell microtissue spheroid.

discs and other parts. Unlike other connective tissues, cartilage does not contain any blood vessels and therefore, heals very slowly. In general, regeneration of adult cartilage is greatly impaired. Whereas children are still able to completely regenerate cartilage defects by differentiation of cells from the perichondrium to chondrocytes and subsequent formation of new cartilage, adult cartilage is usually incompletely repaired by connective tissue cells/scar formation.

Own histological analysis suggests that migration of chondrocytes or their precursor cells may occur even in adult cartilage and may play a role in cartilage regeneration. Therefore, this project examines the migration, regeneration and reparative potential of cartilage cells *in vitro*.

Silica-coated superparamagnetic iron oxide nanoparticles (SPIONs):
A new non-viral drug delivery system
Dr. med. vet. Flurina Clement Frey, PhD

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 control and temporal delivery.

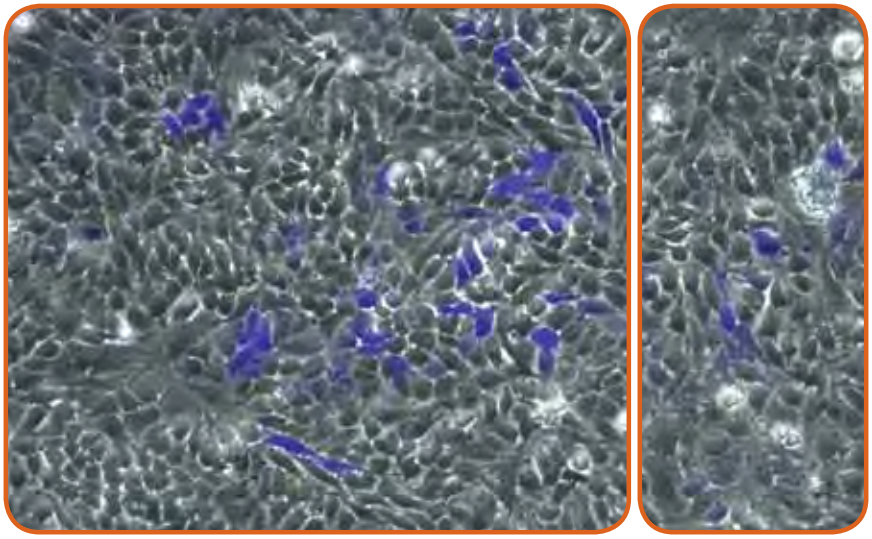
SPIONs are easily incorporated into cells *in vitro* and *in vivo*, but the mechanism of cellular uptake is unknown. Therefore, this project investigates the endocytosis of SPIONs in HeLa cells as well as in ovine chondrocytes and synoviocytes. Surfaceengineered silica-coated fluorescent SPIONs are functionalized with plasmid DNA of tagged marker proteins representing targeted gene delivery to analyze the SPION uptake via the main endocytotic pathways.

Based on the results, *in vitro* studies on the intracellular payload release will be performed, which will allow clinical applications as alternative treatment methods for musculoskeletal diseases, such as osteoarthritis and rheumatoid arthritis.

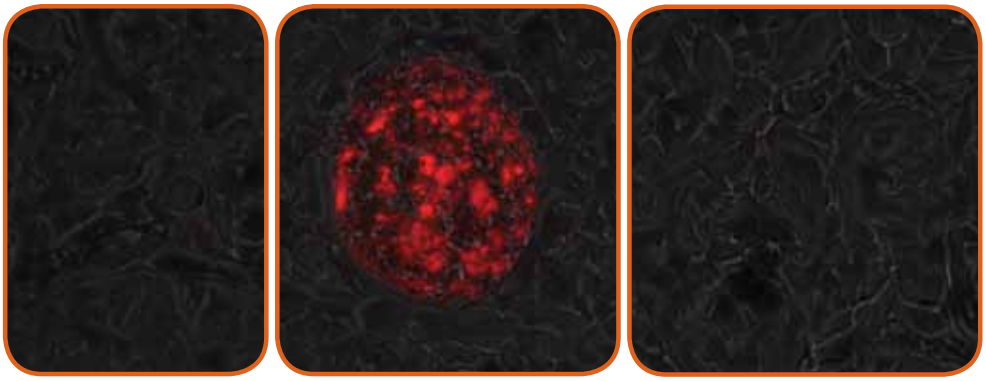
Chondrocytes for the repair of degenerated intervertebral discs
Lena Sara Müller (doctoral student)
Supervised by: Dr. med. vet. Katja Nuss
CABMM collaborator: PD Dr. med. vet. Frank Steffen, Dipl. ECVN

Lack of exercise and weak back muscles lead to an increasing amount of disc protrusions in adults, with back pain as one of the most frequent complaints. In a sound intervertebral disc the nucleus pulposus absorbs pressure, whereas the gelatinous core loses its elasticity and therefore, its absorption capacity in a degenerative or damaged disc.

Different therapies have been invented, with autologous chondrocyte transplantation being one of the most promising.



Fluorescence microscopy of HeLa cells transfected with BFP (blue fluorescent protein).



Fluorescence microscopy of a Qtracker®-labelled ovine mesenchymal stem cell microtissue spheroid.

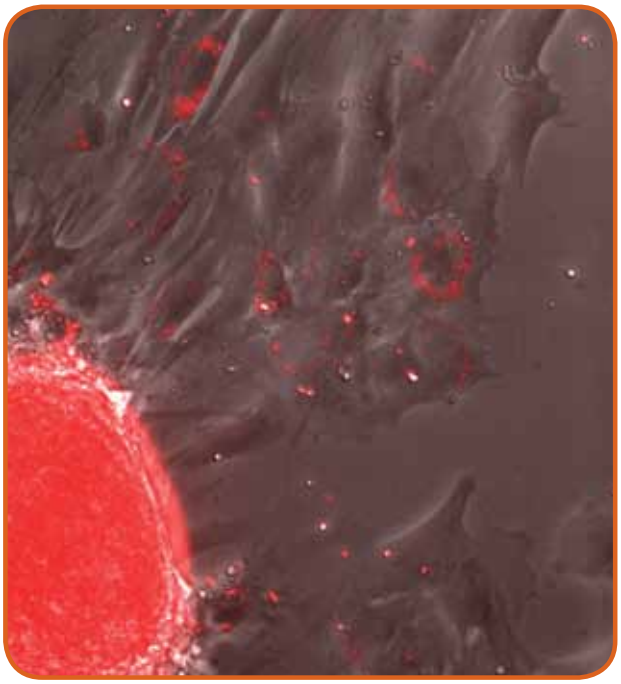
With this technique, chondrocytes from the disc core are harvested and cultivated, with an aim to generating matrix-producing chondrocytes, which can be re-implanted into the damaged intervertebral disc for its morphological and functional repair. One major problem is that the cells do not remain at the site of injection. This problem may be solved by embedding the chondrocytes into a gel, thereby preventing their migration from the repair site.

Therefore, the purpose of this study is to determine the ability of a gel, with or without disc chondrocytes, to repair damaged disc tissue as well as to analyze potential side effects or harmful events.

Mesenchymal stem cells for muscle regeneration
Mario Benn (doctoral student)
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 damage 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.



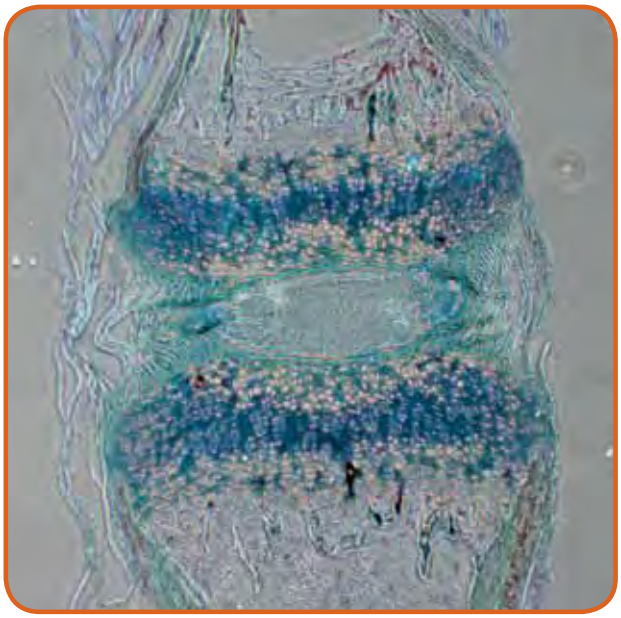
Fluorescence image depicting cellular migration out from a Qtracker®-labelled ovine mesenchymal stem cell microtissue spheroid.

6. Spine Research Group

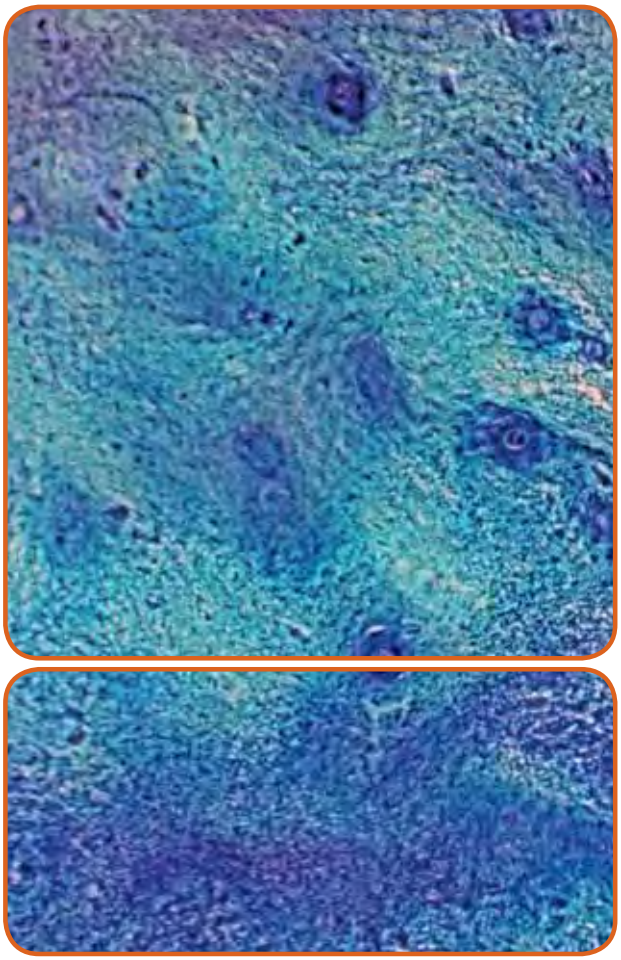
Group leader: Dr. Karin Würtz-Kozak (PhD)
Group member: Lilian Quero (PhD student)

Back pain is one of the most cost-intensive health problems in the world, with an extremely high prevalence. One specific form of back pain is called discogenic back pain, which can arise under certain degenerative conditions of the intervertebral disc. Disc degeneration is a complex process, but a common feature is the accumulation of specific matrix degradation products (e.g. fragmentation products), although quality and quantity of degeneration products can differ in a group with a similar degree of degeneration.

Based on this observation, the overall interest of the Spine Research Group is to elucidate cellular mechanisms during disc degeneration that may underlie the development of discogenic back pain; this knowledge could be used to develop novel treatment options. More specifically, one hypothesis of our research is that certain degradation products may increase the levels of proinflammatory cytokines, which can irritate nerves in the outer part of the disc, thus contributing to pain development. Another hypothesis is that certain biodrugs can interfere in this proinflammatory cascade and can thus be used to treat discogenic back pain in a minimal invasive manner.



FAST staining of a mouse intervertebral disc with the adjacent intervertebral bodies.



Histological image of cultured bovine intervertebral disc cells.

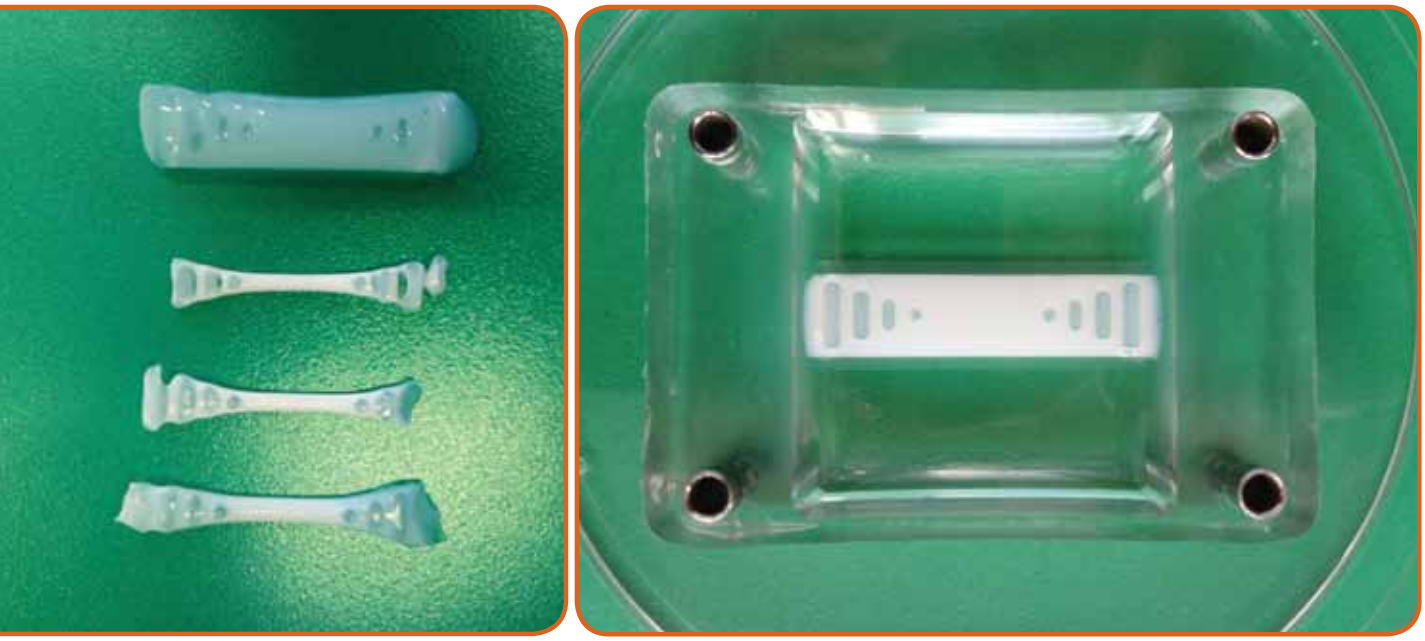
7. Tendon Repair Group

Group leaders: Prof. Dr. med. vet. Anton Fürst, Dipl ECVS
Group members: Dr. med. vet. Felix Theiss, Dipl. ECVS (PhD student)
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 inflammation or irritation of a tendon (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 functionally inferior compared to normal tendon tissue. This has important consequences for the animal in terms of reduced performance and a substantial risk of re-injury.

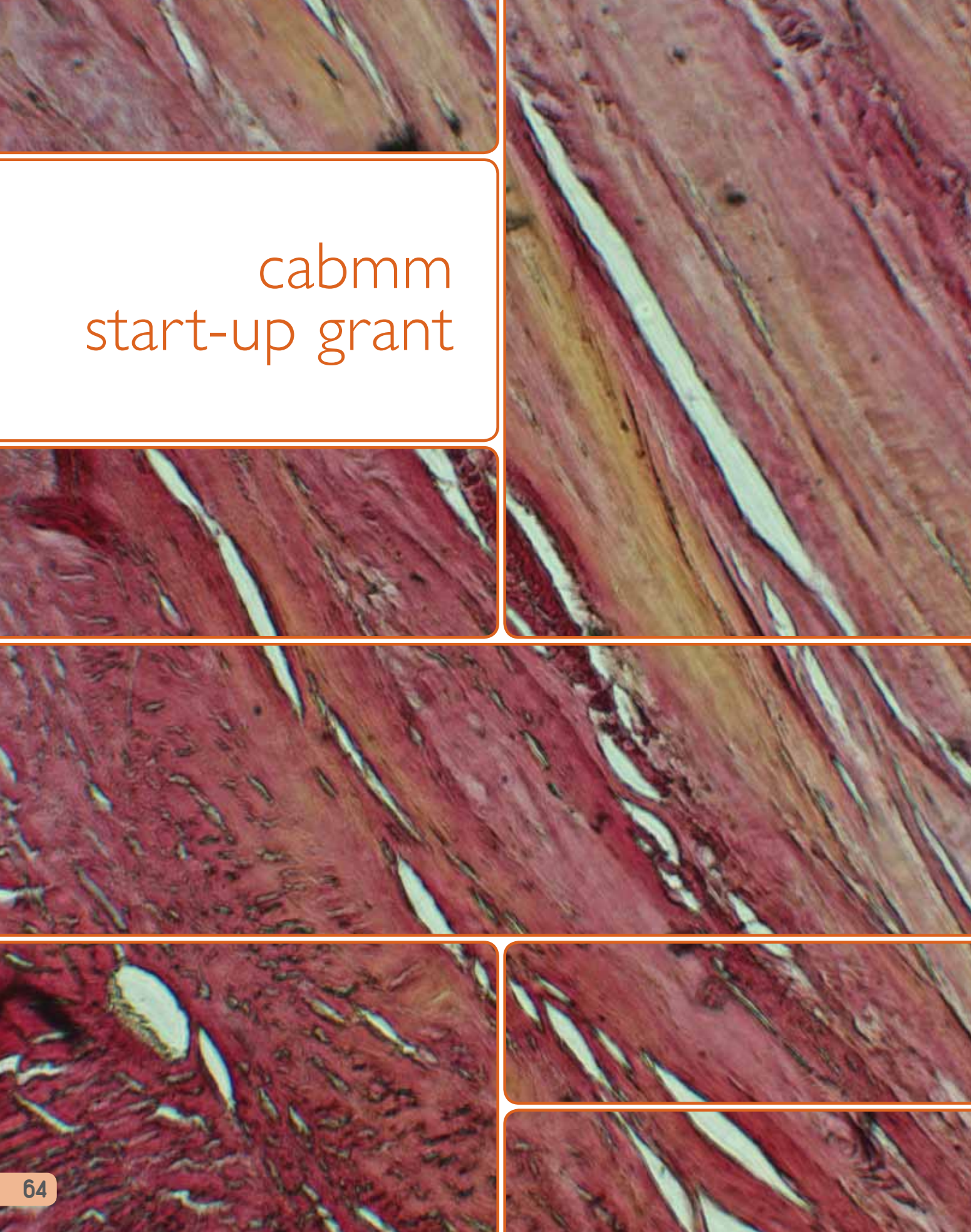
The aim of our group is to develop cell-based treatment strategies to enhance tendon healing in the horse resulting in a shorter convalescence period and an improved quality of repaired tissue, thereby reducing the risk of relapse. To evaluate this therapeutic concept, unanswered questions, like differentiation 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 with and without mechanical stimulation. Possible de-differentiation of tendon cells in culture is a special consideration.

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 fetal cells will be evaluated at the molecular, biochemical and histological level regarding their potential to differentiate into tenocytes in a three-dimensional tendon model system. 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.



Collagen-based scaffolds used for the mechanical stimulation of equine tendon cells.

cabmm start-up grant



The CABMM Start-up Grant is a peer-reviewed funding program designed to support collaborations within the CABMM network and is made possible through the generous financial support of the Mäxi foundation.

The grant supports novel projects within the musculoskeletal and also within the cardiovascular field, with emphasis being placed on proof of principal, potentially 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 on a larger scale 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 members of the Scientific Advisory Board (SAB). The evaluation criteria include amongst others, relevance to the objectives of the CABMM and the Mäxi foundation, originality of the problem(s) addressed and scientific and technical excellence of the proposal and the team.

At the end of the funding period, every project is discussed in line with a SAB Meeting and the project outcome is presented during the CABMM Symposia.

In the reporting period 2012/2013, a total of 13 projects with an estimated total of CHF 470'000.– were funded by a CABMM Start-up Grant. This means that the number of Start-up Grants almost doubled in comparison to the last reporting time and thus, our aim to foster collaborations within the CABMM has been achieved.

A tabular summary of all funded 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 1/2012 and 2/2012

Project Title	Applicants	Amount
Investigation into the regenerative effects of porcine notochordal cells on bovine intervertebral disc cells under co-culture	PD Dr. Benjamin Gantenbein-Ritter*, Dr. Karin Würtz-Kozak	CHF 35'000.–
Mechanisms of mechanotransduction in human intervertebral disc cells upon stimulation with PEMF or strain	Dr. Alfredo Franco-Obregón*, PD Dr. Oliver Hausmann, Dr. Karin Würtz-Kozak*	CHF 37'490.–
Monitoring osteomyelitis by biomarkers following systemic inflammation parameters	Prof. Dr. Regina Hofmann-Lehmann, Prof. Dr. Annette Liesegang, Prof. Dr. Brigitte von Rechenberg*, PD Dr. Raffaella Santoro	CHF 38'790.–
NEMO and IKKbeta: Identifying potential targets for treatment of early osteoarthritis using shRNA technology	Dr. Anne-Kathrin Born* (Prof. Dr. Marcy Zenobi-Wong)**, Dr. Karin Würtz-Kozak, Prof. Dr. Marcy Zenobi-Wong	CHF 39'400.–
Spying on cells: Towards the establishment of a new non-viral drug delivery system using silica-coated superparamagnetic iron oxide nanoparticles (SPIONs)	Dr. Flurina Clement Frey* (Prof. Dr. Brigitte von Rechenberg)**, Prof. Dr. Dr. Michael O. Hottiger	CHF 39'500.-
Identification of RANKL-activated proteins regulating poly-ADP-ribose formation	Prof. Dr. Dr. Michael O. Hottiger*, PD Dr. Peter J. Richards	CHF 39'000.–
	Subtotal 2012	**CHF 229'180.–**

* Main applicant (s)
** corresponding CABMM member

application rounds 1/2013 and 2/2013

Project Title	Applicants	Amount
Role of intrapatellar fat pad on the pathophysiology of the diseased cranial crucial ligament in dogs	Dr. Simone Forterre* (Prof. Dr. David Spreng)**, PD Dr. Peter J. Richards, Prof. Dr. David Spreng	CHF 24'338.-
Investigation of the inflammatory processes associated with canine intervertebral disc herniation	Dr. Franck Forterre* (Prof. Dr. David Spreng)**, Dr. Karin Würtz-Kozak*	CHF 37'950.-
Expression, regulation and relevance of hyaluronidases in the intervertebral disc	PD Dr. Benjamin Gantenbein-Ritter, Dr. Karin Würtz-Kozak*	CHF 29'800.-
Molecular regulation of myogenesis: role of serine protease HTRA1	Dr. Alfredo Franco-Obregón, PD Dr. Peter J. Richards*	CHF 37'000.-
Evaluation of the chondrogenic potential of human epiphyseal chondroprogenitor cells in alginate sulfate hydrogels	Prof. Dr. Lee Ann Laurent-Applegate, Prof. Dr. Marcy Zenobi-Wong*	CHF 35'900.-
Biomechanical characterization of the Luque Trolley System to avoid adjacent segment disease	Prof. Dr. Dr. Patrick R. Kircher, Dr. Sebastian Knell* (Prof. Dr. Dr. Patrick R. Kircher)**, Prof. Dr. Brigitte von Rechenberg	CHF 37'200.-
Analysis of topographic differences in synovial fibroblasts	Prof. Dr. Dr. Michael O. Hottiger, Dr. Caroline Ospelt* (Prof. Dr. Steffen Gay)**	CHF 38'900.-
	Subtotal 2013	**CHF 241'088.–**
	Total amount in the reporting period:	**CHF 470'268.–**

* Main applicant (s)
** corresponding CABMM member

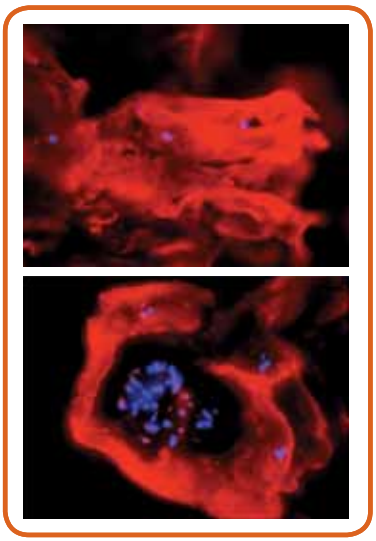
1. Role of serine protease HTRA1 in spinal disc degeneration

Principle Investigator: PD Dr. Peter J. Richards
Collaborator: Dr. Karin Würtz-Kozak
Amount funded: CHF 24'140.–
Funding period: 01/2011 – 12/2011
(application round 1/2010)

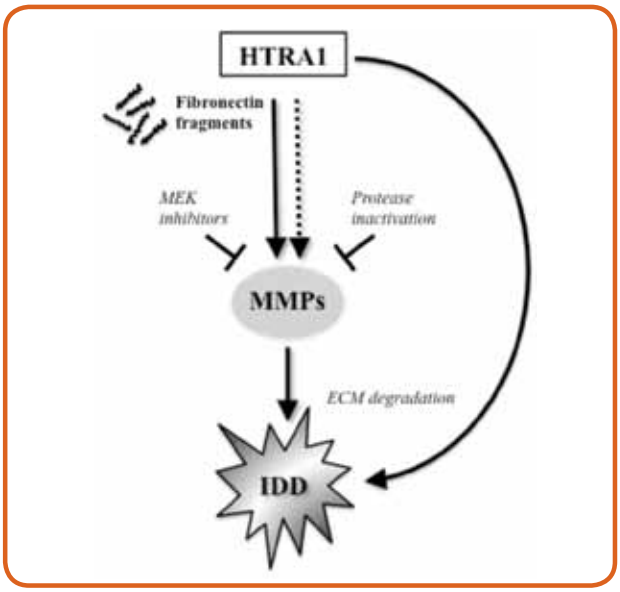
Human HTRA1 is a highly conserved secreted serine protease that degrades numerous extracellular matrix (ECM) proteins. We have previously identified HTRA1 as being up-regulated in osteoarthritic patients and as having the potential to regulate matrix metalloproteinase (MMP) expression in synovial fibroblasts through the generation of fibronectin fragments. In the present report, we have extended these studies and investigated the role of HTRA1 in the pathogenesis of intervertebral disc (IVD) degeneration. HTRA1 mRNA expression was significantly elevated in degenerated disc tissue and was associated with increased protein levels. However, these increases did not correlate with the appearance of rs11200638 single nucleotide polymorphism (SNP) in the promoter region of the HTRA1 gene, as has previously been suggested. Recombinant HTRA1 induced MMP production in IVD cell cultures through a mechanism critically dependent on MEK, but independent of IL-1β signaling. The use of a catalytically-inactive mutant confirmed these effects to be primarily due to HTRA1 serine protease activity. HTRA1-induced fibronectin proteolysis resulted in the generation of various sized fragments, which when added to IVD cells in culture, caused a significant increase in MMP expression. Furthermore, one of these fragments was identified as being the amino-terminal fibrin- and heparin-binding domain, and was also found to be increased within HTRA1-treated IVD cell cultures as well as in disc tissue from patients with IVD degeneration. Our results therefore support a scenario in which HTRA1 promotes IVD degeneration through the proteolytic cleavage of fibronectin and subsequent activation of resident disc cells.

Publication

Tiaden AN, Klawitter M, Lux V, Mirsaidi A, Bahrenberg G, Glanz S, Quero L, Liebscher T, Wuertz K, Ehrmann M, Richards PJ
A detrimental role for human high temperature requirement serine protease A1 (HTRA1) in the pathogenesis of intervertebral disc (IVD) degeneration.
J. Biol. Chem. 2012; 287(25):21335-45



Immunofluorescence staining of HTRA1 in degenerated IVDs



Role of serine protease HTRA1 in spinal disc degeneration

2. Investigating the role of Toll-Like receptor 2 in intervertebral disc degeneration and inflammation

Principle Investigator:	Dr. Karin Würtz-Kozak
Collaborator:	Prof. Dr. Steffen Gay
	PD Dr. Oliver Hausmann
Amount funded:	CHF 35'000.–
Funding period:	10/2011 – 09/2012
	(application round 1/2011)

Purpose: Although inflammatory processes play an essential role in painful intervertebral disc (IVD) degeneration, the underlying regulatory mechanisms are not well understood. This study was designed to investigate the expression, regulation and importance of specific Toll-like receptors (TLRs) – which have been shown to play an essential role e.g. in osteoarthritis – during degenerative disc disease.

Methods: The expression of TLRs in human IVDs was measured in isolated cells as well as in normal or degenerated IVD tissue. The role of IL-1β or TNF-α in regulating TLRs (expression/activation) as well as in regulating activity of down-stream pathways (NF-κB) and expression of inflammation-related genes (IL-6, IL-8, HSP60, HSP70, HMGB1) was analyzed.

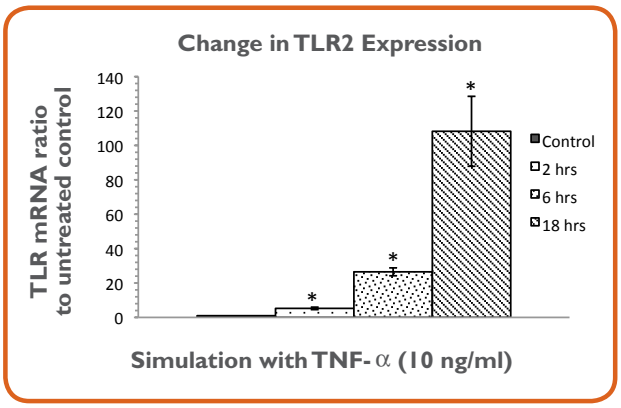
Results: Expression of TLR1/2/3/4/5/6/9/10 was detected in isolated human IVD cells, with TLR1/2/4/6 being dependent on the degree of IVD degeneration. Stimulation with IL-1β or TNF-α moderately increased TLR1/TLR4 mRNA expression (TNF-α only), and strongly increased TLR2 mRNA expression (IL-1β/TNF-α), with the latter being confirmed on the protein level. Stimulation with IL-1β, TNF-α or Pam3CSK4 (a TLR2-ligand) stimulated IL-6 and IL-8, which was inhibited by a TLR2 neutralizing antibody for Pam3CSK4; IL-1β and TNF-α caused NF-κB activation. HSP60, HSP70 and HMGB1 didn't increase IL-6 or IL-8 and were not regulated by IL-1β/TNF-α.

Conclusion: We provide evidence that several TLRs are expressed in human IVD cells, with TLR2 possibly playing the most crucial role.

As TLRs mediate catabolic and inflammatory processes, increased levels of TLRs may lead to aggravated disc degeneration, chronic inflammation and pain development. Especially with the identification of more endogenous TLR ligands, targeting these receptors may hold therapeutic promise.

Publication

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 Jul 5. [Epub ahead of print]

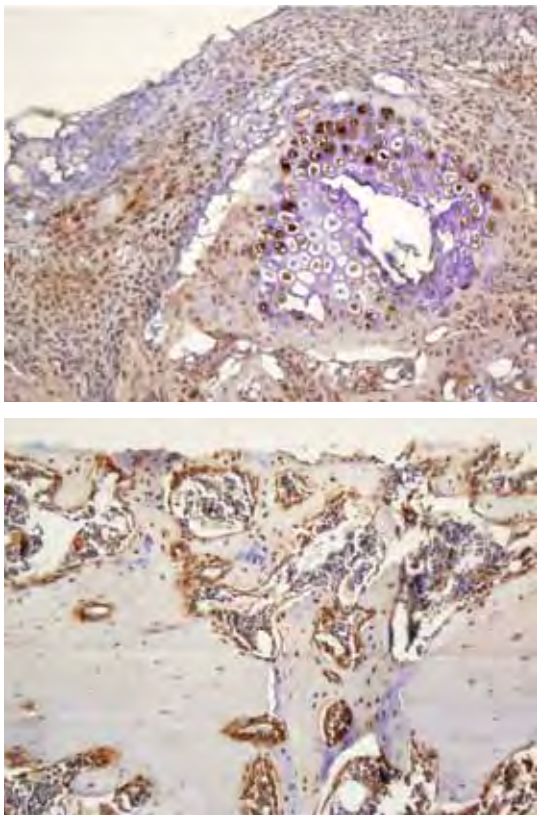


Changes in TLR2 mRNA expression upon stimulation with TNF-α (time course). Fold changes in gene expression of TLR2 after stimulation with 10 ng/ml TNF-α for 2, 6 or 18 hours, measured by Real-time RT-PCR and calculated by the 2^-ΔΔCt method. Changes are calculated relative to untreated control cells. Mean ± SEM of five independent donors. Asterisks indicate statistical significance relative to untreated control with $p < 0.05$.

3. Modulation of extracellular matrix proteins by serine protease HTRA1 and its influence on bone formation

Principle Investigator:	PD Dr. Peter J. Richards
Collaborator:	Prof. Dr. Michael Blauth
Amount funded:	CHF 27'663.–
Funding period:	09/2011 – 08/2012 (application round 1/2011)

Mammalian HTRA1 is a secreted member of the trypsin family of serine proteases, which can degrade a variety of bone matrix proteins and as such, has been implicated in musculoskeletal development. In the present study, we have investigated the role of HTRA1 in mesenchymal stem cell (MSC) osteogenesis and suggest a potential mechanism through which it controls matrix mineralization by differentiating bone-forming cells. Osteogenic induction resulted in a significant elevation in the expression and secretion of HTRA1 in MSCs isolated from human bone marrow (hBMSCs), mouse adipose tissue (mASCs), and mouse embryonic stem cells (mESCs). Recombinant HTRA1 enhanced the osteogenesis of hBMSCs as evidenced by significant changes in several osteogenic markers including integrin-binding sialoprotein (IBSP), bone morphogenetic protein 5 (BMP5) and sclerostin (SOST), and promoted matrix mineralization in differentiating bone-forming osteoblasts. These stimulatory effects were not observed with proteolytically inactive HTRA1 and were abolished by small interfering RNA (siRNA) against HTRA1. Moreover, loss of HTRA1 function resulted in enhanced adipogenesis of hBMSCs. HTRA1 immunofluorescence studies showed co-localization of HTRA1 with IBSP protein in osteogenic mASC spheroid cultures and IBSP was confirmed as being a newly identified HTRA1 substrate in cell cultures and in proteolytic enzyme assays. A role for HTRA1 in bone regeneration *in vivo* was also alluded to in bone fracture repair studies where HTRA1 was found localized predominantly to areas of new bone formation in association with IBSP. These data therefore implicate HTRA1 as having a central role in osteogenesis through modification of proteins within the extracellular matrix.



Immunohistochemical staining of HTRA1 (brown) in paraffin sections of regenerating mouse bone

Publication

Tiaden AN, Breiden M, Mirsaidi A, Weber FA, Bahrenberg G, Glanz S, Cinelli P, Ehrmann M, Richards PJ

Human Serine Protease HTRA1 Positively Regulates Osteogenesis of Human Bone Marrow-Derived Mesenchymal Stem Cells and Mineralization of Differentiating Bone-Forming Cells through the Modulation of Extracellular Matrix Protein

Stem Cells 2012; 30:2271-2282

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

Principle Investigator:	PD Dr. Peter J. Richards
Collaborators:	Dr. Richard A. Lindtner (CABMM member: Prof. Dr. Michael Blauth), Prof. Dr. Michael Blauth
Amount funded:	CHF 23'000.–
Funding period:	01/2012 – 12/2012 (application round 2/2011)

Purpose: The primary aim of this study was to evaluate the influence of aminobisphosphonates on the osteogenesis of hBMSCs and mineralization of differentiating bone-forming cells isolated from osteoporotic patients.

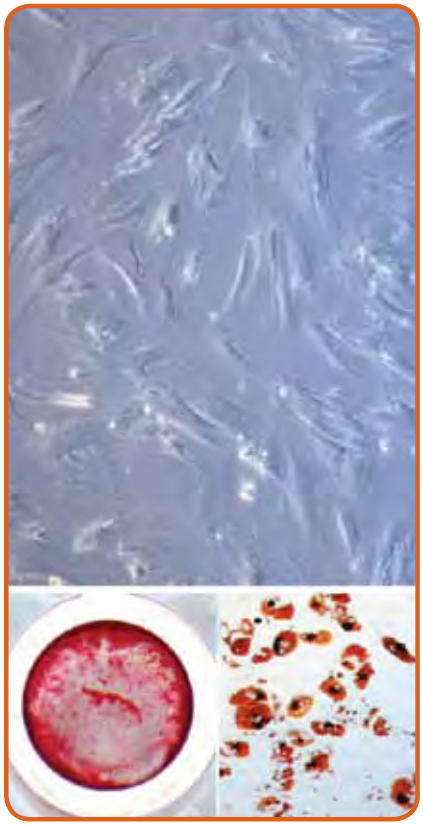
Methods: The influence of aminobisphosphonate treatment on hBMSC osteogenesis was assessed by the quantitative measurement of alkaline phosphatase (ALP) activity, in addition to qRT-PCR and Western blot analysis of known osteogenic markers. Mineralized matrix formation by hBMSC-derived osteoblasts was visualized and quantified using Alizarin red staining.

Results: 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 formation were independent of any alterations in ALP activity, although significant changes in the expression levels of osteopontin (SPP1) were evident in hBMSCs following exposure to aminobisphosphonates. Further analysis revealed osteopontin as having a negative influence on the mineralization of differentiating osteoporotic bone-forming cells.

Conclusions: 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 not only an antiresorptive, but also an osteoanabolic effect in osteoporosis.

Publication

Lindtner RA, Tiaden AN, Genelin K, Ebner HL, Manzl C, Klawitter M, Sitte I, Rechenberg BV, 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.
Osteoporos Int. 2014; 25(3):1151-61



Characterization of osteoporotic patient-derived bone marow stromal cells (BMSCs). *Top panel*, phase contrast image of cultured BMSCs grown under non-differentiating conditions. *Bottom left panel*, cells differentiated towards osteoblasts and stained with Alizarin red at day 21. *Bottom right panel*, cells differentiated towards adipocytes and stained with Oil red O at day 14.

5. Investigation into the regenerative effects of porcine notochordal cells on bovine intervertebral disc cells under co-culture

Principle Investigator:	PD Dr. Benjamin Gantenbein-Ritter
Collaborator:	Dr. Karin Würtz-Kozak
Amount funded:	CHF 35'000.–
Funding period:	09/2012 – 08/2013 (application round 1/2012)

Background. Notochordal cells (NCs) remain in the focus of research for regenerative therapy for the degenerated intervertebral disc (IVD) due to their progenitor status. NCs are thought to release certain factors, thereupon present in notochordal cell conditioned medium (NCCM). These factors have been reported to exert regenerative actions on mature disc cells and prevent structural disruption, inflammation, and neurovascular ingrowth during intervertebral disc degeneration. While NCs represent an interesting cell type that warrants further investigations, their maintenance *in vitro* is challenging, as they are sensitive to changes in nutrient levels and mechanical stimuli. The aim of this study was to establish an optimized culture protocol for porcine NCs by comparing 2D and 3D cell culture systems and by investigating how fetal calf serum (FCS) and oxygen levels affect their phenotype and their ability to activate bovine nucleus pulposus cells (NPCs).

Methods. NCs were cultured in 2D monolayer and in 3D alginate beads for 3 passages and phenotypically characterized over time by flow cytometry and brachyury (T) immunostaining in order to visulaize the notochordal phenotype. To analyse the stimulating effects of NCs on NPCs, indirect co-cultures with no cell contact were maintained at a 1:1 ratio in 3D alginate beads under normoxia (20% oxygen) and hypoxia (2% oxygen) for 7 and 14 days. Additionally, NCs were pre-cultured for 7 days in the presence or absence of FCS. As a positive control, NPCs were stimulated with NCCM. NPC cell activity, glycosaminoglycan content, DNA content and relative gene expression were measured. Mass spectrometry (MS) was conducted on NCCM to determine possible therapeutic agents.

Results. Flow cytometry of unlabeled cells revealed that 3D alginate bead culture maintains NCs in much higher numbers than 2D monolayer culture, in which the number of NCs was already strongly decreased after only one passage.

In 3D culture, NPCs were activated by NCs as indicated by the gene expression ratio of aggrecan to collagen type 2 (ACAN/COL2), both via NCCM or under co-culture with NCs pre-stimulated with FCS. Activation was more pronounced under hypoxia.

NPCs also tended to produce more GAG/DNA after addition of NCCM or in the presence of NCs that had previously been activated with FCS. Hypoxia conditions led to a reduced metabolic activity, but did not lead to a significant change in the glycosaminoglycan/DNA ratio. Annulus fibrosus cells did not respond at all to the presence of NCs or NCCM.

Finally, using MS, connective tissue growth factor (CTGF) was identified as being one of the substances in the NCCM and NC:NPC co-culture.

Conclusions. The results presented here clearly demonstrate that the choice of culture conditions of NCs influences not only their cell number and phenotype, but also their ability to activate NPCs. In 3D alginate bead culture, hypoxia and either indirect co-culture of FCS-stimulated NCs or addition of NCCM resulted in a NPC phenotype, which was most IVD-like considering the ACAN/COL2 ratio (approx. 10:1).

Using MS, connective tissue growth factor (CTGF) was identified to be present in NCCM, a factor that seems to play an essential role in IVD degeneration. This factor has recently been reported in the literature as being a key cytokine involved in relieving painful intervertebral discs through inhibition of neurite outgrowth and vascularization. Although this study supports the potential therapeutic benefit of CTGF, further investigations will be required to specify its mechanism of action, e.g. by performing experiments with recombinant CTGF, CTGF blockers, CTGF receptor blockers or by producing a lentivirus shRNA to silence the gene expression of CTGF in NPCs.

6. Mechanisms of mechanotransduction in human intervertebral disc cells upon stimulation with PEMF or strain

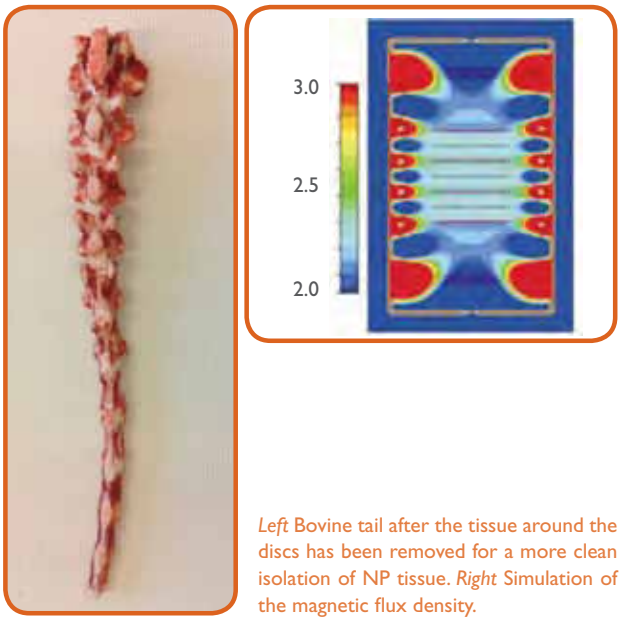
Principle Investigators:	Dr. Karin Würtz-Kozak, Dr. Alfredo Franco-Obregón
Collaborator:	PD Dr. Oliver Hausmann
Amount funded:	CHF 37'490.–
Funding period:	08/2012 – 07/2013 (application round 1/2012)

Purpose: The bulk of our body mass is derived from tissues whose developmental programs are regulated by mechanical input. These tissues include skeletal muscle, bones and connective tissues such as cartilage and tendons. We have previously found that skeletal muscle myoblasts respond to brief exposures of extremely low frequency and low intensity pulsed electromagnetic fields (PEMFs) with an increase in proliferation and enhanced deposition of extracellular matrix. Myogenic gene expression is also enhanced following PEMF exposure downstream of Nuclear factor of activated T-cells (NFAT) calcium-sensitive calcium regulation. Indeed, the majority of consequences of PEMF exposure in myoblasts appear to be situated downstream of calcium influx via transient receptor potential cation (TRPC) channels.

Methods: Given the molecular and mechanistic similarities between the mechanotransduction apparatuses of myoblasts, chondrocytes and intervertebral disc (IVD) cells, we extended our study to entail the analysis of PEMFs over primary IVD cells, specifically of the disc's inner region, the nucleus pulposus (NP). Human as well as bovine NP cells were enzymatically isolated from surgical biopsies and cow tails respectively and cultured either in 2D or 3D (alginate beads). Cells were exposed to different PEMF treatments, using a custom-made PEMF generator and changes in proliferation, viability, gene and protein expression (extracellular matrix, TRP channels) was measured.

Results: PEMF exposure, which did not reduce cell viability, had minor effects on matrix protein expression and cell proliferation in both, human or bovine IVD cells. Variations in field strength, exposure duration, time points of analysis, medium composition or the presence of an inflamed (i.e. diseased) status did not have a significant impact on the cellular response. The observed response varied from sample to sample, i.e. sample history played a big role in determining responsiveness to PEMFs. This was likely due to: 1) inherent differences in tissue trauma and donor age; 2) differences in region of biopsy extraction; 3) subtle differences in handling and processing during isolation and expansion of cells from whole tissue; 4) differences in the ratio of progenitor-like cells and fully differentiated cells isolated from the biopsy; and 5) variations in the expression pattern of TRPC/ Transient Receptor Potential Vanilloid (TRPV) channels.

Conclusion: PEMF treatment with the specific parameters tested so far cannot be used as a method to assist in the regeneration of the IVD. However, longer and repetitive exposure, yet realistic in a clinical context, might stimulate the production of extracellular matrix. It is also possible that progenitor-like disc cells may be more responsive to PEMF (currently under investigation).



Left Bovine tail after the tissue around the discs has been removed for a more clean isolation of NP tissue. *Right* Simulation of the magnetic flux density.

facts & figures

member profiles, joint research projects and publications

In order to promote scientific collaborations and exchange, the CABMM aims to create and continuously strengthen a network of active member groups working together on interdisciplinary and translational research projects. The number and quality of those CABMM members, as well as their collaborative research projects and scientific publications with affiliation to the CABMM, reflect not only the activity within the CABMM network, but also show the success and quality of the CABMM.

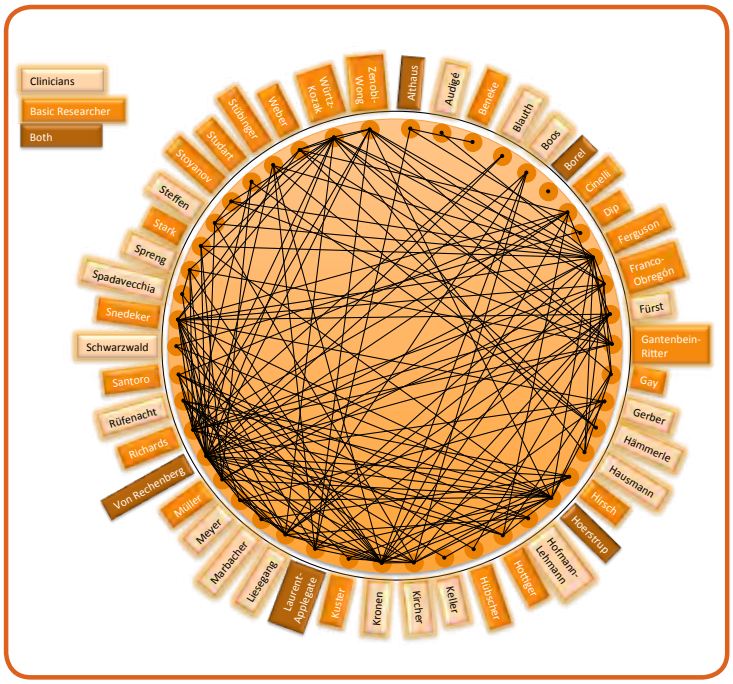
Starting with 16 members in the founding year 2008, the CABMM gained acceptance and reputation in the field of interdisciplinary and translational research in the ensuing years. Nowadays, our network consists of more than 50 active members, and is still continuing to grow. Considering the number of team 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 (e.g. Bern, Lausanne, Lucerne, Nottwil, Wädenswil) as well as in other countries (e.g. Austria), with some of their scientists even using our platform for research.

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 Spring Seminar and Symposium of the CABMM where the presentations of new findings by scientists working within the CABMM allow for the fruitful exchange of scientific knowledge and ideas.

Another testament to the scientific strengths and networking capabilities of our CABMM members is the fact that several joint projects have been successfully completed and more than 40 CABMM-affiliated peer-reviewed research articles have been published in scientific journals within the reporting period.

On the following pages, all CABMM members are introduced with the assistance of short profiles, which we hope will better exemplify both, the range and diversity of research being conducted within the CABMM. Furthermore, we provide tables detailing scientific 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.



Networking within the CABMM: Every collaboration is represented by a line connecting the two collaborating CABMM members.

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 92-96 and 98-103

Name: **Althaus, Felix R.**
Prof. Dr. med. vet.
Institution: Institute of Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich
Grants: Swissmedic
CABMM collaborators: Sascha Beneke, Christian Blenn*, Ramiro Dip, Lee Ann Laurent-Applegate

General research interest:
Our research focuses on the function of enzymes of poly(ADP-ribose) (PAR) metabolism and their involvement in cell death signaling. The poly ADP-ribosylation system represents a target for experimental pharmacotherapy in diabetes, cancer, stroke and inflammation.

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: 51

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: Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich
CABMM collaborators:
Felix Althaus

General research interest:

- Poly(ADP-ribosyl)ation
- DNA repair & genomic stability
- Aging
- Parkinson's disease
- Cell death and Ca2+

* CABMM member until 2014

Name: **Blauth, Michael**
Prof. Dr. med.
Institution: Department for Trauma Surgery, Medical University of Innsbruck
Grants: CABMM, AO
CABMM collaborators:
Jörg Goldhahn, Brigitte von Rechenberg
Peter Richards
CABMM joint projects: 17, 48

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. The stem cells are analyzed by state of the art visualizing techniques, namely electron- and confocal microscopy, as well as biochemical and histological methods.

Name: **Boos, Alois**
Prof. Dr. med. vet.
Institution: Institute of Veterinary Anatomy, Vetsuisse Faculty,
University of Zurich
CABMM collaborators:
Annette Liesegang, Patrick Kircher,
Peter Kronen, Brigitte von Rechenberg
CABMM joint projects: 1, 31

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 Veterinary Office (FVO), Braun Stiftung,
Office International des Epizooties (OIE)
CABMM collaborators: Christian Blenn*
CABMM joint projects: 18

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 acute and chronic wound healing processes in clinical settings. We could recently demonstrate the inhibition of *in vitro* chlamydial infection using wIRA irradiation. Concomitant host cell viability was not affected under wIRA exposure. Treatment experiments with wIRA of *in vitro* persistent chlamydial infections are planned in the future. Effects of wIRA on chlamydiae but also on host cells is studied in collaboration with Dr. Christian Blenn.

* 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: A. Fürst, M. Hottiger, P. Kronen, B. von Rechenberg, P. Richards, R. Santoro, J. Snedeker, F. Weber
CABMM joint projects: 19, 28
Publications with affiliation to the CABMM: 41, 20, 17, 14

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: Novartis Animal Health Inc., Basel and Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich
Grants: Stiftung Forschung für das Pferd, Forschungskredit Nachwuchsförderungskommission der Universität Zürich
CABMM collaborators: Felix Althaus, Colin Schwarzwald

General research interest:
We are interested in elucidating mechanisms of inflammatory down-regulation 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: Institute for Biomechanics, ETH Zurich
Grants: EU, SNF, Mäxi Foundation, AO, CTI, St. Josefs Hospital Fund (Iceland), Industry
CABMM collaborators: L. Audigé, N. Boos, A. Franco-Obregón, B. Gantenbein-Ritter, S. Gay, O. Hausmann, S. Hoerstrup, P. Kronen, A. Liesegang, R. Müller, B. von Rechenberg, J. Snedeker, W. Stark, F. Steffen, J. Stoyanov, S. Stübinger, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 3, 4, 7, 11, 25, 26, 36, 38, 41, 42, 51

Publications with affiliation to the CABMM: 36, 35, 9

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: **Franco-Obregón, Alfredo PhD**
Institution: Rehabilitation and Regenerative Strategies Group (RRSG), Space Biology, ETH Zurich
Grants: Foundation Suisse de Recherche sur les Maladies Musculaires (FSRMM), European Space Agency, Swiss Health Agency (BAG)
CABMM collaborators: N. Boos, S. Ferguson, S. Gay, O. Hausmann, A. Liesegang, R. Müller, P. Richards, J. Snedeker, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 3, 25, 42, 47, 49

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: Paolo Cinelli, Ulrich Hübscher, Patrick Kircher, Lee Ann Laurent-Applegate, Annette Liesegang, Brigitte von Rechenberg, Peter Richards, Jess Snedeker
CABMM joint projects: 22, 28, 58
Publications with affiliation to the CABMM: 34

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 PD Dr. (PhD)**
Institution: Institute of Surgical Technology and Biomechanics, University of Bern
Grants: CABMM, AO Spine, International Scientific Research Networt (SRN), private donation Prof. Dr. Paul Heini, Sonnenhof Clinics
CABMM collaborators: S. Ferguson, B. von Rechenberg, P. Richards, D. Spreng, J. Stoyanov, F. Weber, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 7, 24, 40
Publications with affiliation to the CABMM: 39

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 Masterswitch, EU FP7 PEOPLE-2011-ITN Marie Curie Training Network, EU FP7-TEAM HEALTH.2012.2.4.5-2, IMIBTCure, CABMM, Industry
CABMM collaborators: Norbert Boos, Stephen Ferguson, Alfredo Franco-Obregón, Jörg Goldhahn, Oliver Hausmann, Simon Hoerstrup, Michael Hottiger, Karin Würtz-Kozak
CABMM joint projects: 38, 41

General research interest:
The Center for 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 collaborators: Simon Hoerstrup, Peter Kronen, Dominik Meyer, Brigitte von Rechenberg, Jess Snedeker
CABMM joint projects: 16, 33, 64
Publications with affiliation to the CABMM: 18, 6

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 fifteen 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: **Hämmerle, Christoph**
Prof. Dr. med. dent.
Institution: Center of Dental Medicine, Clinic of Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich
CABMM collaborators: André Studart, Stefan Stübinger, 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 (preclinical 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 tissues.

Name: **Hausmann, Oliver**
PD Dr. med.
Institution: Neurozentrum Zentralschweiz, Hirslanden Hospital St. Anna, Lucerne
Grants: CABMM
CABMM collaborators: Norbert Boos, Alfredo Franco-Obregón, Steffen Gay, Stephen Ferguson, Karin Würtz-Kozak
CABMM joint projects: 4, 38, 41, 47
Publications with affiliation to the CABMM: 15

General research interest:
I am working as a neurosurgeon at the Hirslanden Klinik St. Anna in Lucerne. The research is focused on degeneration of the spine as well as on spinal cord injury. I am collaborating with Dr. Würtz-Kozak in the most recent past. After obtaining ethical approval for the collection of disc biopsies in 2010, I currently provide the Spine Research Group 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: University Hospital Essen
CABMM collaborators: Patrick Kircher, Peter Kronen, Niels Kuster, Serge Marbacher, Brigitte von Rechenberg, Daniel Rüfenacht
Publications with affiliation to the CABMM: 16

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: Clinic for Cardiovascular Surgery, Division of Surgical Research and Swiss Center of Regenerative Medicine, USZ and UZH
Grants: EU FP7, SNF, HSM, Schweizerische Herzstiftung, KTI, Emdo-Stiftung, Olga Mayenfisch Stiftung, BMM, ZürichHeart, SwissTransMed, 3R
CABMM collaborators: S. Ferguson, S. Gay, C. Gerber, M. Hottiger, E. Keller, P. Kircher, P. Kronen, L. Laurent-Applegate, D. Meyer, R. Müller, B. von Rechenberg, P. Richards, D. Rüfenacht, C. Schwarzwald, J. Snedeker, W. Stark, M. Zenobi-Wong
CABMM joint projects: 20, 30, 43, 44, 45, 53, 54, 56
Publications with affiliation to the CABMM: 10

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 collaborators: Annette Liesegang, Brigitte von Rechenberg, Raffaella Santoro
CABMM joint projects: 50

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 recently established the clinical infectiology.

Name: **Hottiger, Michael O.**
Prof. Dr. med. vet. Dr. phil. II
Institution: Institute of Veterinary Biochemistry and Molecular Biology, University of Zurich
Grants: SNF, Oncosuisse, CABMM, Forschungskredit UZH
CABMM collaborators: Paolo Cinelli, Steffen Gay, Simon Hoerstrup, Brigitte von Rechenberg, Peter Richards, Raffaella Santoro
CABMM joint projects: 2, 27, 29, 62
Publications with affiliation to the CABMM: 41, 32, 7, 3

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 post-translational 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: **Hübscher, Ulrich**
Prof. Dr. med. vet. #
Institution: Institute of Veterinary Biochemistry and Molecular Biology, University of Zurich
(host institute of CABMM)
Grants: SNF, UBS
CABMM collaborators:
Anton Fürst, Raffaella Santoro

Prof. emeritus and CABMM Honory Member since 1.2.14

General research interest:
Regulation of DNA repair in animal and human cells, with particular focus on oxidative damages in connection with diseases (cancer, neurodegeneration) and aging.

Name: **Keller, Emanuela**
Prof. Dr. med.
Institution: Neurocritical Care Unit, Department of Neurosurgery, University Hospital Zurich
Grants: CTI
CABMM collaborators: Simon Hoerstrup, Serge Marbacher, Daniel Rüfenacht,

General research interest:
- Development and application of new optical technologies to monitor cerebral hemodynamics and oxygenation in patients at risk for ischemic brain damage (including theoretical and healthy volunteers studies)
- Clinical studies to examine the inflammatory response in patients with subarachnoid hemorrhage
- Application and studies on new neuroprotective treatment strategies, like hypothermia in patients with subarachnoid hemorrhages

Name: **Kircher, Patrick R.**
Prof. Dr. med. vet. PhD, Dipl. ECVDI
Institution: Division of Diagnostic Imaging Vetsuisse Faculty, University of Zurich
Grants: Albert-Heim-Stiftung
CABMM collaborators: Ueli Braun, Alois Boos, Anton Fürst, Sven Hirsch, Simon Hoerstrup, Peter Kronen, Niels Kuster, Annette Liesegang, Brigitte von Rechenberg, Daniel Rüfenacht, Frank Steffen
CABMM joint projects: 8, 15, 31, 37, 56

General research interest:
We are interested in the development of Functional Magnetic Resonance Imaging (fMRI), and MR Spectroscopy 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 W.**
Dr. med. vet., DVM, Dipl. ECVAA
Institution: Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich/Veterinary Anaesthesia Services International, Winterthur
Grants: CTI, 3R, Industry
CABMM collaborators: J. Auer, A. Boos, N. Boos, U. Braun, P. Cinelli, S. Ferguson, A. Fürst, C. Gerber, S. Hirsch, S. Hoerstrup, P. Kircher, L. Laurent-Applegate, A. Liesegang, S. Marbacher, D. Meyer, B. von Rechenberg, D. Rüfenacht, C. Schwarzwald, J. Snedeker, C. Spadavecchia, D. Spreng, S. Stübinger

CABMM joint projects:
6, 14, 15, 34, 35, 36, 37, 56, 59, 63
Publications with affiliation to the CABMM:
44, 35, 33, 24

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: CTI, EU/FP7, nano-tera.ch
CABMM collaborators: Sven Hirsch, Patrick Kircher, Brigitte von Rechenberg, Daniel Rüfenacht

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. (PhD)
Institution: Department of Musculoskeletal Medicine, Service of Plastic and Reconstructive Surgery, Unit of Regenerative Therapy, University Hospital Lausanne
Grants: FRNS, SwissTransMed, CABMM, SCIEX, FP7
CABMM collaborators: Felix Althaus, Anton Fürst, Simon Hoerstrup, Peter Kronen, Brigitte von Rechenberg, Jess Snedeker, Stefan Stübinger, Marcy Zenobi-Wong
CABMM joint projects: 5, 23, 55, 58

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 for all other 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, Schaumann Stiftung
CABMM collaborators: J. Auer, A. Boos, U. Braun, A. Franco-Obregón, S. Ferguson, A. Fürst, R. Hofmann-Lehmann, P. Kircher, P. Kronen, D. Meyer, R. Müller, B. v. Rechenberg, R. Santoro, J. Snedeker, K. Würtz-Kozak
CABMM joint projects: 1, 9, 10, 13, 42, 46, 50
Publications with affiliation to the CABMM: 40, 26

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.
- 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: **Serge Marbacher**
Dr. med. (MSc)
Institution: Cerebrovascular Research Group, Department of Neurosurgery, Kantonsspital Aarau
CABMM collaborators: Sven Hirsch, Emanuela Keller, Peter Kronen, Brigitte von Rechenberg, Daniel Rüfenacht

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 Christoph**
Prof. Dr. med
Institution: Department of Orthopedics, University Hospital Balgrist, Zurich
Grants: SNF, Resortho
CABMM collaborators: Christian Gerber, Jörg Goldhahn, Simon Hoerstrup, Peter Kronen, Annette Liesegang, Brigitte von Rechenberg, Jess Snedeker
CABMM joint projects: 33, 34, 64
Publications with affiliation to the CABMM: 18, 6

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 fifteen 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: Institute for Biomechanics, ETH Zurich,
Grants: EU, NIH, SNF, NFP, SystemsX.ch, CTI, ETHIIRA
CABMM collaborators:
Stephen Ferguson, Alfredo Franco-Obregón, Jörg Goldhahn, Annette Liesegang, Brigitte von Rechenberg, Peter Richards, Jess Snedeker, Wendelin Stark, André Studart
CABMM joint projects: 12

General research interest:
We are interested in characterizing the material properties of musculoskeletal tissues, the quantification of their adaptation from birth to death, with disease, and due to mechanical demands, as well as comparing the kinetics and kinematics of functional and dysfunctional systems. For this purpose, we develop, refine and use biomechanical engineering tools and concepts to explore and understand musculoskeletal organisation, while maintaining a philosophy of respect and compassion for all human and animal life.

Name: **von Rechenberg, Brigitte**
Prof. Dr. med. vet., Dipl. ECVS
Institution: Musculoskeletal Research Unit (MSRU), Vetsuisse Faculty, University of Zurich
Grants: EU, Swiss Transplant, nano-tera.ch
CABMM collaborators: M. Blauth, A. Boos, P. Cinelli, S. Ferguson, A. Fürst, B. Gantenbein-Ritter, C. Gerber, J. Goldhahn, S. Hirsch, S. Hoerstrup, R. Hofmann-Lehmann, M. Hottiger, P. Kircher, P. Kronen, N. Kuster, L. Laurent-Applegate, A. Liesegang, S. Marbacher, D. Meyer, R. Müller, P. Richards, D. Rüfenacht, R. Santoro, J. Snedeker, C. Spadavecchia, D. Spreng, W. Stark, F. Steffen, S. Stübinger, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 3, 5, 6, 8, 13, 20, 21, 22, 30, 31, 32, 33, 34, 35, 36, 37, 43, 44, 45, 46, 50, 55, 57, 59, 62, 63, 64
Publications with affiliation to the CABMM:
38, 36, 35, 33, 30, 24, 21, 18, 9, 6, 4, 2
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 newly embarked in wound healing of deep and infected skin wounds.

Name: **Richards, Peter J.**
PD Dr. (PhD)
Institution: Bone and Stem Cell Research Group, CABMM, University of Zurich
Grants: SNF, Uniscientia Stiftung, Novartis, CABMM
CABMM collaborators: M. Blauth, P. Cinelli, A. Franco-Obregón, A. Fürst, B. Gantenbein-Ritter, M. Hottiger, R. Müller, B. von Rechenberg, R. Santoro, J. Snedeker, S. Spreng, A. Studart, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 10, 12, 17, 28, 29, 48, 60, 61
Publications with affiliation to the CABMM:
42, 39, 32, 25, 17, 8, 7, 5
General research interest:
We are interested in characterizing the functional role played by mesenchymal stem cells in the development of osteoporotic bone through the use of molecular, biochemical and histological techniques. We are currently utilizing stem cells isolated from both human patients and experimental models and have developed the necessary techniques with which to successfully harvest and expand cells from specific stem cell niches.

Name: **Rüfenacht, Daniel A.**
Prof. Dr. med.
Institution: IWR – Interventional Work Research, Neuroradiology, Swiss Neuro Institute SNI, Klinik Hirslanden, Zurich
Grants: SNF, CTI, FP7 (VDHDARE@IT), Industry
CABMM collaborators: Sven Hirsch, Simon Hoerstrup, Emanuela Keller, Patrick Kircher, Peter Kronen, Niels Kuster, Serge Marbacher, Brigitte von Rechenberg
CABMM joint projects: 43, 56
Publications with affiliation to the CABMM: 16
General research interest:
The IWR group is interested in understanding, imaging and visualization of neurological diseases and minimally invasive treatment options (imaging methods, devices and implants). Our work currently focuses on neurovascular 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: **Santoro, Raffaella**
PD Dr. (PhD)
Institution: Institute of Veterinary Biochemistry and Molecular Biology, University of Zurich
Grants: SNF, Oncosuisse, UBS, Promidica-Stiftung
CABMM collaborators: P. Cinelli, R. Hofmann-Lehmann, A. Liesegang, M. Hottiger, U. Hübscher, B. von Rechenberg, P. Richards
CABMM joint projects: 19, 27, 50
Publications with affiliation to the CABMM: 3

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 try to elucidate epigenetic mechanisms that establish and maintain cell identity. Our mission is to define chromatin and epigenetic regulators that contribute to cell differentiation processes like osteoclastogenesis, stem cell-neuronal precursor transition, neoplastic transformation and metastasis.

Name: **Schwarzwald, Colin C.**
Prof. Dr. med. vet. PhD, Dipl. ACVIM, Dipl. ECEIM
Institution: Clinic for Equine Internal Medicine, Equine Department, Vetuisse Faculty, University of Zurich
Grants: SNF, Stiftung Forschung für das Pferd
CABMM collaborators: Ueli Braun, Ramiro Dip, Simon Hoerstrup, Peter Kronen
CABMM joint projects: 53, 54

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, Robert Mathys Foundation
CABMM collaborators: P. Cinelli, S. Ferguson, A. Franco-Obregón, A. Fürst, C. Gerber, S. Hoerstrup, R. Müller, P. Kronen, L. Laurent-Applegate, A. Liesegang, D. Meyer, B. von Rechenberg, P. Richards, F. Weber, K. Würtz-Kozak
CABMM joint projects: 42, 58

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: BLV, 3R, Norwegian School of Veterinary Sciences
CABMM collaborators: Peter Kronen, David Spreng, Brigitte von Rechenberg

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 peri-operative pain treatment in domestic and laboratory animals. Our major areas of interest are pain diagnosis, development of perioperative pain treatment strategies in clinical and experimental settings and optimization of methods to provide local analgesia to treat acute perioperative as well as persistent pain.

Name: **Spreng, David**
Prof. Dr. med. vet.,
Dipl. ECVS, Dipl. ACVECC
Institution: Section of Small Animal Surgery, Vetsuisse Faculty, University of Bern
CABMM collaborators: Benjamin Gantenbein-Ritter, Peter Kronen, Brigitte von Rechenberg, Peter Richards, Claudia Spadavecchia, Karin Würtz-Kozak
CABMM joint projects: 39, 60

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, HCI E 107, ETH Zurich
Grants: SNF, CTI
CABMM collaborators: Stephen Ferguson, Simon Hoerstrup, Peter Kronen, Ralph Müller, Brigitte von Rechenberg, Franz Weber

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 improvement of antibacterial properties of the implants using silver containing TCP nanoparticles without influencing the bioactivity.

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 collaborators: Stephen Ferguson, Patrick Kircher, Brigitte von Rechenberg, Jivko Stoyanov, Karin Würtz-Kozak
CABMM joint projects: 11, 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**
PhD
Institution: Biomedical Laboratories, Swiss Paraplegic Research, Nottwill
Grants: SNF, Swiss Paraplegic Foundation
CABMM collaborators:
Stephen Ferguson,
Benjamin Gantenbein-Ritter,
Frank Steffen, Karin Würtz-Kozak
CABMM joint projects: 11

General research interest:
Use of MSCs for IVD regeneration after trauma and degenerative disease in the context of translational medicine: We investigate the way cells interact with tissue engineering matrices under normoxic and hypoxic conditions for the purpose of IVD differentiation and their use to modulate inflammation in degenerative and traumatic intervertebral discs. We also work on the aging of MSC and the consequences for future cell therapies. We have a substantial collection of cell sets from the same donor(s) – human IVD cells, MSC and peripheral bloods cells.

Name: **Studart, André R.**
Prof. Dr. (PhD)
Institution: Complex Materials, Department of Materials, ETH Zurich
Grants: SNF, Industry
CABMM collaborators:
Christoph Hämmerle, Ralph Müller, Peter Richards

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: Cranio-Maxillofacial Surgery and Implantology Group, CABMM, Musculoskeletal Research Unit (MSRU), Vetsuisse Faculty, University of Zurich
Grants: CTI, EU, Industry
CABMM collaborators: Stephen Ferguson, Christoph Hämmerle, Peter Kronen, Lee Ann Laurent-Applegate, Brigitte von Rechenberg
CABMM joint projects: 6, 14, 21, 35, 36, 57, 59, 63
Publications with affiliation to the CABMM: 43, 37, 36, 31, 29, 28, 23, 19, 13, 2

General research interest:
Our research is aimed at the core points affecting the strong interaction mechanisms and mutual interference at the interface of oral hard and soft tissue structures. Focus is placed on the analysis of principle pathways and reactions that have a vital influence of early inflammatory soft tissue reactions on adjacent bone. A second main topic deals with the development and evaluation of innovative treatment strategies for hard and soft tissue regeneration.

Name: **Weber, Franz E.**
Prof. Dr. rer. nat.
Institution: Division of Cranio-Maxillofacial and Oral Surgery, Oral Biotechnology & Bioengineering, University Hospital Zurich
Grants: SNF, EU-FP7, ITI, AO-CMF grant, CABMM, SSO (Swiss dental Society grant)
CABMM collaborators: Paolo Cinelli, Benjamin Gantenbein-Ritter, Christoph Hämmerle, Jess Snedeker, Wendelin Stark, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 14

General research interest:
The main interest of our research laboratory is the healing of large bone defects in the head region. To that end, we produce and design growth factors to promote bone formation and screen and characterize small molecule enhancers for BMPs. We develop and test titanium based, natural and synthetic bone substitute materials and have a profound expertise on the development and design of biomimetic materials (fibrin gels, platelet rich plasma, synthetic hydrogels, synthetic fibrin, HA/TCP based materials) for *in vitro* and *in vivo* bone tissue engineering.

Name: **Würtz-Kozak, Karin**
PhD
Institution: Institute for Biomechanics (D-HEST), ETH Zurich
Grants: Spine Society of Europe, CABMM, Theodor und Ida Herzog-Egli-Foundation, AO, SAMW
CABMM collaborators: N. Boos, S. Ferguson, A. Franco-Obregón, B. Gantenbein-Ritter, S. Gay, O. Hausmann, A. Liesegang, B. von Rechenberg, P. Richards J. Snedeker, D. Spreng, F. Steffen, J. Stoyanov, M. Zenobi-Wong
CABMM joint projects: 3, 4, 7, 24, 25, 26, 38, 39, 40, 41, 42, 52, 61
Publications with affiliation to the CABMM: 32, 27, 15, 12, 11, 8, 1

General research interest:
We aim to identify and describe the mechanisms leading to phenotypic and biosynthetic changes in musculoskeletal tissues and ultimately to multiple orthopaedic diseases that pose great health problems. A better understanding of the interplay between various external cues and their biomechanical consequences on the cell, tissue and organ level will furthermore allow us to develop non- or minimal-invasive treatment strategies (e.g. molecular therapeutics, mechanical or electrical therapies or scaffolds for tissue engineering) for prevention or treatment. Focus areas: intervertebral disc, cartilage, bone, muscle.

Name: **Zenobi-Wong, Marcy**
Prof. Dr. (PhD)
Institution: Cartilage Engineering & Regeneration, ETH Zürich
Grants: SNF, FP7, AO, CABMM
CABMM collaborators: Stephen Ferguson, Alfredo Franco-Obregón, Benjamin Gantenbein-Ritter, Simon Hoerstrup, Lee Ann Laurent-Applegate, Brigitte von Rechenberg, Peter Richards, Franz Weber, Karin Würtz-Kozak
CABMM joint projects: 23, 52

General research interest:
We engineer 3D cellular systems mainly for cartilage regeneration applications. Natural and synthetic hydrogels are designed to control stem cell and chondrocyte fate. We are also using bioprinting techniques to create layered structures based on extracellular matrix. Other tools for developing functional mimics of the native 3D extracellular environment include photocrosslinkable carbohydrate-based gels and incorporation of adhesion motives into gels. 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

alumni members:

Name: **Boos, Norbert**
Prof. Dr. med. MBA
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 Insitutes for Biomedical Research, Basel

joint research projects (in alphabetical order)

Number	Title	Collaborator (CABMM members only)
1	**Absorption mechanisms in the intestines of goat and sheep**	Alois Boos, Annette Liesegang*
2	**Analysis of the topographic differences in synovial fibroblasts**	Michael Hottiger, Caroline Ospelt*/**
3	**Analyzing the benefit of PEMF treatment in stem-cell based, equine cartilage regeneration**	Stephen Ferguson, Alfredo Franco-Obregón, Brigitte von Rechenberg, Karin Würtz-Kozak*
4	**Annulus fibrosus rupture**	Stephen Ferguson*, Oliver Hausmann, Karin Würtz-Kozak*
5	**B5 SwissTransMed: Biological, Biodegradable and anti-Bacterial Burn-wound Bandages**	Lee Ann Laurent-Applegate*, Brigitte von Rechenberg
6	**Biocompatibility testing of PEEK implants in the pelvic model in sheep**	Peter Kronen, Brigitte von Rechenberg, Stefan Stübinger*
7	**Biological response of the intervertebral disc to repetitive short-term cyclic torsion**	Stephen Ferguson, Benjamin Gantenbein-Ritter*, Karin Würtz-Kozak*
8	**Biomechanical characterization of the Luque Trolley System to avoid adjacent segment disease**	Patrick Kircher*, Brigitte von Rechenberg
9	**Bone marker changes in mice after mechanical stress**	Alfredo Franco-Obregón*, Annette Liesegang
10	**Bone markers in osteoporotic mice**	Annette Liesegang, Peter Richards*
11	**Cell Therapy for Degenerative Disc Disease using Injectable Microcarriers**	Stephen Ferguson, Frank Steffen, Jivko Stoyanov*
12	**Characterization of bone turnover and remodeling in experimental mouse models**	Ralph Müller*, Peter Richards
13	**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
14	**Development of an animal model to study the osteonecrosis of the jaw**	Peter Kronen, Stefan Stübinger*, Franz Weber

* Principal Investigator
** CABMM member since 2014

Number	Title	Collaborator (CABMM members only)
15	**Development of a transvascular bypass operation technique in pigs**	Patrick Kircher, Peter Kronen*
16	**Diagnosis and minimally invasive treatment of rotator cuff tendon tear**	Christian Gerber*, Dominik Meyer, Jess Snedeker
17	**Effect of bisphosphonates on the differentiation potential of mesenchymal stem cells isolated from osteoporotic patients**	Michael Blauth, Peter Richards*
18	**Effect of water-filtered infrared A (wIRA) on chlamydial infections**	Christian Blenn, Nicole Borel*
19	**Epigenetic rRNA gene silencing during ESC differentiation**	Paolo Cinelli, Raffaella Santoro*
20	**Establishment of a cell- and tissue biobank**	Simon Hoerstrup*, Brigitte von Rechenberg
21	**Evaluation of a new saw blade for atraumatic bone cutting**	Brigitte von Rechenberg, Stefan Stübinger*
22	**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 subchondrals cystic lesions (SCLs) in horses**	Anton Fürst*, Brigitte von Rechenberg
23	**Evaluation of the chondrogenic potential of human epiphyseal chondroprogenitor cells in alginate sulfate hydrogels**	Lee Ann Laurent-Applegate, Marcy Zenobi-Wong*
24	**Expression, regulation and relevance of hyaluronidases in the intervertebral disc**	Benjamin Gantenbein-Ritter, Karin Würtz-Kozak*
25	**Expression, regulation and role of the TRP channel family in disc and muscle**	Norbert Boos, Stephen Ferguson, Alfredo Franco-Obregón*, Karin Würtz-Kozak
26	***Ex vivo* biological evaluation of trabecular bone response to injectable ceramic based cements under mechanical loading**	Stephen Ferguson*, Karin Würtz-Kozak*

* Principal Investigator

Number	Title	Collaborator (CABMM members only)
27	**Functional analysis of non-coding RNA in osteoclastogenesis**	Michael Hottiger, Raffaella Santoro*
28	**Identification of tenocytic specific markers in the horse**	Paolo Cinelli*, Anton Fürst, Peter Richards
29	**Identification of RNKL-activated proteins regulating poly-ADP-ribose formation**	Michael Hottiger*, Peter Richards
30	**ImaValve**	Simon Hoerstrup*, Brigitte von Rechenberg
31	**Impingement syndrome in hip joints**	Alois Boos*, Patrick Kircher, Brigitte von Rechenberg
32	**Implantation of allogenic discs chondrocytes embedded in Albugel into pre-damaged nuclei pulposi in sheep**	Frank Steffen, Brigitte von Rechenberg*
33	**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
34	**Improved Soft Tissue Anchorage for Anterior Cruciate Reonstruction**	Peter Kronen, Dominik Meyer, Jess Snedeker*, Brigitte von Rechnenberg
35	**Influence of a new polymer dowel on primary stability and osseointegration of dental implants**	Peter Kronen, Brigitte von Rechenberg, Stefan Stübinger*
36	**Influence of different surface modifications and macro-designs of dental implants on the osseointegration**	Stephen Ferguson, Peter Kronen, Brigitte von Rechenberg, Stefan Stübinger*
37	**Intracranial tissue perfusion, pressure and temperature**	Patrick Kircher, Peter Kronen*, Brigitte von Rechenberg
38	**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*
39	**Investigation of the inflammatory processes associated with canine intervertebral disc herniation**	David Spreng*, Karin Würtz-Kozak*

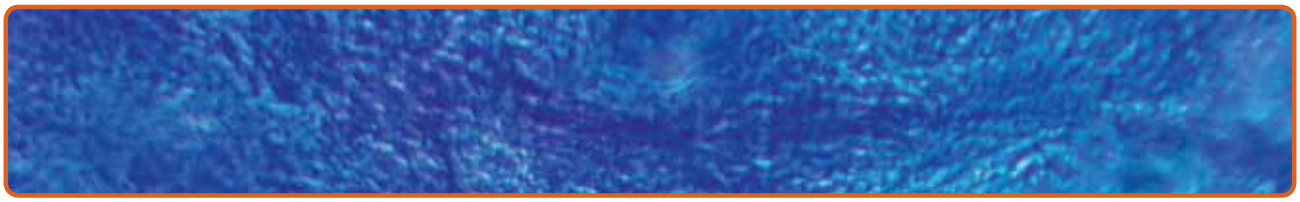
* Principal Investigator

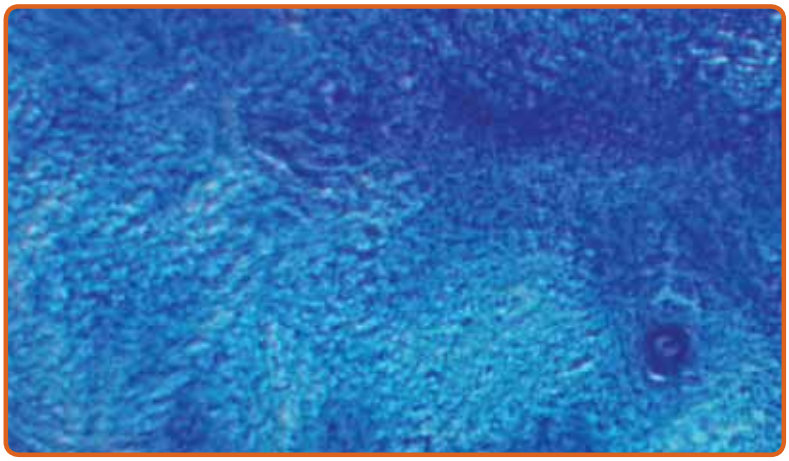
Number	Title	Collaborator (CABMM members only)
40	**Investigation of the Regenerative Effects of porcine Notochordal Cells onto bovine Intervertebral Disc Cells under Co-culture**	Benjamin Gantenbein-Ritter*, Karin Würtz-Kozak
41	**Investigation the anti-inflammatory, anti-catabolic, anti-apoptotic and anti-senescence properties of Epigallo-catechin gallate (EGCG) in human disc cells**	Norbert Boos, Stephen Ferguson, Steffen Gay, Oliver Hausmann, Karin Würtz-Kozak*
42	**Investigation the effects of PEMF in a murine *in vivo* model**	Stephen Ferguson, Alfredo Franco-Obregón*, Annette Liesegang, Jess Snedecker, Karin Würtz-Kozak
43	***In vitro* point-of care blood clot profiling by thromboelastography**	Simon Hoerstrup, Brigitte von Rechenberg, Daniel Rüfenacht*
44	**iValve**	Simon Hoerstrup*, Brigitte von Rechenberg
45	**LifeValve**	Simon Hoerstrup*, Brigitte von Rechenberg
46	**Local mechanisms in the growth plate of young growing animals**	Annette Liesegang*, Brigitte von Rechenberg
47	**Mechanisms of mechanotransduction in human intervertebral disc cells upon stimulation with PEMF or strain**	Alfredo Franco-Obregón*, Oliver Hausmann, Karin Würtz-Kozak*
48	**Modulation of extracellular matrix proteins by serine protease HtrA1 and its influence on bone formation**	Michael Blauth, Peter Richards*
49	**Molecular regulation of myogenesis: role of HTRA1**	Alfredo Franco-Obregón, Peter Richards*
50	**Monitoring osteomyelitis by biomarkers following ystemic inflammation parameters**	Regina Hofmann-Lehmann, Annette Liesegang, Brigitte von Rechenberg*, Raffaella Santoro
51	**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

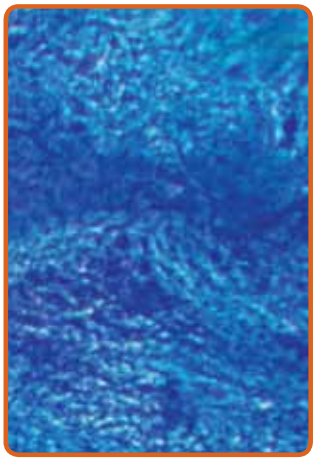
* Principal Investigator

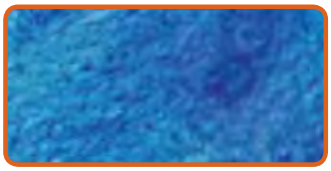
Number	Title	Collaborator (CABMM members only)
52	**NEMO and IKKb: Identifying potential targets for the treatment of early osteoarthritis using shRNA technology**	Karin Würtz-Kozak, Marcy Zenobi-Wong*
53	**Novel heterotopic working heart transplantation in rodents as a model for orthotopic *in vivo* investigation of tissue engineered heart valves**	Simon Hoerstrup*, Colin Schwarzwald
54	**Novel "stretched" PGA / PCL dip coated co-polymer stented scaffold: biomaterial *in vivo* evaluation in a rodent animal model**	Simon Hoerstrup*, Colin Schwarzwald
55	**Osteochrondral bone stimulation with fetal progenitor cells**	Lee Ann Laurent-Applegate*, Brigitte von Rechenberg
56	**Performance and safety of a new embolizing device in a pig model**	Simon Hoerstrup, Patrick Kircher, Peter Kronen*, Daniel Rüfenacht
57	**Photodynamic laser application for bisphosphonate-induced avascular bone necrosis**	Brigitte von Rechenberg, Stefan Stübinger*
58	**Regeneration of equine weight bearing tendons**	Anton Fürst*, Lee Ann Laurent-Applegate, Jess Snedeker
59	**Rekonstruktion von Knochendefekten durch lokale Wirkstofffreisetzung aus dem bioabbaubaren synthetischen Knochenersatzmaterial easy-graft®**	Peter Kronen, Brigitte von Rechenberg, Stefan Stübinger*
60	**Role of the infrapatellar fat pad on the pathophysiology of the diseased cranial cruciate ligament in dogs**	Peter Richards, David Spreng*
61	**Role of serine protease HtrA1 in spinal disc degeneration**	Peter Richards*, Karin Würtz-Kozak
62	**Spying on cells: Towards the establishment of a new non-viral drug delivery system using silica-coated superparamagnetic iron odixe nanoparticles (SPIONs)**	Michael Hottiger, Brigitte von Rechenberg*
63	**STEP – Sensing peri-implant disease**	Peter Kronen, Brigitte von Rechenberg, Stefan Stübinger*
64	**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

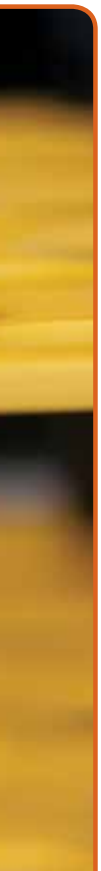
* Principal Investigator

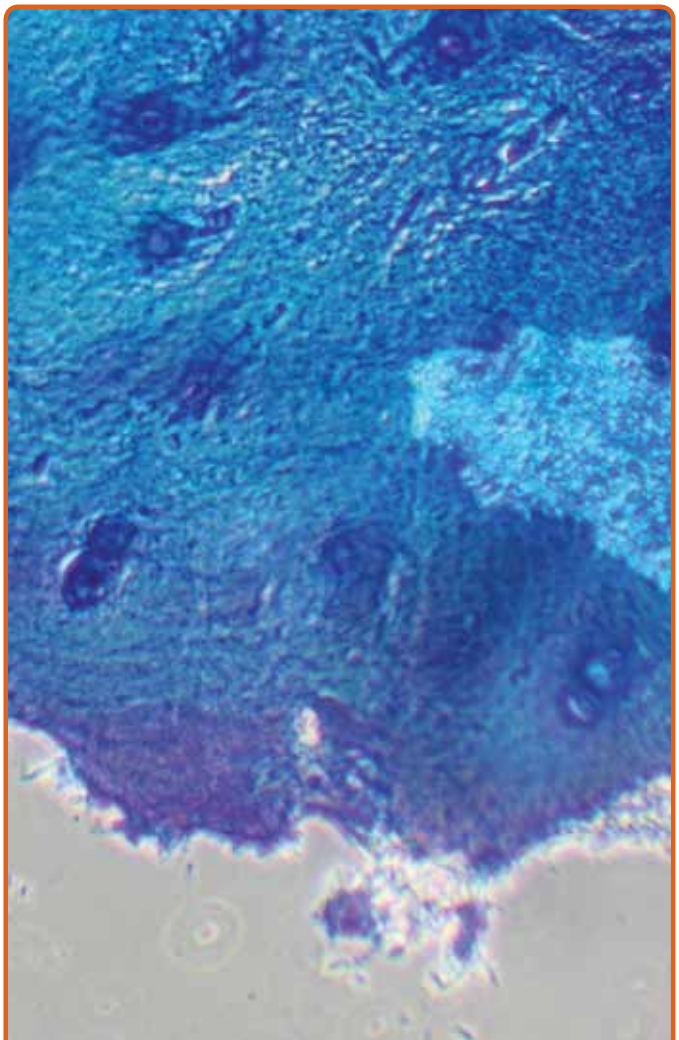












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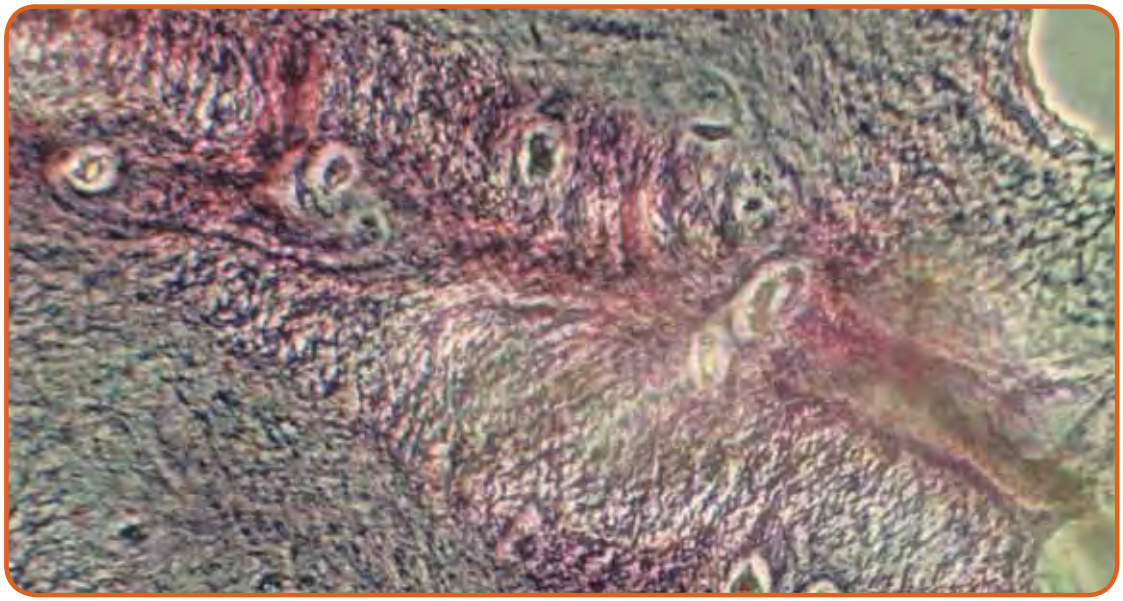

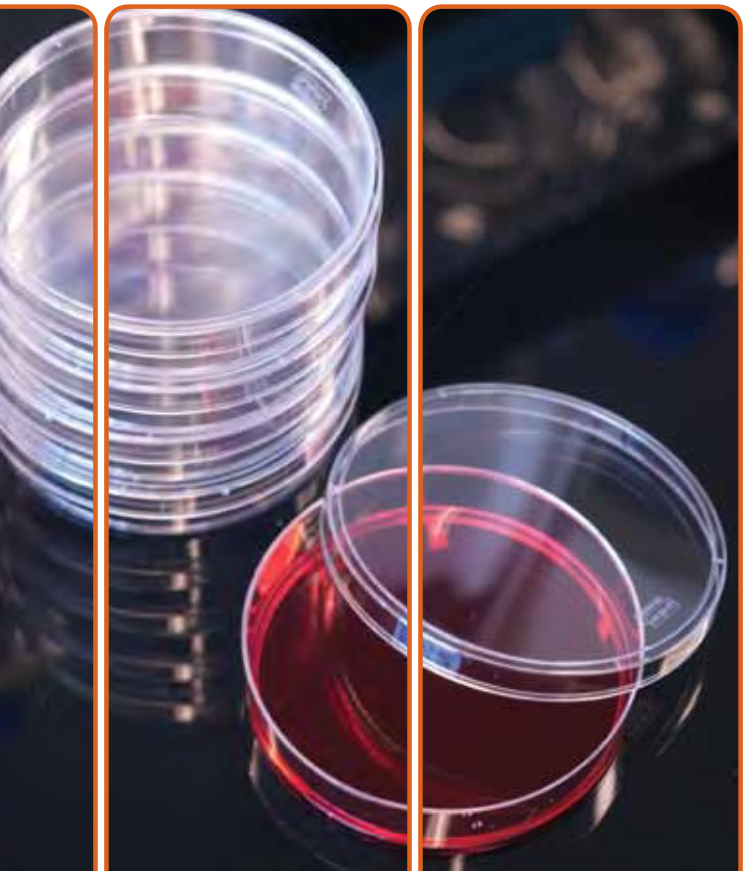

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