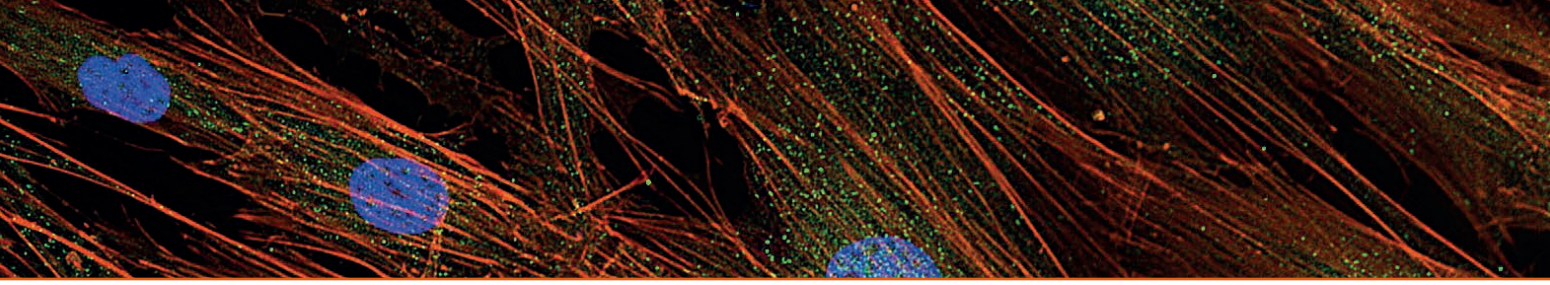
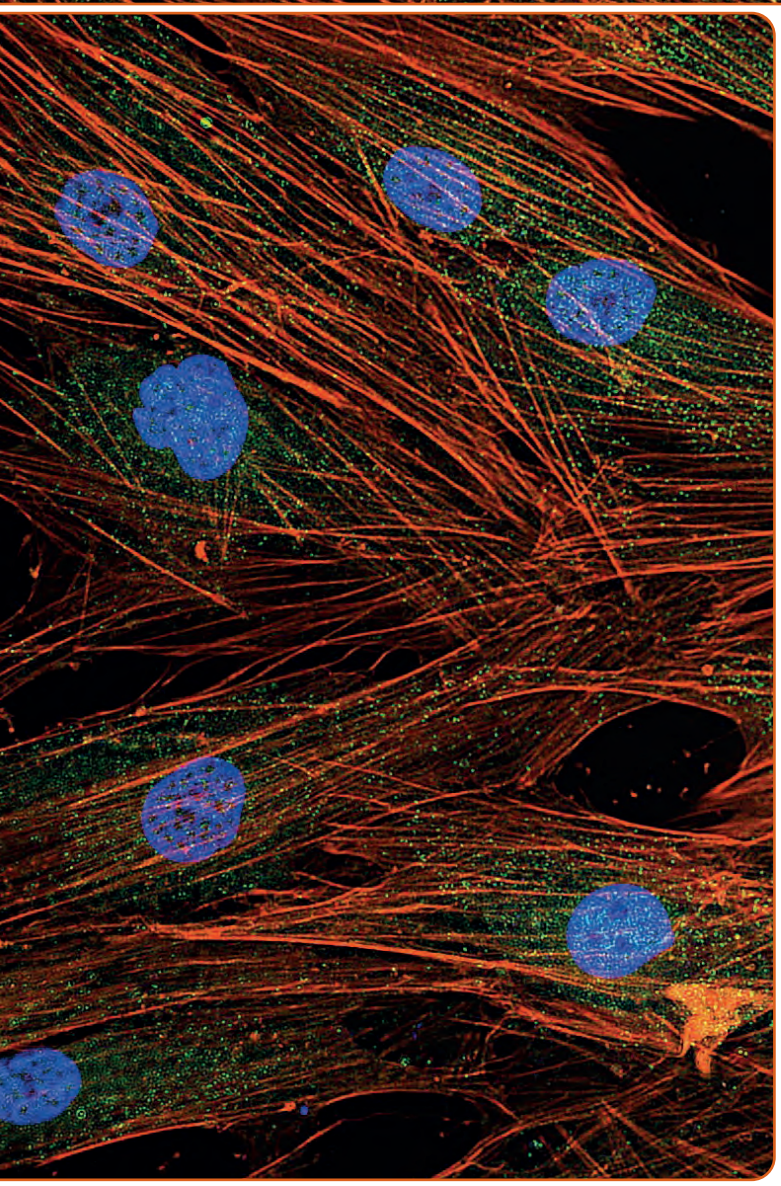
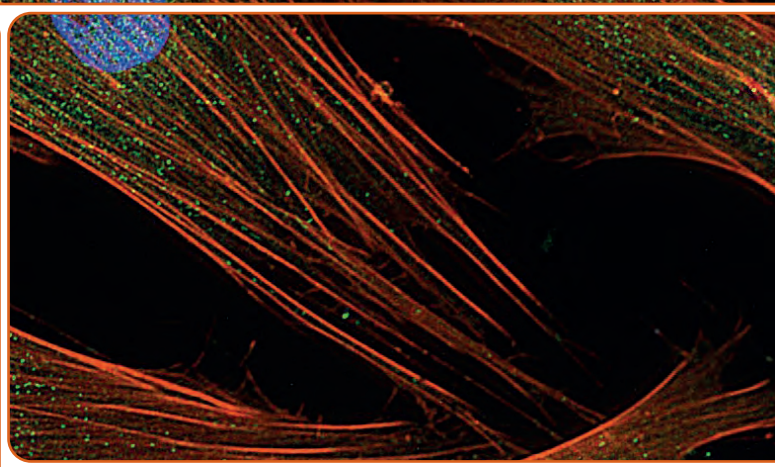
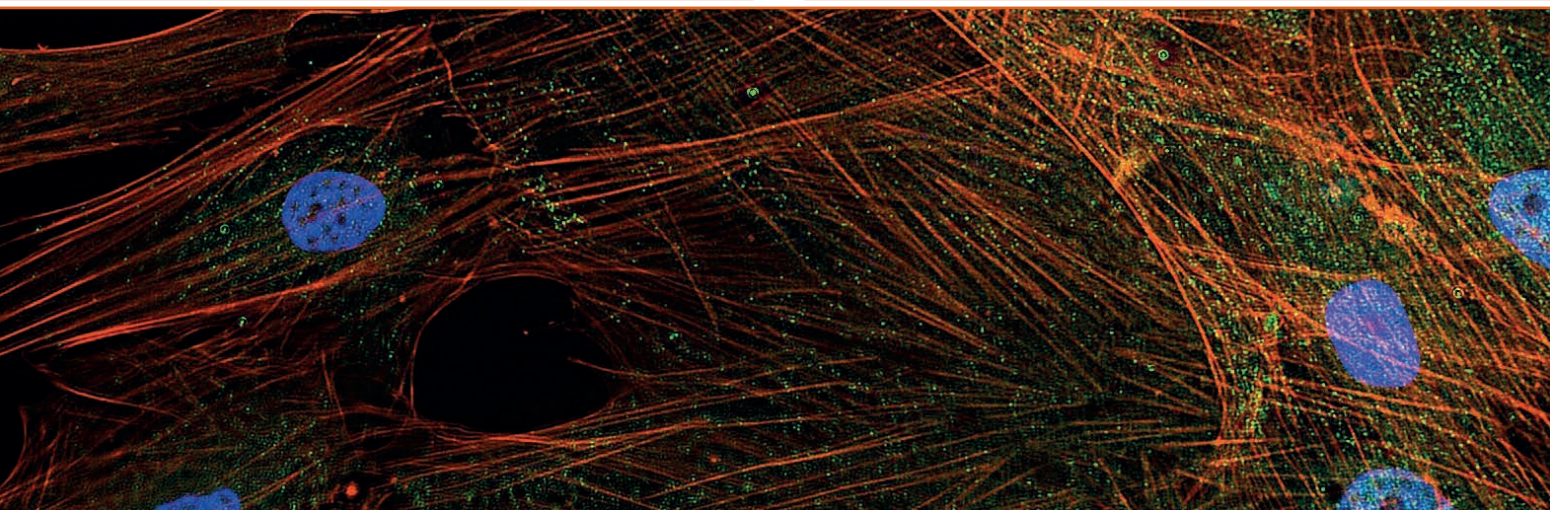




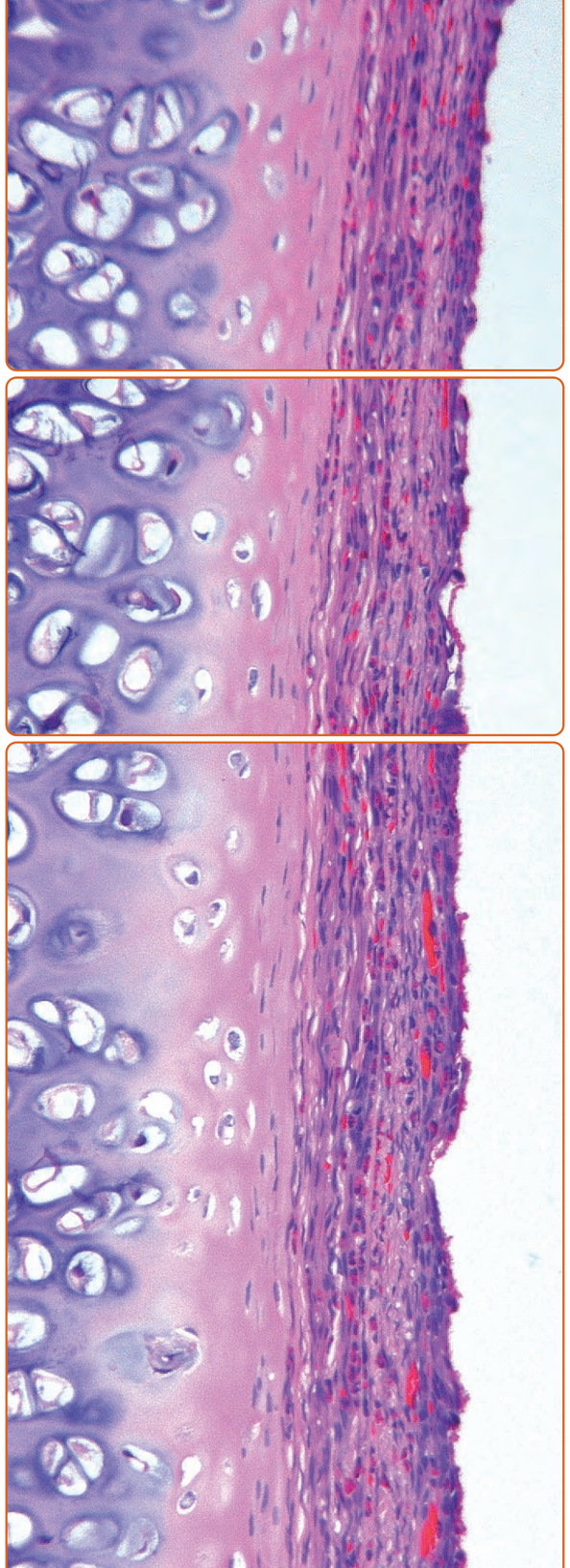


cabmm
center for applied biotechnology and molecular medicine

report 2020 / 2021



cabmm report
2020 / 2021



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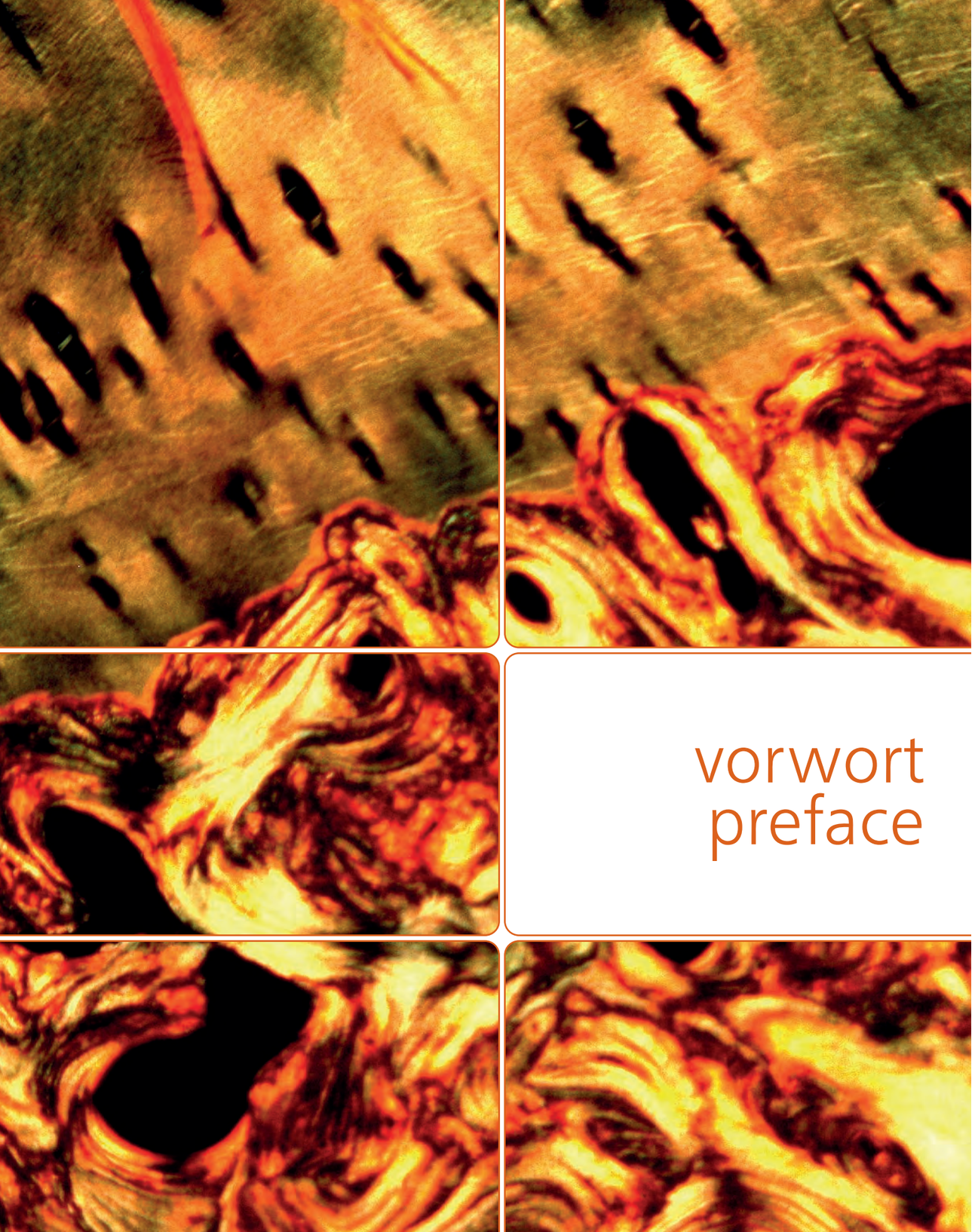


vorwort
preface

Liebe Leserin, lieber Leser,

„Zusammenkommen ist ein Beginn, Zusammenbleiben ein Fortschritt, Zusammenarbeiten ein Erfolg."
Henry Ford

Zusammenarbeit – das ist es, was das CABMM ausmacht.

Am CABMM herrscht Freude am Wissensaustausch und an der Entwicklung gemeinsamer Ideen und Projekte. Die Diversität in unserem Netzwerk und die interdisziplinäre Zusammenarbeit laden ein, einen Blick über den eigenen Tellerrand zu riskieren und auch einmal neue Wege zu gehen, was letztendlich die Voraussetzung für Innovationen und erfolgreiche, translationale Forschung ist.

Einen kleinen Einblick in die Welt des CABMM gewährt Ihnen der vorliegende CABMM Report. Neben allgemeinen Informationen und wissenschaftlichen Forschungsberichten erhält der Report mit Porträts von Personen aus dem CABMM Netzwerk auch wieder eine ganz persönliche Note.

Ich freue mich auf die zukünftige Zusammenarbeit und viele, neue, spannende Projekte innerhalb des CABMM und wünsche Ihnen viel Spass mit unserem Rückblick auf bereits Erreichtes im neuen CABMM Report!

Dr. Silke Kalchofner-Mark
Geschäftsführerin CABMM

Dear reader,

"Coming together is a beginning, staying together is progress, and working together is success."
Henry Ford

Working together – that's what characterizes the CABMM.

At the CABMM, people really enjoy exchanging their knowledge and expertise and jointly developing ideas and projects. The diversity within our network and plenty of interdisciplinary collaborations entice one to risk a look beyond everyday business and to explore new horizons. And eventually, that's a prerequisite for innovation and successful translational research.

The present CABMM Report allows you a little insight into the world of the CABMM. In addition to general information and scientific research reports, it also comprises again portraits of people connected to the CABMM network, adding a special personal touch.

I am very much looking forward to future collaborations and many new exciting projects within the CABMM, and hope you enjoy the review of our accomplishments compiled in the new CABMM Report!

Dr. Silke Kalchofner-Mark
Managing Director CABMM

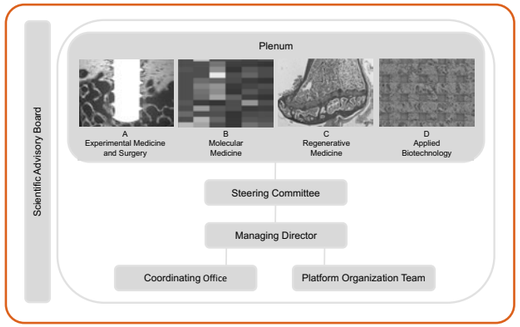
about us

cabmm bodies and events

ABOUT US

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

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



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

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

Furthermore, the CABMM offers expertise in regulatory affairs: Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) were established through two founding members of the CABMM, Prof. Dr. Brigitte von Rechenberg and Prof. Dr. Dr. Simon P. Hoerstrup, respectively. As Good Clinical Practice (GCP) has already been running at the University Hospital for several years, the University of Zurich now combines all regulatory requirements for the development, production, and first clinical trials of new drugs and therapies. The CABMM now continues its efforts in regulatory affairs by providing a platform that allows for intensifying the interaction between the three responsible groups, e.g., by promoting the exchange of ideas and discussions about the interfaces of their regulatory fields.

In order to strengthen the CABMM network and enhance collaborations between CABMM members from a variety of research disciplines, so far, two major events were organized every year. Unfortunately, in the reporting period, we could not hold any on-site events due to the COVID-19 pandemic. As the CABMM events primarily thrive on personal interactions and discussions, and real-life meetings make them what they are and cannot be adequately replaced by a virtual setting, no major CABMM event took place in the reporting period. However, the CABMM Scientific Seminar, a lecture series organized by the CABMM, could be continued and even profited by the change to an online format, as also CABMM member groups from outside Zurich were able to participate, allowing for the continuation of a lively exchange within the CABMM member network and beyond.

On the following pages, the Steering Committee represented by Prof. Dr. Dr. Simon P. Hoerstrup and the Scientific Advisory Board represented by Prof. em. Dr. Brigitte von Rechenberg are looking back on the achievements and obstacles that have been overcome within the reporting period. Additionally, a tabular summary of the CABMM Scientific Seminar in 2020 and 2021 can be found.

from the cabmm steering committee

from left to right: Prof. Dr. Dr. Simon P. Hoerstrup, Prof. Dr. Dr. Michael O. Hottiger, Prof. Dr. Annette Liesegang, Prof. Dr. Janine Reichenbach, Prof. Dr. Marcy Zenobi-Wong, Dr. Silke Kalchofner-Mark

The reporting period of 2020/2021 was very much influenced by the corona pandemic. Despite this challenging time, the CABMM looks back on two successful years.

In 2020, we received renewed approval as official competence center of the University of Zurich for the time period of 2020-2023 by the University leadership. Thanks to the diligent preparation of all the information and necessary documents by Dr. Silke Kalchofner-Mark and the CABMM Coordinating Office, the approval process went very smoothly. I would like to thank all involved people for doing such a great job, and express my special thanks to Prof. Roger Stephan, Dean of the Vetsuisse Faculty, and Prof. Rainer Weber, former Dean of the Medical Faculty, for their support.

Moreover, the Musculoskeletal Research Unit (MSRU) as one of the core groups in the CABMM member network received **re-accreditation by Swissmedic** to conduct studies **in compliance with the principles of GLP** and was able to expand its portfolio: In addition to testing biocompatibility and efficacy of medical devices and pharmaceuticals, the MSRU is now also able to perform toxicity studies under GLP. Congratulations! This further strengthens not only the Zurich location as hub for translational research but also the CABMM network and reflects the ongoing success of the CABMM in establishing and optimizing a GxP compliant environment.

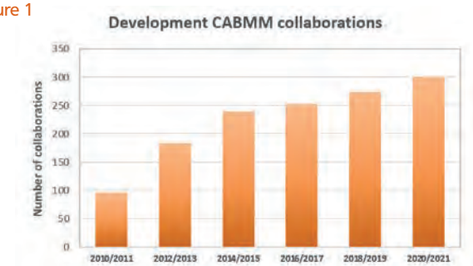
The important role of the CABMM as translational center for innovative and applied research was further underlined by the fact that the **first prize for the best investor pitch** was awarded to our CABMM Research Platform users Dr. Scott Finlay and Dr. Salim Darwiche by a jury of entrepreneurial experts as part of the BioEntrepreneurship & Innovation (BEI) program of UZH in 2021. They presented a novel cartilage repair technology, that is currently being developed on the CABMM Research Platform in a collaborative project between two CABMM member groups – the Musculoskeletal Research Unit, University of Zurich, and the Regenerative Therapy Unit, CHUV, Lausanne – as well as Swiss and international industrial partners, showcasing one of many successful collaborations in translational and applied research within the CABMM network.

In general, the achievements and the development of our competence center and, particularly, its **networking and collaborative character** are impressive. Despite the corona pandemic, the number of collaborations within the CABMM network was increasing in the reporting period (300 collaborations; 10% higher compared to the last reporting period; Fig. 1). This is particularly remarkable, as the number of memberships was only slightly growing (82 members at the end of December 2021 compared to 78 at the end of the last reporting period), and also the work on the CABMM Research Platform had to be temporarily stopped due to the pandemic situation. Nevertheless, our member network stayed active, and 90 related scientific publications were published in the reporting period.

Unfortunately, we were not able to hold the main CABMM events, but the weekly CABMM Scientific Seminar has been continued in an online format. This virtual setting was very well received, and we decided to continue our lecture series in this way, as it allows people from outside Zurich to participate and thus, fosters a broader and lively interdisciplinary exchange within our global network.

New Steering Committee member: Prof. Dr. Marcy Zenobi-Wong

Figure 1



Furthermore, we are glad to inform that we had the pleasure to welcome a new member to the CABMM Steering Committee: Prof. Marcy Zenobi-Wong joined our board at the beginning of 2021, and we are very happy to have her with us. My thanks to her and all other Steering Committee members for their commitment and continuous support of our center.

In the name of the CABMM Steering Committee, I would like to close with thanking all of you, who made the CABMM what it is today. The CABMM would not have been possible without the fantastic support of its members, the CABMM Coordinating Office, the CABMM Scientific Advisory Board, and various key supporters, such as Dr. h. c. mult. Hansjörg Wyss and the Mäxi Foundation. We can be very proud of the CABMM's achievements within the past years.

Zurich, November 2022
Prof. Dr. med. Simon P. Hoerstrup, PhD
Chairman of the CABMM Steering Committee

cabmm steering committee

Name and affiliation	Application field
Prof. Dr. med. Simon P. Hoerstrup, PhD (chairman) Medical Faculty, University of Zurich	C – Regenerative Medicine
Prof. Dr. med. vet. Dr. phil. II Michael O. Hottiger (vice-chairman) Vetsuisse Faculty and Faculty of Science, University of Zurich	B – Molecular Medicine
Prof. Dr. med. vet. Annette Liesegang Vetsuisse Faculty, University of Zurich	A – Experimental Medicine and Surgery
Prof. Dr. med. Janine Reichenbach Medical Faculty, University of Zurich and University Children`s Hospital Zurich	B – Molecular Medicine
Prof. Dr. Marcy Zenobi-Wong (PhD) ETH Zurich	C – Regenerative Medicine
Dr. Silke Kalchofner-Mark (PhD) Vetsuisse Faculty, University of Zurich	Managing Director

the scientific advisory board of the cabmm

from left to right: Prof. em. Dr. Brigitte von Rechenberg, Prof. em. Dr. Dr. Dr. Hans-Florian Zeilhofer, Prof. em. Walter Schaffner, Prof. em. Dr. Markus Aebi

The aim of the Scientific Advisory Board (SAB) is to critically evaluate the quality of the CABMM activities and to review grant applications for a CABMM Start-up Grant. Furthermore, all SAB members offer general support in all scientific questions and participate in the training and promotion of young academics. The participation in the yearly CABMM Seminar and CABMM Symposium allows the SAB to get insights into the quality of the network and to contribute to fruitful discussions. The SAB represents various scientific disciplines and fields of medical practice and is supported by the Deans of the Medical and the Vetsuisse Faculty of the University of Zurich who are *ex officio* members.

cabmm scientific advisory board

Name and affiliation	Representing
Prof. em. Dr. med. vet. Brigitte von Rechenberg (chairwoman) University of Zurich	Application field A – Experimental Medicine and Surgery
Prof. em. Dr. Walter Schaffner (PhD) University of Zurich	Application field B – Molecular Medicine
Prof. em. Dr. med. Dr. med. dent. Dr. h. c. Hans-Florian Zeilhofer University Hospital Basel	Application field C – Regenerative Medicine
Prof. em. Dr. Markus Aebi (PhD) ETH Zurich	Application field B – Molecular Medicine
Prof. Dr. med. Frank Rühli, PhD Dean of the Medical Faculty, University of Zurich	*(ex officio)*
Prof. Dr. med. vet. Dr. h. c. Roger Stephan Dean of the Vetsuisse Faculty, University of Zurich	*(ex officio)*

"Tempora mutantur, nos et mutamur in illis – Times change and we change with them…" a hexameter created by Ovid in Roman times and since the 16th century known as a proverb in our culture. It is not only true for the world, but also for the CABMM. During the off-time due to corona, everything came to a halt including our activities at the CABMM. Labs were closed, experiments could not be conducted and also many collaborations went into hibernation, as well as the activities of the Scientific Advisory Board (SAB).

The duties of the SAB are twofold: on one side the evaluation of the CABMM Start-up Grants, on the other side the evaluation of the overall scientific activities of the CABMM. Both activities were coming to a halt, though for different reasons. The SAB met once every year in the reporting period, but only for discussing CABMM Start-up Grant projects. Due to the overall situation during the corona-crisis, the evaluation of the overall CABMM activities was put on hold. Nevertheless, we are all back on track again and will get involved in the CABMM evaluation in the coming months.

The CABMM Start-up Grant, however, will have to get new funding before this successful path can be reiterated. With the final year of the Mäxi Foundation's support, there are no longer resources left for financing grants. All we can promise at this time point is that we are exploring new ways. Let's cross our fingers that we will be successful.

Changes also occurred with the members of the SAB. Our chairman, Prof. Felix Althaus, retired from the SAB with our great thanks for his proficient leadership during his time at the Board. Prof. Brigitte von Rechenberg was elected as his follower as chairwoman of the Board.

We are also very pleased to announce that we could win Prof. Markus Aebi as new SAB member. Furthermore, Prof. Frank Rühli joined the Board as *ex officio* member in his function as new Dean of the Medical Faculty. We would like to welcome both new SAB members and thank Prof. Rainer Weber as previous *ex officio* representative of the Medical Faculty for his support during his term in office.

Zurich, November 2022
Prof. em. Dr. med. vet. Brigitte von Rechenberg
Chairwoman of the CABMM Scientific Advisory Board

cabmm scientific seminar

The CABMM Scientific Seminar is a lecture series organized by the CABMM that is held each spring and autumn semester.

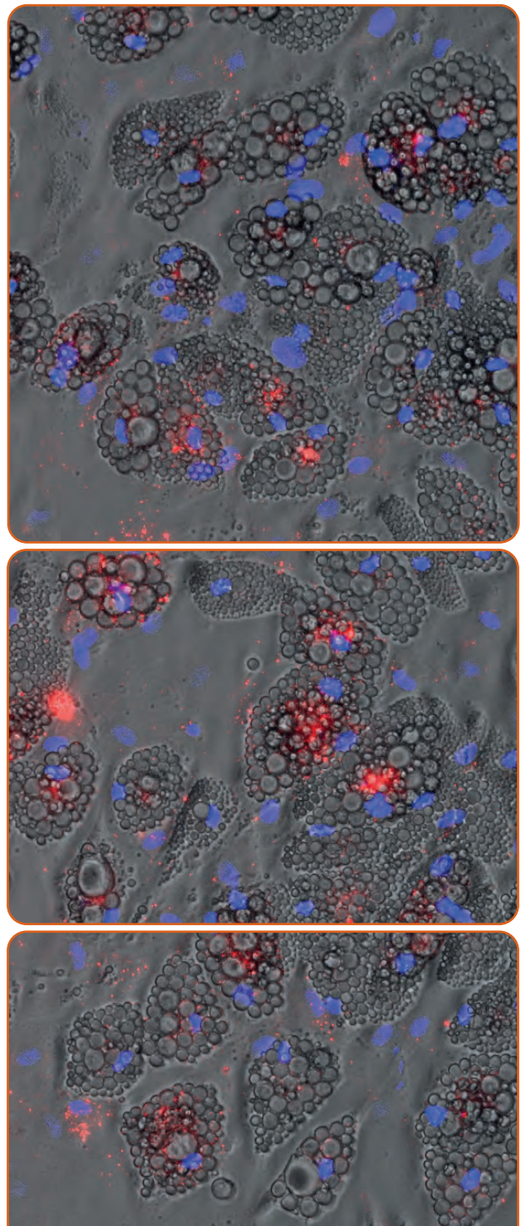
It has a special structure consisting of different mini-series, each of which representing a specific research group of the CABMM network or highlighting a collaborative project or a special topic in the field of translational research that is considered to be of importance to our network.

In general, every mini-series starts with an overview talk given by the principal investigator that is followed by presentations of research projects or topic-related articles by group members. After each presentation, a discussion takes place that encourages scientific brainstorming.

The lectures are an integral part of the University's course catalogue (FWB82).

We would like to highlight that, well in line with the CABMM's commitment to animal welfare, two mini-series were recognized for continuing education credit by the Veterinary Office of the Canton of Zurich in this reporting period: the mini-series "Anesthesia and Analgesia" in the spring semester of 2020 that was held by the Office for Animal Welfare and 3R of the University of Zurich, the Musculoskeletal Research Unit and Section Anaesthesiology of the University of Zurich; and the mini-series "The Swiss Association of Veterinarians in Industry and Research (SAVIR)" in the autumn semester of 2020 dealing, inter alia, with legislation in the field of animal welfare. Both topics attracted numerous attendees, also from outside of the CABMM.

A tabular summary of all mini-series given during the reporting period can be found on the following pages.



spring semester 2020

Mini-series	Speaker(s)	Title
Anesthesia / Analgesia *	Dr. med. vet. Peter Kronen	*Animal experimentation: an obvious case for analgesia?*
	PD Dr. med. vet. Simone Ringer, PhD	*Sequelae of anesthetic complications in small animals*
	Dr. med. vet. Rima Bektas	*Einfluss der Anästhesieführung auf die Sauerstoffversorgung*
	Dr. Paulin Jirkhof (PhD)	*Side effects of untreated pain and analgesia in animal experimentation*

autumn semester 2020

Mini-series	Speaker(s)	Title
Clinical and pathopysiological relevance of Modic type 1 changes in chronic low back pain	Dr. Stefan Dudli (PhD)	*Modic type 1 changes in chronic low back pain: basic research and clinical implication*
	Irina Heggli, MSc	*Bone marrow stromal cells contribute to fibrosis in Modic type 1 changes*
Collagen cross-linking (CXL): research in sight saving technology	Prof. Simon Pot, DVM	*From concept to clinic: The Corneal Cross-linking (CXL) Story*
	Malwina Kowalska, DVM	*PACK-CXL protocol optimization: effects of acceleration, fluence and riboflavin concentration on tissue stability, treatment and antibacterial efficacy*
	Prof. Dr. med. Farhad Hafezi, PhD	*PACK-CXL Phase III clinical trial in human patients*
Swiss Association of Veterinarians in Industry and Research *	Dr. med. vet. Maike Heimann	*The Swiss Association of Veterinarians in Industry and Research (SAVIR) and introduction to the SVLAS expert title for vets in laboratory animal science*
	Dr. med. vet. Maike Heimann	*Animal experiment in Switzerland - reality and public opinion*
	Dr. Birgit Ledermann (PhD)	*The Swiss Laboratory Animal Science Association (SGV) – a partner association of SAVIR*
	Dr. med. vet. Maike Heimann	*The Swiss Transparency Agreement on Animal Research (STAAR)*

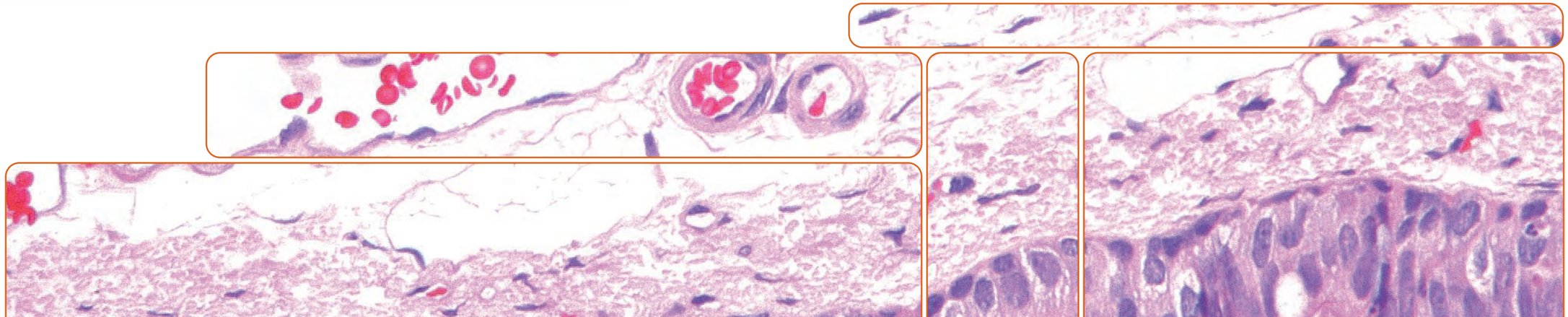
* recognition for continuing education credit

spring semester 2021

Mini-series	Speaker(s)	Title
BioMed Entrepreneurship Ecosystem at UZH	Dr. Marion Haug (PhD) Dr. Christina Sina (PhD)	*Programs in BioMed Entrepreneurship: BioEntrepreneurship & Innovation (BEI) program and Minor in BioMed Entrepreneurship*
	Dr. Eva Maria Håkanson (PhD) Matthias Herrmann, MSc	*UZH entrepreneurship ecosystem at a glance: UZH Innovation and USZ Health Innovation Hub*
	Dr. Roch Ogier (PhD, MD)	*Early fundraising for life science projects (Translational Development Accelerator, TDA)*
	Dr. Sina Reckel (PhD) Dr. Melanie Wiesel (PhD) Lukas Langenegger, MSc Robin Müller	*Translation of scientific discoveries into new therapies: Wyss Zurich*
At the Interplay of Bone Morphogenic Proteins and their Antagonists with respect to improved fracture healing or spinal fusion	Prof. Benjamin Gantenbein (PhD)	*Bone Morphogenic Proteins and their inhibitors and their potential role for improved spinal fusion*
	Fatemeh Safari	*The role of BMP and BMP antagonists in bone remodeling*
	Franziska Silvia Strunz, MSc	*Repair of a critical size defect in osteoporotic bone*
	Andreas Shaun Croft, MSc	*Effect of Different Cryopreservation Media on Human Nucleus Pulposus Cells' Viability and Trilineage Potential*
Advances in Cartilage Regeneration: Lab to Clinic (and vice versa)	Dr. Philippe Abdel-Sayed (PhD)	*Models for pre-clinical safety for cartilage tissue engineering*
	Alexis Laurent, Pharm.	*Optimal cell sources for industrial transposition*
	Dr. Virginie Philippe (PhD)	*Autologous cartilage cell therapy transplantation: GMP implementation*

autumn semester 2021

Mini-series	Speaker(s)	Title
New strategy to treat cartilage and intervertebral disc pathologies: from models to patients	Prof. Andrea Barbero (PhD)	*Cartilage Tissue Engineering*
	Jesil Kasamkattil, MSc	*Spheroids generated by human nasal chondrocytes for scaffold-free nucleus pulposus augmentation*
	Andrea Mainardi, MSc	*Mechanically active Organs-on-Chip as advanced models of osteoarthritis*
	Laura Dönges, MSc	*In vitro model to study cartilage hypertrophy in osteoarthritic conditions*
Insights from Multiscale Functional Imaging of Tendon	Prof. Jess Snedeker (PhD)	*Tendon in Disease, Injury, and Rehabilitation*
	Tobias Götschi, MSc	*PIEZO1 Gain-of-Function is Associated with Increased Tendon Stiffness in Humans*
Veterinary Clinical Infectiology – An Insight in Research Projects at the Clinical Laboratory	Prof. Dr. med. vet. Regina Hofmann-Lehmann	*The Clinical Laboratory: Introduction and Research in Clinical Infectiology*
	Dr. sc. nat. Marina Meli	*Cytauxzoon europaeus n. sp. infections in domestic cats, lynx and wildcats in Switzerland and in wildcats in France: a tale that started more than two decades ago*
	Dr. med. vet. Andrea Spiri	*Rehoming of research cats – important considerations to make the story a success*
	med. vet. Julia Klaus	*SARS-CoV-2 from One Health perspective: current data on infections in animals and potential risks*



portraits

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

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

Prof. Dr. med. vet. Franck Forterre

- Professor for small animal and neurosurgery at the University of Bern
- Structured and self-disciplined team player
- Nature lover with a great sense of humor
- Well-trained and crazy about sports
- Part of a very ambitious family

Prof. Dr. med. Frank Rühli, PhD

- Founder of the Institute of Evolutionary Medicine
- Dean of the Medical Faculty of the University of Zurich
- Member of the CABMM Scientific Advisory Board
- Member of the City Council of Zurich
- Family man

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.

„gut gelaunter teamplayer“

franck forterre, porträt von paula lanfranconi

Franck Forterre ist Ausserordentlicher Professor für Kleintier- und Neurochirurgie an der Universität Bern sowie Leiter der Kleintierklinik. Seit 2014 ist er Mitglied des CABMM. Der Teamplayer hat viel Humor. Und er ist ziemlich sportverrückt.

Die grosse hölzerne Katzenskulptur auf seinem Schreibtisch springt sofort ins Auge. Ja, er sei ein Katzentyp, bestätigt Franck Forterre mit einem leichten französischen Akzent. „Ich mache viel Sport und brauche eine Tierbeziehung mit viel Freiheit.“ Mit einem Hund wäre er gebunden. Rund um sein Pult streben Pflanzen in die Höhe. „Mein Dschungel, und der Affe sitzt mittendrin“, kommentiert Forterre lachend. Die geometrischen Bilder des Op-Art-Künstlers Victor Vasarely stehen hingegen für seine strukturierte Art.

Franck Forterres Hauptforschungsinteresse gilt Rückenmarkserkrankungen bei Hunden, aber auch bei Katzen. Seine Forschungsideen stammen aus seiner chirurgischen Tätigkeit und befassen sich mit der einfachen Frage: Warum? Insbesondere das, was „nicht klappt“, weckt seinen Forschergeist. Forterre versteht sich als Teamplayer, legt Wert auf richtiges Delegieren: „Die Aufgabe wird besprochen und dann komplett delegiert.“ Anders wäre sein Workload auch gar nicht zu stemmen. Klinikleitung, Forschung und Betreuung beanspruchen viel Zeit. Dazu kommt noch eine Gastprofessur in Uppsala. Doch dem durchtrainierten 54-Jährigen scheint vieles leicht zu fallen. Die Lehre bezeichnet er als eines seiner Steckenpferde und die Chirurgie als „eine der schönsten Pausen in meinem Arbeitsalltag“.

Zum CABMM stiess Neurochirurg Franck Forterre 2014, auf der Suche nach Kooperationspartnern. Als Kliniker, erläutert er, könne er gut analysieren, wo die Forschung ansetzen müsste, doch für die Umsetzung im Labor brauche man Support. Zweimal erhielt Forterre einen CABMM Start-up Grant. Beide Male ging es um Entzündungsprozesse nach Bandscheibenvorfall bei Hunden: „Ich hatte und habe einen sehr guten Austausch mit Karin Würtz-Kozak.“ Aktuell forscht er an Mini Pigs und Hunden über Wirbelfusion. Die ersten Resultate seien viel versprechend, das Interesse der Humanmedizin gross. „Aber eine Schwalbe macht noch keinen Sommer“, relativiert der erfahrene Forscher.

Dass es ihn in die Tiermedizin verschlagen würde, stand keineswegs fest: Sein Traumberuf war Bergführer. Doch der Vater, Gymnasialdirektor im südfranzösischen Antibes, fand, der Filius habe zu gute Noten. Wenn du Tiermedizin studierst, versprach man ihm, kannst du in einem Nationalpark in den Alpen arbeiten. Das motivierte den Naturfreak. Er studiert in Toulouse, da sind die Pyrenäen nicht weit. Danach wechselt er mit einem DAAD (Deutscher Akademischer Austauschdienst)-Stipendium an die Münchner Ludwig-Maximilians-Universität und spezialisiert sich auf Neurochirurgie. Es folgt eine Einladung der Freien Universität Berlin. Und 2005 kommt der Anruf aus Bern. „Ein Traum!“ Bern war das europäische Mekka der Neurologie, mit Koryphäen wie André Jaggy. Und Berge gab es da auch zuhauf.

Auf Forterres Pult steht ein Familienfoto. Vier strahlende Gesichter. Und alle ganz schön ambitioniert. Im Vergleich zu ihm, stellt Forterre fest, sei seine Frau Simone eine Triathletin von Beruf. Zuerst studierte sie Ernährungswissenschaften, doktorierte und forschte dann in Tiermedizin. Letztes Jahr setzte sie noch einen Master in Medical Education obendrauf. „Dieser Studiengang“, sagt Forterre mit gespielter Gequältheit, „muss ihr Letzter sein“. Ebenso strebsam ist Tochter Florine. Die 18-Jährige ist im Nationalkader Moderner Fünfkampf – Fechten, Schwimmen, Laufen, Schiessen, Reiten. Nach der Matur will sie in Bern Humanmedizin studieren.

Spätestens jetzt drängt sich der Besucherin die Frage auf, wie das Forterresche Powercouple Familie und Beruf auf die Reihe kriegt. Simone und er seien „eine sehr gute Symbiose“, antwortet Forterre. Seine Frau habe ihm den Rücken freigehalten, als er es gebraucht habe. Heute, wo Simone als Studienkoordinatorin jedes Wochenende arbeite, um das neue veterinärmedizinische Curriculum umzusetzen, habe er den Haushalt mehr oder weniger übernommen: „Ich mache das gerne. Heute kann ich meine Zeit freier einteilen.“ Zudem seien die Kinder bereits unabhängiger.

Aber nochmals: Wie bringt man so vieles unter einen Hut? Forterres Antwort kommt rasch: „Strukturieren. Und viel Selbstdisziplin.“ Es gibt Leute, die sagen, er sei ein bisschen verrückt. Wenn er morgens in die Klinik kommt, ist er oft schon von seinem Wohnort Schwarzenburg auf den Gurnigelpass geradelt. Das sind satte 800 Höhenmeter. Und an Wochenenden geht’s per Rennrad über Alpenpässe. Doch das Radfahren ist nur Vorbereitung auf den Winter, denn Forterres Leidenschaften sind Langlauf und Biathlon. „Ich bin vom mediterranen Sonnenkind zum Wintermenschen geworden“, stellt er fest. Fast 2000 Kilometer habe er letzte Saison auf den schmalen Latten zurückgelegt.

So viel Leistung könnte nach Verbissenheit klingen, doch für Franck Forterre scheint Sport reine Erholung zu sein: „Egal, welchen Ärger der Tag bringt – dank dem Training habe ich frühmorgens etwas erlebt, was mir niemand nehmen kann.“ So sei er fast immer gut gelaunt. Bei studentischen Feiern, fügt er schmunzelnd bei, mache er „oft den Pausenclown“. Und er spiele bei Theaterstücken mit. Zum Beispiel als Gnom Gollum. Aber es kann auch eine Fee sein.

Die Zukunft? Franck Forterre wäre sich selber untreu, würde er sich nicht bereits mit seiner Nachfolge befassen. Bis 60 will er an der vordersten Front bleiben, danach einen Schritt zurücktreten, um seine potentiellen Nachfolgerinnen oder Nachfolger zu unterstützen. Er habe in Bern verschiedene Prozesse in Gang gesetzt, die wolle er begleiten: „Ich bin ein bisschen wie ein Terrier. Kein böser, aber ich bleibe dran.“

Und privat? Da will er seinen Kindern zur Seite stehen und sportlich noch etwas mithalten mit ihnen. Bei Fünfkämpferin Florine habe er allerdings dieses Jahr verloren, räumt er ein. Und er wird seine Frau Simone unterstützen. „Sie hat es wirklich verdient!“ Seine Stimme klingt warm.

Es geht gegen 11.40 Uhr, die Interviewstunde ist vorbei. Ein Patient wartet. Ein Hund. Nichts Dringliches. „Aber“, fragt Franck Forterre beim Abschied, „was ist wirklich dringend im Leben?“

"good-humored team player"

franck forterre, portrait by paula lanfranconi

Franck Forterre is an associate professor for small animal and neurosurgery at the University of Bern and head of its Small Animal Clinic. He has been a CABMM member since 2014. The team player has a great sense of humor, and he is rather crazy about sports.

The big wooden cat sculpture on his desk directly catches one's eye. Yes, he would be the cat type, confirms Franck Forterre with a slight French accent. "I am doing a lot of sports and need a lot of freedom in a relationship with an animal." With a dog, he would be bound. All around his desk, plants are growing upwards. "My jungle, and the monkey is right in the middle" comments Forterre, laughing. In contrast, the geometrical pictures of the Op Art artist Victor Vasarely represent his structured nature.

Franck Forterre's main research interest are diseases of the spinal cord in dogs, but also in cats. His research ideas develop from his surgical work and address a simple question: Why? Things that "do not work" especially stimulate his inquisitive mind. Forterre sees himself as a team player and highlights the importance of properly delegating tasks: "The task is discussed and subsequently entirely delegated." Otherwise, he would not be able to manage his workload. Clinic management, research, and supervision need a lot of time. On top of that comes a visiting professorship in Uppsala. But a lot of things seem to come easily to the well-trained 54-year-old. He thinks of teaching as one of his hobbies and surgery as "one of the nicest breaks during his working day".

The neurosurgeon Franck Forterre joined the CABMM in 2014, when he was looking for collaborative partners. As a clinician, he explains, he could very well analyze which issues need to be addressed in a research project, but he would need support for their realization in the lab. Forterre was twice supported by a CABMM Start-up Grant. Both times it was about inflammatory processes after disc herniation in dogs: "I had and still have a very good exchange with Karin Würtz-Kozak." He currently investigates spinal fusion in minipigs and dogs. First results would be promising, and of high interest to human medicine. "But it takes more than one swallow to make a summer", relativizes the experienced researcher.

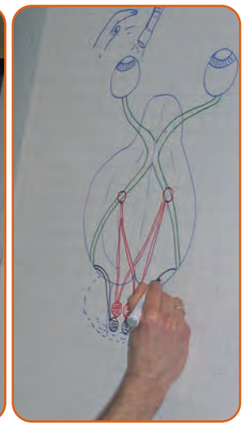
That he ended up in veterinary medicine was by no means predetermined: the job of his dreams was to be a mountain guide. But his father, director of a secondary school in Antibes in Southern France, thought that his junior's grades were too good. If you would study veterinary medicine, he was told, you could work in an alpine national reserve. That motivated the nature lover. He studied

in Toulouse, not far from the Pyrenees. Then he went to Ludwig Maximilian University of Munich supported by a DAAD (Deutscher Akademische Austauschdienst, German Academic Exchange Service) stipendium and specialized in neurosurgery. Subsequently, he was invited to the Free University of Berlin. Finally, in 2015, he received a phone call from Bern. "A dream!" Bern was the European Mecca for Neurobiology, with experts like André Jaggy. And with many mountains.

On Forterre's desk is a family picture. Four happy faces. And all very ambitious. Compared to him, Forterre states, his wife Simone would be a professional triathlete. First, she studied nutritional sciences, then did a doctorate and started to do research in veterinary medicine. On top of this, she completed her master's degree in medical education last year. "This degree", says Forterre with feigned distress "has to be her last one". His daughter Florine is equally ambitious. The 18-year-old is a member of the national squad in modern pentathlon – fencing, swimming, running, shooting, and horse riding. After school, she wants to study human medicine in Bern.

At this stage, the visitor is compelled to ask herself how the Forterre power couple manages to keep their family and working life in order. Simone and he have "a good symbiosis", answers Forterre. His wife took the load off from him when he needed it. Nowadays, as Simone is working every weekend as study coordinator to implement the veterinary curriculum, he would pretty much take care of the household: "I am happy to do this. Today, I have more flexibility in managing my time." Additionally, the kids would be already more independent.

But again: How is it possible to balance so many things? Forterre's answer follows immediately: "Structure. And a lot of self-discipline." Some people say that he would be a little crazy. When he arrives at the clinic in the morning, he has often already gone by bike from his home in Schwarzenburg to the Gurnigelpass. That means an 800 meters difference in altitude. And, during the weekends, he is riding his racing bike over alpine passes. But all this cycling is only in preparation for the winter season, as Forterre's real passion is cross-country skiing and biathlon. "I changed from a Mediterranean child of the sun to a winter person", he states. During the last season, he covered almost 2'000 kilometers on cross-country skis.



That much activity could sound like doggedness, but for Franck Forterre, doing sports seems to be pure relaxation: "No matter what kind of trouble the day might bring – thanks to the training early in the morning, I experience something that no one can take away from me." Thus, he would be almost always in a good mood. At student parties, he adds smiling, he would often be the "comic relief". He would also act in theatre plays. For example, as the gnome Gollum. Or as a fairy.

The future? Franck Forterre would not remain true to himself if he would not have already addressed the question about his succession. Until the age of 60, he will continue playing the leading role. Then, he wants to take one step back in order to support his potential successor. He has set processes in motion in Bern, and he would like to accompany them: "I am little bit like a terrier. Not a bad one, but I keep at it."

And in private life? He wants to support his children and keep up with them in sports for some time. But he concedes that he already lost against pentathlete Florine this year. Furthermore, he wants to support his wife Simone. "She really deserves it!" His voice shows affection.

11:40 am is approaching, the interview is over. A patient is waiting. A dog. Nothing really urgent. "But what", Franck Forterre asks when saying goodbye, "is really urgent in life?"

„geerdeter mumienforscher – und dekan“

frank rühli, porträt von paula lanfranconi

Professor Frank Rühli ist Gründungsdirektor des Instituts für Evolutionäre Medizin der Universität Zürich. Als Dekan der Medizinischen Fakultät gehört er dem Wissenschaftlichen Beirat des CABMM an. An Sitzungen liebt es der eloquente Mumienforscher, mit einem provokativen Spruch abgehobene Egos in die Realität zurückzuholen.

Der Blick seiner grossen blauen Augen geht in die Weite. So, als schaue der weltbekannte Mumienforscher auf einen fernen Zeithorizont – viele seiner „Patienten” sind schliesslich etliche tausend Jahre alt. Sein Büro an der Universität Zürich Irchel zieren Fotos von altägyptischen Denkmälern und kleine Repliken von Skulpturen. Mumie findet sich keine. Mumien in einem Büro, das wäre in Frank Rühlis Augen unethisch.

Eigentlich hätte der Vielbeschäftigte gar keine Zeit. Heute ist der letzte Tag des Sommersemesters. In einer Stunde steht eine Dekanatssitzung mit den Spitzen von Universität und Universitätsspital Zürich an. Doch für das CABMM hat Rühli eine halbe Stunde frei geschaufelt. Er schätze das CABMM als sehr interdisziplinäre, auf akademische Exzellenz und Innovation ausgerichtete Institution, sagt er. „Das sind die klassischen Parameter, die wichtig sind für die Universität.”

Was empfiehlt er dem CABMM als Wissenschaftlicher Beirat? Sein Grundanliegen, antwortet er, sei, dass man mit anderen ähnlichen Institutionen zusammenarbeite, innerhalb der Universität, aber auch extern. „So, dass man nicht in einem Bubble drinsteckt, sondern versucht, durch das Konglomerat unterschiedlicher Wissenschaftlerinnen und Wissenschaftler einen Mehrwert zu schaffen – ausserhalb der bereits bestehenden Pfade.” Wichtig ist ihm auch die Nachwuchsförderung.

Professor Frank Rühli, 51, ist Gründungsdirektor des Instituts für Evolutionäre Medizin der UZH. Die Evolutionäre Medizin versuche, aus der Vergangenheit für die Gegenwart und die Zukunft zu lernen, erläutert er. Einerseits durch entsprechende Datensätze. Aber auch durch konzeptionelle Überlegungen. „Es ist ein holistischer Blickwinkel, der über das rein Technische hinausgeht: Warum wird jemand krank? Warum ist diese Krankheit noch nicht ausgemerzt?” Ziel sei letztlich, Erkenntnisse für die heutige Medizin zu gewinnen.

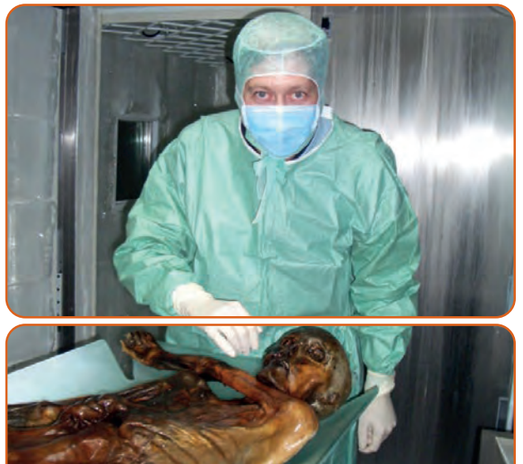
Der gebürtige Zürcher interessierte sich schon als Kind für das alte Ägypten, studierte dann aber nicht Ägyptologie, sondern Medizin. Im Rahmen seiner ersten Doktorarbeit untersuchte er eine Mumie und machte an der University of Adelaide ein PhD-Studium. Dabei ging es vertiefter um Evolution. Rühlis erste Forschungsprojekte an der UZH kamen rasch voran, auch dank der Unterstützung durch die Mäxi-Stiftung, eine Gemeinsamkeit mit dem CABMM. Inzwischen hat Rühli so berühmte Mumien wie Tutanchamun oder Ötzi untersucht. Die alten Ägypter seien einerseits an Infektionskrankheiten gestorben. „Interessanterweise aber auch an ähnlichen Leiden wie wir Heutigen: degenerative oder kardiovaskuläre Krankheiten.”

Zu Rühlis Forschung gehört auch die Evolution von Erregern. So beforscht sein Institut historische Gewebe nach Infektionsfaktoren oder man untersucht das Public Health-Verhalten während der Spanischen Grippe von 1918, der letzten grossen Pandemie in der Schweiz. Um zu zeigen, dass die UZH als Volluniversität sehr viele Krisenszenarien – nicht nur Covid – abdecken könne, gründete Rühli 2021 das UZH Center for Crisis Competence (CCC). „Nebenher” fungierte der Professor zudem als Mitherausgeber des „Weissbuch Corona. Die Schweiz nach der Pandemie”. Darin beleuchten 40 Expertinnen und Praktiker aus allen Lebens- und Wissensbereichen die mittel- und langfristigen Auswirkungen der Pandemie auf die Schweiz.

Den grössten Teil seiner Arbeitszeit – wohl bis zu 80 Prozent – nimmt heute sein Amt als Dekan der Medizinischen Fakultät ein. „Da haben wir wirklich Leverage und können für eine gute akademische Medizin einstehen”, freut sich Rühli. Dass er als Dekan kein klassischer Mediziner sei, habe vielleicht Nachteile. Aber auch Vorteile. Als Mumienforscher bewege er sich in einem Paralleluniversum – es gebe weniger Interessenkonflikte. Und: Wenn man sich mit tausendjährigen Körpern befasse, relativiere sich so einiges: „In Sitzungen, bei denen es hoch zu und her geht, habe ich öfter Lust, die Leute daran zu erinnern, dass die meisten von ihnen wohl in 50 Jahren alle unter dem Boden liegen werden”, sagt Rühli schmunzelnd.

„Zum Ausgleich” engagiert sich der 51-jährige Freisinnige im Gemeinderat der Stadt Zürich. Er setzt sein Wissen zum Beispiel in der Aufsichtsfunktion über das Stadtspital ein. Da steht dessen Ausgliederung aus der Stadtverwaltung an. Es stelle sich die Frage: Wie garantiert man eine gute Gesundheitsversorgung und besteht trotzdem im Markt? Als Milizoberst befasst sich Rühli mit Entwicklungsszenarien wie beispielsweise Pandemien. Das alles erde ihn. „Und es macht auch meinen Reiz aus.”

Last but not least ist der Vielbeschäftigte auch Familienvater. Seine beiden Kinder sind noch klein, doch sie zeigen bereits eine gewisse Affinität zur Tätigkeit ihres Vaters: „Zum Beispiel wickeln sie sich in einen Teppich ein und sagen: Ich bin eine Mumie ... .” Bloss: Bleibt bei dieser Agenda noch Zeit für die Familie? Man müsse sich halt relativ konsequent Zeit nehmen und zu gewissen Zeitfenstern keine Sitzungen machen und das Wochenende freihalten. Sagt er. Doch die Abgrenzung zwischen Beruf und Hobby falle ihm schwer. So sei er schon mal an einem Wochenende nach Ägypten geflogen zum Forschen, verrät er.



Theaterbesuche? Nur noch sehr begrenzt. Und auch zum Lesen komme er nicht mehr oft. Sein Favorit ist Albert Camus. Der Existentialist beschreibe eindrücklich, wie wenig die Menschen das Leben reflektieren. „Zusammen mit seinen Landschaftsbeschreibungen ist das einmalig.”

Für die Zukunft ist dem Forscher wichtig, dass sein Institut gut läuft und dass es valablen Nachwuchs generiert. Während seiner Zeit als Dekan will er dafür einstehen, dass die verschiedenen Akteure – UZH, Universitätsspitäler und ETHZ – gemeinsam auf einen exzellenten Medizinstandort Zürich hinarbeiten. Und was wünscht er sich als Mensch? Seine Antwort kommt rasch und überzeugend: „Ein glückliches Familienleben!”

Der 51-Jährige, so scheint es, ist mit sich im Reinen. Er habe, sagt er zum Schluss, immer ein reichhaltiges Leben gewollt. „Da kann ich mich nicht beklagen.”

Die Zeit drängt. Schon bald beginnt die Dekanatssitzung, drunten in der Stadt. Für ein Mittagessen reichts wohl nicht mehr, ein starker Kaffee muss genügen.

"down-to-earth mummy researcher – and dean"

frank rühli, portrait by paula lanfranconi

Professor Frank Rühli is founding director of the Institute of Evolutionary Medicine at the University of Zurich. As Dean of the Medical Faculty, he is a member of the CABMM Scientific Advisory Board. In meetings, the eloquent mummy researcher loves to bring out-of-touch egos back to reality with a provocative statement.

The gaze of his big blue eyes goes into space. As if the world-famous mummy researcher were looking at a far time horizon – after all, many of his "patients" are several thousands of years old. His office at University Zurich-Irchel is decorated with pictures of ancient Egyptian monuments and small replicas of sculptures. There is no mummy. A mummy in an office, that would be unethical in Frank Rühli's view.

Actually, the extremely busy professor barely has any time at all. Today is the last day of the spring semester. The deanship meeting with the leaders of the University and University Hospital Zurich will start in one hour. But for the CABMM he made some time. He values the CABMM as a very interdisciplinary institution focusing on academic excellence and innovation, he says. "These are the classical parameters that are important for the University."

What does he recommend to the CABMM as member of its Scientific Advisory Board? His basic concern, he answers, would be to collaborate with similar institutions within the University, but also externally. "So one does not live in a bubble, but tries to create added value through the conglomerate of different scientists – off the beaten track." Moreover, the promotion of young scientists would be important to him.

Professor Frank Rühli, 51, is founding director of the Institute of Evolutionary Medicine at UZH. Evolutionary Medicine tries to learn from the past for the present and future, he explains. On the one hand, by systematic data sets, but also by conceptual thinking. "It is a holistic view which goes beyond the pure technical perspective. Why does someone fall sick? Why is this disease still existing?" In the end, the aim would be to gain insights for today's medicine.

The Zurich-born had already been interested in ancient Egypt since his childhood but then studied medicine and not Egyptology. During his first doctorate, he investigated a mummy, and then did a PhD study at the University of Adelaide where he gained deeper insights into evolution. Rühli's first research projects at the UZH quickly made progress, also thanks to the support of the Mäxi Foundation, one thing in common with the CABMM. In the meantime, Rühli investigated such famous mummies as Tutanchamun or Ötzi. On the one hand, the ancient Egyptians died of infectious diseases, "but, interestingly, also of similar diseases like today's people: degenerative or cardiovascular diseases".

Rühli's research also includes the evolution of pathogens. Thus, his institute is looking for infectious factors in historical tissues or studying public health behavior during the Spanish flu in 1918, the last big pandemic in Switzerland. In order to show that the UZH as a comprehensive university could cover many crisis scenarios – and not only Covid – Rühli founded the UZH Center for Crisis Competence (CCC) in 2021. "Alongside", the professor is co-editor of the "Weissbuch Corona. Die Schweiz nach der Pandemie" (White Paper Corona. Switzerland after the Pandemic). In this book, 40 experts and practicians from all areas of life and science describe medium- and long-term impacts of the pandemic on Switzerland.

Nowadays, he dedicates most of his time at work – up to 80 percent – to his function as Dean of the Medical Faculty. "There, we really have leverage and can stand for good academic medicine", Rühli says happily. Perhaps it would have disadvantages that he as Dean would not be a classical physician. But it would also have advantages. As mummy researcher, he would move in a kind of parallel universe – there would be less conflicts of interest. Furthermore, if someone deals with thousands year-old bodies, a lot of things would be put in a different perspective: "In meetings where arguments heat up, I often have the desire to remind people that most likely most of them will be six feet under in 50 years", Rühli says with a smile.

"For counterbalancing" the 51-year-old liberal is committed to the City Council of Zurich. He uses his knowledge for example in the supervisory function over the city hospital, which is going to be spun off from the city administration. The question is: How can good healthcare be guaranteed and remain competitive? As military colonel, Rühli is working on development scenarios such as pandemics. All that grounds him. "And that's also what makes it appealing."

Last but not least, the very busy man is also father of a family. His two children are still young, but both already show some affinity for their father's work: "For example, they are wrapping themselves in a carpet and saying: I am a mummy… ." But, does his agenda allow any time for his family? You would have to take time rather consequently, not schedule any meetings at certain times and keep the weekends free, so he says. But the clear boundaries between work time and personal time would sometimes be difficult for him to hold. It already happened that he went to Egypt on a weekend to do research, he reveals.

Visits to a theatre? Only very limited. And he would only rarely get to read. His favorite writer is Albert Camus. The existentialist impressively describes how little humans would reflect on their life. "Together with his description of landscapes, this is unique."

For the future, it is important for the researcher that his institute is doing well and generates eligible young academics. During his time as Dean, he wants to drive the different players – UZH, University Hospitals, and ETHZ – to work together on Zurich as an excellent location for medicine. And what does he wish for himself as a human being? The answer comes at once and in a convincing way: "A happy family life!"

It seems that the 51-year-old is at peace with himself. At the end, he says that he always wanted a rich life. "I cannot complain."

Time is short. Soon the deanship meeting will start, down in the city center. There won't be enough time for having lunch anymore, a strong coffee will have to do.

Photo: University of Basel Kings' Valley Project

research reports

cabmm research platform

The CABMM Research Platform is a multidisciplinary organisation embedded within the Department of Molecular Mechanisms of Disease (DMMD) at the University of Zurich. Our main objectives are to foster translational, clinically oriented research and to promote scientific collaborations between CABMM members. The CABMM Research Platform is well equipped and provides a stimulating environment, where basic scientists and clinicians can discuss their research and ideas and work shoulder to shoulder for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissues.

During the reporting period 2020/2021, there have been a total of four research groups and 15 people using the CABMM Research Platform. As the idea behind the CABMM Research Platform is to offer all CABMM members the possibility to rent a space for a certain time and/or project, personnel changes are rather common, and only three of the groups listed below used the CABMM Research Platform during the complete reporting period. For the other group, the time of finishing its work on our platform is indicated.

1. **Cancer Epigenome Group**
   Group leader: Michael O. Hottiger (until 12 / 2020)

2. **Musculoskeletal Research Unit**
   Group leaders: Katja Nuss, Karina Klein, Salim Darwiche

3. **Ocular Cell Biology Group**
   Group leader: Farhad Hafezi

4. **Skin Engineering Group**
   Group leader: Maurizio Calcagni

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

Moreover, at the beginning of this chapter, we present one research project of the Musculoskeletal Research Unit (MSRU) from the Vetsuisse Faculty, University of Zurich, in more detail in the leading article. The MSRU has been using the CABMM Research Platform since its creation in 2008. That is why numerous projects were performed on our platform and/or in collaboration with other CABMM member groups during the past years. In the leading article, Dr. Salim Darwiche and Dr. Karina Klein from the the MSRU leadership consortium present their research project **"Electromagnetic field therapy to enhance fracture healing"** and conclude with some general considerations about evaluation strategies in preclinical research and the clinical translation of positive preclinical outcomes.

Electromagnetic field therapy to enhance fracture healing

Dr. Salim Darwiche (PhD) and
Dr. med. vet. Karina Klein, PhD
Group members (in alphabetical order): Dr. med. vet. Flurina Clement Frey, PhD, Ljubica Dimbrek, med. vet. Simon Dolert, Dr. Scott Finlay (PhD), Rikke Grundtvig, med. vet. Isabel Heel, Andrew Hicks (animal caretaker), Dr. med. vet. Agnieszka Karol, Dr. med. vet. Peter Kronen, Dipl. ECVAA, med. vet. Felix Lehner, Aymone Lenisa (lab technician), Tatiana Müller, Dr. med. vet. Katja Nuss, Joanna Schmid, med. vet. Sarah Schleich, med. vet. Milena Tegelkamp, Prof. em. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS, Rosita Walther, med. vet. Christina Wiezorek, med. vet. Paula Zscherpe

Delayed or non-unions remain at the forefront of outstanding challenges in fracture healing. The incidence can vary depending on the fractured bone location and other comorbidities, with associated significant economic and clinical impacts. Therapies using electromagnetic field technology have shown evidence of enhanced bone growth and regeneration at the fracture site, but the modalities of treatment vary greatly, so do the outcomes.

Testing a new technology for fracture healing in a preclinical *in vivo* model

The Musculoskeletal Research Unit (MSRU) tested a new technology using combined electric and magnetic field (CEMF) therapy and its potential to enhance bone healing in two standardized tibia osteotomy models in sheep. The technology was designed by Neue Magnetodyn GmbH (Munich, Germany) and the pre-clinical *in vivo* study was funded by Johnson & Johnson Family of Companies. The CEMF technology tested in this study was different from standard electromagnetic field devices: it used a combination of magnetic and *in situ*-amplified electric stimulation. A primary external magnetic field activated an implanted transducer by electromagnetic induction, which generated an electric voltage between connected screws, placed across a fracture gap (Fig. 1). The CEMF technology was designed to expand the functionality of already existing standard orthopedic and trauma implants (in this case, a locking compression plate stabilizing two long bone fragments) to an on-demand, active stimulation device for bone healing. The challenge was to test this technology in an animal model which would be translatable to the human clinical situation, using standardized, precise and well-controlled surgical and post-surgical protocols as well as a multidisciplinary approach to evaluating bone healing in order to reliably detect any potential enhancement from using CEMF.

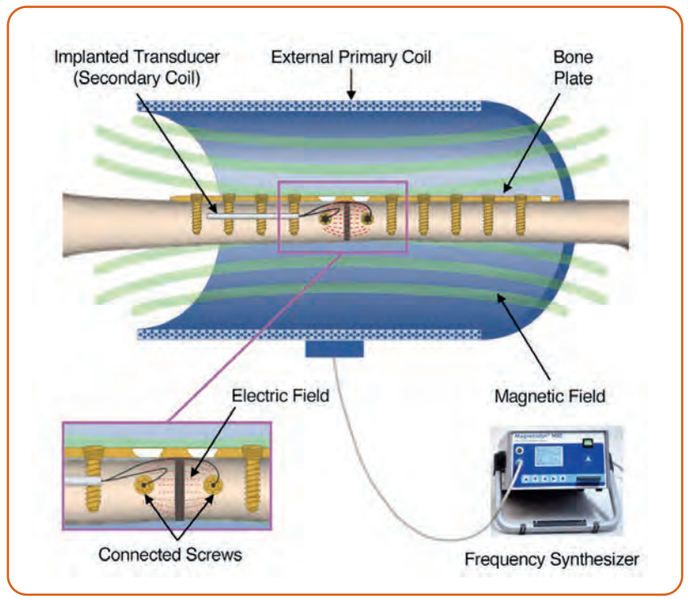


Figure 1: Schematic representation of the CEMF technology, showing the primary external coil, the magnetic field it generates when connected to the frequency synthesizer, the implanted transducer (secondary coil), which is connected to two screws placed on either side of the defect. The magnetic field generated by the primary coil induces an electrical field at the defect area, between the connected screws, without any physical transcutaneous connection to implanted components, thereby reducing infection risks.

Schematische Darstellung der CEMF-Technologie: Die primäre externe Spule generiert das elektromagnetische Feld, welches durch die Verbindung zum Frequenzsynthesizer und durch die sekundäre Transducer Spule bei den zwei verbundenen Schrauben auf je einer Seite des Frakturspaltes das elektrische Feld am Frakturspalt verursacht. Das System funktioniert ohne physische, transkutane Verbindung zwischen den Komponenten, womit die Gefahr einer Infektion deutlich reduziert wird.

The novel CEMF treatment was therefore evaluated in two standardized sheep tibia osteotomy models: a 3 mm non-critical size gap model and a 17 mm critical size defect model augmented with autologous bone grafts, both stabilized with locking compression plates. CEMF treatment was delivered across the fracture gap twice daily for 90 mins, starting 4 days post-surgery until sacrifice (9 or 12 weeks post-OP for the 3 mm and 17 mm defect model, respectively). Control groups received no CEMF treatment. Various evaluation methods were employed to assess bone healing:

- Regular radiographic follow-up from surgery to the 9-week or 12-week endpoints were performed together with semi-quantitative radiographic scoring;
- Morphometric analysis using post-mortem micro-CT data was used to assess callus volume and density;
- Micro-CT data was then analyzed using finite element modeling to perform virtual torsion tests and generate virtual torsional rigidity data;
- Regular intravital fluorescent injections were used to later detect histologically the deposited calcium at different stages of healing;
- Post-mortem torsional rigidity was also assessed as a primary biomechanical outcome;
- Qualitative and semi-quantitative histological analysis was performed to assess biocompatibility (according to ISO10993-6 guidelines) and evaluate bone healing.

In the 3 mm gap model, the CEMF group (n = 6) exhibited higher callus mineral density compared to the control group (n = 6), two-fold higher biomechanical torsional rigidity and a histologically more advanced callus maturity, but no statistically significant differences were detected (Fig. 2 and 3). This was likely due to the 9-week investigative endpoint, a stage at which differences in healing kinetics may not be easily detected in non-critical defects, particularly in a model in which healing was not otherwise impaired (as is the case in delayed and non-unions). The timepoint at 12 weeks in the 17 mm defect group, however, was ideal to distinguish a clear effect of CEMF therapy. Indeed, differences between the control (n = 6) and CEMF group (n = 6) were more pronounced. The CEMF group showed a radiologically more advanced callus, a higher callus volume ($p = 0.003$), higher virtual torsional rigidity ($p = 0.007$) and a 2.6x higher biomechanical torsional rigidity ($p = 0.024$), combined with a histologically more advanced callus maturity and healing (Fig. 4 and 5).

Overall, the CEMF technology tested in this study notably enhanced bone healing, particularly in larger defects, resulting in better new bone structure, callus morphology and superior biomechanical properties. This technology could therefore be an important addition to a surgeon's toolbox for accelerated healing and regeneration. The advantage of the CEMF technology tested in this study is that it can be applied separately and independently from the standard fixation technique. The outer coil component can easily be placed when therapy is needed and, therefore, could be easily integrated into routine postoperative care. Indeed, the CEMF technology tested in this study could be applied in revision cases or after a delayed union has manifested.

The advantage of multi-disciplinary evaluation strategies in preclinical *in vivo* studies

This study employed a wide range of pre-clinical evaluations (e.g., radiographs, CT morphometry, virtual torsional rigidity, biomechanical testing, histology) in order to comprehensively evaluate the effect of CEMF technology on bone healing. In this animal model, the CEMF-treated groups were hypothesized to show improved healing, but the control groups were also expected to heal (the 3 mm gap model is a non-critical size model and the 17 mm graft model augmented with autologous bone grafts is also expected to heal fully, albeit slower than the 3 mm gap model). The choice of evaluation tools was therefore important, so was the choice of endpoint.

Some of the evaluation tools used are translationally relevant (radiographs, CT scans, virtual torsional rigidity), while

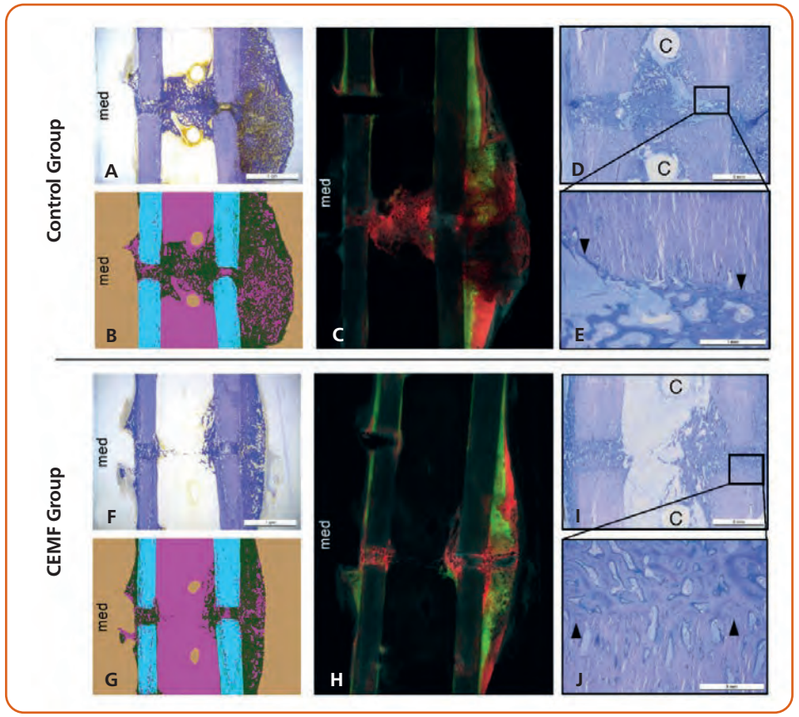


Figure 2: Representative histological, histomorphometric and fluorescent pictures of the 3 mm gap model, showing toluidine blue surface-stained ground sections (A, F), their respective histomorphometric segmentation (B, G) as well as the corresponding native section showing fluorescent dye deposition (C, H). The histomorphometric pictures (B and G) show background in beige, old bone in cyan, new bone in dark green and non-bone tissue in magenta. The fluorescent pictures (C and H) show overlays of Calcein green 3-week deposition in green, Xylenol orange 6-week deposition in red and Oxytetracycline 9-week deposition in blue. Overall, the interfragmentary healing and remodeling was more advanced in the CEMF group, associated with a smoother callus, versus a more irritated callus and less mature healing in the control sample. Toluidine blue-stained thin sections are also shown at low (D, I) and high (E, J) magnification. CEMF screw holes are indicated with the letter "C". Black arrows indicate the fracture line, specifically the transition between old and new bone, and point towards the fracture gap, showing an organized and integrated new bone formation at the fracture gap, particularly in the CEMF sample.

Repräsentative histologische, histomorphometrische und fluoreszierende Bilder des 3 mm Defektes: mit Toluidinblau Oberflächen-gefärbte Dickschnitte (A, F), die Segmentierung für die verschiedenen Knochensegmente (B, G), sowie die entsprechenden Fluoreszenzschnitte (Native Schnitte) (C, H). Die histomorphometrischen Schnitte (B und G) zeigen den Hintergrund in beige, alten Knochen in hellblau, neuen Knochen in grün und weichen Kallus in magenta. Die Fluoreszenzbilder (C und H) zeigen die Kalziumablagerung von Calceingrün (3 Wochen), Xylol-Orange in rot (6 Wochen) und Oxytetracyclin in blau (9 Wochen). Insgesamt war die interfragmentäre Frakturheilung und das Remodeling bei der CEMF-Gruppe ausgeprägter. Der Kallus war schmaler, regelmässiger und glatt verglichen mit einem dickeren, unregelmässigen, und weniger weit entwickelten Kallus bei den Kontrolltieren. Dünnschnitte (Toluidinblau) mit geringer (D und I) und hoher Vergrösserung (E und J) zeigen das Kallusgewebe am Frakturspalt. Die CEMF Schrauben sind gekennzeichnet mit C, die schwarzen Pfeile bezeichnen die Frakturlinie, speziell zwischen dem Übergang vom alten zum neuen Knochen des Kallus, und sind gegen den Frakturspalt gerichtet. Der neue Knochen im Kallus ist besser strukturiert in der CEMF-Gruppe.

others cannot be translated to human clinical situations and can only be applied in preclinical animal studies (biomechanical tests, histology). Biomechanical testing can reveal important differences between healing outcomes at certain time points in the healing process. In secondary fracture healing in large mammals and humans, the rigidity of a healing long bone progresses through a well-known S-shaped curve that corresponds to the stages of mineralization and remodeling of the callus. Excluding nonunions, all fractures eventually reach equivalence with its intact state, although the timeline for this process can vary substantially based on the biological and mechanical conditions. A biomechanical test alone could detect for example a substantial difference in torsional rigidity between a fast healer and a slow healer at an earlier timepoint, but that difference would be difficult to detect at a later timepoint, even though the pathways of healing were different. In this situation, other analysis approaches such as histology become critically important for assessing the maturing of the bridging and progress of late-stage remodeling. This highlights the importance of a multi-disciplinary evaluation strategy, particularly in pre-clinical *in vivo* studies, in order to analyze all facets of bone healing and generate a holistic assessment of the effect of the new technology.

Overcoming hurdles to clinical translation despite positive preclinical outcomes

Despite positive preclinical outcomes from the described CEMF study, the question remains whether such active devices can be widely deployed in the current economic, regulatory, and clinical landscape. Clinical evidence for the efficacy of existing electromagnetic field devices is mixed, making it difficult for new technologies to distinguish themselves from the fold. The challenge lies in the focus on binary union/nonunion as a primary efficacy outcome in clinical studies, which may in fact create a barrier to regulatory approval. Indeed, inconclusive clinical findings may not necessarily reflect a lack of efficacy of the devices and therapies tested, but rather an inability to measure the full continuum of treatment-related responses. There is therefore a real need to test new technologies clinically in difficult fractures using modernized research tools, in order to translate the promising findings in ovine studies, such as the one herein, into promising clinical outcomes. While the gamut of methodologies employed in preclinical studies cannot all be used in human trials (e.g., post-mortem biomechanics, histology), complementing existing clinical research assessment methods (radiographic assessment, CT morphometric analyses) with virtual structural analyses such as virtual torsional rigidity assessment could be very valuable to get quantitative measures of healing. Moving away from nonunion rate as a primary measure of efficacy may therefore not only decrease the cost of clinical trials but also bring devices more efficiently through regulatory approval and widespread clinical use.

Acknowledgements

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Magnetfeldtherapie zur Beschleunigung der Frakturheilung

Dr. Salim Darwiche (PhD) und
Dr. med. vet. Karina Klein, PhD
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Eine verzögerte Knochenheilung bleibt eine grosse Herausforderung in der Frakturheilung. Ihr Vorkommen hängt von verschiedenen Faktoren ab, wie dem Ort der Fraktur und anderen, zusätzlichen Krankheitsfaktoren, und hat erhebliche klinische und wirtschaftliche Konsequenzen. Magnetfeldtherapien zeigten bereits eine verbesserte Knochenheilung und Regeneration, die Modalitäten der Behandlungen wie auch die Resultate variieren jedoch deutlich.

Untersuchung einer neuen Technologie zur Frakturbehandlung in einem *in vivo* Tiermodell

Die Musculoskeletal Research Unit (MSRU) hat eine neue Technologie untersucht, welche eine Kombination von elektrischer und magnetischer Feldtherapie (CEMF) zur Beschleunigung der Knochenheilung in zwei standardisierten Tibiaosteotomie-Modellen bei Schafen zum Thema hatte. Die neue Technologie wurde von der Firma Neue Magnetodyn GmbH (München, Deutschland) entwickelt und die präklinische Studie von der Firma Johnson & Johnson (Depuy Synthes) finanziert. Die CEMF-Technologie unterscheidet sich von herkömmlichen Magnetfeldtherapie-Geräten, indem sie magnetische und *in situ*-amplifizierte elektrische Stimulation kombiniert. Ein primäres, externes magnetisches Feld wird über dem Frakturspalt erzeugt und aktiviert einen implantierten Transducer durch elektromagnetische Stimulation, was eine elektrische Stromspannung an den verbundenen Schrauben zur Folge hat (Abb. 1). Die CEMF-Technologie wurde entwickelt, um die Funktionalität von bereits bestehenden, standardisierten orthopädischen und Trauma-Implantaten zu erweitern und auf Abruf durch Aktivierung des Gerätes zur Beschleunigung der Knochenheilung beizutragen (im vorliegenden Fall einer sogenannten „Locking Compression Plate (LCP)" über einem Frakturspalt). Die Herausforderung bestand darin, in einem validen Tiermodell die klinische Situation beim Menschen mit präzisen, standardisierten Protokollen zur Operationstechnik wie auch die Evaluation der Resultate zu simulieren, um das Potential und den Effekt der CEMF-Technologie zur beschleunigten Knochenheilung zu dokumentieren.

Die neue CEMF-Technologie wurde in zwei standardisierten Osteotomie-Modellen mit entweder 3 mm oder 17 mm grossen Knochendefekten in der Tibia von Schafen getestet. Beim 17 mm, kritischen Defekt wurde autologe Spongiosa als Knochenersatz verwendet, während der 3 mm Defekt nicht zusätzlich augmentiert wurde. Beide Osteotomien wurden mit LCP und sogenannten „Locking Screws" stabilisiert. Die CEMF-Therapie wurde zweimal täglich für jeweils 90 Minuten über dem Frakturspalt durchgeführt, wobei die Behandlung 4 Tage nach der Operation begann und bis zum Ende des Versuchs angewendet wurde (9 Wochen für die 3 mm und 12 Wochen für die 17 mm Knochendefekte). Bei den Kontrollgruppen wurden die gleichen Geräte und Implantate verwendet, allerdings wurde keine Stimulation ausgelöst.

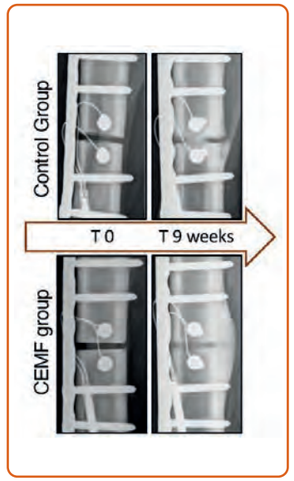

Figure 3: Representative radiographs in the 3 mm gap model from a Control group sheep and a CEMF group sheep, showing the status at time 0 (T0, post-OP, day of surgery) and 9 weeks post-OP (T 9 weeks). The radiographs shown were taken in the antero-posterior plane.

Repräsentative Röntgenaufnahmen (anterior-posterior) des 3 mm Defektmodells eines Tieres der Kontrollgruppe und der CEMF Gruppe zum Zeitpunkt 0 (T0, Tag des Eingriffs, postoperativ) und 9 Wochen postoperativ (T 9 weeks).

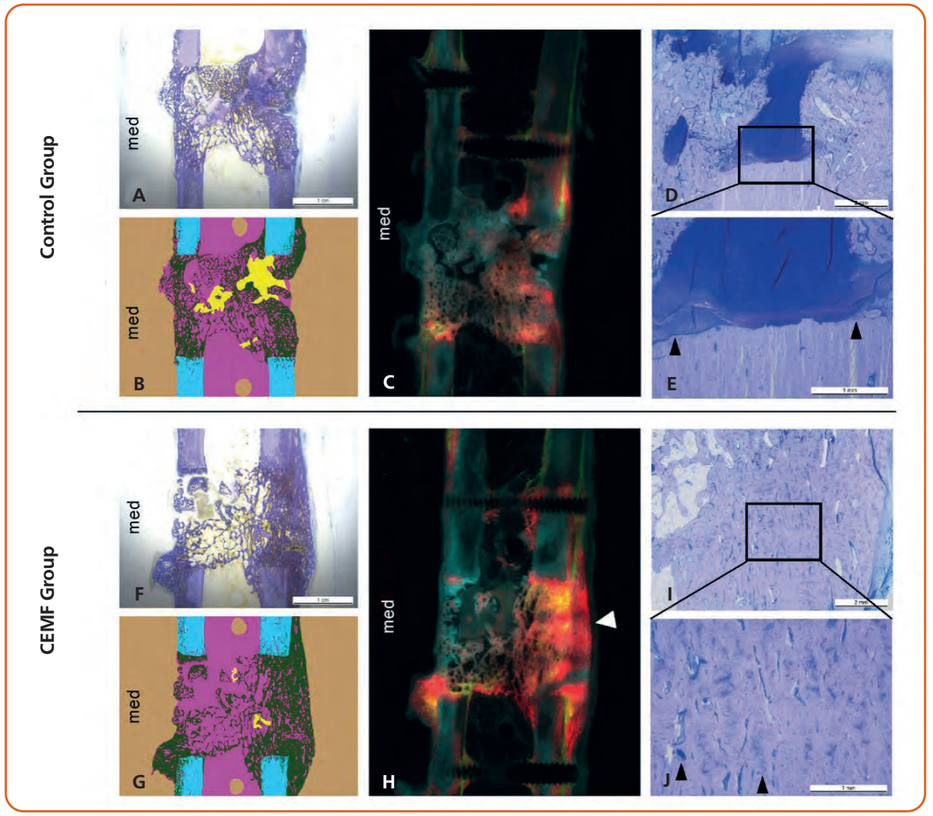

Figure 4: Representative histological, histomorphometric and fluorescent pictures of the 17 mm graft model, toluidine blue surface-stained ground sections (A, F), their respective histomorphometric segmentation (B, G) as well as the corresponding native section showing fluorescent dye deposition (C, H). The histomorphometric pictures (B and G) show background in beige, old bone in cyan, new bone in dark green, cartilaginous tissue in yellow and non-bone tissue in magenta. The fluorescent pictures (C and H) show overlays of Calcein green 3-week deposition in green, Xylenol orange 6-week deposition in red and Oxytetracycline 12-week deposition in blue. Deposition of bone at 6-weeks was more prominent at the trans-cortex in the CEMF group (white arrow, panel H). Toluidine blue-stained thin sections are also shown at lower (D, I) and higher (E, J) magnification. Black arrows indicate the fracture line, specifically the transition between old and new bone, and point towards the fracture gap. New bone formation in the fracture gap was more advanced in the CEMF group, versus the control group, which showed notable cartilaginous tissue (dark purple staining glycosaminoglycan-rich tissue islets) in the fracture gaps, indicating a less advanced healing stage.

Repräsentative histologische, histomorphometrische und fluoreszierende Bilder des 17 mm Defektmodells: mit Toluidinblau Oberflächen-gefärbte Dickschnitte (A, F), die Segmentierung für die verschiedenen Knochensegmente (B, G), sowie die entsprechenden Fluoreszenzschnitte (Native Schnitte; C, H). Die histomorphometrischen Schnitte (B und G) zeigen den Hintergrund in beige, alten Knochen in hellblau, neuen Knochen in grün und weichen Kallus in magenta. Die Fluoreszenzbilder (C und H) zeigen die Kalziumablagerung von Calceingrün (3 Wochen), Xylol-Orange in rot (6 Wochen) und Oxytetracyclin in blau (9 Wochen). Die Knochenbildung mit 6 Wochen war prominenter am Trans-Cortex bei der CEMF-Gruppe (weisser Pfeil, H). Dünnschnitte (Toluidinblau) mit geringer (D und I) und hoher Vergrösserung (E und J) zeigten vermehrte Knochenbildung in der CEMF-Gruppe im Vergleich zur Kontrollgruppe, welche deutlich Knorpelbildung im Frakturspalt (violette Färbung der Glycosaminoglycan-reichen Gewebeinseln) und damit einen unreiferen Kallus aufwies. Die schwarzen Pfeile bezeichnen die Frakturlinie und spezifisch den Übergang zwischen altem und neuem Knochen und zeigen in Richtung des Frakturspaltes.

Zur Evaluation der Knochenheilung wurden folgende Methoden angewendet:

- Regelmässige, wöchentliche Röntgenkontrollen vom Zeitpunkt des Eingriffs bis zum Endpunkt (9 bzw. 12 Wochen) mit semi-quantitativer Auswertung der Kallusbildung;
- Morphometrische Analyse anhand von post-mortem Mikro-CT Daten zur Bestimmung von Volumen und Dichte des Frakturkallus;
- Die Mikro-CT Daten wurden mittels „finite element modeling" zur Bestimmung von virtuellen Torsions- und Steifigkeits-Daten weiter analysiert;
- Regelmässige Applikation von intravitalen Fluoreszenz-Markern, um die zeitliche Abfolge von abgelagertem Kalzium am Frakturspalt in den verschiedenen Stadien der Knochenheilung histologisch verfolgen zu können;
- Die postmortalen, nicht-destruktiven Torsions- und Steifigkeits-Tests wurden ebenfalls zur primären Bestimmung der biomechanischen Festigkeit der Knochenheilung verwendet;
- Qualitative und semi-quantitative histologische Analysen wurden durchgeführt, um die Biokompatibilität (nach ISO10993-6 Richtlinien) der verwendeten Technologie und die Art der Knochenheilung zu bestimmen.

Die Kallusdichte und Mineralisierung war beim 3 mm Defekt höher in der CEMF (n=6) als in der Kontrollgruppe (n=6). Auch die Torsions-Steifigkeit war zweimal höher, und das Kallusgewebe zeigte sich reifer bzw. besser strukturiert, allerdings ohne statistische Signifikanz (Abb. 2 und 3). Letzteres hing wahrscheinlich mit dem Zeitpunkt der histologischen Untersuchung (9 Wochen) zusammen, an welchem Unterschiede in der Kinetik der Knochenheilung in nicht-kritischen Knochendefekten von 3 mm schon nicht mehr detektiert werden können, vor allem in einem Tiermodell, in welchem keine Störung der Knochenheilung vorliegt (wie dies beispielsweise bei Non-Unions der Fall ist). Im Gegensatz dazu schien der Zeitpunkt von 12 Wochen bei der 17 mm Defekt-Gruppe ideal zu sein, weil dort ein klarer Effekt der CEMF-Therapie zu beobachten war. Die Unterschiede zwischen der Kontroll- und der CEMF-Gruppe (n=6 pro Gruppe) zeigte sich darin, dass die CEMF-Gruppe radiologisch einen ausgeprägteren Kallus, ein höheres Kallusvolumen (p=0.003), eine höhere virtuelle (p=0.007) und eine 2.6 mal höhere biomechanische Torsions-Steifigkeit (p= 0.024) zeigte. Ausserdem waren histologisch reifere Kallus-Strukturen und verbesserte Knochenheilung erkennbar (Abb. 4 und 5).

Zusammenfassend zeigte die CEMF-Gruppe eine deutlich verbesserte Knochenheilung, vor allem bei grösseren Defekten, wo eine reifere Knochenstruktur und Kallus-Morphologie sowie bessere biomechanische Eigenschaften beobachtet wurden. Deshalb ist zu erwarten, dass diese Technologie ein wichtiger Zusatz zur Frakturbehandlung werden könnte. Der Vorteil der in dieser Studie getesteten Technologie liegt darin, dass sie separat und unabhängig von jeder Standardfixation bei Knochenbrüchen angewendet werden kann. Die äussere Spule kann leicht angebracht und für eine postoperative Behandlung verwendet werden, wenn die CEMF-Therapie benötigt wird, z. B. in Revisionen oder bei fehlender Frakturheilung (Non-Unions).

Der Vorteil von multi-disziplinären Evaluations-Strategien in präklinischen *in vivo* Studien

Diese Studie beinhaltete verschiedene präklinische Evaluationsmethoden (z.B. Radiologie, CT-Morphometrie, virtuelle Torsions-Steifigkeit, biomechanische Tests, Histologie), um den Effekt der CEMF-Therapie auf die Knochenheilung umfassend zu untersuchen. Die Hypothese war, dass die mit CEMF behandelten Gruppen eine verbesserte Knochenheilung aufweisen würden. Bei den beiden Kontrollgruppen wurde auch eine gute Knochenheilung erwartet, jedoch etwas langsamer im Zeitverlauf. Deshalb waren die Evaluationsmethoden wie auch die Wahl des Endzeitpunktes wichtig.

Einige der Evaluationsmethoden sind auch in klinischen Fällen relevant (Radiologie, CT-Scans, virtuelle Torsions-Steifigkeit), während andere nicht in den humanen Bereich übertragen werden können (biomechanische Tests, Histologie). Biomechanische Tests können allerdings wichtige Unterschiede der Knochenheilung zu verschiedenen Zeitpunkten zeigen. Während der sekundären Knochenheilung in grossen Säugetieren und dem Menschen nimmt die Steifigkeit des Kallusgewebes progressiv in einer bekannten Sinuskurve zu, welche dem Status der Mineralisation und des Remodelings des neuen Knochengewebes entspricht. Ausser bei Non-Unions ist der Status der geheilten Fraktur schliesslich äquivalent zum intakten Knochen, allerdings hängt der Zeitverlauf für diesen Prozess substanziell von den biologischen und mechanischen Konditionen ab. Wenn z. B. nur biomechanische Tests verwendet werden, dann könnte eventuell ein wichtiger Unterschied in der Torsions-Steifigkeit zwischen einer schnelleren und langsameren Heilung zu einem früheren Zeitpunkt gefunden werden. Zu einem späteren Zeitpunkt wäre dieser nur noch schwerlich zu entdecken, auch wenn die Wege der Heilung unterschiedlich waren. In solchen Situationen werden andere Evaluationsmethoden sowie die Histologie um so wichtiger, um die Überbrückung des Frakturspaltes und die Reifung der Kallusstruktur zu bestimmen. Dies zeigt die Wichtigkeit der multidisziplinären Evaluationsstrategie, speziell in präklinischen *in vivo*-Studien, um alle Facetten der Knochenheilung in einer holistischen Anschauungsweise zu betrachten.

Das Überwinden von Hindernissen zur klinischen Translation trotz positiver Resultate

Trotz positiver Resultate in der CEMF-Studie bleibt die Frage offen, ob solche aktiven Geräte angesichts der ökonomischen, regulatorischen und klinischen Situation weitverbreitet angewendet werden können. Klinische Resultate mit ähnlichen elektromagnetischen Geräten sind gemischt, was es für neue Geräte schwierig macht, sich positiv davon abzuheben. Eine weitere Herausforderung besteht darin, dass in humanklinischen Studien der Fokus oft auf binären Unions/Non-Unions als primärem Endpunkt liegt, was in der Realität ein Hindernis für die Zulassung sein kann. Nicht eindeutige Resultate sprechen nicht unbedingt für die Unwirksamkeit der Geräte und Therapien, sondern können darin begründet sein, nicht die volle Bandbreite der Auswirkungen zu erfassen. Deswegen ist es notwendig, diese neuen Technologien klinisch an komplizierten Frakturen zu testen, um allenfalls eine Translation der Ergebnisse der Schafstudie zu ermöglichen. Die gesamte Bandbreite, der in der präklinischen Studie verwendeten Methoden kann bei klinischen Studien am Menschen nicht angewendet werden (z. B. post-mortem biomechanische Tests, Histologie). Hingegen könnten klinische Untersuchungsmethoden, wie Radiologie und CT-morphologische Analysen, dafür verwendet werden, virtuelle Torsions-Steifigkeits-Tests auszuführen, und damit die klinischen Heilung zu quantifizieren. Wenn solche neuen Techniken angewendet werden könnten, anstatt nur die Non-Union-Rate als primären Endpunkt für die Beurteilung der Heilung heranzuziehen, könnte dies nicht nur die Kosten von klinischen Studien reduzieren, sondern auch die Zulassung und damit die klinische Verwendung von neuen Geräten beschleunigen.

Danksagung

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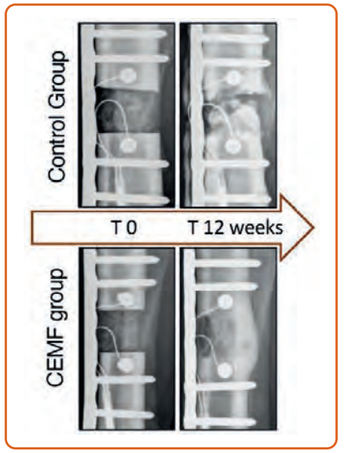


Figure 5: Representative radiographs in the 17 mm gap model from a control group sheep and a CEMF group sheep, showing the status at time 0 (T0, post-OP, day of surgery) and 12 weeks post-OP (T 12 weeks). The radiographs shown were taken in the antero-posterior plane.

Repräsentative Röntgenaufnahmen (anterior-posterior) des 17 mm Defektmodells eines Tieres der Kontrollgruppe und der CEMF Gruppe zum Zeitpunkt 0 (T0, Tag des Eingriffs, postoperativ) und 12 Wochen postoperativ (T 12 weeks).

overview cabmm research platform

1. Cancer Epigenome Group

Group leader: Prof. Dr. med. vet. Dr. phil. II Michael O. Hottiger
Platform users: Dr. Lorenza P. Ferretti (PhD), Alessandra Cereghetti (PhD student)

Genome instability is a cancer hallmark that leads to a wide spectrum of genetic changes, including mutations in epigenetic modifiers. Disruption of the "epigenome" as a result of alterations in epigenetic regulators such as the 'writers', 'readers', or 'editors' of DNA methylation and/or chromatin states, is a fundamental mechanism in oncogenesis. In fact, changes in the epigenome can profoundly influence many hallmarks of cancer as well as clinical responses to anticancer therapies. Moreover, epigenetic mechanisms modulate a variety of transcriptional pathways resulting in a dynamic heterogeneous tumor cell population. Although much has been learned about the relationship between the epigenome and cancer, many cancer drugs in use have not been linked to specific biomarkers that could guide therapies to maximize patient benefit. The observation that epigenetic inhibitors lead to dramatic effects in malignant cells, although their normal counterparts remain largely unaltered, underlines their potential as anti-cancer therapeutics. Moreover, recent studies revealed that some epigenetic inhibitors alter only a few hundred genes depending on cell type indicating that these compounds can disrupt a selective set of genes. Elucidating the networks of epigenetic regulators in different cancer types will provide a further mechanistic understanding of the interplay between genetic and epigenetic alterations.

Identifying novel epigenome-targeted anticancer agents in patient-derived 3D melanoma cultures

During the last two years, we carried out an epigenetic drug screen in 3D patient-derived melanoma cultures to identify a possible epigenetic mechanism of resistance to Mitogen-activated protein kinase inhibitor (MAPKi), one of the first-line treatments for melanoma. We demonstrated that in 3D patient-derived cultures a poly(ADP-ribose) polymerase inhibitor (PARPi) restores MAPKi sensitivity in malignant melanomas with frequently mutated genes (BRAF (Rapidly Accelerated Fibrosarcoma B-type) and NRAS (Neuroblastoma Rat Sarcoma; Fig. 1)). It is not surprising that the synergistic activity of PARPi and MAPKi was not observed in monolayer (2D) cultures, since 3D culturing better represents *in vivo* tumors by preserving chemical gradients and cell-cell interactions. Surprisingly, however, the PARPi does not appear to act through modulation of the DNA damage response in these melanoma cells. Strikingly, through integrated transcriptomic and proteomic analyses, we discovered that PARP inhibition restores BRAFi-sensitivity by affecting lysosomal-autophagy biogenesis as well as by restoring the EMT (epithelial-mesenchymal transition)-like phenotype switching, one of the major epigenetic driven drug resistance mechanisms. Moreover, PARP inhibition enhances MAPKi response in patient-derived xenograft mice models by decreasing tumor growth and improving the survival rate. Taken together, these findings delineate how alterations in chromatin ADP-ribosylation may reshape transcriptional pathways and the lysosomal-autophagy biogenesis to overcome MAPKi resistance revealing a new promising combinatorial therapy for the treatment of resistant melanoma as well as other BRAF- or NRAS-mutated cancer types.

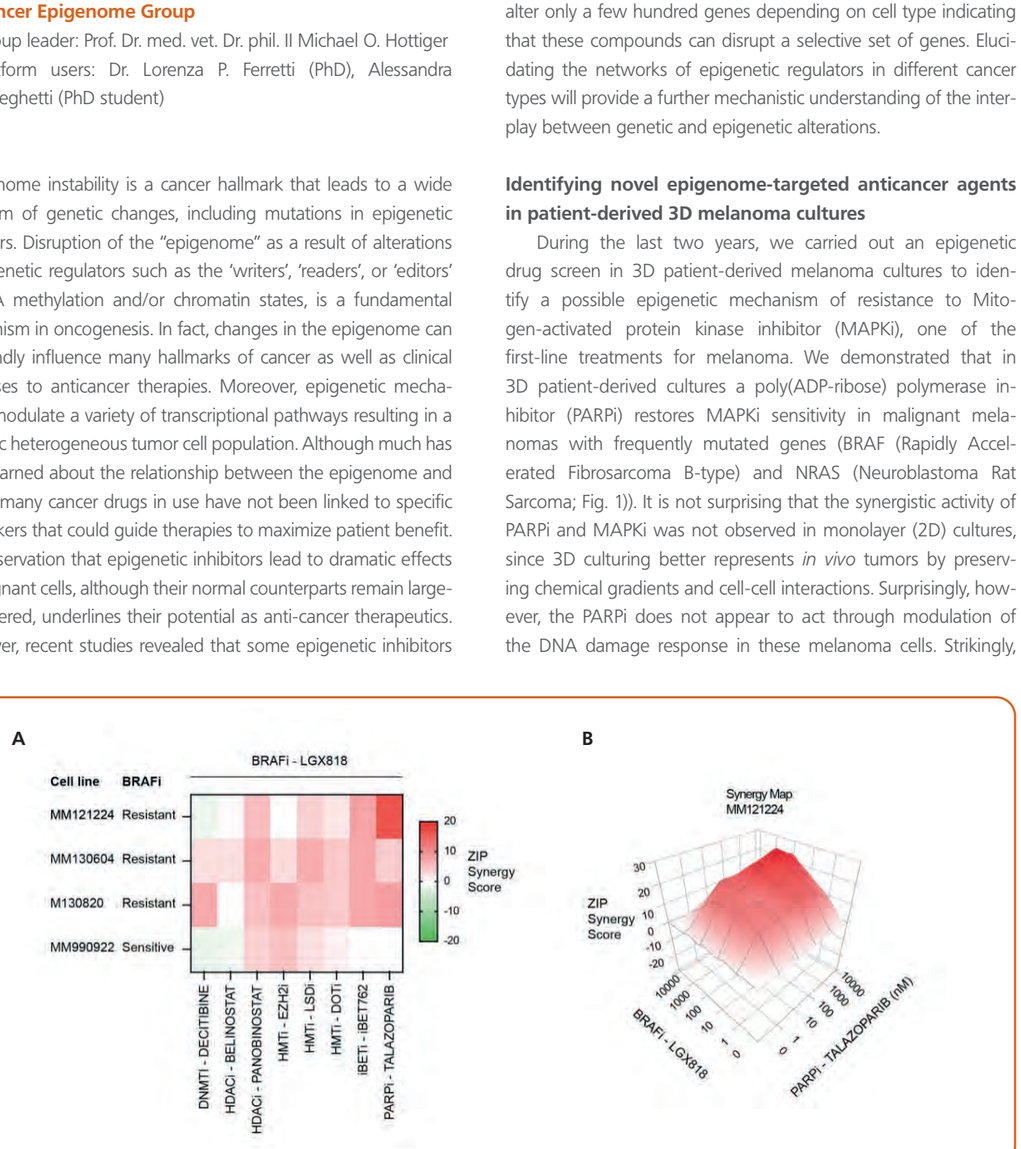


Figure 1: PARP inhibition enhances the efficacy of BRAF/MEK pathway inhibitors.

Because the second major treatment modality for metastatic melanoma patients is immunotherapy, we have investigated in a second set of experiments whether epigenetic regulation affects melanoma response to immunotherapy. We performed a surface marker screening of a NRAS-mutated melanoma cancer culture identifying ICAM-1 (CD54) as upregulated after treatment with the DNA methylation inhibitor decitabine (Fig. 2). Specifically, we showed that administration of DNMTi (DNA methyltransferase inhibitors) upregulated the expression of the antigen-presenting machinery, HLA Class I/II as well as the secretion of the pro-inflammatory Th1 chemokines CXCL9 and CXCL10. Moreover, increased ICAM-1 expression positively correlated with increased immunogenicity of human melanoma cells and correlated with increased immune cell infiltration in a public dataset and human primary melanoma sample cohort. Collectively, these findings describe the potential of DNMTi in improving melanoma immunogenicity, hence supporting DNMTi as an adjuvant for the treatment of advanced melanoma patients.

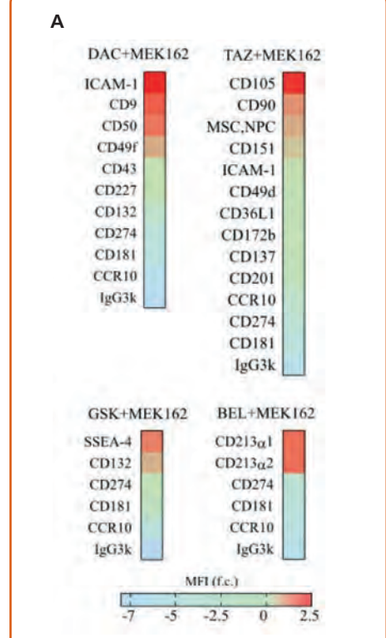


Figure 2: DNMTi modulates melanoma surfaceome by upregulating the costimulatory molecule ICAM-1.

2. Musculoskeletal Research Unit (MSRU)

Group leaders: Dr. med. vet. Katja Nuss, Dr. med. vet. Karina Klein, PhD, Dr. Salim E. Darwiche (PhD)
Platform users: Dr. Scott Finlay (PhD), Aymone Lenisa (lab technician), Juliette Blankesteijn (master student), Prof. em. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS

The MSRU is specialized in the design, implementation, and evaluation of *in vivo* preclinical investigations, particularly in large animal models. The areas of investigation are centered on the musculoskeletal system, but also extend to cardiovascular and wound healing applications. It has also established expertise in histology processing and analysis including non-decalcified plastic embedded ground and thin sections, cryosections, paraffin embedded sections as well as immunohistochemistry. A special feature of the MSRU is its successful implementation of Good Laboratory Practice (GLP). The MSRU facility has received and maintained its GLP accreditation by Swissmedic since 2014. Thus, together with Good Manufacturing Practice (GMP) established at Wyss Zurich and human clinical trials performed under Good Clinical Practice (GCP) at the University Hospital Zurich and the close collaboration of the involved institutions, the University of Zurich is able to offer the complete quality chain for research and development of new therapeutics.

Engineered Biological Implant for Canine Disc Replacement

Dr. Scott Finlay (PhD), Juliette Blankesteijn (master student),
Prof. em. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS,
Dr. Salim E. Darwiche (PhD)

Degeneration of the intervertebral disc (IVD) involves progressive structural and functional failure of the disc tissue, which can result in significant pain and neurological deficits. Dogs frequently suffer from spontaneous degenerative IVD disease and associated pain. Total disc replacement using a mechanical IVD prosthesis has been somewhat successfully applied in humans in order to preserve motion of the spinal segment. Complications such as heterotopic ossification, wear debris and implant failure are, however, still common occurrences. It may be argued that the fundamental source of failure of IVD prostheses may be tied to their inability to biologically interact with the surrounding tissue and therefore curb the degenerative inflammatory processes. Unlike non-biological implants, tissue engineered IVDs may both biologically integrate and remodel with the surrounding tissue, particularly by maintaining the structure and biological activity of adjacent endplates, thereby enabling long-term function and maturation.

A successful IVD tissue engineering strategy relies on the creation of a biomechanically and biologically compatible construct. Regarding biological compatibility, autologous nucleus pulposus and annulus fibrosus cells, while biologically matching, are difficult to source from a healthy tissue and often do not maintain their phenotype *in vitro*. Synoviocytes, however, which can be harvested relatively minimally invasively from synovial joints (e.g., during a planned joint arthroscopy), are easily isolated, grown and can be differentiated *in vitro* to engineer collagen II and glycosaminoglycan-rich matrices.

The main aim of this project was, therefore, to produce canine-sized tissue engineered disc constructs for IVD replacement in dog patients, starting with canine synoviocytes. To that end, the cells were sourced, in collaboration with Dr. med. vet. Luc Smolders, Dipl. ECVS, and CABMM member Prof. Dr. med. vet. Frank Steffen, Dipl. ECVN, of the small animal clinic at the Vetsuisse Faculty in Zurich, from synovial tissue collected during crucial ligament repair surgeries in dog patients needing ligament repair. The synovial tissue samples were taken from otherwise discarded tissue from surgery. Thus far, a cell bank from seven canine donors was created with millions of cells (Fig. 1). Afterwards, cells from one donor were seeded onto smaller and larger non-woven polyester scaffold discs (2 mm thick x 7 mm diameter and 4 mm thick x 15 mm diameter, respectively). The constructs were grown in chondrogenic medium in a non-loaded environment for 4 or 6 weeks, to assess their capability to deposit matrix, in the preliminary stages of tissue engineering. Overall, the biomechanical analysis of the constructs at this stage showed that the matrix formation was still very preliminary. This observation was confirmed by the glycosaminoglycan and collagen deposition assays, which also showed evidence of preliminary extracellular deposition. The histological assessment of constructs at this stage confirmed the biomechanical and biochemical assay findings, and further showed that the cell seeding was homogenous throughout the scaffolds.

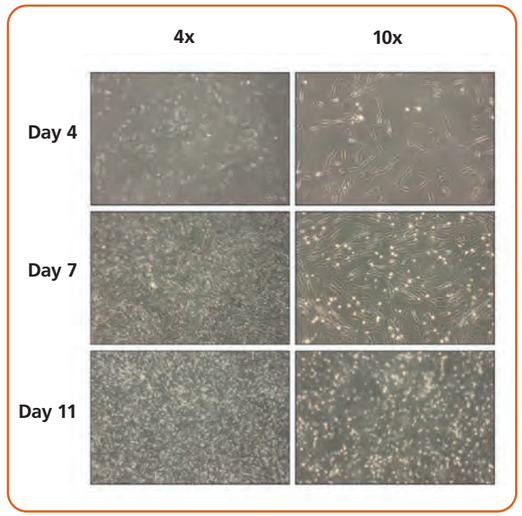


Figure 1: Microscopic images (4x, 10x) of canine synoviocytes in monolayer culture at various time points of expansion.

Although preliminary in nature, the results of the project thus far showed that synoviocytes could be successfully harvested from discarded tissue from canine patients, enough to create cell banks for every patient. Furthermore, the synoviocytes expanded well in culture, could be successfully seeded, and attached well onto the scaffold material. Finally, although the extracellular matrix deposition from the cells particularly from this donor was too preliminary to form a tissue engineered matrix ready for biomechanical stimulation in our custom made IVD bioreactor, the challenge seems to lie more on the variability seen in cell behavior from donor to donor, which merits further characterization, as well as seeding density improvements, which would maximize the potency of cells, once seeded in 3D.

The next phase of the project Is looking to characterize the matrix deposition potency of cells from all donors, using micropellet or microspheroid assays as well as improving the seeding protocol to ensure the cells are at a sufficiently high density in the scaffold to produce functional extracellular matrix.

Articular Cartilage Tissue Engineering

Dr. Salim E. Darwiche (PhD), Dr. Scott Finlay (PhD), Aymone Lenisa (lab technician), Prof. em. Dr. med. vet. Brigitte von Rechenberg, Dipl. ECVS

Restoration of hyaline cartilage after a traumatic or developmental lesion is still one of the most challenging problems in orthopedic surgery. Once a lesion in the hyaline cartilage is present, cartilage matrix degradation is inevitable and in the long term will always result in osteoarthritis of the affected joint. Various surgical interventions have been attempted to repair articular cartilage (e.g., microfracture, osteochondral transplants, mosaicplasty, autologous chondrocyte implantation). Although acceptable clinical outcomes between 87-90 % are reported initially for some of these technologies, decline of success is also reported after the first 5 years. Limitations are indeed still considerable for all these technologies.

Tissue engineered cell-based technologies may provide a solution, but despite recent advances, such technologies are still not widely available clinically. A fundamental aspect to consider is the choice of cell source. Choosing an allogeneic cell source would ensure batch reliability and avoid a second surgery, but adult allogeneic cells would cause immune rejection if the recipient is not matched to a donor. Human chondroprogenitor cells (hCPs, provided by CABMM member Prof. Lee Ann Laurent-Applegate and LAM Biotechnologies in Lausanne) circumvent this challenge due to their immunoprivileged phenotype. Additionally, they have the capacity to produce cartilage tissue and maintain that ability after multiple population doublings, unlike adult cells. Furthermore, *in vitro*, hCPs had significantly lower expression of hypertrophic markers (collagen X, Ihh, PTH1R) than those displayed by adult mesenchymal stem cells (findings from CABMM member Prof. Marcy Zenobi-Wong's lab). *In vivo*, hCPs outperformed adult chondrocytes with higher glycosaminoglycan and collagen II content, whilst not triggering an immune response, and showing no signs of calcification.

This project was therefore designed to combine the potency, reliability, and translatability of human chondroprogenitor cells with a tissue engineering technology and an implantation technology that could resolve challenges currently faced by other cartilage treatment techniques. To that end, hCPs were tested for

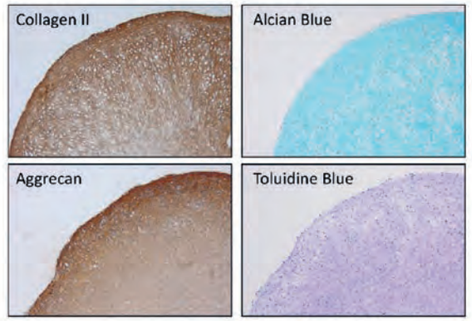


Figure 2: Example of micropellet culture of human chondroprogenitor cells, in this case grown in chondrogenic medium without dexamethasone, in hypoxic conditions, showing good deposition of collagen II, aggrecan as well as glycosaminoglycans.

their matrix producing properties in micropellet assays, looking at various passages and culture conditions. These series of tests were done in close collaboration with LAM Biotechnologies, with assays running in parallel with those run by the team at LAM Biotechnologies, and information shared openly in order to identify the best window and conditions to grow tissue from these cells (Fig. 2). The results showed that the cells could deposit cartilaginous matrix both after a pre-expansion in 2D, or even after thawing them from liquid nitrogen storage and placing them directly in 3D in chondrogenic medium. The cells were also potent up to passages that are higher (up to P7) than those normally used with adult chondrocytes (up to P3-4), without losing potency with expansion rounds.

As a second step, the cells were seeded on non-woven polyester scaffolds with integrated fixations – a technology specifically designed to be easily implantable in a cartilage defect down the line (Fig. 3). The hCPs attached very well to the polyester scaffolds, homogenously throughout, and deposited cartilage-like matrix in various tested conditions and passages. Some constructs were also placed in a custom-made bioreactor, which can apply daily physiological loading for weeks, in order to drive the constructs to maturity and better mechanical and biochemical properties (Fig. 4).

Although the results were very promising thus far, the mechanical and biochemical properties of the final constructs could still need some improvement and maturation. One of the aspects of the technology that, although on the long run provides a major advantage, presented some challenges on the short run, is the integrated fixation feature. Indeed, growing the constructs without an integrated fixation first, then attaching the fixation at a later stage, may allow the tissue engineering process to go to higher levels of maturation and reduce interference during cell seeding and biomechanical stimulation, making the whole process more reliable and reproducible.

Based on the promising results thus far, the next phase of the project is focusing on optimizing seeding, testing the most promising media formulations, which can maximize extracellular matrix deposition, and biomechanically stimulating the constructs to maturation before adding the fixation feature as a last step prior to implantation.

Figure 3: Engineered cartilage constructs with integrated fixation.

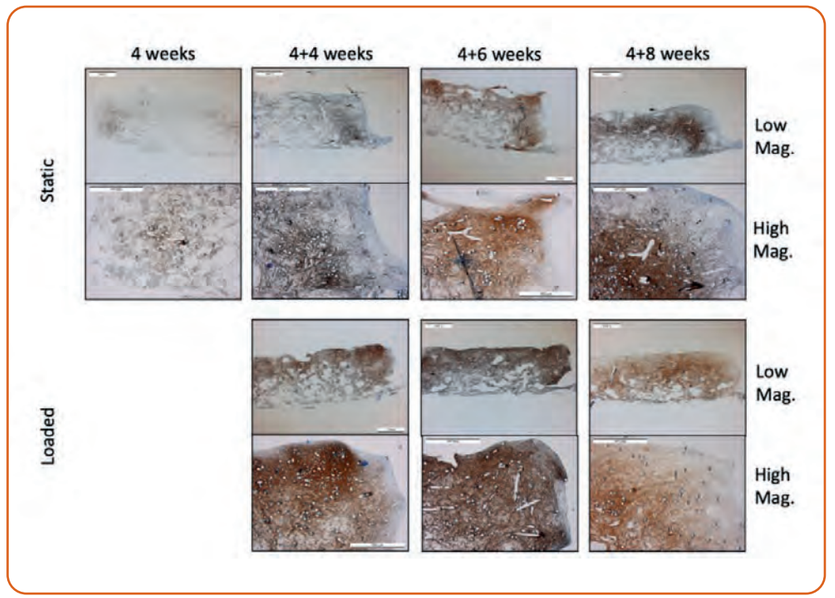


Figure 4: Collagen type II immunohistochemical staining of constructs cultured with hCPs for 4 weeks in chondrogenic medium, followed by up to 8 weeks with or without mechanical stimulation in a bioreactor.

We thank CABMM member Prof. Lee Ann Laurent-Applegate and the team at LAM Biotechnologies (Lausanne, Switzerland) for the fruitful and open collaboration to drive forward this scalable allogenic cell-based cartilage treatment technology. Our thanks also go to Prof. Bahaa Seedhom and the team at Xiros, Ltd. (Leeds, UK) for the funding, guidance, contribution in developing the technology and support throughout the project and for providing the custom-designed surgical tools, scaffolds, seeding chambers, and bioreactors.

3. Ocular Cell Biology Group

Group leader: Prof. Dr. med. Farhad Hafezi, PhD
Platform users: Dr. Emilio Torres (MD), Dr. Reyhaneh Abrishamchi (MD), Dr. Hormoz Abdshahzadeh (MD), Christian Funck (MSc), Daniel Eckert (MSc)

The Ocular Cell Biology (OCB) group, led by Prof. Farhad Hafezi, has been dedicated to a number of both clinical and experimental research projects. The group's aim is to develop new and innovative therapeutic approaches for ocular diseases, mainly related to the cornea. Key research topics include:

- Diagnosis and treatment of keratoconus,
- Corneal biomechanics,
- New technologies of corneal cross-linking in keratoconus,
- Corneal cross-linking for the treatment of infectious keratitis, and
- Improvement of current excimer and femtosecond laser technology.

In the reporting period, the group was engaged in several projects simultaneously, and peer-reviewed publications were the result of these efforts. Below, we describe the research projects performed by the OCB group on the CABMM Research Platform:

High Fluence Increases the Antibacterial Efficacy of PACK Cross-Linking

According to the World Health Organization (WHO), corneal infections constitute one of the leading causes of blindness worldwide. It can result from minor ocular trauma, because of occupational risk combined with poor hygiene. Particularly, in the absence of immediate and adequate medical care, which is often the case in developing countries, it is a vision-threatening disease. Although the incidence rate in industrialized countries is significantly lower, infectious keratitis can arise from improper contact lens wear, dry eyes, recent ocular surgery, or systemic immunosuppression.

Photoactivated chromophore for keratitis cross-linking (PACK-CXL) is used as an adjunct therapy to antibiotic medication in infectious keratitis. This experimental study aimed at quantifying the PACK-CXL efficacy as a function of UV fluence using several bacterial strains and irradiated volumes.

We have determined the impact of UV fluence (i.e., UV energy) and the size of the irradiated volume on the bacterial killing achieved with current clinical PACK-CXL protocols. In contrast to an earlier study, we found that the administered UV fluence, not the overall irradiation time, determined the extent of bacterial killing.

In summary, the efficacy of PACK-CXL can be further improved by using a higher UV fluence: increasing the currently used UV fluence by a factor of 3 led to an increase in the amount of bacterial killing from 50% to 100% in low-bacterial concentrations.

Accelerated Corneal Cross-linking as an Adjunct Therapy in the Management of Presumed Bacterial Keratitis: A Cohort Study

Our purpose was to evaluate the effect of PACK-CXL to treat bacterial corneal infections clinically. In this non-randomized cohort study, we evaluated the effect of PACK-CXL as an adjunct to the standard antimicrobial treatment of presumed bacterial keratitis by comparing cases prior to and following the implementation of a PACK-CXL protocol at the ELZA Institute, a private eye clinic in Dietikon.

Our results show that adjunct treatment with accelerated PACK-CXL resulted in a significantly shorter time to re-epithelialization, fewer follow-up visits, and a shorter total follow-up when compared to standard antimicrobial therapy alone. Moreover, accelerated PACK-CXL significantly reduced the need for tectonic urgent corneal transplantation.

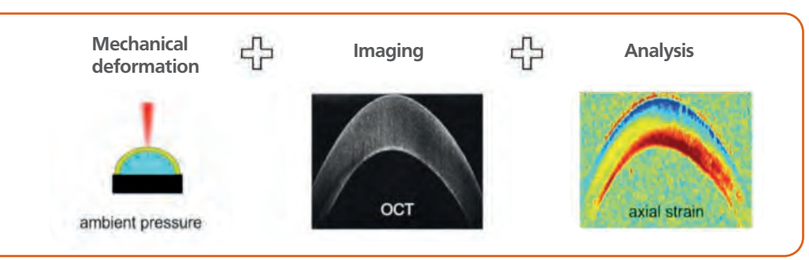


Figure 1: Principles and imaging acquisition example of quasi-static optical coherence elastography (OCE).

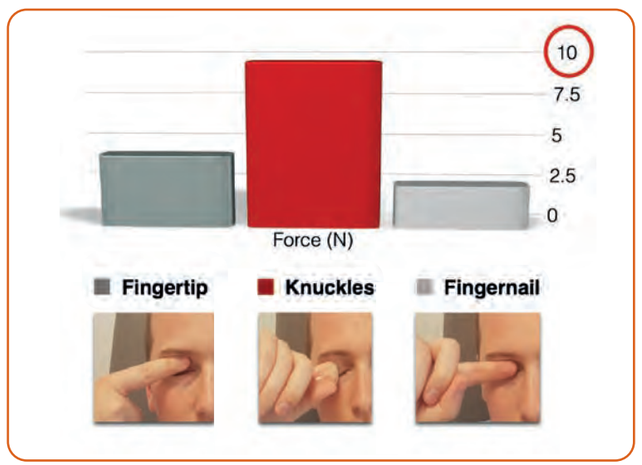


Figure 2: Assessment of the mechanical forces applied during eye-rubbing. The greatest force was exerted when the knuckle was used. This was around 10 N and was in average 2.2 and 3.7 times greater when compared to fingertip or fingernail eye-rubbing.

Detecting alterations in corneal strain distribution might be a useful diagnostic and screening parameter for corneal pathologies, as well as a follow-up tool to determine the progression of keratoconus and to quantify the effect of corneal cross-linking after treatment.

Quasi-Static Optical Coherence Elastography to Characterize Human Corneal Biomechanical Properties

Quasi-static optical coherence elastography (OCE) is an emerging technology to investigate corneal biomechanical behavior in situations like physiological stress conditions (Fig. 1). OCE was applied to evaluate previously inaccessible biomechanical characteristics of human corneal tissue and to study the role of Bowman's layer in corneal biomechanics. The intraocular pressure (IOP) is the major mechanical load imposed on ocular tissues. It undergoes physiological diurnal fluctuations which induces radial expansion/contraction and accordingly corneal elongation/compression strain. OCE is based on subpixel displacement tracking to record such corneal strain maps with high-spatial resolution. Tissue strain is a property that is inherently related to its elastic modulus, which determines corneal shape and refractive power. Assuming a homogenous stress distribution across the corneal tissue, strain maps represent a direct measure of the elastic modulus.

In the present study, we were able to record spatially resolved corneal strain distribution over the entire stromal thickness in response to a physiological stress stimulus, with pressure loading amplitudes matching a clinically relevant IOP range (10-30 mm Hg). We demonstrated that strain maps could be retrieved from a single pressure change as little as 1 mm Hg. This high sensitivity makes the technique particularly interesting for future clinical applications.

Assessment of the mechanical forces applied during eye rubbing

Keratoconus (KC) is a potentially sight threatening corneal disease characterized by a progressive corneal protrusion with irregular astigmatism and corneal thinning. The exact etiology of keratoconus remains unclear. Besides genetic predisposition, intense and prolonged eye rubbing may play important roles in the pathogenesis of the disease. There is a hypothesis that repetitive and prolonged eye rubbing may alter corneal biomechanics and trigger keratoconus onset or exacerbate its clinical presentation, as postulated in a number of recent publications. So, the present study evaluated the amount and type of mechanical forces applied to the lids of keratoconus patients during eye rubbing.

Major variations were detected in the force exerted on the globe during eye rubbing. Of all types of eye rubbing, knuckle rubbing exerts the highest force on the globe (Fig. 2). In this study's group of patients with keratoconus, those patients who rubbed with their fingernail exerted the lowest force, whereas patients that rubbed their eyes with the fingertips applied an intermediate force. Thus, the force exerted on the eye in rubbing is strongly related to the eye rubbing type.

In the future, experimental eye rubbing models can be used to better understand the impact of repetitive eye rubbing on corneal biomechanics and the potential correlation between applied force and keratoconus levels. Our data gathered will help determine the amount of force that should be used in such models to mimic the human condition.

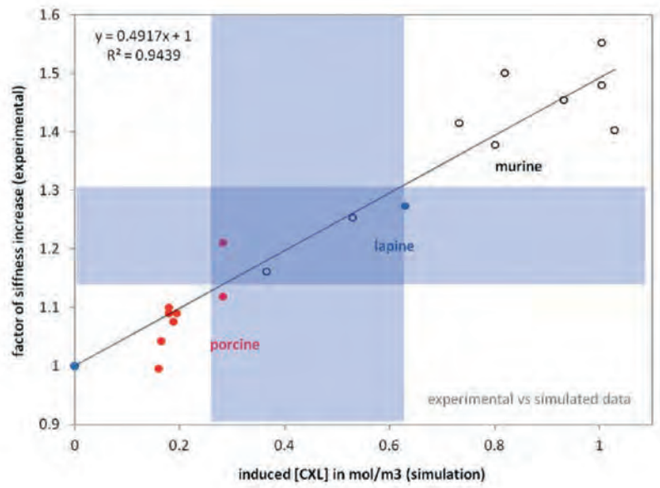


Figure 3: Predicting CXL efficacy with a model. The nomogram for ultra-thin corneas was based on the cross-linking density after performing corneal cross-linking in animal models.

Individualized corneal cross-linking with riboflavin and UV-A in ultra-thin corneas: the Sub400 protocol

This clinical trial was based on our group's experimental model, published as recently as 2017 (Fig. 3), and represents a major advance for ophthalmology by allowing keratoconus treatment for patients who previously had no therapeutic option. The study evaluated a series of cases in which the novel 'sub400' algorithm of individualized CXL treatment for ultrathin corneas was used. Corneas with keratoconus as thin as 212 µm could be treated without signs of endothelial decompensation. The algorithm named 'sub400' adapts the total fluence applied to each individual's stromal thickness. This fluence allows corneas thinner than 400 µm to be treated without alternative solutions of artificial corneal thickening.

In 2009, the first approach to be developed was with the induction of preoperative corneal edema with hypo-osmolar riboflavin. However, there are questions about the duration of the edema effect after the start of UV-A irradiation (the cornea may shrink through desiccation), which could theoretically increase the risk of postoperative complications. Furthermore, the effect of CXL seems to be smaller than in corneas > 400 µm treated with Dresden protocol. In another approach, an isoosmolar riboflavin-soaked contact lens is placed over the cornea to increase the total corneal thickness. The greatest stiffening effect of CXL occurs in the most anterior part of the cornea, and the contact lens-assisted CXL approach has also been shown to result in a reduced corneal stiffening effect.

The individualized 'sub400' CXL protocol uses an experimentally validated algorithm that considers the stromal availability of riboflavin, oxygen, and UV-A during the CXL procedure. The model allows predicting not only the amount of biomechanical strengthening achieved after CXL, but also the duration of UV irradiation required to achieve the desired penetration depth. The accuracy of the theoretical model was previously verified in preclinical experiments, and the nomogram was able to predict the biomechanical effectiveness of CXL in porcine, murine, and lapine corneas. The nomogram requires the value of the corneal – stromal – intraoperative thickness to determine the individualized patient fluence. The goal is to obtain a demarcation line 70 µm above the corneal endothelium. In order to facilitate clinical application with individualized fluences, irradiation intensity was kept fixed at 3 mW/cm², while the treatment time was modified. The aim of the current study was to verify the efficiency in preventing progression after one year of the procedure, and this confirmation was possible in 89 % of the cases. One could argue that the failure rate of 11 % at one year would be high. However, it is worth remembering that such patients would until then be contraindicated to treatment with CXL and as a consequence, the disease may have potentially progressed.

Impact of hypothermia on the biomechanical effect of epithelium-off corneal cross-linking

The corneal cross-linking (CXL) photochemical reaction is essentially dependent on oxygen and hypothermia, which usually leads to higher dissolved oxygen levels in tissues, with potentially greater oxygen availability for treatment. For this project, we evaluated whether a reduction of corneal temperature during CXL may increase oxygen availability, and therefore, enhance the CXL biomechanical stiffening effect in *ex vivo* porcine corneas.

Considering that (a) the availability of tissue oxygen may vary at different temperatures, and (b) oxygen is essential for CXL reactions, this study aimed to assess whether a reduction in the surface temperature of the cornea during CXL could cause an additional stiffening effect. In order to measure such eventual response, extensometry measurements were carried out after CXL performed at cold (4 °C) or standard (24 °C) temperatures.

The results did not show any temperature-dependent effect: no significant differences were found between corneas treated with CXL at cold or at standard temperature-controlled rooms.

In conclusion, while oxygen plays an essential role in corneal cross-linking, the results suggest that corneal stromal temperature does not affect the biomechanical effect of epithelium-off accelerated CXL in *ex vivo* porcine corneas.

Contribution of Bowman layer to corneal biomechanics

Corneal biomechanics play an important role not only in ocular pathologies such as keratoconus (KC) but also after corneal surgical procedures, whether for therapeutic or refractive purposes. Recent surgical techniques suggest a role of Bowman layer in corneal biomechanics. These findings have direct implications for refractive surgery and for the management of patients with KC.

Bowman layer is found between the epithelial basal membrane and the anterior stroma and is typically described as an acellular condensation of the anterior corneal stroma, with primary composition of collagen types I, III, and V. Therefore, the purpose of this study was to compare the elastic modulus (E-modulus)

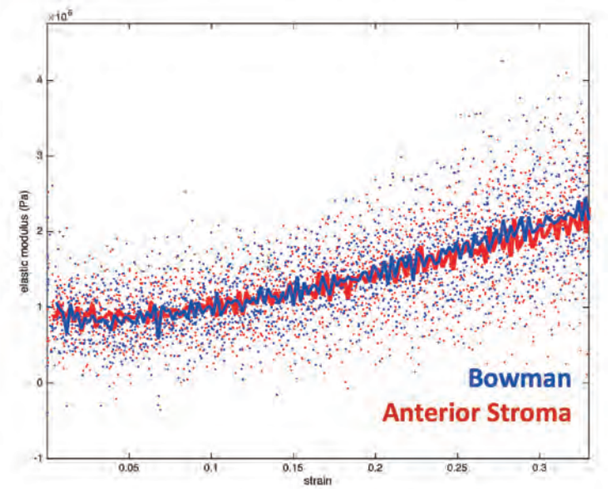


Figure 4: No measurable difference was observed in the Elastic modulus in accordance with corneal strain in both groups, with (blue) or without Bowman membrane (red).

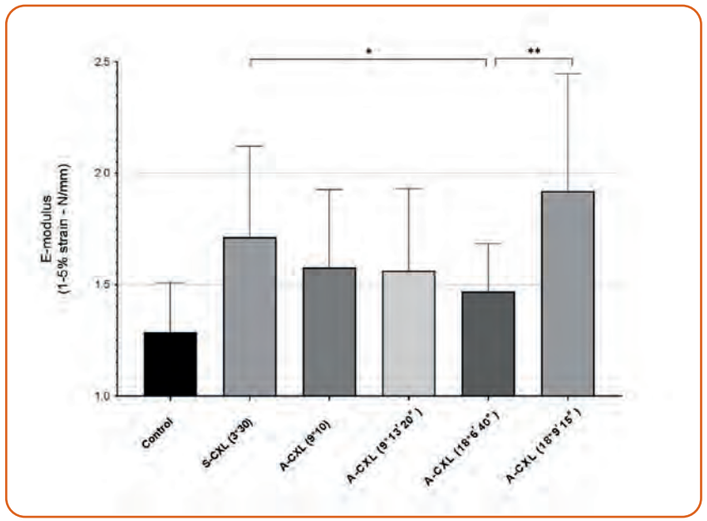


Figure 5: Accelerated high-fluence epi-off without supplemental oxygen provide more stiffening effect. Elastic modulus of accelerated high-fluence setting of 18 mW/cm² for 9 minutes and 15 seconds provides the highest stiffening effect (represented by the last column on the right).

using 2D stress–strain extensometry in healthy *ex vivo* human corneal lamellas with or without the presence of Bowman layer.

In summary, the presence or absence of Bowman layer did not alter the stiffness of an approximately 160 µm postmortem corneal lamella (Fig. 4). Unlike previous experiments, where whole corneas were analyzed, our measurements were performed in thin corneal flaps so that the relative biomechanical contribution of Bowman layer should be greater. These results may have implications not only for refractive laser surgery procedures but also for the new technique of Bowman layer transplantation in KC.

High-Fluence Accelerated Epithelium-Off Corneal Cross-Linking Protocol Provides Dresden Protocol–Like Corneal Strengthening

The normal human cornea shows a considerable degree of structural anisotropy. It is characterized by two preferred collagen fibril orientations orthogonal to each other. Alteration of the regular orthogonal arrangement of the fibrils in keratoconus may be related to the biomechanical instability of the tissue. Reduction of collagen cross-links and a reduction of molecular bonds between neighboring stromal proteoglycans are thought to be relevant to decreased stiffness of keratoconus corneas.

As mentioned previously, the Dresden protocol CXL has remained the Gold Standard for cross-linking in ectatic corneas since its introduction over 20 years ago.

Interestingly, the initial Dresden protocol had a total UV fluence of 5.4 J/cm². At that time, this fluence was chosen along with a minimal corneal stromal thickness of 400 µm to ensure that the published UV damage threshold level of 0.36 J/cm² for corneal endothelial cells was not reached. However, newer studies suggest that the irradiation damage threshold for the corneal endothelium is far higher than previously assumed, and the total fluence that could be delivered safely to the cornea during a CXL procedure may be substantially higher than the limits specified in the Dresden protocol.

So, this finding opened the floodgates for a high-fluence accelerated CXL protocol. Now, the challenge was to identify an epi-off protocol that puts all elements of CXL (UV-A intensity, irradiation time, total fluence) into a working relationship to accelerate the CXL procedure, while maintaining sufficient oxygen supply to the cornea. Oxygen availability ensures the biomechanical results achieved with the original Dresden protocol. And this outcome was precisely the purpose of the present study: to identify such a protocol.

In our *ex vivo* experiments using stress-strain, 300 porcine eyes were used for evaluating different elastic moduli of several CXL protocols. The ideal settings were achieved when using an accelerated high-fluence (10 J/cm²) setting of 18 mW/cm² of intensity for a duration of 9 minutes and 15 seconds, which provided a significantly greater stiffening effect than any other accelerated protocols evaluated (Fig. 5).

Collagen V insufficiency in a mouse model for Ehlers Danlos-syndrome affects viscoelastic biomechanical properties explaining thin and brittle corneas

Ehlers–Danlos syndrome (EDS) is a genetic disease leading to abnormalities in mechanical properties of different tissues. With this project, we quantified corneal biomechanical properties in an adult classic EDS mouse model using two different measurement approaches suited for murine corneal mechanical characterization. We related differences in biomechanical properties to stromal structures using Second Harmonic Generation (SHG) microscopy. Quasi-static Optical Coherence Elastography (OCE) was conducted non-invasively during ambient pressure modulation by – 3 mm Hg. As a result, we propose that disturbed collagen fibril structure in Col5a1+/– corneas affects the viscoelastic properties.

In summary, a reduced expression of Col5a1+/– in the cornea seems to predominantly affect the viscoelastic properties of the tissue. The results support and rationalize the notion that thin corneas with altered extracellular matrix composition maintain a normal corneal shape during homeostasis. Further studies are needed to evaluate if long-term stress on an abnormal matrix worsens alterations in corneal thickness and facilitates tissue protrusion.

Smartphone-Based Keratograph (SBK Project)

Keratoconus, a corneal disease, is the most common cause for preventable blindness among children and adolescents. Since the vision loss caused by the disease cannot be recovered, early detection and prompt treatment are key to limiting the impact of the disease. Recent studies suggest that keratoconus prevalence varies by region of the world but can be particularly high in humid and desert regions according to Gokhale *et al.* In fact, the prevalence of keratoconus in pediatric patients in Riyadh, Saudi Arabia, was found to be 4.79 % in a study performed by Torres-Netto *et al.*

The Smartphone-Based Keratograph (SBK) project establishes the basis for early intervention by developing an inexpensive, simple to operate and portable screening device. Simplicity is an important factor for extensive screening as access to medical professionals may be the first limiting factor in public health. The SBK project has been developed at the CABMM Ocular Cell Biology group since December 2020, and is funded by two Swiss foundations, Fondation Botnar (Basel) and the Light for Sight Foundation (Dietikon).

The first phase of the project was completed in June 2021, with the generation of a proof-of-concept prototype screening device (Fig. 6, center). The prototype displayed improved keratoconus screening capabilities compared with other low-cost screening methods, like eye examination with a slit lamp or a skiascope. The prototype provides an accurate topographic map of the cornea, which enables eye specialists to examine for the presence of keratoconus as a basis for the diagnosis. The benefit of a keratography map is that it gives objective information on the state (and shape)

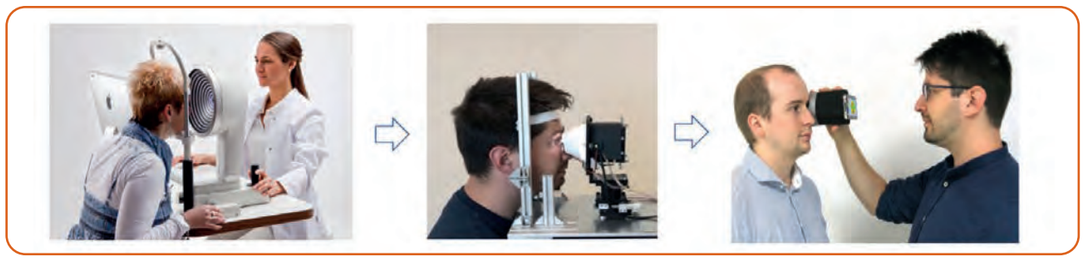


Figure 6: The SBK project develops an affordable corneal topographer for keratoconus screening. A typical corneal topographer (left), the proof-of-concept prototype developed in 2021 (center), and a mock-up of the fully portable prototype currently under development (right).

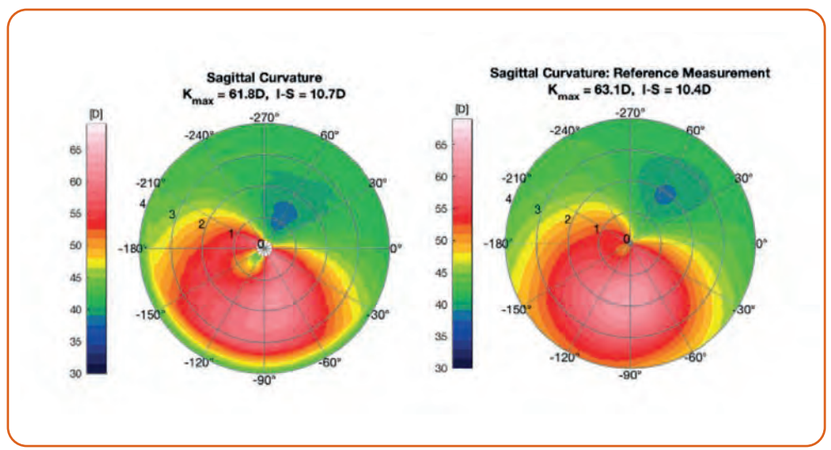


Figure 7: Topographic curvature maps of a cornea with keratoconus. Measurement with the prototype (left) shows good accuracy compared to the reference instrument (right).

of the cornea, which is an improvement over the older methods, which are qualitative, subjective, and dependent on the experience of the person operating the instruments. Furthermore, the topographic measurement data can be used for automated (software-based) detection of keratoconus, and thereby it can help remove bias from the operator.

Our proof-of-concept prototype is providing topographic maps with sufficient accuracy to distinguish keratoconic eyes from healthy eyes.

Furthermore, automated evaluation successfully identified all keratoconus cases in the recorded dataset (total 18 eyes, 9 with keratoconus, 9 healthy). Figure 7 shows a comparison between measurements with the prototype and a high-end reference instrument. Despite inaccuracies in the absolute values of the prototype's measurement, the topographic maps look qualitatively very similar, making the diagnosis of keratoconus possible.

Absolute accuracy of measured topographies has been evaluated on known reference surfaces, showing curvature errors <0.4 and <1.7 diopters (D), for root-mean-square (RMS) error and maximum error, respectively. Repeatability has been tested on real eyes, showing a standard deviation of <0.2 and <0.7 diopters for mean and maximum curvatures, respectively.

The proof-of-concept showed the feasibility of constructing a corneal topographer with inexpensive components. However, the prototype in the first project phase is not fully portable, as it requires a fixed head rest and a laptop for operation. The current, second project phase, seeks to improve on these points and develop a compact, fully portable prototype, by using a smartphone as a user interface and processing unit. The intended use is depicted in the mock-up in Figure 6, right. A simple screening device like the one shown is key to enable widespread early detection of the disease.

4. Skin Engineering Group

Group leader: Prof. Dr. med. Maurizio Calcagni
Platform users: Dr. Laura Frese (PhD), Ursula Steckhholzer (lab technician)

Keratinocytes for the treatment of severe burns and other difficult healing wounds

The skin provides an invaluable protective barrier for the human body. However, if the skin is seriously injured, e.g., by extensive burns or wound healing disorders such as chronically open wounds, the patients suffer from the dramatic loss of their epidermal and dermal skin layers. In these cases, the skin's natural ability to regenerate and repair defective skin is impaired. In addition, in severe burn patients, remaining unaffected skin areas are often not sufficient to provide an autograft coverage.

For the treatment of severe skin damage, cultivated patient-specific keratinocyte grafts have been clinically used since the 1970s. They can be produced *in vitro* from the patient's own (autologous) cells in order to avoid rejection reactions. An approx. 4 cm^2 skin biopsy of the patient is used as starting material to produce cell-based transplants. Keratinocytes can be isolated from this skin biopsy, which, after successful expansion, are transplanted to the patient in order to repair the defective skin layer. However, despite significant developments in the past years, successful and sustainable treatment is still a challenge, especially for deep and infected wounds. In order to improve the clinical outcome, reliable, high-quality grafts with faster availability and a flexible time window for transplantation are required. In order to develop such new therapies, intensive basic scientific research is essential. Thus, the main aim of the Skin Engineering Group is to produce reliable, safe, and traceable autologous keratinocyte sheets (cultivated epidermal autograft, CEA) to treat patients, all the while providing the surgeons with a window of flexibility in order to optimize the grafting date to the health of the patient.

Our team has established a method to produce cultured autologous keratinocyte grafts from human skin biopsies without the need for any xenogenic risk components such as a feeder layer (murine or others) or bovine serum (Fig. 1). The methodology has been reliable in over 100 biopsies processed to date. Furthermore, we have also established a protocol to produce a live graft as early as 18 days after biopsy harvest, which is stable and can therefore be transplanted for the following 7 days (day 25 after biopsy harvest). This, we anticipate, will give surgeons a much wider window to graft their patients. We are currently working on the translation of our production protocol into the standards of Good Manufacturing Practice (GMP). Additionally, we are developing further products based on autologous keratinocytes from our own production within the UZH / USZ enabling the treatment of a larger population of patients needing wound-healing enhancement.

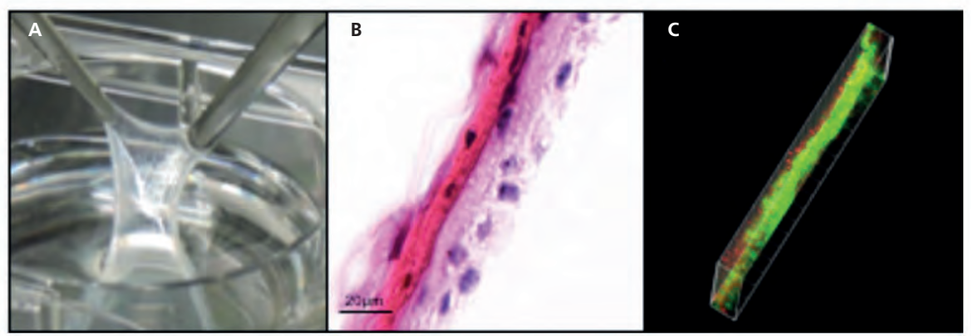


Figure 1: (A) Cultivated Epidermal Autograft, CEA, (B) Hematoxylin-eosin staining, (C) Live (green)-Dead (red) staining.

In addition to our main research project, our research group is working on further technologies and is involved in other research projects in which we seek to better understand and enhance skin wound healing:

Investigation of hypercortisolemia-induced wound healing disorders in an *in vitro* skin model

In this project our research group is focusing on the investigation of hypercortisolemia-induced wound healing disorders caused by chronic immunosuppressive treatment with glucocorticoids (GC). The exact underlying mechanisms of hypercortisolemia-induced wound healing disorders have not yet been completely understood. However, there are indications that at the molecular level, among other things, a downregulation of Nrf2 (nuclear factor (erythroid-derived 2) -like 2) might be involved. To prove the involvement of Nrf2, three *in vitro* skin models with increasing complexity based on human keratinocytes are used (Fig. 2).

In collaboration with Prof. Dr. Felicitas Boretti (Vetsuisse Faculty, University of Zurich) and Prof. Dr. Nadja Sieber-Ruckstuhl (Vetsuisse Faculty, University of Zurich), our research group is analyzing whether chronic GC treatment downregulates the Nrf2 pathway. Furthermore, it is tested whether Nrf2 activity can be rescued after chronic GC treatment by specific therapeutic treatments. To that end, three *in vitro* models with three levels of increasing complexity, will be used. The first, and simplest, model consists of an *in vitro* 3D engineered epidermal culture in which human keratinocytes are grown in an air-liquid interface. This simplified system is used to specifically look at the epidermal layer of the skin (Fig. 2 A and B). The second and third *in vitro* models introduce more complexity by culturing full thickness human skin samples in an air-liquid interface chamber (Fig. 2 C and D), with the third model artificially creating a traumatic "injury" to the skin *in vitro* (Fig. 2 E and F). In all models, GC treatment is applied for various durations in culture using dexamethasone. As end point analyses for all models, tissue samples are processed histologically and stained with hematoxylin-eosin staining to examine the effect of GC treatment. Tissues are also processed by RNA extraction, and RT-PCR analysis will determine the activity of the Nrf2 pathway and its target genes in response to chronic GC treatment.

The study will provide essential insights into chronic GC-induced wound healing disorders as well as the effect of Nrf2 induction on wound healing. In addition, a possible treatment with a physiological compound is under investigation. The results of this study can make not only a significant contribution to basic research but also provide significant added value for the treatment of chronic wounds with hypercortisolemia.

Safety of UV-based disinfection on human skin

Our collaboration partner Aseptuva GmbH, a MedTech startup based in Technopark Winterthur, is developing a medical device to combat hospital acquired infections through guided delivery of Far-UV-C radiation at infection-prone regions around catheters and tubes which are inserted into patients. Conventional UV-based disinfection lamps use 254 nm wavelength, which is known to be carcinogenic due to DNA damage of skin cells in the form of premutagenic DNA lesions, which can be assessed by quantifying the amount of cyclobutane pyrimidine dimers (CPD). Aseptuva's technology aims to introduce a new safety aspect by exploiting a narrow window of Far-UV-C wavelengths (~220 nm), which are strongly absorbed by the stratum corneum and by the larger cytoplasm of human skin cells, thus shielding the nuclei from potential DNA damage. As previously described, 50 % CPD formation was measured for a very high UV dosage of 157 mJ/cm² at 254 nm on a human skin model EpiDerm-FT (MatTek Corp.) consisting of stratum corneum and 8–12 human cell layers to reproduce human epidermis and dermis. Furthermore, 254 nm Far-UV-C led to 90 % cell death at a dose of 2 mJ/cm². Using the same dose of the two wavelengths on mice skin (SKH1-Elite strain 477), 254 nm radiation produced CPD in over 80 % of the epidermal keratinocytes after 2 days, while no significant increase was observed by radiation at 222 nm. To date, there has been no study that has assessed the effect of Far-UV-C on human skin *ex vivo* obtained through biopsy within the International Commission on Non-Ionizing Radiation Protection (ICNIRP) limits. Therefore, in collaboration with Aseptuva, we carried out a preliminary investigation concerning the same, in order to test safety of Far-UV-C technology at limiting exposure values of ~ 25mJ/cm² on human skin tissue, and therewith, the feasibility of Aseptuva's technology.

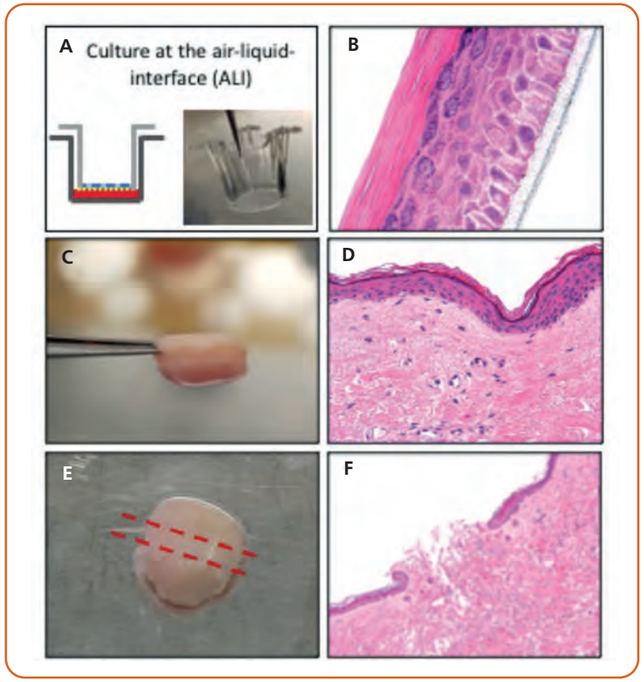
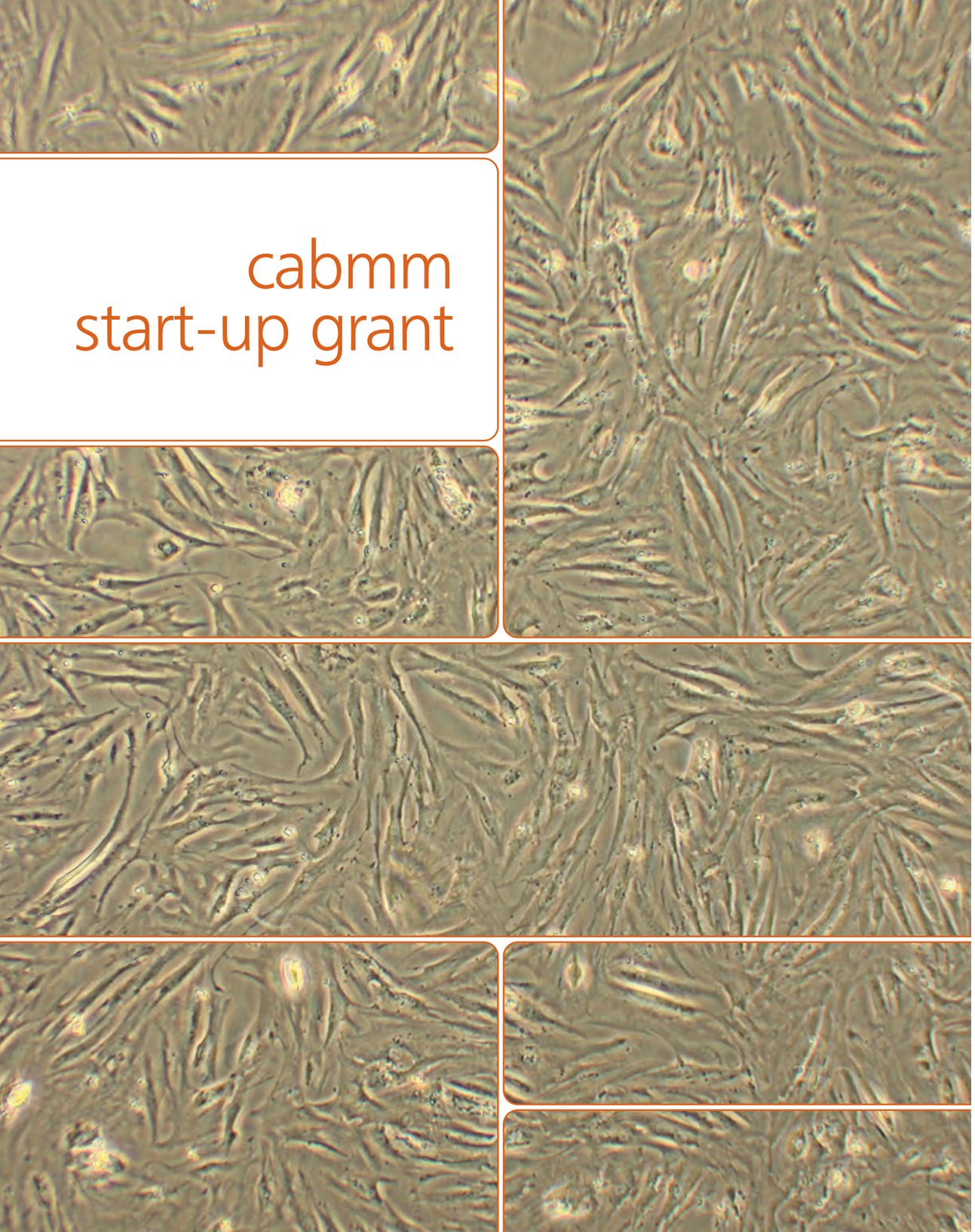


Figure 2: Overview of the three *in vitro* skin models with increasing complexity: 3D epidermal skin model using Transwell® (A), skin organ culture model (C) and artificial "wound" model (E). The corresponding hematoxylin-eosin staining shows the tissue architecture of each model (B, D, F).

Native human skin samples, collected from adult patients undergoing plastic surgery at the Division of Plastic Surgery and Hand Surgery of the University Hospital Zurich, were used to apply UV radiation using the Aseptuva's technology. Different illumination periods were used in order to reach specific total Far-UV-C intensities: Approx. 6 mJ/cm² of 222 nm UV light was applied once for 5 mins on the skin sample (with filter) as well as 72 mJ/cm² of 222 nm UV light for 69 min (with filter) and 47 mJ/cm² for 9 min (without filter). Biochemical assays were performed on skin samples to assess DNA damage in the form of premutagenic DNA lesions. Therefore, the amount of CPD was assessed using ELISA. It could be shown that the Aseptuva technology, the application of Far-UV-C wavelengths (220 nm) to human skin, causes no significant DNA damage in the form of CPD formation compared to untreated samples.



cabmm start-up grant

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

The grants support novel projects within the musculoskeletal and the cardiovascular field, with emphasis being placed on proof of principle, high-risk studies, which would most likely not be supported by other more competitive funding agencies. It is expected that the findings generated from these initial studies should be sufficient to enable further applications to be submitted to more competitive funding agencies. Application requirements include, amongst others, CABMM membership and an affiliation to a Swiss institution of the principal investigator. At least one applicant needs to be affiliated with the University of Zurich and preference is given to young academics. Under no circumstances can applications be considered that involve industrial partners or animal experimentation.

The applicants can receive a maximum amount of CHF 40'000.– over a period of one year.

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

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

Until the end of 2021, a total amount of more than CHF 1.7 Mio was allocated to our funding program. In total, 52 projects were approved, and 40 associated articles have been published in peer-reviewed scientific journals, amongst others, in high-ranking journals such as Nature Communications, Molecular Cell, or the Nature Partner Journal Regenerative Medicine. Some projects even resulted in two or even more publications, illustrating the importance of our funding program as well as the scientific excellence of the supported projects. Additionally, the results obtained in those preliminary studies have allowed in approximately 70% of the cases for the support of continuative studies by larger funding agencies, proving our strategy successful.

In this reporting period, a total of three projects with an overall amount of CHF 94'181,10 was funded by a CABMM Start-up Grant. A tabular summary of these projects can be found on the following page. Additionally, short summaries of selected, already successfully completed projects are presented. If the project has already been published in a scientific journal, the corresponding citation is indicated.

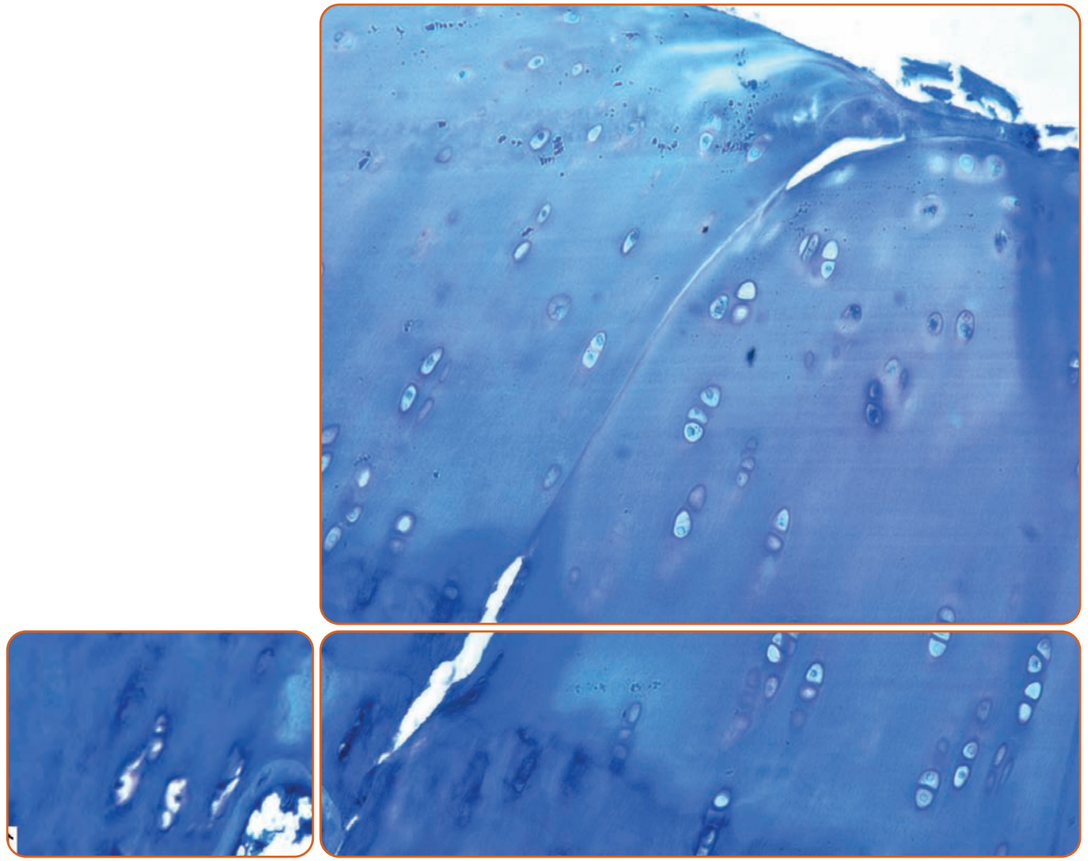
summary of newly approved projects in the reporting period

applications 2020

Project title	Applicants	Amount
Toward the combination of epigenetics and tissue engineering to generate cartilage *in vitro*	PD Dr. Paolo Cinelli Dr. Killian Flégeau * (Prof. Dr. Marcy Zenobi-Wong **) Prof. Dr. Lee Ann Laurent-Applegate Prof. Dr. Marcy Zenobi-Wong	**CHF 30'908.10**
	Subtotal 2020	**CHF 30'908.10**

applications 2021

Project title	Applicants	Amount
Nucleus pulposus-on-a-chip as a model for mechanobiology research and therapeutic testing	Dr. Salim Darwiche (Dr. Katja Nuss **) Dr. Olga Krupkova * (Prof. Dr. Andrea Barbero **)	**CHF 33'620.00**
REVEAL-FS: Characterization of novel targets for near infrared fluorescence-guided surgery of fibrosarcomas	Prof. Dr. Franco Guscetti (Prof. Dr. Anja Kipar **) Prof. Dr. Dr. Enni Markkanen * PD Dr. Mirja Nolff (Prof. Dr. Antonio Pozzi **)	**CHF 29'653.00**
	Subtotal 2021	**CHF 63'273.00**
	Total amount in the reporting period	**CHF 94'181.10**



* main applicant, ** corresponding CABMM member

1. Identification of HSP70-dependent factors involved in response to thermoradiotherapy in osteosarcoma

Principle investigator: Dr. Katarzyna Nytko-Karouzakis (Prof. Dr. Carla Rohrer Bley **)
Collaborators: Prof. Dr. Stephan Bodis ***
Prof. Dr. Niels Kuster
Prof. Dr. Carla Rohrer Bley
Amount funded: CHF 20'040.–
Funding period: 11 / 2017 – 10 / 2018

Background: Radiotherapy resistance is one of the major obstacles in clinical cancer treatment of various tumor types, including osteosarcomas. Intrinsic resistance is caused by high levels of tumor hypoxia and the presence of cancer stem cells, which are highly radio-resistant and responsible for tumor relapse after treatment. Pre-treatment of tumors with hyperthermia is often used to increase the efficacy of radiotherapy. One of the main proteins induced in response to hyperthermia is heat shock protein 70 (HSP70). We have previously shown that Abrams canine osteosarcoma cell line was radiosensitized by hyperthermia pre-treatment. Moreover, Abrams cells have low basal but strongly heat-inducible levels of HSP70.

Aim: The aim of our study was to investigate up- and down-regulated genes in response to (thermo)radiotherapy in a HSP70 proficient and deficient canine osteosarcoma cell line (Abrams), and the functional role of HSP70 in the mechanism of thermoradiosensitization. We used RNA sequencing technology and quantitative RT-PCR to identify down- and up-regulated factors, clonogenic cell survival and proliferation assays to measure the response to treatment, and apoptosis/necrosis assay to investigate cell death after treatment.

Results: We could identify genes differentially expressed in HSP70 knockdown cells (Fig. 1). Moreover, hyperthermia and thermoradiotherapy, but not radiotherapy alone, induced differential gene expression. We identified genes differentially expressed only in HSP70 knockdown (thus HSP70-dependent) cells in response to hyperthermia and thermoradiotherapy. Interestingly, cell proliferation but not clonogenicity and apoptosis/necrosis was affected by HSP70 knockdown in response to thermoradiotherapy.

Conclusion / Significance: The results suggest that HSP70 regulates expression of specific genes in response to hyperthermia and thermoradiotherapy. Further investigations into the role of specific genes regulated in a HSP70-dependent manner in response to thermoradiotherapy could pave a way into new, combinatorial treatment options for (canine) osteosarcoma and other cancer types.

Publication:
Nytko KJ, Thumser-Henner P, Russo G, Weyland MS, Rohrer Bley C
"Role of HSP70 in response to (thermo)radiotherapy: analysis of gene expression in canine osteosarcoma cells by RNA-seq"
Sci Rep, 2020 Jul 29;10(1):12779

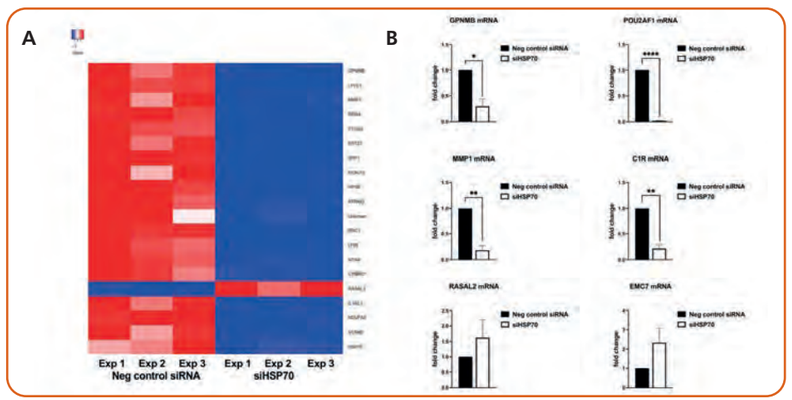


Figure 1: (A) GPNMB, LYVE1, and MMP1 are the most significantly downregulated genes in HSP70 knockdown cells. Heatmap of normalized counts of the top 20 differentially expressed genes and HSP70 in negative control and HSP70 knockdown cells in experimental replicates (n=3). (B) mRNA levels of selected differentially expressed genes analyzed by qRT-PCR.

** corresponding CABMM member, *** no CABMM member

2. Automated and High-throughput Production of hiPSC-derived Human Cardiac Microtissues for *in vitro* Disease Modeling

Principal investigators: Dr. Bramasta Nugraha (Prof. Dr. Dr. Simon P. Hoerstrup **)
Prof. Dr. Maximilian Emmert (Prof. Dr. Dr. Simon P. Hoerstrup **)
Collaborator: Prof. Dr. Dr. Simon P. Hoerstrup
Amount funded: CHF 40'000.–
Funding period: 03 / 2018 – 02 / 2019

Background: Genetic cardiomyopathies are characterized by changes in the function and structure of the myocardium. The development of a novel *in vitro* model could help to better emulate healthy and diseased human heart conditions and may improve the understanding of disease mechanisms.

Aim: Our study aimed to elucidate the suitability of cardiac organoids as a novel *in vitro* model for genetically healthy and hypertrophic cardiomyopathy (HCM) heart conditions.

Results: We demonstrated the generation of cardiac organoids using a triculture approach of human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) from healthy subjects or cardiomyopathy patients, human cardiac microvascular endothelial cells (HCMECs), and human cardiac fibroblasts (HCFs). We assessed the organoids' suitability as a 3D cellular model for the representation of phenotypical features of healthy and cardiomyopathic hearts. We observed clear differences in structure and beating behavior between the organoid groups, depending on the type of hiPS-CMs (healthy versus cardiomyopathic) used.

Conclusion / Significance: The proposed *in vitro* organoid model may represent a physiological-like human heart mini-tissue, which retains the geno- and phenotypical characteristics of the corresponding donor tissue. Therefore, our organoids may represent a robust model system, suitable for medium- to large-scale production, for studying and modeling cardiac disease. Feasibility assays for producing organoids in a more size-controlled, automated, and high-throughput fashion is envisioned. Although this system cannot entirely replace animal models due to the bypassing of critical composite features of human diseases, such as complex sensory and feedback systems, it is expected to contribute to the reduction of animal experiments needed.

Publication:
Filippo Buono M, von Boehmer L, Strang J, Hoerstrup SP, Emmert MY, Nugraha B
"Human Cardiac Organoids for Modeling Genetic Cardiomyopathy"
Cells, 2020 Jul 20;9(7):1733

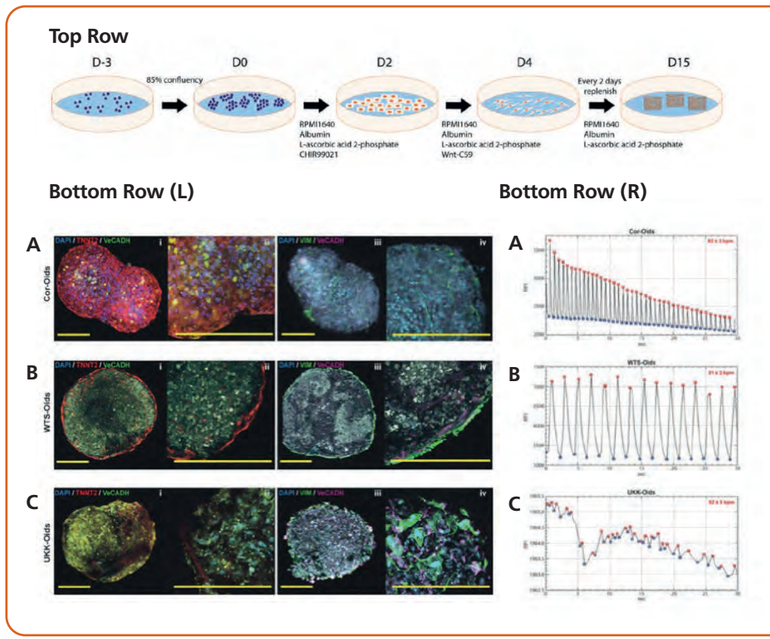


Figure 1: Top Row: Optimized adopted hiPSCs differentiation protocol towards cardiomyocyte lineage. Bottom Row, left: Immunofluorescence staining shows localization differences in the tri-culture cardiac microtissues among control (Cor-oids), healthy (WTS-Oids) and cardiomyopathic organoid (UKK-Oids) types. Bottom Row, right: Analysis of the beating pattern and rates of the different cardiac organoids.

** corresponding CABMM member

3. Intraoperative tissue and fluid analysis using radiofrequency plasma spectroscopy

Principle investigator: Prof. Dr. Dominik Meyer ****
Collaborators: Prof. Dr. Christian Gerber
Dipl.-Ing. Sebastian Valet ***
Prof. Dr. Annelies Zinkernagel
Dr. Frédéric Cornaz ***
Amount funded: CHF 24'353.–
Funding period: 09 / 2016 – 12 / 2017

Background: Electrosurgical bipolar radio frequency (RF) devices are primarily used for soft tissue ablation and coagulation in arthroscopic surgeries. During the procedure a plasma field is formed. The emitted light spectra can be analyzed by optical emission spectroscopy (OES) which allows the deduction of chemical elements (Fig. 1). The method can potentially be applied intraoperatively to diagnose the treated tissue in real time. Applications of interest aim at the detection of particles of prosthetic debris, different types of tissue, degenerative diseases like calcifying tendinitis, bacterial infections in biofilms, and other pathologies.

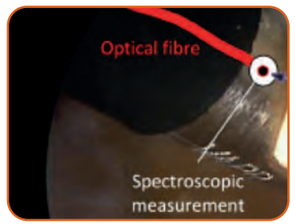
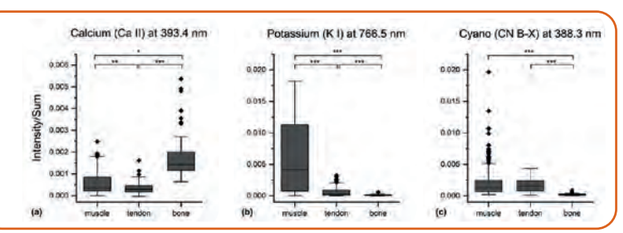


Figure 1: Electrode of the bipolar RF device used in an arthroscopic surgery (arthroscopic camera) with plasma discharge in contact with soft tissue under irrigation of saline solution.

Aim: Proof of hypothesis that plasma spectroscopy during surgical radio frequency (RF) tissue ablation allows for the characterization of biological tissue or chemical components.



Results: The main results from spectroscopic measurements are based on the analysis of elements such as Na, Cl, K, and Ca in liquids as well as in porcine tissue samples. Post-processing of spectral measurement data was carried out using a specifically developed MATLAB algorithm. The optical intensity was determined for a varied concentration of sodium (range from 0-154 mmol/l) and potassium (0-130 mmol/l). The peak intensity at 589 nm for sodium and at 766 nm for potassium showed a linear correlation with the ion concentration (R^2=0.986 and R^2=0.963, respectively). RF-OES measurement during porcine tissue ablation revealed that the distinction between different types of biological tissue is possible using indicator elements such as Ca, K, and C-N (Fig. 2). The minimal limit of detection (LOD) for calcium in tissue using RF-OES was estimated with 122 ± 51 µg/g (mean calcium concentration in porcine tendon measured with ICP-OES, n=30). The calcium content of randomized tissue samples (including tendon, muscle, and cartilage tissue) of human subjects ranged from 80 µg/g (healthy tendon) to 162'700 µg/g (tendon calcification) with a mean of 35'266 µg/g (analyzed by ICP-OES, n=12) and lies well in the range of the estimated LOD for RF-OES. Pilot studies on bacterial cultures were conducted with the aim to identify bacterial growth to give the surgeon real time feedback on the presence of bacterial infection.

Conclusion / Significance: The findings demonstrate the feasibility and potential of optical emission spectroscopy for intraoperative real-time analysis of ablated tissue. Detection of chemical elements, distinction between different tissue types, tissue contact detection, and control of the ablation process is possible by means of RF-OES. The variation of calcium content in human tissue is considerably larger than the LOD and reveals the potential for the intraoperative differentiation using RF-OES.

Publication:
Cornaz F, Valet S, Meyer DC
"Spectroscopic characterization of tissue and liquids during arthroscopic radio-frequency ablation"
Med Phys, 2020 Aug;47(8):3703-3709

Figure 2: Figure from Cornaz *et al.* 2020: Emission intensities of calcium (a), potassium (b), and cyanido radical (c) peaks during ablation of different porcine tissue samples are plotted (each: duration 5s, n=5, 500 frames). Significant differences between measurements are marked with asterisks (*p < 0.05, **p < 0.01, ***p < 0.001).

4. Microbiota and metabolic endotoxemia: the missing culprit of Osteoarthritis

Principle investigator: Dr. Gonçalo Barreto
(Prof. Dr. Marcy Zenobi-Wong **)
Collaborators: Prof. Dr. Marcy Zenobi-Wong
Prof. Dr. Dr. Caroline Ospelt
Amount funded: CHF 40'000.–
Funding period: 01 / 2018 – 12 / 2018

Background: Osteoarthritis (OA), the most common form of arthritis, is estimated to be in the top 5 leading causes of disability worldwide. Alarmingly, OA incidence is estimated to continue growing partly due to the overall worldwide trend of increased obesity and aging population. Furthermore, OA is now considered as a disorder of the joint as a whole, with inflammation driving many pathologic changes. The inflammation in OA is distinct from that in rheumatoid arthritis and other autoimmune diseases: it is chronic, comparatively low-grade, and mediated primarily by the innate immune system.

Aim: Microbiota, the new frontier in medicine, plays a fundamental role on the induction, training, and function of the host immune system with connections to a variety of diseases. We aimed to evaluate (1) the role of metabolic endotoxemia, a key pro-inflammatory product of the microbiota, in inducing low-grade inflammation and innate immunity activation mechanisms of osteoarthritis as well as (2) the association of endotoxemia with epidemiological data of osteoarthritis.

Results: We have been able to explore several mechanisms which may contribute to the pathogenic mechanism of endotoxemia in OA. We demonstrated that the glycoprotein lumican is a mediator of lipopolysaccharide (LPS)-induced TLR4 (toll-like receptor) activation of inflammation, cartilage degradation, and macrophage polarization in the OA joint. Our systematic analysis identified bacterial species such as Clostridium and Firmicutes as potential regulators of OA. Lastly, the CABMM Start-up Grant support enabled us to collect further preliminary data and refine our project and future experiments which have now been successfully funded by an ETH Grant (Fig. 1).

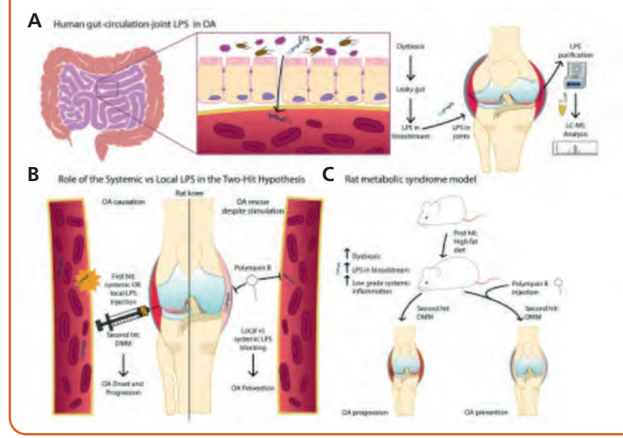


Figure 1: Schematic of the proposed follow-up experiments funded by an ETH Grant. (A) LPS types in synovial fluid samples from end stage OA patients will be identified using Liquid Chromatography - Mass Spectrometry (LC-MS). LPS enters the joint through the gut-joint axis, first into general circulation through the leaky gut, and then into the joint space via blood vessels in the subchondral bone or synovium. (B) In a rat OA model, we test the 'two-hit' hypothesis, namely that both low-grade inflammation (intraarticular or systemic LPS injection) and structural damage (from Destabilization of Medial Meniscus (DMM)) are required to potentiate the disease. (C) We hypothesize that a high-fat diet can also create the inflammatory conditions to potentiate the DMM OA model. We also test the hypothesis that Polymyxin B can ameliorate OA severity, by inactivating LPS.

Conclusion / Significance: Understanding the impact and molecular mechanism the gut microbiome exerts in osteoarthritis disease, could pave the way for new clinical therapeutic strategies, as well as provide the society with further evidence for dietary guidelines for OA patients, and the rest of the population at risk of developing OA.

Publication:
Barreto G, Senturk B, Colombo L, Brück O, Neidenbach P, Salzmann G, Zenobi-Wong M, Rottmar M
"Lumican is upregulated in osteoarthritis and contributes to TLR4-induced pro-inflammatory activation of cartilage degradation and macrophage polarization"
Osteoarthritis Cartilage, 2020 Jan;28(1):92-101

*** no CABMM member, **** former CABMM member

** corresponding CABMM member

5. Canine spontaneous meniscal degeneration: A suitable model for translational medicine?

Principle investigator: Prof. Dr. Antonio Pozzi
Collaborator: Dr. Olga Krupkova
(Prof. Dr. Karin Würtz-Kozak **)
Amount funded: CHF 39'000.–
Funding period: 12 / 2017 – 11 / 2018

Background: Approximately 25 % of people over the age of 55 are known to have suffered from a significant episode of knee pain due to osteoarthritis (OA). Meniscal pathology contributes to knee OA by altering load distribution and lowering knee flexibility. However, the biological contribution of meniscal pathology to OA is unclear, also due to the absence of chronic pro-inflammatory conditions in animal models.

Aim: The study aims were (1) to investigate whether spontaneous (chronic) meniscal pathology in privately owned dogs contributes to joint inflammation and (2) to assess whether this model replicates chronic meniscal pathology and OA traits.

Results: Menisci, synovial membranes, and synovial fluids were isolated from 14 privately owned dogs with spontaneous meniscal pathology (MP) and 5 healthy controls. Synovial fluids from stifles with MP contained increased levels of inflammation/pain markers (IL-6, NGF, VEGF), suggesting ongoing disease. MP tissues showed significantly upregulated gene expression of NGF and COX-2 but not of other pro-inflammatory genes (IL-6/8, IL-1β, TNF-α) and pathways (NF-κB and p38 signaling), indicating that MP might contribute to pain. On the other hand, cultured primary cells isolated from MP significantly upregulated pro-inflammatory mediators (IL-6/8, IL-1β, TNF-α, NGF, COX-2 mRNA) in response to IL-1β or TNF-α and activated NF-κB and p38 signaling pathways, suggesting their sensitivity to inflammation.

Conclusion / Significance: While previous studies mainly focused on canine synovial fluid, our study confirmed that biological changes in spontaneous MP partially correspond to alterations documented in human MP (NGF, COX-2). It has been suggested that pain associated with OA is mostly related to bone and periarticular tissue rather than cartilage and meniscus, due to their aneural nature. However, based on our results, MP may be a source of molecules involved in pain. Complete surgical resection of degenerated meniscal tissue is not feasible and not recommended because of the detrimental effects of meniscectomy on biomechanical stability. Our findings support the use of new therapies (e.g., drugs targeting NGF) to reduce pain signals arising from MP. Additional studies are needed to confirm whether the spontaneous canine model of MP can be suitable for translational research.

Publication:
Krupkova O, Smolders L, Wuertz-Kozak K, Cook J, Pozzi A
"The Pathobiology of the Meniscus: A Comparison Between the Human and Dog"
Front Vet Sci, 2018 Apr 16;5:73

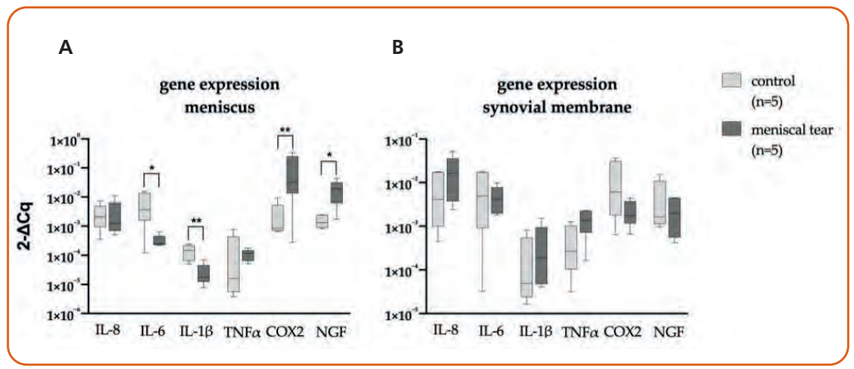


Figure 1: The expression of inflammation-associated genes in the meniscus (A) and synovial membrane (B) isolated from canine patients with meniscal tear (dark grey) and the healthy donors (light grey). IL-1β, IL-6, IL-8, TNF-α, COX2, and NGF mRNA was quantified by RT-qPCR and normalized to the housekeeping gene (GAPDH) ($2^{-\Delta Cq}$). Asterisks indicate statistically significant differences with *$p<0.05$ and **$p<0.01$ (linear mixed models).

6. The Role of Fibronectin Fragments in Immune Modulation and Inflammaging during Canine Disc Disease

Principle investigators: Prof. Dr. Franck Forterre
Prof. Dr. Benjamin Gantenbein
Amount funded: CHF 19'715.–
Funding period: 08 / 2018 – 07 / 2019

Background: Canine intervertebral disc disease (IVDD) is a prevalent disorder and shares many similarities with the human pathology. While the molecular disease mechanisms in humans are well-investigated, considerably less is known about the pathobiology of canine IVDD. Nevertheless, similarly to humans, increased expression of proinflammatory cytokines can be found in herniated canine IVDs compared to non-herniated IVDs. The production and release of proinflammatory factors may be mediated through toll-like receptors (TLR) by numerous stimuli. One group of these stimuli are certain host-derived damage-associated molecular patterns like fibronectin fragments (FnF). These fragments develop during tissue dysfunction and may be of specific relevance to IVD pathologies by inducing an inflammatory response in resident cells.

Aim: The project aimed to demonstrate the presence of FnF in herniated IVD material collected during surgery from dogs suffering from IVDD by Western Blotting. Furthermore, the proinflammatory and catabolic potential of 30 kDa FnF *in vitro* in canine IVD was investigated by exposing canine nucleus pulposus (NP) cell cultures to 30 kDa FnF. Involvement of TLRs was evaluated by their blocking through Sparstolonin B (TLR 2/4 antagonist) during the exposition to FnF. Gene and protein expression of proinflammatory cytokines by NP cells was evaluated with qPCR and ELISA, respectively.

Results: Amongst multiple sized FnF (30, 35, 45, and >170 kDa), N-terminal fragments at a size of ~30 kDa were most consistently expressed in herniated IVDs. Importantly, these fragments were exclusively present in herniated, but not in non-herniated IVDs (Fig. 1).

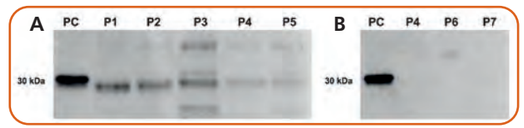


Figure 1: Detection of fibronectin fragments in herniated (A, patients 1-5) and non-herniated (B, patients 4-7) canine nucleus pulposus material using a mouse monoclonal antibody specific for N-terminal fibronectin (PC=positive control).

At the gene level, exposure of canine NP cells to 500 nM 30 kDa FnF caused a significant upregulation of IL-6 and IL-8. Donor-donor variation was observed in response to FnF treatment, whereby this phenomenon was most evident for COX-2, with three donors demonstrating a significant downregulation and three donors showing upregulation. Protein production of IL-6 and PGE2 was inconclusive. Insufficient sensitivity of the used commercial ELISA kits was suspected to be responsible for the lack of response. Blocking of TLR did not alter the expression and protein production of NP cells upon FnF exposure. Cell cultures of donors with a less prominent response or downregulation were derived from cryopreserved cell cultures, whereas the others were freshly established cell cultures, indicating that the process of cryopreservation may affect their sensitivity to FnF.

Conclusion / Significance: Given the presence of the 30 kDa FnF in canine herniated IVDs and the proinflammatory effect of 30 kDa FnF on NP cells, we concluded that the accumulation of FnF may be involved in the pathogenesis of canine IVDD. These results correspond to the findings in humans with IVDD.

Publication:
Schmidli MR, Sadowska A, Cvitas I, Gantenbein B, Lischer HEL, Forterre S, Hitzl W, Forterre F, Wuertz-Kozak K
"Fibronectin Fragments and Inflammation During Canine Intervertebral Disc Disease"
Front Vet Sci, 2020 Nov 16;7:547644

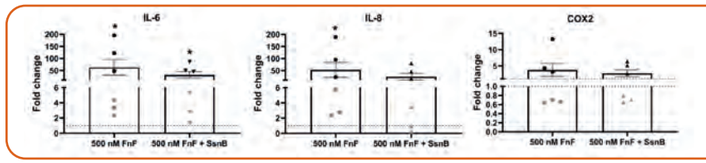


Figure 2: Gene expression of IL-6, IL-8 and COX2 after 18 h exposure to 30 kDa fibronectin fragments alone (points) and in combination with the TRL-2/TRL-4 inhibitor Sparstolonin B (triangles). Values were normalized to GAPDH reference gene and are shown as fold change compared to untreated control or Sparstolonin B alone. Asterisks denote statistically significant differences with $p < 0.05$. Black symbols indicate high responders (n=3), grey symbols indicate low responders (n=3).

** corresponding CABMM member

facts & figures

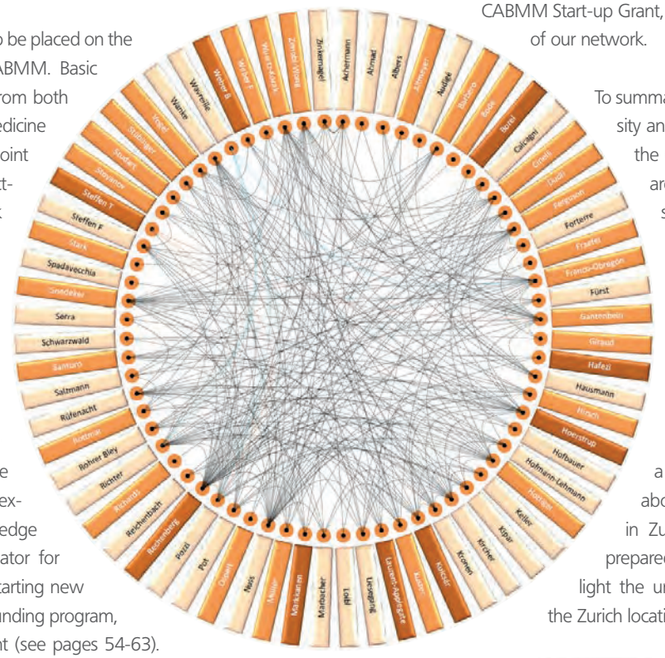
member profiles, joint research projects and publications

Performance, coordination and promotion of interdisciplinary and translational research – these are the main objectives of the CABMM. Therefore, we aim to create and continuously strengthen a network of active member groups from different fields. The number and quality of those members as well as their collaborative research projects and scientific publications reflect not only the activity within the CABMM network, but also show the success and quality of the CABMM.

Since its foundation in 2008, the CABMM has gained acceptance and reputation in the field of interdisciplinary and translational research. Amongst others, this is illustrated by a continuously growing number of CABMM members. At the end of 2021, our network consisted of 82 members. Considering the number of team members behind every person, this makes for an impressive network! Although the majority of associated scientists belong to institutions in Zurich, we also have strong affiliations with other institutions located elsewhere in Switzerland as well as in other countries. In this respect, it is nice to see that our members who leave Switzerland for professional purposes or retire usually want to stay connected with the CABMM and often retain a close working relationship.

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. One of the most important instigators for starting a new collaboration is the yearly CABMM Seminar and the CABMM Symposium where the presentations of new findings by scientists working within the CABMM allow for fruitful exchange of scientific knowledge and ideas. Another stimulator for scientific discussions and starting new collaborations is our own funding program, the CABMM Start-up Grant (see pages 54-63). And even though we were not allowed to organize any in person events within the reporting period due to the Covid-19 pandemic, the number of collaborations among CABMM members as well as the number of joint research projects nevertheless increased by 10 % and 13 %, respectively, demonstrating that a solid network was established during the past years.

Another testament to the scientific strengths and networking capabilities of our CABMM members is the fact that almost 350 peer-reviewed research articles with affiliation to the CABMM have been published in scientific journals since its creation, thereof almost 100 in the reporting period. More than half of these publications are connected either to the CABMM Research Platform or to the CABMM Start-up Grant, again showing the success of our network.



To summarize and illustrate the diversity and multifaceted work within the CABMM, all our members are introduced with the assistance of short profiles on the following pages. Additionally, we provide tables detailing research projects performed within the CABMM as well as CABMM-affiliated articles published in scientific journals. Furthermore, a public relations brochure about "Translational Research in Zurich" is listed, which was prepared by the CABMM to highlight the unique GxP competence at the Zurich location.

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 90-97 and 98-108

Name: **Achermann, Yvonne**
PD Dr. med.
Institution: Department of Dermatology, University Hospital Zurich; Internal Medicine and Infectious Diseases, Spital Zollikerberg
Grants: Jubiläumsstiftung Swiss Life, Stiftung für wissenschaftliche Forschung an der Universität Zürich, USZ Foundation, Vontobel-Stiftung
CABMM collaborators: Stefan Dudli, Oliver Hausmann, Niels Kuster, Katja Nuss, Brigitte von Rechenberg, Karin Würtz-Kozak, Annelies Zinkernagel
CABMM joint projects: 29, 49, 76, 81
CABMM-affiliated publications: 17, 67

General research interest:
PD Dr. Yvonne Achermann is a medical doctor specialized in internal medicine and infectious diseases. Since 2008, her scientific focus is on implant-associated infections, mainly prosthetic joint infections. She combines basic research in the field of "prevention, diagnostic, and treatment of implant-associated infections" and clinical research in collaboration with the University Hospital Zurich, University Hospital Balgrist, and Schulthess Clinic. Her current experimental research focus is on prevention and treatment of periprosthetic joint infections using photodynamic therapy.

Name: **Ahmad, Sufian S.**
PD Dr. med.
Institution: BG-Center for Trauma & Reconstructive Surgery, University of Tübingen, Germany (until 06/2020); Center for Musculoskeletal Surgery, Charité, University of Berlin, Germany
Grants: Insel-Grant, Smith & Nephew Grant, Swiss Orthopaedics
CABMM collaborators: Benjamin Gantenbein, Brigitte von Rechenberg
CABMM joint projects: 73
CABMM-affiliated publications: 27

General research interest:
Sufian S. Ahmad's research focus is on mechanobiology of cruciate ligaments, cellular biology for treatment of ligament ruptures as well as clinical studies. As a clinician, he emphasizes the need for providing clinically relevant research questions to the basic research laboratory, which would subsequently allow for smooth translation back into clinical practice.

Name: **Albers, Christoph E.**
PD Dr. med.
Institution: Department of Orthopaedic Surgery and Traumatology, University Hospital Bern
Grants: DePuy Synthes, Icotec, ORTHO-TEAM, Swiss Orthopaedics
CABMM collaborators: Stefan Dudli, Benjamin Gantenbein, Oliver Hausmann
CABMM joint projects: 7
CABMM-affiliated publications: 8, 42

General research interest:
Christoph Albers is a spine surgeon at the Department of Orthopaedic Surgery and Traumatology, University Hospital Bern. His scientific background includes bone metabolism, osteogenesis, and bone healing. Current research projects aim at improving and augmenting spinal fusion and intervertebral disc regeneration. As a clinician, he is interested in translating knowledge from basic science directly to clinical application.

Name: **Altmeyer, Matthias**
Prof. Dr. sc. nat.
Institution: Department of Molecular Mechanisms of Disease, University of Zurich
Grants: Comprehensive Cancer Center Zurich, ERC, Novartis Foundation for Medical-Biological Research, Pfizer CTI, SNF, Stiftung zur Krebsbekämpfung, Swiss Cancer Research Foundation
CABMM collaborators: Michael Hottiger, Enni Markkanen, Brigitte von Rechenberg

General research interest:
Research in our laboratory is aimed at elucidating cellular mechanisms of genome integrity maintenance and their deregulation in human diseases such as cancer. Currently, our work is focused on cell cycle regulation of DNA repair events and on the role of chromatin in modulating repair reactions, including those required for genome editing and gene therapy.

Name: **Audigé, Laurent**
Prof. Dr. (DVM), PhD
Institution: Research and Development Department, Shoulder and Elbow Surgery, Schulthess Clinic, Zurich
Grants: SNF
CABMM collaborators: Stephen Ferguson, Christian Gerber
CABMM joint projects: 53, 71

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.
Furthermore, we contribute to 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: **Barbero, Andrea**
Prof. Dr. (PhD)
Institution: Cartilage Engineering Group, Department of Biomedicine, University of Basel and University Hospital Basel
Grants: Fondazione Cariplo, SNF
CABMM collaborators: Katja Nuss, Antonio Pozzi, Brigitte von Rechenberg, Gian Salzmann, Jivko Stoyanov, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 47, 54, 55, 57
CABMM-affiliated publications: 33, 74

General research interest:
Prof. Barbero's research is related to the establishment of 3D culture systems, combining cell biology, engineered technologies, and materials science. These systems are used to investigate fundamental aspects of cartilage development, and as grafts to induce tissue regeneration. A special focus lies in the use of nasal cartilage grafts for the treatment of nasal and articular cartilage and their potential use for intervertebral disc repair.

Name: **Bode, Jeffrey**
Prof. Dr. sc. nat.
Institution: Laboratory of Organic Chemistry, ETH Zurich
Grants: ERC Synergy Grant, industry, Innosuisse, NCCR Catalysis, NIBR Global Scholars Program, SNF, SNF Sinergia
CABMM collaborators: Marcy Zenobi-Wong
CABMM joint projects: 1

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

Name: **Borel, Nicole**
Prof. Dr. med. vet., Dipl. ECVP, FVH pathology
Institution: Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich
Grants: AgroVet-Strickhof, CSF ETHZ, Dr. med. h. c. Erwin Braun Stiftung, OIE, Sefunda AG, SNF, Stiftung für wissenschaftliche Forschung an der Universität Zürich
CABMM collaborators: Anton Fürst, Regina Hofmann-Lehmann
CABMM joint projects: 18, 63, 84
CABMM-affiliated publications: 1, 39, 84

General research interest:
We focus on new therapeutic strategies for intracellular bacteria such as chlamydiae. Application of water-filtered infrared A irradiation (wIRA) strongly inhibits chlamydial infection *in vitro* and reduces ocular pathology and chlamydial load in a guinea pig conjunctivitis model. Future studies will investigate the working mechanism of wIRA, its effect on chronic chlamydial infections and possible future clinical applications. The final goal is to establish wIRA as a novel therapeutic device to combat blinding trachoma, a devastating neglected tropical disease, affecting 41 million people globally.

Name: **Calcagni, Maurizio**
Prof. Dr. med.
Institution: Department of Plastic Surgery and Hand Surgery, University Hospital Zurich
Grants: BioSilk, Evi Diethelm-Winteler-Stiftung, Georg und Bertha Schwyzer-Winiker-Stiftung, Karitative Stiftung Dr. Gerber-ten Bosch, LaColline, Medartis, Stiftung für Naturwissenschaftliche und Technische Forschung, Stiftung Propter Homines, SUVA
CABMM collaborators: Paolo Cinelli, Simon Hoerstrup, Lee Ann Laurent-Applegate, Katja Nuss, Brigitte von Rechenberg, Jess Snedeker, Viola Vogel
CABMM joint projects: 25, 39, 45, 61
CABMM-affiliated publications: 61

General research interest:
The team led by Maurizio Calcagni works on the following projects:
- Tendon healing and adhesion
- 3D motion analysis of the hand and wrist, biomechanics of the wrist and hand
- Tissue engineering of skin and production of cultivated keratinocytes
- Patient reported outcome measurements in hand and wrist surgery

Name: **Cinelli, Paolo**
PD Dr. sc. nat.
Institution: Clinic for Trauma Surgery, University Hospital Zurich; Center for Surgical Research, University Hospital Zurich and University of Zurich
Grants: CABMM, Gottfried und Julia Bangerter-Rhyner Stiftung, Novartis Foundation for Medical-Biological Research, Olga Mayenfisch Stiftung, SNF
CABMM collaborators: Maurizio Calcagni, Alfredo Franco-Obregón, Benjamin Gantenbein, Simon Hoerstrup, Michael Hottiger, Brigitte von Rechenberg, Raffaella Santoro, Jess Snedeker, Wendelin Stark, Benedikt Weber, Franz Weber, Marcy Zenobi-Wong
CABMM joint projects: 5, 26

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: **Dudli, Stefan**
Dr. (PhD)
Institution: Center of Experimental Rheumatology, University Hospital Zurich and Balgrist University Hospital Zurich
Grants: Balgrist-Stiftung, FOREUM, NIH Back Pain Consortium (BACPAC), Velux Stiftung, USZ Health Innovation Hub, UZH BioEntrepreneur-Fellowship
CABMM collaborators: Yvonne Achermann, Christoph Albers, Stephen Ferguson, Benjamin Gantenbein, Oliver Hausmann, Katja Nuss, Caroline Ospelt, Jess Snedeker, Annelies Zinkernagel
CABMM joint projects: 4, 7, 41, 56

General research interest:
Modic type 1 changes (MC1) are fibrotic-inflammatory vertebral bone marrow lesions adjacent to rapidly degenerating intervertebral discs. Disc degeneration is mostly pain-free but MC1 are highly specific for chronic low back pain (cLBP). Treatment and work absenteeism due to chronic LBP accounts for 1-2 % of the gross domestic product in western countries. About 10 % of all patients with chronic LBP have MC1, but there is no specific treatment for MC1. We are part of the NIH Back Pain Consortium (BACPAC) and the Clinical Research Priority Program "Pain" of the UZH to stratify patients with cLBP in order to provide better and targeted treatments. Our particular interest is the development of biomarkers for cLBP and MC1 and to develop a novel cell-based therapy for patients with MC1.

Name: **Ferguson, Stephen**
Prof. Dr. (PhD)
Institution: Laboratory for Orthopaedic Technology, Institute for Biomechanics, ETH Zurich
Grants: ETH Zürich Foundation, EU, industry, SNF
CABMM collaborators: Laurent Audigé, Stefan Dudli, Franck Forterre, Alfredo Franco-Obregón, Jörg Goldhahn, Oliver Hausmann, Niels Kuster, Markus Loibl, Ralph Müller, Katja Nuss, Antonio Pozzi, Brigitte von Rechenberg, Markus Rottmar, Jess Snedeker, André Studart, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 30, 32, 41, 53, 62, 82
CABMM-affiliated publications: 26, 40, 57

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: **Forterre, Franck**
Prof. Dr. med. vet.
Institution: Department of Clinical Veterinary Medicine, Small Animal Surgery, Vetsuisse Faculty, University of Bern
Grants: AO Foundation, Biologische Heilmittel Heel GmbH, CABMM, Formas, Marie-Louise von Muralt-Stiftung für Kleintiere, Novartis Animal Health, SNF
CABMM collaborators: Stephen Ferguson, Benjamin Gantenbein, Carla Rohrer Bley, Claudia Spadavecchia, David Spreng, Karin Würtz-Kozak
CABMM joint projects: 46, 75
CABMM-affiliated publications: 36

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

Name: **Fraefel, Cornel**
Prof. Dr. sc. nat.
Institution: Institute of Virology, Vetsuisse Faculty, University of Zurich
Grants: SNF
CABMM collaborators: Michael Hottiger, Raffaella Santoro

General research interest:
Viruses are potent tools to address specific questions in cell biology, immunology, and molecular biology. They are effective vehicles for applications in molecular medicine, such as vaccination and gene therapy. The focus of Prof. Fraefel's research group is the analysis of the molecular mechanisms of virus replication and the use of this information for applying viruses in biomedical research.

Name: **Franco-Obregón, Alfredo**
Prof. Dr. (PhD)
Institution: Institute for Health Innovation & Technology (iHealthTech) and Department of Surgery, National University Hospital Singapore
Grants: MOE Academic Research Funding Tier2, MOE Tier 1, NHIC Innovation to Develop, NIC on Active and Confident Ageing, Healthy Longevity Catalyst Awards, National Medical Research Council Centre Grant, National University Healthy Systems Seed Fund, NUS Biomedical Institute for Global Health Research Technology
CABMM collaborators: P. Cinelli, S. Ferguson, B. Gantenbein, M. N. Giraud, A. Liesegang, R. Müller, P. Richards, C. Rohrer Bley, G. Salzmann, J. Snedeker, F. Steffen, J. Stoyanov, V. Vogel, V. Wavreille, K. Würtz-Kozak, M. Zenobi-Wong
CABMM-affiliated publications: 26

General research interest:
Skeletal muscle evolved to regulate whole body regeneration and metabolism. Muscle loss because of inactivity or old age is associated with metabolic and cardiovascular dysfunctions, compromised immunity and recovery from injury and increased risks of cancer. These healthful attributes of muscle are initiated by mitochondrial activation, upstream of myokine release, rendering systemic adaptations. The BICEPS (Biolonic Currents Electromagnetic Pulsing Systems) lab's main focus is to develop new therapeutic strategies to maintain muscle health in the elderly and clinically immobilized via a novel process of Magnetic Mitohormesis.

Name: **Fürst, Anton**
Prof. Dr. med. vet., Dipl. ECVS
Institution: Equine Hospital, Vetsuisse Faculty, University of Zurich
CABMM collaborators: Jörg Auer, Nicole Borel, Patrick Kircher, Brigitte von Rechenberg, Henning Richter, Jess Snedeker
CABMM joint projects: 63

General research interest:
Our technical expertise and interests cover all fields of equine surgery. Currently, our research focuses mainly on equine orthopedics, 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, Benjamin**
Prof. Dr. phil. nat.
Institution: Department for BioMedical Research (DBMR), University of Bern; Department of Orthopaedic Surgery and Traumatology, Inselspital, University of Bern
Grants: CABMM, H2020 iPSpine, Marie Skłodowska Curie International Training Network (ITN) "Disc4All", SNF
CABMM collaborators: Sufian Ahmad, Christoph Albers, Paolo Cinelli, Stefan Dudli, Franck Forterre, Alfredo Franco-Obregón, Marie-Noëlle Giraud, Oliver Hausmann, Simon Hoerstrup, Brigitte von Rechenberg, Jess Snedeker, David Spreng, Thomas Steffen, Jivko Stoyanov, Benedikt Weber, Franz Weber, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 7, 48, 73, 75
CABMM-affiliated publications: 8, 27, 28, 36, 42

General research interest:
The Tissue Engineering for Orthopaedics & Mechanobiology (TOM) group, Bone & Joint Program, of the Department for BioMedical Research (DBMR) is performing basic research in the area of tissue engineering using a cross-disciplinary approach of biology and mechanics in collaboration with the Department of Orthopaedic Surgery and Traumatology, Inselspital, University of Bern. 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, the anterior cruciate ligament and the enthesis of the rotator cuff.

Name: **Giraud, Marie-Noëlle**
PD Dr. phil. nat.
Institution: Faculty of Science and Medicine, University of Fribourg
Grants: SNF, University of Fribourg
CABMM collaborators: Martin Flück, Alfredo Franco-Obregón, Benjamin Gantenbein, Daniel Rüfenacht
CABMM joint projects: 80
CABMM-affiliated publications: 86

General research interest:
Acute coronary syndromes are associated with high morbidity and mortality rates. Associated myocardial infarction results in maladaptive remodeling as the hallmark of chronic heart failure. My laboratory focuses on the development of cell-matrix combination as new therapeutic tools for cardiovascular diseases. In particular, we investigate the regenerative capacity of the vessels and the myocardium.

Name: **Hafezi, Farhad**
Prof. Dr. med., PhD, FARVO
Institution: ELZA Institute AG, Dietikon; CABMM, University of Zurich; Department of Ophthalmology, University of Southern California, Los Angeles, California, USA; Department of Ophthalmology, Wenzhou Medical University, Wenzhou, China
Grants: Fondation Botnar, Light for Sight Foundation, SCHWIND eye-tech solutions, Velux Stiftung
CABMM collaborators: Katja Nuss, Simon Pot, Brigitte von Rechenberg
CABMM joint projects: 38, 59
CABMM-affiliated publications: 5, 10, 14, 15, 22, 25, 34, 38, 43, 44, 48, 49, 50, 52, 56, 59, 66, 69, 70, 71, 73, 80, 85, 88

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

Name: **Hausmann, Oliver**
Prof. Dr. med.
Institution: Neuro- and Spine Center, Hirslanden Klinik St. Anna, Lucerne
Grants: CABMM
CABMM collaborators: Yvonne Achermann, Christoph Albers, Norbert Boos, Stefan Dudli, Stephen Ferguson, Benjamin Gantenbein, Karin Würtz-Kozak, Annelies Zinkernagel
CABMM joint projects: 7, 43, 76
CABMM-affiliated publications: 17

General research interest:
I am chair of the Neuro- and Spine Center at the Hirslanden Klinik St. Anna in Lucerne. The focus of my clinical work is on degenerative changes of the adult spine.
Over the last years, a successful collaboration with the Tissue Regeneration and Mechanobiology Lab of Prof. Dr. Karin Würtz-Kozak could be established. With a translational bench-to-bedside approach, inflammatory reactions within the degenerated human disc were analyzed and correlated to the clinical presentation.

Name: **Hirsch, Sven**
Prof. Dr. (PhD)
Institution: Institute of Applied Simulation, Zürcher Hochschule für Angewandte Wissenschaften (ZHAW), Wädenswil
Grants: Innosuisse
CABMM collaborators: Zsolt Kulcsár, Niels Kuster, Katja Nuss, Daniel Rüfenacht, Jess Snedeker, Stefan Stübinger, Isabel Wanke
CABMM joint projects: 24

General research interest:
Prof. 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., PhD
Institution: Institute for Regenerative Medicine, University of Zurich; Wyss Zurich, ETH Zurich and University of Zurich
Grants: CABMM, Hartstichting, Horizon 2020, Krebsliga Zürich, Kurt und Senta Herrmann-Stiftung, Mäxi-Stiftung, Olga Mayenfisch Stiftung, Schweizerische Herzstiftung, SNF, Stichting Life Sciences & Health, Stiftung zur Krebsbekämpfung
CABMM collaborators: M. Calcagni, P. Cinelli, B. Gantenbein, M. Hottiger, P. Kircher, P. Kronen, Z. Kulcsár, L. A. Laurent-Applegate, K. Nuss, B. von Rechenberg, J. Reichenbach, H. Richter, D. Rüfenacht, C. Schwarzwald, A. Studart, V. Vogel, I. Wanke, B. Weber
CABMM joint projects: 5, 8, 11, 16, 19, 25, 37, 67, 78, 79
CABMM-affiliated publications: 21, 37, 61

General research interest:
The research expertise of Prof. Simon P. Hoerstrup lies in the fields (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: **Hofbauer, Günther**
Prof. Dr. med.
Institution: Department of Dermatology, University Hospital Zurich
Grants: SNF
CABMM collaborators: Daniel Rüfenacht, Andreas Serra, Isabel Wanke, Benedikt Weber
CABMM joint projects: 9

General research interest:
The focus of Prof. Hofbauer's research group is on squamous cell carcinoma of the skin and their potential prevention and treatment. He is the head of the working group for dermatology and organ transplantation within the SGDV (Swiss Society for Dermatology and Venereology) and represents this group within the scientific committee of the Swiss Transplant Cohort Study.

Name: **Hofmann-Lehmann, Regina**
Prof. Dr. med. vet.
Institution: Clinical Laboratory, Department of Clinical Diagnostics and Services and Center for Clinical Studies, Vetsuisse Faculty, University of Zurich
Grants: BAFU, BAG, BLV, industry, SNF, Stiftung für wissenschaftliche Forschung an der Universität Zürich
CABMM collaborators: Nicole Borel, Ueli Braun, Michael Hottiger, Anja Kipar, Annette Liesegang, Katja Nuss, Brigitte von Rechenberg, Carla Rohrer Bley, Raffaella Santoro, Colin Schwarzwald
CABMM joint projects: 18, 34, 52

General research interest:
Our main research interests are clinical infectiology and clinical pathology. We apply animal models to investigate host-pathogen interactions and have developed diagnostic assays for infectious and immunological parameters. Current research focuses on SARS-CoV-2 in a one health approach (COVID households, domestic/wild animals). Our clinical pathologists (Dipl. ECVCP) are experts for laboratory animal hematology, chemistry, cytology etc. Finally, in the Center for Clinical Studies we provide support for laboratory-based clinical research.

Name: **Hottiger, Michael O.**
Prof. Dr. med. vet., Dr. phil. II
Institution: Department of Molecular Mechanisms of Disease, University of Zurich
Grants: Cancer Research Center, Forschungskredit UZH, Huggenberger-Bischoff Stiftung, Innosuisse, Marlis Geiser-Lemken Stiftung, NIH, SNF, URPP Translational Cancer Research
CABMM collaborators: Matthias Altmeyer, Paolo Cinelli, Cornel Fraefel, Simon Hoerstrup, Regina Hofmann-Lehmann, Anja Kipar, Patrick Kircher, Katja Nuss, Antonio Pozzi, Brigitte von Rechenberg, Janine Reichenbach, Henning Richter, Daniel Rüfenacht, Raffaella Santoro, Jess Snedeker, Isabel Wanke
CABMM joint projects: 15

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, but if chronic, inflammation may lead to cancer. My laboratory is interested in the molecular regulation of inflammation by ADP-ribosylation, a posttranslational modification of proteins. Our current work focuses on the activation and function of the enzymes that catalyze ADP-ribosylation and the identification of their target proteins as well as on their biological role e.g., in cancer.

Name: **Keller, Emanuela**
Prof. Dr. med.
Institution: Neurocritical Care Unit, Department of Neurosurgery, University Hospital Zurich
Grants: Innosuisse, SNF
CABMM collaborators: Patrick Kircher, Peter Kronen, Zsolt Kulcsár, Henning Richter
CABMM joint projects: 33

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

Name: **Kipar, Anja**
Prof. Dr. med. vet.
Institution: Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich
Grants: Biotechnology and Biological Sciences Research Council UK, Natural Sciences and Engineering Research Council of Canada, UK Research and Innovation
CABMM collaborators: Regina Hofmann-Lehmann, Michael Hottiger, Patrick Kircher, Annette Liesegang, Enni Markkanen, Katja Nuss, Simon Pot, Antonio Pozzi, Henning Richter
CABMM joint projects: 34, 65

General research interest:
Main areas of research are a) the pathogenesis of viral infectious diseases, like Boid Inclusion Body Disease of snakes, Feline Infectious Peritonitis and, most recently, COVID-19 using small animal models; b) the pathogenesis of cardiomyopathies with specific emphasis on remodeling processes. Our animal work stretches from viral and bacterial diseases to toxicopathology. With the Laboratory for Animal Model Pathology (LAMP) we maintain a research platform that offers technical service and expert pathologist input to animal studies with a morphological component. Such collaborative, interdisciplinary approaches maximize the outcome.

Name: **Kircher, Patrick R.**
Prof. Dr. med. vet., PhD, EMBA UZH
Institution: Division of Diagnostic Imaging, Vetsuisse Faculty, University of Zurich
Grants: Innosuisse
CABMM collaborators: Anton Fürst, Simon Hoerstrup, Michael Hottiger, Emanuela Keller, Anja Kipar, Peter Kronen, Zsolt Kulcsár, Annette Liesegang, Katja Nuss, Simon Pot, Antonio Pozzi, Brigitte von Rechenberg, Henning Richter, Carla Rohrer Bley, Daniel Rüfenacht, Frank Steffen, Isabel Wanke
CABMM joint projects: 33, 66, 68, 69

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

Name: **Kronen, Peter**
Dr. med. vet., DVM, Dipl. ECVAA
Institution: Department of Molecular Mechanisms of Disease, Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich; Veterinary Anaesthesia Services International, Winterthur
Grants: EU, industry, Innosuisse, SNF Sinergia
CABMM collaborators: Christian Gerber, Simon Hoerstrup, Emanuela Keller, Patrick Kircher, Zsolt Kulcsár, Serge Marbacher, Katja Nuss, Brigitte von Rechenberg, Henning Richter, André Studart, Stefan Stübinger, Franz Weber
CABMM joint projects: 21, 33, 44, 66
CABMM-affiliated publications: 12, 51, 58

General research interest:
- Improvement of anesthetic 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
- Alternative administration techniques of anesthetic and analgesic drugs

Name: **Kulcsár, Zsolt**
PD Dr. med., Dr. sc. nat.
Institution: Department of Neuroradiology, University Hospital Zurich
CABMM collaborators: Sven Hirsch, Simon Hoerstrup, Emanuela Keller, Patrick Kircher, Peter Kronen, Serge Marbacher, Katja Nuss, Brigitte von Rechenberg, Henning Richter, Daniel Rüfenacht, Isabel Wanke
CABMM joint projects: 33
CABMM-affiliated publications: 29, 63

General research interest:
PD Dr. Dr. Kulcsár is leading the Neurointerventional Unit at the Department of Neuroradiology of the University Hospital Zurich. Besides the clinical work in minimally invasive management of neurovascular and spinal diseases, his major scientific research interest focuses on the development and evolution, hemodynamic aspects, and treatment modalities of cerebral aneurysms and also on imaging and invasive management of acute ischemic stroke.

Name: **Kuster, Niels**
Prof. Dr. sc. ETH Zurich
Institution: Foundation for Research on Information Technologies in Society (IT'IS), Zurich
Grants: ANSES, BAFU, BAG, BAKOM, Bertarelli Foundation, BFS, COST, ETH, EUREKA, EUROSTARS, Imperial College London, industry (several), Innosuisse, INERIS, Monique Dornonville de la Cour-Stiftung, NIEHS, NIH, Novartis FreeNovation, SBFI, SNF, UBE, UZH, Wyss Center, Geneva
CABMM collaborators: Yvonne Achermann, Stephen Ferguson, Sven Hirsch, Brigitte von Rechenberg, Henning Richter, Carla Rohrer Bley, Daniel Rüfenacht, Isabel Wanke
CABMM joint projects: 35, 81

General research interest:
Core research areas: development of 1) functionalized computational human anatomical models, 2) multi-physics and multi-scale simulation methods and technologies to model interactions between physical agents and biological processes and structures, and 3) tissue models (e.g., neuro, perfusion models) and their application for optimizing treatment planning and therapeutic techniques. Additional competencies: hyperthermia, MR safety, validation procedures.

Name: **Laurent-Applegate, Lee Ann**
Prof. Dr. med.
Institution: Department of Musculoskeletal Medicine, Service of Plastic and Reconstructive Surgery, Unit of Regenerative Therapy, Lausanne University Hospital; OSCAR, Oxford University, Suzhou, China
Grants: CABMM, Flavie, FRNS, Lausanne Hospital Priority Project Funding, LORF, Loterie Romande, Marie Skłodowska-Curie Fellowship
CABMM collaborators: M. Calcagni, S. Hoerstrup, K. Nuss, B. von Rechenberg, G. Salzmann, J. Snedeker, K. Würtz-Kozak, M. Zenobi-Wong
CABMM joint projects: 17, 22, 31, 42, 58, 77
CABMM-affiliated publications: 2, 16, 32, 45, 46, 47, 53, 54, 58, 65, 72, 77, 78, 79, 82, 89, 90, 91

General research interest:
We are interested in addressing clinical problems of 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 established cell banks of progenitor cells harvested from human bone, cartilage, disc, muscle, tendon, and skin, and some of these cell sources are being used to successfully develop cellular therapies for severely burned patients, acute and chronic wounds, and for all other musculoskeletal tissues. We work closely with the CABMM to develop GLP large animal models for pre-clinical investigations for innovative APIs (active pharmaceutical ingredients) and cellular therapeutics. In addition to the routine clinical use of cellular therapies for burn patients, we have clinical studies on-going for autologous chondrocyte cell therapy in the CHUV within the Swissmedic accredited GMP Cell Production Center.

Name: **Liesegang, Annette**
Prof. Dr. med. vet., Dipl. ECVCN, IVAS
Institution: Institute of Animal Nutrition and Dietetics, Vetsuisse Faculty, University of Zurich
Grants: Innosuisse, Lehrkredit, Royal Canin (Schweiz) AG, Stiftung Pro Pferd, SVWZH
CABMM collaborators: Alois Boos, Ueli Braun, Alfredo Franco-Obregón, Regina Hofmann-Lehmann, Anja Kipar, Patrick Kircher, Brigitte von Rechenberg, Henning Richter, Raffaella Santoro, Stefan Stübinger
CABMM joint projects: 3, 13, 34, 40, 52, 83
CABMM-affiliated publications: 83

General research interest:
Focus on cartilage, bone and mineral research, energy metabolism and sustainability of different feed (from feed to food)
- Physiological and nutritional influences on bone metabolism and cartilage metabolism
- Bone and cartilage markers and bone mineral density (pQCT) during growth, gestation, and lactation
- Calcium resorption mechanisms in the intestines
- Mechanisms of longitudinal growth regulation within growth plates
- Hormones of calcium metabolism
- Osteoporosis
- Vitamin D metabolism in skin
- Bone metabolism in cats
- Energy and protein metabolism in cats
- Trace element metabolism and the influences on absorption

Name: **Loibl, Markus**
PD Dr. med.
Institution: Schulthess Clinic, Zurich
CABMM collaborators: Stephen Ferguson, Karin Würtz-Kozak
CABMM joint projects: 30

General research interest:
Preclinical trials led to a better understanding of the demands of the native environment in the degenerating disc. I am interested in the regenerative effect of cell-based applications and locally applicable drugs in the intervertebral disc niche to prevent disc degeneration and promote disc regeneration. As a clinician, I am interested in translating basic science knowledge to develop appropriateness criteria for regenerative treatments in a clinical setting.

Name: **Marbacher, Serge**
Prof. Dr. med., PhD
Institution: Cerebrovascular Research Group, Department of Neurosurgery, Kantonsspital Aarau
Grants: Research Council Kantonsspital Aarau, SNF
CABMM collaborators: Peter Kronen, Zsolt Kulcsár, Katja Nuss, Brigitte von Rechenberg, Daniel Rüfenacht, Isabel Wanke

General research interest:
The Cerebrovascular Research Group focuses on cerebral aneurysms, e.g., endovascular treatment options to prevent aneurysm rupture and sequels of subarachnoid hemorrhage after their rupture. We currently work with a sidewall rat and rabbit bifurcation aneurysm model using degenerated arterial grafts to investigate treatment options and inflammatory processes eventually leading to aneurysm growth and rupture. It is our ultimate goal to find novel endovascular modalities that completely exclude the aneurysm from the circulation and reconstruct the diseased arterial segment. Furthermore, we explore non-occlusive endovascular bypass options.

Name: **Markkanen, Enni**
Prof. Dr. med. vet., Dr. sc. nat.
Institution: Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich
Grants: Albert-Heim-Stiftung, CABMM, Sassella-Stiftung, SNF, Wolferman-Nägeli-Stiftung
CABMM collaborators: Matthias Altmeyer, Anja Kipar, Simon Pot, Antonio Pozzi, Henning Richter, Viola Vogel
CABMM joint projects: 65

General research interest:
Our vision is to leverage the power of comparative oncology between humans, cats, and dogs to improve the diagnosis and therapy of cancer in all three species – from patient to the bench and back. Currently, our research is focused on understanding the mechanisms by which stroma influences growth and malignancy of tumors, and the identification of novel targets for improved imaging and therapy of soft tissue sarcomas in human, canine, and feline patients.

Name: **Müller, Ralph**
Prof. Dr. sc.
Institution: Laboratory for Bone Biomechanics, Institute for Biomechanics, ETH Zurich
Grants: COST, ERC, EU, SNF
CABMM collaborators: Michael Blauth, Stephen Ferguson, Alfredo Franco-Obregón, Jörg Goldhahn, Jess Snedeker, André Studart, Karin Würtz-Kozak, Marcy Zenobi-Wong
CABMM joint projects: 6

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

Name: **Nuss, Katja**
Dr. med. vet.
Institution: Department of Molecular Mechanisms of Disease, Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich
Grants: Industry, Innosuisse, SNF, SNF Sinergia
CABMM collaborators: Yvonne Achermann, Andrea Barbero, Maurizio Calcagni, Stefan Dudli, Stephen Ferguson, Farhad Hafezi, Sven Hirsch, Simon Hoerstrup, Regina Hofmann-Lehmann, Michael Hottiger, Anja Kipar, Patrick Kircher, Peter Kronen, Zsolt Kulcsár, Lee Ann Laurent-Applegate, Serge Marbacher, Simon Pot, Antonio Pozzi, Brigitte von Rechenberg, Janine Reichenbach, Henning Richter, Markus Rottmar, Daniel Rüfenacht, Jess Snedeker, Stefan Stübinger, Isabel Wanke, Marcy Zenobi-Wong
CABMM joint projects: 2, 4, 12, 16, 17, 20, 25, 27, 29, 38, 45, 47, 50, 55, 57, 60, 61, 62, 64, 66, 70, 78, 79, 82
CABMM-affiliated publications: 9, 53, 58, 75

General research interest:
Dr. Katja Nuss is one of three leaders of the Musculoskeletal Research Unit (MSRU). She is a specialist in veterinary surgery and in veterinary anesthesiology with a huge experience in clinical and experimental surgery. Special scientific interest includes intracranial aneurysms and its animal models; wound healing; bone, muscle, tendon, ligament biomaterials, and cartilage degeneration. The MSRU is a GLP accredited facility for preclinical studies.

Name: **Ospelt, Caroline**
Prof. Dr. med., PhD
Institution: Center of Experimental Rheumatology, University Hospital Zurich
Grants: Carigest, Gebauer Stiftung, Novartis Foundation for Medical-Biological Research
CABMM collaborators: Stefan Dudli, Marcy Zenobi-Wong
CABMM joint projects: 51

General research interest:
In one of the leading centers worldwide for the analysis of synovial fibroblasts in rheumatoid arthritis, Prof. Ospelt's track record is the analysis of genetic and epigenetic changes within this complex field. Furthermore, the group uses single cell and spatial transcriptomics to analyze the role of specific fibroblasts subtypes in arthritis development.

Name: **Pot, Simon**
Prof. Dr. (PhD), Dipl. ACVO/ECVO
Institution: Ophthalmology Section, Equine Department, Vetsuisse Faculty, University of Zurich
Grants: ACVO Vision for Animals Foundation Founders Clinical Research Grant, American Kennel Club Canine Health Foundation, ECVO Research Grant, Stiftung für wissenschaftliche Forschung an der Universität Zürich, Velux Stiftung
CABMM collaborators: Farhad Hafezi, Anja Kipar, Patrick Kircher, Enni Markkanen, Katja Nuss, Henning Richter, Carla Rohrer Bley, Markus Rottmar, Frank Steffen, Viola Vogel
CABMM joint projects: 59
CABMM-affiliated publications: 9

General research interest:
Simon Pot's main research interests are on the following topics:
- Mechanobiology of corneal wound healing: Understanding the basic mechanisms governing the reciprocal force balance between fibroblasts and their extracellular matrix, an important regulator of wound healing and fibrosis.
- Infectious corneal disease: Evaluating the elimination of corneal infections and stabilization of the corneal stroma through pharmacological (antibacterial and antifungal agents) and physical (UV-A/Riboflavin corneal crosslinking – CXL) means.
- Ocular imaging: Evaluating the use of high-resolution advanced imaging technologies (ultrasound biomicroscopy, microcoil assisted MRT and Optical Coherence Tomography) for ocular imaging.

Name: **Pozzi, Antonio**
Prof. Dr. med. vet., Dipl. ECVS/ACVS, Dipl. ACVSMR
Institution: Clinic for Small Animal Surgery, Vetsuisse Faculty, University of Zurich
Grants: Albert-Heim-Stiftung, American Kennel Club Canine Health Foundation, industry, Legat Bachofner, Forschungskredit UZH
CABMM collaborators: Andrea Barbero, Stephen Ferguson, Michael Hottiger, Anja Kipar, Patrick Kircher, Enni Markkanen, Katja Nuss, Brigitte von Rechenberg, Henning Richter, Carla Rohrer Bley, Jess Snedeker, Frank Steffen, Thomas Steffen, Stefan Stübinger, Vincent Wavreille, Karin Würtz-Kozak
CABMM joint projects: 47, 50, 64, 65

General research interest:
My main interest is musculoskeletal research with focus on joint physiology and pathophysiology, including knee, meniscus and cartilage injuries using animal models to understand diseases and develop novel treatments. As chair of the Clinic for Small Animal Surgery, I lead the clinic research program. The major goal of the research teams of the Clinic for Small Animal Surgery is to study clinical problems in companion animals that provide naturally occurring models for human diseases, including areas such as joint, spine, trauma, and oncologic surgery.

Name: **von Rechenberg, Brigitte**
Prof. em. Dr. med. vet., Dipl. ECVS
Institution: Department of Molecular Mechanisms of Disease, Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich (until 2020); Brigitte von Rechenberg Consulting GmbH
Grants: Hans Jegen Stiftung, Meier-Birkel Stiftung, Stiftung Pro Pferd
CABMM collaborators: Y. Achermann, S. Ahmad, M. Altmeyer, A. Barbero, M. Calcagni, P. Cinelli, S. Ferguson, M. Flück, A. Fürst, B. Gantenbein, C. Gerber, F. Hafezi, S. Hoerstrup, R. Hofmann-Lehmann, M. Hottiger, P. Kircher, P. Kronen, Z. Kulcsár, N. Kuster, L. A. Laurent-Applegate, A. Liesegang, S. Marbacher, K. Nuss, A. Pozzi, J. Reichenbach, H. Richter, M. Rottmar, D. Rüfenacht, R. Santoro, C. Schwarzwald, J. Snedeker, F. Steffen, T. Steffen, A. Studart, V. Vogel, I. Wanke, M. Zenobi-Wong, A. Zinkernagel
CABMM joint projects: 2, 12, 13, 17, 20, 25, 27, 29, 37, 39, 42, 44, 49, 52, 58, 60, 62, 64, 67, 72, 82, 83
CABMM-affiliated publications: 18, 40, 51, 53, 55, 57, 58, 61, 64, 67, 74, 86, 87

General research interest:
Our main interest in musculoskeletal research is focusing on bone and cartilage, including fracture and defect healing, the influence of inflammation in bone and cartilage healing as well as physiological remodeling of subchondral bone and cartilage. With our collaborators, we expanded in wound healing, aneurysm research, experimental anesthesia and pain management. Our facility is GLP-accredited by the Swissmedic and in this capacity, we have broadened our scope to other fields of experimental medicine and support other CABMM members with their animal experiments.

Name: **Reichenbach, Janine**
Prof. Dr. med.
Institution: Institute for Regenerative Medicine, University of Zurich; Division of Somatic Gene Therapy, University Children's Hospital Zurich
Grants: CRPP ImmuGene, UFSP ITINERARE, SNF, Wyss Zurich
CABMM collaborators: Simon Hoerstrup, Michael Hottiger, Katja Nuss, Brigitte von Rechenberg
CABMM joint projects: 19, 60

General research interest:
The research group of Prof. Reichenbach is focused on the development of new therapeutic concepts and therapeutic correction by first-in-man clinical gene therapy for inborn errors of the immune and nervous system.

Name: **Richards, Peter J.**
PD Dr. (PhD)
Institution: Novartis Institutes for BioMedical Research, Basel
CABMM collaborators: Alfredo Franco-Obregón
CABMM-affiliated publications: 26

General research interest:
I'm principally involved in research into pharmacotherapeutic options for osteoarthritis treatment.

Name: **Richter, Henning**
Dr. sc. med. vet., PhD, Dipl. SVLAS
Institution: Diagnostic Imaging Research Unit (DIRU), Clinic for Diagnostic Imaging, Vetsuisse Faculty, University of Zurich
Grants: Albert-Heim-Stiftung, Innosuisse
CABMM collaborators: Anton Fürst, Simon Hoerstrup, Michael Hottiger, Emanuela Keller, Anja Kipar, Patrick Kircher, Peter Kronen, Zsolt Kulcsár, Niels Kuster, Annette Liesegang, Enni Markkanen, Katja Nuss, Simon Pot, Antonio Pozzi, Brigitte von Rechenberg, Daniel Rüfenacht, Frank Steffen, Thomas Steffen, Isabel Wanke, Vincent Wavreille
CABMM joint projects: 33, 40, 66, 68, 69

General research interest:
Dr. Richter is leading the Diagnostic Imaging Research Unit (DIRU), which serves as a platform for internal and external research groups interested in veterinary and translational clinical studies. DIRU offers a broad range of imaging modalities, highest expertise in clinical imaging as well as in study organization and laboratory animal science. Scientific interest mainly focuses on MRI as well as on interventional imaging.

Name: **Rohrer Bley, Carla**
Prof. Dr. med. vet.
Institution: Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich
Grants: Albert-Heim-Stiftung, Marie-Louise von Muralt-Stiftung für Kleintiere, SNF
CABMM collaborators: Franck Forterre, Alfredo Franco-Obregón, Regina Hofmann-Lehmann, Patrick Kircher, Niels Kuster, Simon Pot, Antonio Pozzi, Frank Steffen
CABMM joint projects: 35
CABMM-affiliated publications: 20, 23

General research interest:
My group's research is focused on radiation therapy in all aspects (basic and clinical radiobiology, radiotherapy). Our clinic is well equipped, counting to one of the most state-of-the-art veterinary cancer treatment facilities in Europe. While treating animal patients with spontaneously occurring tumors we believe that with research focusing on diseases or conditions similar to those occurring in human patients, we can make our contribution to increasing the complex knowledge about cancer.

Name: **Rottmar, Markus**
Dr. sc.
Institution: Cell-/Tissue Material Interactions, Lab for Biointerfaces, Swiss Federal Laboratories for Materials Science and Technology (Empa), St. Gallen
Grants: Helmut Horten Stiftung, Innosuisse, ITI Foundation, Novartis FreeNovation, SNF, Strategic Focus Area Advanced Manufacturing
CABMM collaborators: Stephen Ferguson, Katja Nuss, Simon Pot, Brigitte von Rechenberg, Gian Salzmann, Viola Vogel, Marcy Zenobi-Wong
CABMM-affiliated publications: 4

General research interest:
The team of Dr. Rottmar is interested in gaining a better understanding of how cells and tissues interact with biomaterials. The research focus is to elucidate the role of blood-material interaction and immune cell responses on downstream cell fate decisions and how this knowledge can be exploited to steer a desired tissue response (i.e., facilitating or preventing hard/soft tissue integration, enhance wound healing) by materials design.

Name: **Rüfenacht, Daniel A.**
Prof. Dr. med.
Institution: Neuroradiology, Klinik Hirslanden & SNRI/SCNSI, Zurich; Interventional-WorkResearch (IWR), SwissNeuroFoundation
Grants: Industry, SwissNeuroFoundation, University of Essen
CABMM collaborators: Marie-Noëlle Giraud, Sven Hirsch, Simon Hoerstrup, Günther Hofbauer, Michael Hottiger, Patrick Kircher, Zsolt Kulcsár, Niels Kuster, Serge Marbacher, Katja Nuss, Brigitte von Rechenberg, Henning Richter, Andreas Serra, Isabel Wanke
CABMM joint projects: 9, 68, 69

General research interest:
The IWR group is interested in understanding, imaging, and visualization of neurovascular diseases and minimally invasive treatment options. Research focuses on vessel wall pathologies (esp. intracranial aneurysms), AVM, and vascular dementia. Biological pathways of interest include angiogenesis (mTOR) and degeneration (NF-κB). Translational research efforts include supporting exploratory workshops (iNEW), multiscale modeling, and methods connecting biomechanics with biological effects at cellular and organ system level. We support development of methodologies to investigate disease understanding and therapeutic effects and the development of a sustainable databank for neurovascular diseases (AneuX, SwissNeuroFoundation).

Name: **Salzmann, Gian**
Prof. Dr. med.
Institution: Orthopaedics, Lower extremities, Schulthess Klinik, Zurich
Grants: Alwin Jäger Stiftung, GOTS, SNF, Stiftung Lindenhof Bern
CABMM collaborators: Andrea Barbero, Alfredo Franco-Obregón, Lee Ann Laurent-Applegate, Markus Rottmar, Marcy Zenobi-Wong
CABMM joint projects: 74
CABMM-affiliated publications: 4

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

Name: **Santoro, Raffaella**
Prof. Dr. rer. nat.
Institution: Department of Molecular Mechanisms of Disease, University of Zurich
Grants: ERC Advanced Grant, Krebsliga Schweiz, SNF Sinergia, SNFS Excellence
CABMM collaborators: Paolo Cinelli, Cornel Fraefel, Regina Hofmann-Lehmann, Michael Hottiger, Annette Liesegang, Brigitte von Rechenberg
CABMM joint projects: 26, 52

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

Name: **Schwarzwald, Colin C.**
Prof. Dr. med. vet., PhD, Dipl. ACVIM / ECEIM
Institution: Clinic for Equine Internal Medicine, Equine Department, Vetsuisse Faculty, University of Zurich
Grants: SHK Stiftung für Herz- und Kreislaufkrankheiten
CABMM collaborators: Simon Hoerstrup, Regina Hofmann-Lehmann, Brigitte von Rechenberg
CABMM joint projects: 8

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

Name: **Serra, Andreas**
Prof. Dr. med., MPH
Institution: Department of Internal Medicine and Nephrology, Klinik Hirslanden, Zurich; Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich
Grants: Industry
CABMM collaborators: Christian Gerber, Jörg Goldhahn, Günther Hofbauer, Daniel Rüfenacht, Isabel Wanke
CABMM joint projects: 9

General research interest:
Prof. Serra's research focus lies on mammalian target of rapamycin (mTOR) signaling pathway, therapies for autosomal dominant polycystic kidney disease (ADPKD) and treatment for tuberous sclerosis (TSC). As a result of his scientific background, he is head of the Suisse ADPKD cohort (www.adpkd.ch) and co-director of the Swiss TSC network (www.swissTSCnetwork.ch).

Name: **Snedeker, Jess G.**
Prof. Dr. (PhD)
Institution: Department of Orthopaedic Biomechanics, University of Zurich; Institute for Biomechanics, ETH Zurich
Grants: Balgrist Foundation, Chan Zuckerberg Initiative, ETH Zurich Research Grant, Innosuisse, Novartis Foundation, SNF
CABMM collaborators: Maurizio Calcagni, Paolo Cinelli, Stefan Dudli, Stephen Ferguson, Martin Flück, Alfredo Franco-Obregón, Anton Fürst, Benjamin Gantenbein, Christian Gerber, Jörg Goldhahn, Sven Hirsch, Michael Hottiger, Lee Ann Laurent-Applegate, Ralph Müller, Katja Nuss, Antonio Pozzi, Brigitte von Rechenberg, Franz Weber, Karin Würtz-Kozak, Marcy Zenobi-Wong, Annelies Zinkernagel

CABMM joint projects: 2, 14, 23, 56

General research interest:
The Snedeker Lab is a leading research group focused on tendon mechanobiology and regenerative orthopedic surgery. Beyond basic research, the group actively develops and clinically translates next-generation orthopedic devices for improved patient outcomes and better quality of life.

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: Institut Analgesia, SNF Spark, UniBern Forschungsstiftung
CABMM collaborators: Franck Forterre

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 behavior and at refining procedures and techniques to improve pain treatment in domestic and laboratory animals. Our major areas of interest are 1) neurophysiological characterization of acute and persistent pain to provide evidence in the context of animal welfare, 2) development of perioperative pain treatment strategies in clinical and experimental settings and 3) optimization of methods to treat acute perioperative and chronic pain.

Name: **Stark, Wendelin J.**
Prof. Dr. (PhD)
Institution: Functional Materials Laboratory, Institute for Chemical and Bioengineering, ETH Zurich
Grants: Gebert Rüf Stiftung
CABMM collaborators: Paolo Cinelli

General research interest:
We develop biodegradable additives to make inert materials bioactive. This makes soft tissue implants adhere better to the implanted material and reduces friction, tear off and may potentially reduce risks for infections.
Since 2013, we have worked on soft implants, particularly with 3D printed heart like pumps, as part of the Zurich Heart Project.
Since 2016, we have developed biosensors containing living materials, and enabling local read out of complex chemical or, potentially biological samples.

Name: **Steffen, Frank**
Prof. Dr. med. vet., Dipl. ECVN
Institution: Section of Neurology, Department of Small Animals, Vetsuisse Faculty, University of Zurich
Grants: Legat Bachofner
CABMM collaborators: Alfredo Franco-Obregón, Patrick Kircher, Simon Pot, Antonio Pozzi, Brigitte von Rechenberg, Henning Richter, Carla Rohrer Bley, Jivko Stoyanov, Karin Würtz-Kozak
CABMM joint projects: 27, 36

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 exploring a new methodology for treating regeneration of intervertebral discs *in vitro*. This technology is then intended to be introduced in clinical applications.

Name: **Steffen, Thomas**
Prof. Dr. med., PhD, MBA
Institution: Department of Molecular Mechanisms of Disease, Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich (until 11/2020); Orthopaedic Research Laboratory, Division of Orthopaedic Surgery, McGill University, Montréal General Hospital, Montréal, Canada
Grants: AO Foundation
CABMM collaborators: Benjamin Gantenbein, Antonio Pozzi, Brigitte von Rechenberg, Henning Richter

General research interest:
Thomas Steffen received basic training in orthopedic surgery in Bern, Switzerland, then worked 28 years in basic and applied spinal research at McGill University in Montréal, Canada. His expertise is in biomechanics of the musculoskeletal system, bone and bone substitutes, intervertebral disc degeneration and organ culture models, orthopedic implant development, animal models and translational research at large.

Name: **Stoyanov, Jivko**
Prof. Dr. (PhD), EMBA
Institution: SCI Population Biobanking & Translational Medicine Group, Swiss Paraplegic Research, Nottwil; Institute of Social and Preventive Medicine, University of Bern
Grants: SPHN, SSPH, Swiss Paraplegic Foundation
CABMM collaborators: Andrea Barbero, Alfredo Franco-Obregón, Benjamin Gantenbein, Frank Steffen, Karin Würtz-Kozak
CABMM joint projects: 28, 54
CABMM-affiliated publications: 33

General research interest:
Jivko Stoyanov leads the group of SCI Population Biobanking and Translational Medicine at Swiss Paraplegic Research and is head of the Swiss Spinal Cord Injury Cohort Study Biobank. The group is interested in optimizing cell interaction with tissue engineering matrices for the purpose of regeneration of pressure injuries following spinal cord injury and modulation of inflammation in intervertebral discs (IVD). They isolate and culture human and canine IVD cells and mesenchymal stem cells (MSCs) and have knowledge in hypoxic cell culture, molecular and biochemical methods, and live cell imaging. Furthermore, they have a substantial collection of matched (from same donor) cell sets – IVD cells, MSCs and PBMCs (peripheral blood mononuclear cells). Other focus areas are lifestyle modifications and their influence on the urinary, skin, and fecal microbiome as well as immunosenescence in persons with SCI.

Name: **Studart, André R.**
Prof. Dr. (PhD)
Institution: Complex Materials, Department of Materials, ETH Zurich
Grants: Industry, SCCER Mobility, SNF, Strategic Focus Area Advanced Manufacturing
CABMM collaborators: Stephen Ferguson, Simon Hoerstrup, Peter Kronen, Ralph Müller, Brigitte von Rechenberg
CABMM-affiliated publications: 51

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

Name: **Stübinger, Stefan**
PD Dr. med. dent.
Institution: Hightech Research Center of Cranio-Maxillofacial Surgery, Department of Biomedical Engineering, Medical Faculty, University of Basel and University Hospital Basel
Grants: Fondation Botnar, industry, Innosuisse, Swiss Nanoscience Institute
CABMM collaborators: Sven Hirsch, Peter Kronen, Annette Liesegang, Katja Nuss, Antonio Pozzi, Franz Weber
CABMM joint projects: 21, 24

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

Name: **Vogel, Viola**
Prof. Dr. (PhD), Dr. h. c.
Institution: Laboratory of Applied Mechanobiology, Department for Health Sciences and Technology, ETH Zurich
Grants: Industry, NCCR, SNF
CABMM collaborators: Maurizio Calcagni, Alfredo Franco-Obregón, Jörg Goldhahn, Simon Hoerstrup, Enni Markkanen, Simon Pot, Brigitte von Rechenberg, Markus Rottmar, Benedikt Weber, Marcy Zenobi-Wong
CABMM joint projects: 10
CABMM-affiliated publications: 37

General research interest:
The focus of Prof. Vogel's laboratory is to learn how mechanical forces are sensed by bacteria, cells, and tissues, how forces stretch proteins and thereby switch their structure-function relationships and how this in turn regulates cell signaling. By combining physical, engineering, and biological tools, we are asking how the mechanobiology of extracellular matrix and of macrophages directs homeostasis versus pathologies in human tissues and in *de novo* grown microtissues, and how such insights can be exploited for applications in bioengineering and regenerative medicine.

Name: **Wanke, Isabel**
Prof. Dr. med.
Institution: Neuroradiology, Klinik Hirslanden & SNRI/SCNSI, Zurich; InterventionalWork-Research (IWR), SwissNeuroFoundation; Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Germany
Grants: Industry, SwissNeuroFoundation, University of Essen
CABMM collaborators: Sven Hirsch, Simon Hoerstrup, Günther Hofbauer, Michael Hottiger, Patrick Kircher, Zsolt Kulcsár, Niels Kuster, Serge Marbacher, Katja Nuss, Brigitte von Rechenberg, Henning Richter, Daniel Rüfenacht, Andreas Serra
CABMM joint projects: 9, 69

General research interest:
The IWR group is interested in understanding, imaging, and visualization of neurovascular diseases and minimally invasive treatment options. Research focuses on vessel wall pathologies (esp. intracranial aneurysms), AVM and vascular dementia. The biological pathways of interest include angiogenesis (mTOR) and degeneration (NF-κB). Translational research efforts include supporting exploratory workshops (iNEW), multiscale modeling and methods connecting biomechanics with biological effects at cellular and organ system level. We support development of methodologies to investigate disease understanding and therapeutic effects and the development of a sustainable databank for neurovascular diseases (AneuX, SwissNeuroFoundation).

Name: **Wavreille, Vincent**
Dr. med. vet.
Institution: Clinic for Small Animal Surgery, Vetsuisse Faculty, University of Zurich (new affiliation: VetSpecialistes, Grand-Sacconex)
Grants: Intramural Grant – The Ohio State University, Steps for Sarcoma, VSSO
CABMM collaborators:
Alfredo Franco-Obregón, Antonio Pozzi, Henning Richter

General research interest:
My primary research interest is surgical oncology with focus on animal models for cancer research. The similarities between veterinary and human patients provide naturally occurring models for human cancer. Our research aims at the development of novel cancer treatments: minimally invasive approaches, new multimodal protocols combining radiation therapy and surgery to treat bone cancer and novel surgical reconstructive techniques.

Name: **Weber, Benedikt**
Prof. Dr. med., Dr. sc. nat.
Institution: Skin and Endothelium Research Division, Medical University of Vienna, Austria
Grants: FWF, Medizinisch-Wissenschaftlicher Fonds der Bundeshauptstadt Wien, WWTF
CABMM collaborators: Paolo Cinelli, Benjamin Gantenbein, Simon Hoerstrup, Günther Hofbauer, Viola Vogel
CABMM-affiliated publications: 37

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

Name: **Weber, Franz E.**
Prof. Dr. rer. nat.
Institution: Oral Biotechnology & Bioengineering, Center of Dentistry / MKG, University of Zurich
Grants: Innosuisse, SNF
CABMM collaborators: Paolo Cinelli, Benjamin Gantenbein, Peter Kronen, Jess Snedeker, Stefan Stübinger
CABMM joint projects: 21
CABMM-affiliated publications: 6, 30, 31, 35, 41, 68, 81

General research interest:
The main interest of our research laboratory is the healing of large bone defects of the mandible and the cranium by personalized bone substitutes. At present, we mainly focus on the micro- and nanostructure of 3D-printed bone substitutes to optimize osteoconduction and realize this topic by additive manufacturing of calcium phosphates and bioglass. Moreover, we started to evaluate micro- and nanoarchitectures optimal for bone augmentations, mainly needed for the placement of dental implants. Epigenetics, pulp regeneration and bone regeneration by osteoinduction are other subjects of research.

Name: **Würtz-Kozak, Karin**
Prof. Dr. hum. biol., MBA
Institution: Department of Biomedical Engineering, Rochester Institute of Technology, Rochester, New York, USA
Grants: EUROSPINE, NIH, RIT, SNF
CABMM collaborators: Yvonne Achermann, Andrea Barbero, Norbert Boos, Stephen Ferguson, Franck Forterre, Alfredo Franco-Obregón, Benjamin Gantenbein, Oliver Hausmann, Lee Ann Laurent-Applegate, Markus Loibl, Ralph Müller, Antonio Pozzi, Jess Snedeker, David Spreng, Frank Steffen, Jivko Stoyanov, Annelies Zinkernagel
CABMM joint projects: 6, 14, 28, 32, 36, 43, 46, 48, 76
CABMM-affiliated publications: 7, 17, 26, 36

General research interest:
My research aims to improve the understanding of the cellular mechanisms underlying specific pathologies (predominantly musculoskeletal and skin disorders), with a focus on inflammation and inflammaging. This information is then utilized for the development of novel treatment options that allow for tissue regeneration and pain reduction, applying engineering principles (e.g., genome engineering, engineering of functional biomaterials) as well as principles from molecular medicine (e.g., pathway modulation).

Name: **Zenobi-Wong, Marcy**
Prof. Dr. (PhD)
Institution: Tissue Engineering and Biofabrication, Institute for Biomechanics, ETH Zurich
Grants: CABMM, ETH Zürich Foundation, SNF
CABMM collaborators: Andrea Barbero, Jeffrey Bode, Paolo Cinelli, Stephen Ferguson, Alfredo Franco-Obregón, Benjamin Gantenbein, Lee Ann Laurent-Applegate, Ralph Müller, Katja Nuss, Caroline Ospelt, Brigitte von Rechenberg, Markus Rottmar, Gian Salzmann, Jess Snedeker, Viola Vogel
CABMM joint projects: 1, 12, 20, 22, 31, 42, 51, 70, 74, 77
CABMM-affiliated publications: 4, 87, 89

General research interest:
We use biomaterials and biofabrication techniques to create 3D cellular systems, primarily for cartilage regeneration. Biomimetic hydrogels are designed to control stem cell and chondrocyte fate, having engineered adhesion and growth factor binding properties. We use bioprinting to create complex functional mimics of cartilage tissue.

Name: **Zinkernagel, Annelies**
Prof. Dr. med., PhD
Institution: Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich
Grants: NCCR AntiResist, SNF, KFSP BacVivo
CABMM collaborators: Yvonne Achermann, Stefan Dudli, Oliver Hausmann, Brigitte von Rechenberg, Jess Snedeker, Karin Würtz-Kozak
CABMM joint projects: 76

General research interest:
The scientific interest of Prof. Zinkernagel's group are bacterial pathogenesis, increasing antibiotic resistance and therefore possible new treatment strategies. Special focus lies on the role of virulence factors during pathogenesis, persistence of *Staphylococcus aureus* that goes along with antibiotic tolerance and high relapse rates and the characterization of bacteria within biofilms.

honorary members

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

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

Name: **von Rechenberg, Brigitte**
Prof. em. Dr. med. vet., Dipl. ECVS
Institution: Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich

alumni members

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

Name: **Blauth, Michael**
Prof. Dr. med.
Institution: Department for Trauma Surgery, Medical University of Innsbruck, Austria

Name: **Boos, Alois**
Prof. em. Dr. med. vet.
Institution: Institute of Veterinary Anatomy, Vetsuisse Faculty, University of Zurich

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

Name: **Braun, Ueli**
Prof. em. 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: **Dip, Ramiro**
PD Dr. med. vet., PhD
Institution: Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich; Swiss Reinsurance Company Ltd.

Name: **Flück, Martin**
Prof. Dr. (PhD)
Institution: Faculty of Science and Medicine, University of Fribourg

Name: **Gay, Steffen**
Prof. em. Dr. med.
Institution: Center of Experimental Rheumatology, University Hospital Zurich

Name: **Gerber, Christian**
Prof. em. Dr. med.
Institution: Department of Orthopaedics, University Hospital Balgrist, Zurich

Name: **Goldhahn, Jörg**
Prof. Dr. med.
Institution: Department of Health Sciences and Technology, ETH Zurich

Name: **Spreng, David**
Prof. Dr. med. vet.
Institution: Department of Veterinary Medicine, Vetsuisse Faculty, University of Bern

joint research projects 2020 / 2021 (in alphabetical order)

Number	Title	Collaborators (CABMM members)
1	**3D Patterning of Proteins on Hydrogels**	Jeffrey Bode Marcy Zenobi-Wong *
2	**A novel patch to repair a partial tear of the infraspinatus muscle in sheep**	Katja Nuss / Salim Darwiche * Brigitte von Rechenberg Jess Snedeker
3	**Absorption mechanisms in the intestines of goat and sheep**	Alois Boos **** Annette Liesegang *
4	**Activated neutrophils at the vertebral bone-disc junction promote cartilage endplate damage in Modic changes**	Stefan Dudli * Katja Nuss
5	**Aging hallmarks in human mesenchymal stromal cells: rejuvenation strategies for next generation therapies #**	Paolo Cinelli Melanie Generali (Simon Hoerstrup **) Debora Kehl * (Simon Hoerstrup **)
6	**Alterations in bone following early life stress**	Ralph Müller * Karin Würtz-Kozak *
7	**Analyzing the Transcriptome of Cells in Intervertebral Discs with Modic Changes and its Relevance for Spinal Fusion #**	Christoph Albers Stefan Dudli Benjamin Gantenbein * Oliver Hausmann
8	**Aortic and pulmonic annulus measurements pre-operatively in sheep**	Simon Hoerstrup * Colin Schwarzwald
9	**Arteriovenous malformations**	Günther Hofbauer Daniel Rüfenacht * Andreas Serra Isabel Wanke
10	**Assess the potency of a peptide-based probe to identify progressive stages of vascular atherosclerotic plaques: a first histological analysis #**	Vahid Hosseini * (Viola Vogel **) Viola Vogel
11	**Bio-printed 3D artery analogues for modeling atherosclerosis #**	Simon Hoerstrup Anna Mallone * (Simon Hoerstrup **)
12	**Biphasic implants for osteochondral tissue repair and regeneration**	Katja Nuss / Salim Darwiche * Brigitte von Rechenberg Marcy Zenobi-Wong
13	**Bone metabolism of cats**	Annette Liesegang * Brigitte von Rechenberg
14	**Calcium Flux Imaging in 3D constructs and tissue samples**	Jess Snedeker * Karin Würtz-Kozak *
15	**Cancer Epigenome**	Michael Hottiger * Mitchell Levesque */***
16	**Cardiovascular Tissue Engineering**	Simon Hoerstrup * Katja Nuss
17	**Cartilage and IVD replacement using constructs with integrated fixation**	Lee Ann Laurent-Applegate Katja Nuss / Salim Darwiche * Brigitte von Rechenberg
18	**Clamydiales and hemotropic mycoplasma in captive and free-living bats**	Nicole Borel * Regina Hofmann-Lehmann
19	**Clinical phase I/II study for p47phox Chronic Granulomatous Disease (CGD)**	Simon Hoerstrup Janine Reichenbach *
20	**Combination of a Collagen Scaffold and an Adhesive Hyaluronan-Based Hydrogel for Cartilage Regeneration**	Katja Nuss / Salim Darwiche Brigitte von Rechenberg Marcy Zenobi-Wong *
21	**Development of an animal model to study the osteonecrosis of the jaw**	Peter Kronen Stefan Stübinger * Franz Weber
22	**Development of an antimicrobial hydrogel for the prevention and treatment of multi-drug resistant prosthetic joint infections #**	Philippe Abdel-Sayed * (Lee Ann Laurent-Applegate **) Shawna McCallin (Lee Ann Laurent-Applegate **) Marcy Zenobi-Wong
23	**Diagnosis and minimally invasive treatment of rotator cuff tendon tear**	Christian Gerber */**** Dominik Meyer **** Jess Snedeker

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

Number	Title	Collaborators (CABMM members)
24	**Digitale Simulation zur individualisierten Fertigung von 3D Nanofaserfilter und Integration in Vollschutzanzug für Pandemiefälle**	Christian Adlhart */*** Sven Hirsch Stefan Stübinger
25	**Effect of hypothermal conditioning on the quality and growth potential of *in vitro* cultured keratinocytes for skin grafts**	Maurizio Calcagni * Simon Hoerstrup Katja Nuss / Salim Darwiche Brigitte von Rechenberg
26	**Elucidation of mechanisms regulating ground state pluripotency**	Paolo Cinelli Raffaella Santoro *
27	**Engineered biological implant for canine disc replacement**	Katja Nuss / Salim Darwiche * Brigitte von Rechenberg * Frank Steffen
28	**Erythrocyte-based nanotechnology for personalized delivery of naturally derived anti-inflammatory drugs #**	Olga Krupkova * (Karin Würtz-Kozak **) Jivko Stoyanov *
29	**Establishment of a localized acute implant-associated *Staphylococcus aureus* bone infection model in sheep**	Yvonne Achermann Katja Nuss / Salim Darwiche * / Karina Klein Brigitte von Rechenberg
30	**Evaluating the influence of global sagittal alignment on proximal segment loading using musculoskeletal modeling**	Stephen Ferguson Markus Loibl *
31	**Evaluation of the chondrogenic potential of human epiphyseal chondroprogenitor cells in alginate sulfate hydrogels #**	Lee Ann Laurent-Applegate Marcy Zenobi-Wong *
32	**Expression, regulation, and role of the TRP channel family in disc**	Stephen Ferguson Karin Würtz-Kozak *
33	**Haptoglobin administration into the subarachnoid space prevents hemoglobin-induced cerebral vasospasm**	Michael Hugelshofer */*** Emanuela Keller Patrick Kircher Peter Kronen Zsolt Kulcsár Henning Richter * Dominik Schaer */***
34	**Hematology, biochemistry, and morphological features of peripheral blood cells in captive Boa constrictor**	Regina Hofmann-Lehmann Anja Kipar * Annette Liesegang

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

Number	Title	Collaborators (CABMM members)
35	**Identification of HSP70-dependent factors involved in response to thermoradiotherapy in osteosarcoma #**	Stephan Bodis *** Niels Kuster Katarzyna Nytko-Karouzakis * (Carla Rohrer Bley **)
36	**Identification of inflammatory and pain markers in degenerative spinal disease #**	Luc Smolders * (Frank Steffen **) Frank Steffen Karin Würtz-Kozak *
37	**ImaValve**	Simon Hoerstrup * Brigitte von Rechenberg
38	**Induction of cross-links in corneal tissue by sunlight exposure**	Farhad Hafezi * Katja Nuss
39	**Influence of electrotherapy on the stratification of keratinocytes and epidermal regeneration**	Maurizio Calcagni * Brigitte von Rechenberg
40	**Influence of phosphorus source on kidney health in cats**	Annette Liesegang * Henning Richter
41	**Injectability of carriers for cell delivery in porous bone**	Stefan Dudli * Stephen Ferguson
42	**Injectable hyaluronan based adhesive technology for cartilage regeneration using epiphyseal chondroprogenitor cells**	Lee Ann Laurent-Applegate Brigitte von Rechenberg Marcy Zenobi-Wong *
43	**Intervertebral disc inflammaging**	Oliver Hausmann * Karin Würtz-Kozak *
44	**Intracranial tissue perfusion, pressure, and temperature**	Peter Kronen * Brigitte von Rechenberg
45	**Investigating hypercortisolemia-induced wound healing disturbances and the therapeutic potential of heme in skin models *in vitro***	Felicitas Boretti */*** Maurizio Calcagni Katja Nuss Nadja Sieber-Ruckstuhl ***
46	**Investigation of the inflammatory processes associated with canine intervertebral disc herniation #**	Franck Forterre * David Spreng **** Karin Würtz-Kozak

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

Number	Title	Collaborators (CABMM members)
47	**Laser Assisted Robot Guided Cartilage Regeneration**	Andrea Barbero Katja Nuss / Salim Darwiche Antonio Pozzi Georg Rauter */***
48	**Marie Skłodowska Curie International Training Network (ITN) Disc4All**	Benjamin Gantenbein Jérôme Noailly */*** Karin Würtz-Kozak
49	**Marvel: electromagnetic pulsed stimulation to prevent osteomyelitis**	Yvonne Achermann Beat Lechmann *** Brigitte von Rechenberg *
50	**Meniscal Strain in Normal and Degenerated Canine Menisci**	Katja Nuss / Salim Darwiche Antonio Pozzi *
51	**Microbiota and metabolic endotoxemia: the missing culprit of Osteoarthritis #**	Gonçalo Barreto * (Marcy Zenobi-Wong **) Caroline Ospelt Marcy Zenobi-Wong
52	**Monitoring osteomyelitis by biomarkers following systemic inflammation parameters #**	Regina Hofmann-Lehmann Annette Liesegang Brigitte von Rechenberg * Raffaella Santoro
53	**Motion analysis of the proximal interphalangeal joint in healthy hands, as well as in osteoarthritis hands following implantation with the new CapFlexPIP implant compared with silicone implants**	Laurent Audigé * Stephen Ferguson
54	**Nanoghosts as drug delivery platform in intervertebral disc repair #**	Olga Krupkova * (Andrea Barbero **) Jivko Stoyanov *
55	**Nasal chondrocytes for the treatment of cartilage and disc pathologies**	Andrea Barbero * Katja Nuss / Salim Darwiche
56	**Neuronal growth and angiogenesis in Modic type 1 changes #**	Ulrich Blache (Jess Snedeker **) Stefan Dudli *
57	**Nucleus pulposus-on-a-chip as a model for mechanobiology research and therapeutic testing #**	Salim Darwiche (Katja Nuss **) Olga Krupkova * (Andrea Barbero **)

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

Number	Title	Collaborators (CABMM members)
58	**Osteochondral bone stimulation with fetal progenitor cells**	Lee Ann Laurent-Applegate * Brigitte von Rechenberg
59	**PACK-CXL for infectious keratitis**	Farhad Hafezi * Simon Pot *
60	**Preclinical GLP animal study on p47phox CGD mice to prepare IMPD for above clinical trial**	Katja Nuss Brigitte von Rechenberg Janine Reichenbach *
61	**Preliminary study to assess the impact of Far-UVC on human skin tissue**	Maurizio Calcagni * Katja Nuss / Salim Darwiche
62	**Pulsed electromagnetic field therapy enhances bone repair and regeneration in two tibia osteotomy models in sheep**	Stephen Ferguson Katja Nuss / Salim Darwiche * / Karina Klein Brigitte von Rechenberg
63	**Quantitative assessment of blood vessels in the superficial digital flexor tendons of horses**	Nicole Borel Anton Fürst *
64	**Regeneration of meniscus using injectable biomaterial**	Katja Nuss / Salim Darwiche * Antonio Pozzi Brigitte von Rechenberg
65	**REVEAL-FS: Characterization of novel targets for near infrared fluorescence-guided surgery of fibrosarcomas #**	Franco Guscetti (Anja Kipar **) Enni Markkanen * Mirja Nolff (Antonio Pozzi **)
66	**Scavenging of cell-free hemoglobin in the subarachnoid space: Proof of therapeutic concept in chronic hemoglobin exposure**	Michael Hugelshofer */*** Patrick Kircher Peter Kronen Katja Nuss / Karina Klein Henning Richter
67	**Skin regeneration using MSC**	Simon Hoerstrup Brigitte von Rechenberg *
68	**Steam device in transrectal interventional MRI usage on canine prostates**	Patrick Kircher Henning Richter * Daniel Rüfenacht

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

Number	Title	Collaborators (CABMM members)
69	**Steam effects on tissue – simulation and validation**	Patrick Kircher Henning Richter * Daniel Rüfenacht Isabel Wanke
70	**Subcutaneous implantation of polymeric or metal implants for auricular reconstruction**	Katja Nuss / Salim Darwiche Marcy Zenobi-Wong *
71	**Surgical safety and effectiveness in orthopedics: Swiss-wide multicenter evaluation and prediction of core outcomes in arthroscopic rotator cuff reconstruction**	Laurent Audigé * Christian Gerber ****
72	**The effect of pharmacological and mechanical stimulation on the chronically retracted torn rotator cuff muscle – An experimental study in sheep**	Christian Gerber */**** Dominik Meyer **** Brigitte von Rechenberg Karl Wieser ***
73	**The importance of plasmin in synovial fluid for the healing of ACL ruptures #**	Sufian Ahmad Benjamin Gantenbein *
74	**The *in vitro* chondrogenic differentiation of human bMSCs within gel or sponge-type 3D matrices – a comparative approach #**	Gian Salzmann * Marcy Zenobi-Wong
75	**The role of Fibronectin Fragments in immune Modulation and Inflammaging during Canine Disc Disease #**	Franck Forterre * Benjamin Gantenbein *
76	**The role of *Propionibacterium acnes* infection in intervertebral disc inflammation #**	Yvonne Achermann * Oliver Hausmann Karin Würtz-Kozak * Annelies Zinkernagel
77	**Toward the combination of epigenetics and tissue engineering to generate cartilage *in vitro* #**	Killian Flégeau * (Marcy Zenobi-Wong **) Lee Ann Laurent-Applegate Marcy Zenobi-Wong
78	**Transcatheter aortic valve implantation of cell-free tissue engineered heart valves in sheep**	Simon Hoerstrup * Katja Nuss / Karina Klein
79	**Transcatheter pulmonary valve replacement of cell-free tissue engineered heart valves in sheep**	Simon Hoerstrup * Katja Nuss / Karina Klein
80	**Transplantation of autologous mesenchymal stem cells halts fatty atrophy of detached rotator cuff muscle after tendon repair: results from an ovine model**	Martin Flück */**** Marie-Noëlle Giraud
81	**Treatment of periprosthetic joint infections using photodynamic therapy**	Yvonne Achermann * Markus Grob *** Niels Kuster Peter Wahl *** Patrick Zingg ***
82	**Virtual mechanical tests out-perform morphometric measures for assessment of mechanical stability of fracture healing *in vivo***	Hannah Dailey */*** Stephen Ferguson Katja Nuss / Salim Darwiche / Karina Klein Brigitte von Rechenberg
83	**Vitamin D metabolism in goat and sheep**	Annette Liesegang * Brigitte von Rechenberg
84	**Water-filtered infrared A (wIRA): new therapeutic strategies for treatment of chlamydial infections in humans and animals**	Christian Blenn **** Nicole Borel *

* principal investigator(s), ** corresponding CABMM member, *** no CABMM member, **** former CABMM member
# CABMM Start-up Grant project

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1	Borel N, Sauer-Durand AM, Hartel M, Kuratli J, Vaupel P, Scherr N, Pluschke G **wIRA: hyperthermia as a treatment option for intracellular bacteria, with special focus on Chlamydiae and Mycobacteria** *Int J Hyperthermia, 2020;37(1):373-383*
2	Laurent A, Darwiche SE, Hirt-Burri N, Scaletta C, Michetti M, Laurent P, Raffoul W, de Buys Roessingh AS, Applegate LA **Banking Progenitor Cells for Hippiatric Regenerative Medicine: Optimized Establishment of Safe and Consistent Cell Sources for Standardized Veterinary Therapeutic Protocols** *Am J Biomed Sci Res, 2020;8(4)*
3	Meier AF, Laimbacher AS **HSV-1 Amplicon Vectors as Genetic Vaccines** *Methods Mol Biol, 2020;2060:111-130*
4	Barreto G, Senturk B, Colombo L, Brück O, Neidenbach P, Salzmann G, Zenobi-Wong M, Rottmar M **Lumican is upregulated in osteoarthritis and contributes to TLR4-induced pro-inflammatory activation of cartilage degradation and macrophage polarization** *Osteoarthritis Cartilage, 2020 Jan;28(1):92-101*
5	Torres-Netto EA, Spiru B, Kling S, Gilardoni F, Lazaridis A, Sekundo W, Hafezi F **Similar Biomechanical Cross-linking Effect After SMILE and PRK in Human Corneas in an Ex Vivo Model for Postoperative Ectasia** *J Refract Surg, 2020 Jan 1;36(1):49-54*
6	Siegenthaler B, Ghayor C, Ruangsawasdi N, Weber FE **The Release of the Bromodomain Ligand *N,N*-Dimethylacetamide Adds Bioactivity to a Resorbable Guided Bone Regeneration Membrane in a Rabbit Calvarial Defect Model** *Materials (Basel), 2020 Jan 21;13(3):501*
7	Krupkova O, Greutert H, Boos N, Lemcke J, Liebscher T, Wuertz-Kozak K **Expression and activity of hyaluronidases HYAL-1, HYAL-2 and HYAL-3 in the human intervertebral disc** *Eur Spine J, 2020 Mar;29(3):605-615*
8	May RD, Frauchiger DA, Albers CE, Hofstetter W, Gantenbein B **Exogenous Stimulation of Human Intervertebral Disc Cells in 3-Dimensional Alginate Bead Culture With BMP2 and L51P: Cytocompatibility and Effects on Cell Phenotype** *Neurospine, 2020 Mar;17(1):77-87*
9	Voelter K, Tappeiner C, Riond B, Nuss K, Bruetsch D, Pot SA **Evaluation of D-dimer levels in aqueous humor of rabbit eyes with and without induced intraocular fibrin and fibrinolytic treatment** *Vet Ophthalmol, 2020 Mar;23(2):212-218*

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10	Knyazer B, Krakauer Y, Tailakh MA, Achiron A, Hecht I, Lifshitz T, Torres-Netto EA, Hafezi NL, Hafezi F **Accelerated Corneal Cross-linking as an Adjunct Therapy in the Management of Presumed Bacterial Keratitis: A Cohort study** *J Refract Surg, 2020 Apr 1;36(4):258-264*
11	McLuckie M, Robotti F, Sanchez-Macedo N, Enderlin D, Frese L, Cheng PF, Levesque MP, Egaña JT, Poulikakos D, Ferrari A, Lindenblatt N **Lipoconstruct surface topography grating size influences vascularization onset in the dorsal skinfold chamber model** *Acta Biomater, 2020 Apr 1;106:136-144*
12	Wright B, Kronen PW, Lascelles D, Monteiro B, Murrell JC, Robertson S, Steagall PVM, Yamashita K **Ice therapy: cool, current and complicated** *J Small Anim Pract, 2020 May;61(5):267-271*
13	Schwarzenberg P, Darwiche S, Yoon RS, Dailey HL **Imaging Modalities to Assess Fracture Healing** *Curr Osteoporos Rep, 2020 Jun;18(3):169-179*
14	Kling S, Torres-Netto EA, Spiru B, Sekundo W, Hafezi F **Quasi-Static Optical Coherence Elastography to Characterize Human Corneal Biomechanical Properties** *Invest Ophthalmol Vis Sci, 2020 Jun 3;61(6):29*
15	Aslanides IM, Hafezi F, Chen S, Mukherjee H, Selimis V, Maragkos I, Lu N, Kymionis G **5-year efficacy of all surface laser ablation with cross-linking (ASLA-XTRA) for the treatment of myopia** *Eye Vis (Lond), 2020 Jun 11;7:31*
16	Laurent A, Lin P, Scaletta C, Hirt-Burri N, Michetti M, de Buys Roessingh AS, Raffoul W, She BR, Applegate LA **Bringing Safe and Standardized Cell Therapies to Industrialized Processing for Burns and Wounds** *Front Bioeng Biotechnol, 2020 Jun 19;8:581*
17	Schmid B, Hausmann O, Hitzl W, Achermann Y, Wuertz-Kozak K **The Role of *Cutibacterium acnes* in Intervertebral Disc Inflammation** *Biomedicines, 2020 Jun 30;8(7):186*
18	Flück M, Fitze D, Ruoss S, Valdivieso P, von Rechenberg B, Bratus-Neuenschwander A, Opitz L, Hu J, Laczko E, Wieser K, Gerber C **Down-Regulation of Mitochondrial Metabolism after Tendon Release Primes Lipid Accumulation in Rotator Cuff Muscle** *Am J Pathol, 2020 Jul;190(7):1513-1529*
19	Sadoughifar R, Goldust M, Abdshahzadeh H, Abrishamchi R, Rudnicka L, Jafferany M, Gupta M **Artificial intelligence in diagnosis and management of COVID-19 in dermatology** *Dermatol Ther, 2020 Jul;33(4):e13794*

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24	Cornaz F, Valet S, Meyer DC **Spectroscopic characterization of tissue and liquids during arthroscopic radio-frequency ablation** *Med Phys, 2020 Aug;47(8):3703-3709*
25	Kling S, Hufschmid FS, Torres-Netto EA, Randleman JB, Willcox M, Zbinden R, Hafezi F **High Fluence Increases the Antibacterial Efficacy of PACK Cross-Linking** *Cornea, 2020 Aug;39(8):1020-1026*
26	Tai YK, Ng C, Purnamawati K, Yap JLY, Yin JN, Wong C, Patel BK, Soong PL, Pelczar P, Fröhlich J, Beyer C, Fong CHH, Ramanan S, Casarosa M, Cerrato CP, Foo ZL, Pannir Selvan RM, Grishina E, Degirmenci U, Toh SJ, Richards PJ, Mirsaidi A, Wuertz-Kozak K, Chong SY, Ferguson SJ, Aguzzi A, Monici M, Sun L, Drum CL, Wang JW, Franco-Obregón A **Magnetic fields modulate metabolism and gut microbiome in correlation with Pgc-1α expression: Follow-up to an in vitro magnetic mitohormetic study** *FASEB J, 2020 Aug;34(8):11143-11167*
27	Bakirci E, Tschan K, May RD, Ahmad SS, Kleer B, Gantenbein B **The importance of plasmin for the healing of the anterior cruciate ligament** *Bone Joint Res, 2020 Sep 3;9(9):543-553*
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30	Khera N, Ghayor C, Lindholm AK, Pavlova E, Atanassova N, Weber FE **N, N-Dimethylacetamide, an FDA approved excipient, acts post-meiotically to impair spermatogenesis and cause infertility in rats** *Chemosphere, 2020 Oct;256:127001*
31	Bhattacharya I, Ghayor C, Pérez Dominguez A, Weber FE **From Influenza Virus to Novel Corona Virus (SARS-CoV-2)-The Contribution of Obesity** *Front Endocrinol (Lausanne), 2020 Oct 6;11:556962*
32	Laurent A, Hirt-Burri N, Scaletta C, Michetti M, de Buys Roessingh AS, Raffoul W, Applegate LA **Holistic Approach of Swiss Fetal Progenitor Cell Banking: Optimizing Safe and Sustainable Substrates for Regenerative Medicine and Biotechnology** *Front Bioeng Biotechnol, 2020 Oct 23;8:557758*
33	Capossela S, Mathew V, Boos M, Bertolo A, Krupkova O, Stoyanov JV **Novel Fast and Reliable Method for Nano-Erythrosome Production Using Shear Force** *Drug Des Devel Ther, 2020 Oct 28;14:4547-4560*
34	Zhang H, Roozbahani M, Piccinini AL, Hafezi F, Scarcelli G, Randleman JB **Brillouin microscopic depth-dependent analysis of corneal crosslinking performed over or under the LASIK flap** *J Cataract Refract Surg, 2020 Nov;46(11):1543-1547*
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37	Mallone A, Gericke C, Hosseini V, Chahbi K, Haenseler W, Emmert MY, von Eckardstein A, Walther JH, Vogel V, Weber B, Hoerstrup SP **Human induced pluripotent stem cell-derived vessels as dynamic atherosclerosis model on a chip** *bioRxiv, 2020.11.27.401034*
38	Belin MW, Alizadeh R, Torres-Netto EA, Hafezi F, Ambrósio R Jr, Pajic B **Determining Progression in Ectatic Corneal Disease** *Asia Pac J Ophthalmol (Phila), 2020 Dec;9(6):541-548*

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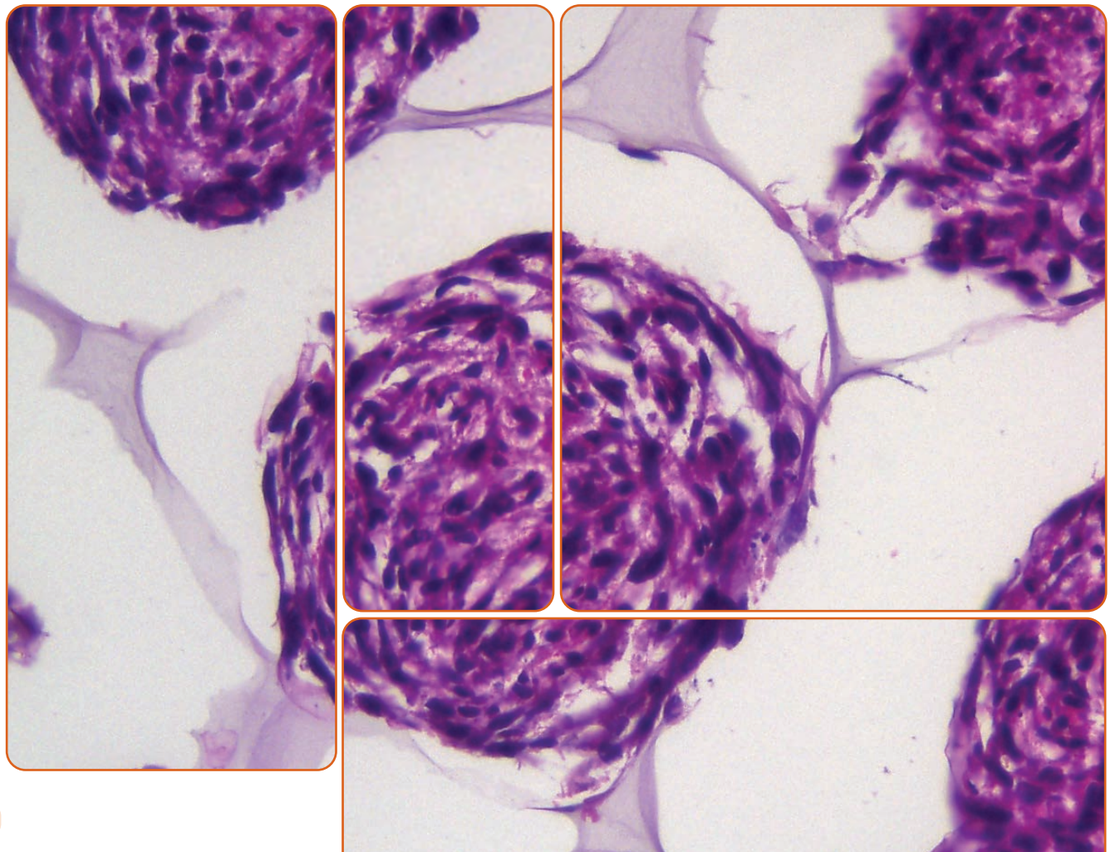
39	Kuratli J, Leonard CA, Nufer L, Marti H, Schoborg R, Borel N **Maraviroc, celastrol and azelastine alter *Chlamydia trachomatis* development in HeLa cells** *J Med Microbiol, 2020 Dec;69(12):1351-1366*
40	Plecko M, Klein K, Planzer K, Wähnert D, Behm P, Ferguson SJ, Brianza S, Stadelmann VA, von Rechenberg B **Variable fixation promotes callus formation: an experimental study on transverse tibial osteotomies stabilized with locking plates** *BMC Musculoskelet Disord, 2020 Dec 3;21(1):806*
41	Ghayor C, Chen TH, Bhattacharya I, Özcan M, Weber FE **Microporosities in 3D-Printed Tricalcium-Phosphate-Based Bone Substitutes Enhance Osteoconduction and Affect Osteoclastic Resorption** *Int J Mol Sci, 2020 Dec 4;21(23):9270*



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43	Hafezi F, Torres-Netto EA, Randleman JB, Hafezi NL, Mazzotta C, Ambrósio Jr R, Kollros L **Corneal Cross-linking for Keratoglobus Using Individualized Fluence** *J Refract Surg Case Rep, 2021;1(1):e10-e14*
44	Knyazer B, Hillen M, Hafezi F **Corneal Cross-linking for Infectious Keratitis at the Slit Lamp in Wheelchair Users** *J Refract Surg Case Rep, 2021;1(3):e36-e39*
45	Laurent A, Scaletta C, Hirt-Burri N, Raffoul W, de Buys Roessingh AS, Applegate LA **Swiss Fetal Transplantation Program and Non-enzymatically Isolated Primary Progenitor Cell Types for Regenerative Medicine** *Methods Mol Biol, 2021;2286:1-24*
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47	Laurent A, Scaletta C, Michetti M, Hirt-Burri N, Flahaut M, Raffoul W, de Buys Roessingh AS, Applegate LA **Progenitor Biological Bandages: An Authentic Swiss Tool for Safe Therapeutic Management of Burns, Ulcers, and Donor Site Grafts** *Methods Mol Biol, 2021;2286:49-65*
48	Hafezi F, Torres-Netto EA, Hillen MJP **Re: Prajna et al.: Cross-Linking-Assisted Infection Reduction: a randomized clinical trial evaluating the effect of adjuvant cross-linking on outcomes in fungal keratitis (Ophthalmology. 2020;127:159-166)** *Ophthalmology, 2021 Jan;128(1):e6*
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50	Hafezi F, Richoz O, Torres-Netto EA, Hillen M, Hafezi NL **Corneal Cross-linking at the Slit Lamp** *J Refract Surg, 2021 Feb 1;37(2):78-82*
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53	Laurent A, Abdel-Sayed P, Ducrot A, Hirt-Burri N, Scaletta C, Jaccoud S, Nuss K, Roessingh ASB, Raffoul W, Pioletti D, Rechenberg BV, Applegate LA, Darwiche S **Development of Standardized Fetal Progenitor Cell Therapy for Cartilage Regenerative Medicine: Industrial Transposition and Preliminary Safety in Xenogeneic Transplantation** *Biomolecules, 2021 Feb 9;11(2):250*
54	Al-Dourobi K, Laurent A, Deghayli L, Flahaut M, Abdel-Sayed P, Scaletta C, Michetti M, Waselle L, Simon JP, Ezzi OE, Raffoul W, Applegate LA, Hirt-Burri N, Roessingh ASB **Retrospective Evaluation of Progenitor Biological Bandage Use: A Complementary and Safe Therapeutic Management Option for Prevention of Hypertrophic Scarring in Pediatric Burn Care** *Pharmaceuticals (Basel), 2021 Feb 28;14(3):201*
55	Schwarzenberg P, Ren T, Klein K, von Rechenberg B, Darwiche S, Dailey HL **Domain-independent simulation of physiologically relevant callus shape in mechanoregulated models of fracture healing** *J Biomech, 2021 Mar 30;118:110300*
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57	Schwarzenberg P, Klein K, Ferguson SJ, von Rechenberg B, Darwiche S, Dailey HL **Virtual mechanical tests out-perform morphometric measures for assessment of mechanical stability of fracture healing in vivo** *J Orthop Res, 2021 Apr;39(4):727-738*
58	Laurent A, Abdel-Sayed P, Grognuz A, Scaletta C, Hirt-Burri N, Michetti M, de Buys Roessingh AS, Raffoul W, Kronen P, Nuss K, von Rechenberg B, Applegate LA, Darwiche SE **Industrial Development of Standardized Fetal Progenitor Cell Therapy for Tendon Regenerative Medicine: Preliminary Safety in Xenogeneic Transplantation** *Biomedicines, 2021 Apr 3;9(4):380*
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70	Hafezi F **Corneal Cross-linking for Keratoconus: Exploring the Issues Regarding Accelerated Protocols and Thin Corneas** *J Ophthalmic Vis Res, 2021 Jul 29;16(3):314-316*
71	Hafezi F, Richoz O, Torres-Netto EA, Hillen M, Hafezi N **Reply: Corneal Cross-linking at the Slit Lamp: Concern About Risk of Corneal Ulcer** *J Refract Surg, 2021 Aug;37(8):572-573*
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Steffen Zeisberger, Martin Kayser, Flurina Clement Frey,
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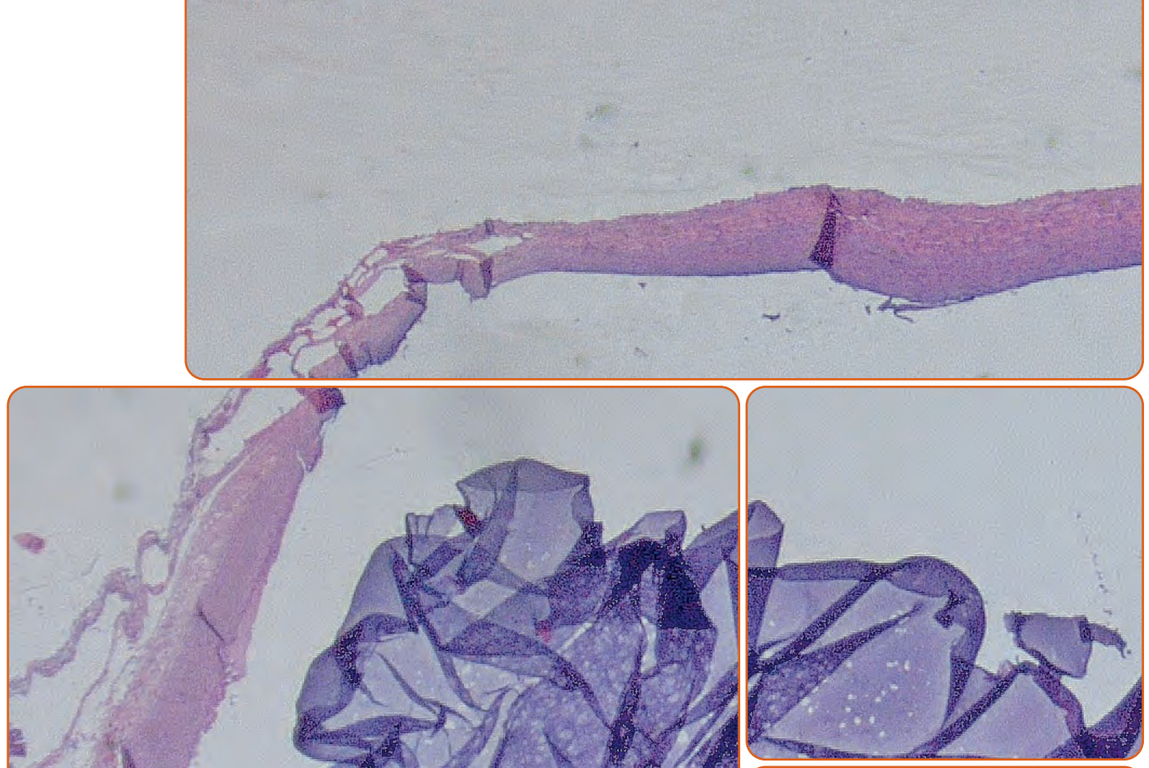

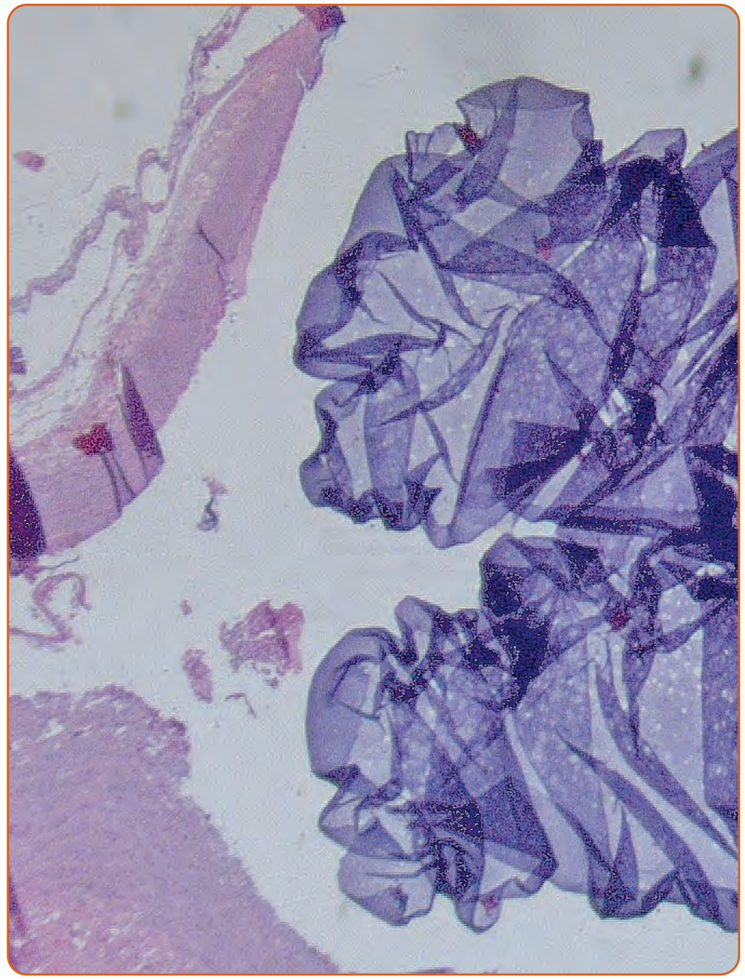

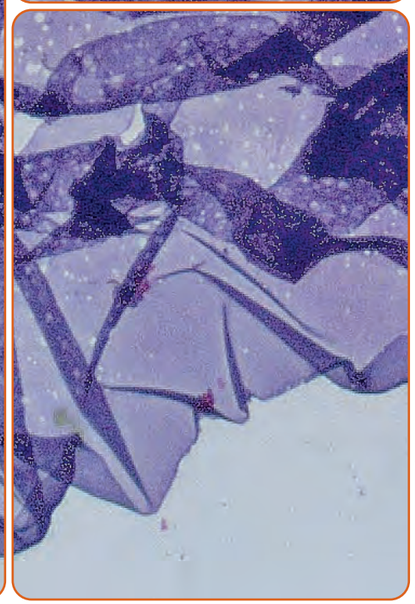

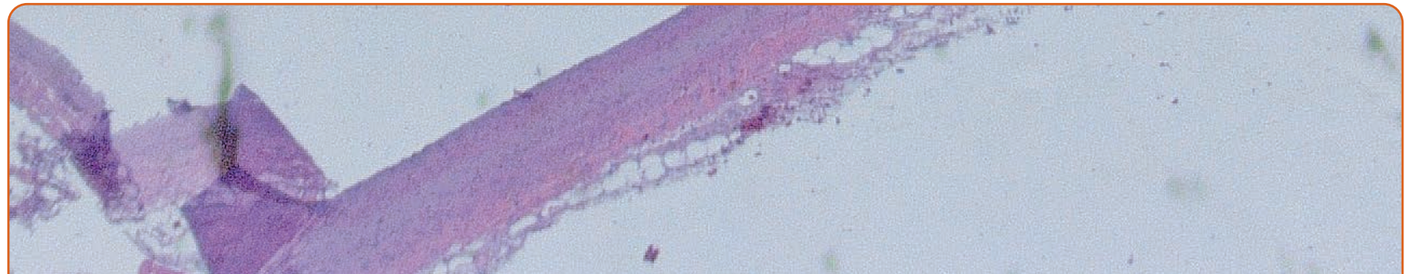

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