CABMM'S **PROFESSOR BRIGITTE VON RECHENBERG** ON THE ADVANTAGES OFFERED BY THE COMPETENCE CENTRES AT THE UNIVERSITY OF ZURICH

Excellence through co-operation

"'Centres of Competence' are scientific networks where university institutes or institute departments co-ordinate their work according to strategic objectives."

This is the official definition of successful scientific networks that are accepted through the leading university authorities as competence centres at the University of Zurich. Prerequisites are a developmental plan that demonstrates the overall benefit, as well as the strategic focus and pertinent rules and guidelines of the network. The centre must first be acknowledged and supported through the leading faculty, after which it has to apply for re-certification every three years, where its national and international success and added scientific value to the university has to be demonstrated and, in case of doubt, be reviewed by external reviewers in the field.

By nature, these competence centres are focused on a more general topic where different specialists contribute and elucidate specific questions from various perspectives (e.g. ethics, gerontology, linguistics, etc.).

CABMM

The CABMM is one of these official competence centres. Its focus is placed on applied biotechnology and translational medicine. From 'bench to beside…and back' is the slogan which covers basic research from enhancing current understanding of (molecular) mechanisms to *in vitro* cell culture work, with or without bioreactors, to provide optimal environmental conditions for organ regeneration on natural or synthetic scaffolds before implantation into experimental animals and, finally, in clinical trials into human patients.

The centre provides an interdisciplinary research platform on which basic scientists and clinicians are able to exchange scientific information and create collaborations for the purpose of developing novel therapeutic approaches for the treatment of dysfunctional and diseased tissues.

Development

The CABMM developed naturally over time when the three founders (Brigitte von Rechenberg, Michael Hottiger, Simon Hoerstrup) started to collaborate in translational research projects. This bundling of expertise led to an immediate higher output of results and success, since board-certified veterinary anaesthesiologists and veterinary professionals with clinical experience and those engaged in animal care reduced intra and post-operative complications and the overall mortality rate of experimental animals significantly, while the highly specialised cardiologists could concentrate on their work with the pulmonary artery grafts (project headed by Professor Hoerstrup).

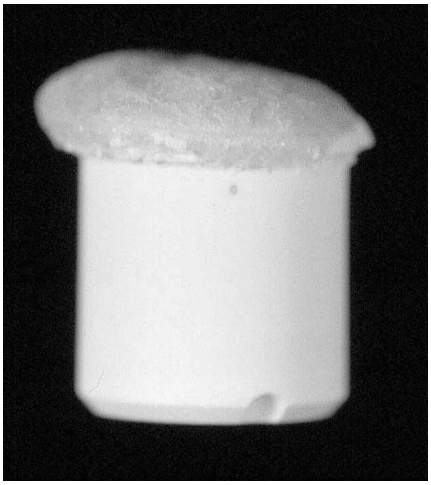

Fig. 1 The dual scaffold for hyaline cartilage resurfacing shows a calcium phosphate based matrix for the subchondral bone part and a porous PLGA for the hyaline cartilage part

Combined effort

The study design and planning was a combined effort, as well as from the analysis of results and discussions of unexpected complications and/or outcomes. From this, it was shown that the clinical expertise of the veterinary group helped tremendously in the solving of problems with experimental animals, especially when nothing could be found in the pertinent experimental literature.

Although the various experts initially seemed to be far away from each other, it soon was found that there were many common interests. Apart from clinical experiences that are instrumental for good study designs in preclinical studies, the sharing of the technology platform and expertise in basic sciences such as biochemistry and molecular medicine turned out to be a real asset.

With these positive experiences, the decision was made to formalise the already existing network and form a technology and expert platform at the University of Zurich, which is now known and acknowledged as the Competence Center for Applied Biotechnology and Molecular Medicine. The CABMM was founded in August 2008, and re-certified in August 2011.

Biotechnology

Biotechnology is interdisciplinary and highly complex. In order to regenerate dysfunctional tissue, basic science is needed to understand the underlying mechanisms of failure and an understanding of whether molecular pathways need to be inhibited or stimulated to bring back normal function is also required.

While many basic cellular mechanisms can be studied in cell cultures *in vitro,* tissue composition is more intricate, and cell functionality can only be studied in more sophisticated systems such as organ cultures or experimental animals.

In particular, the possibility to modify gene expression in animals helps to understand the function and dysfunction of cellular and tissue interactions. The design of intelligent biomaterials or tissue-engineered products is only possible if these interactions are respected and valued. Otherwise, failure is inevitable.

One of the classic examples of this is the resurfacing of hyaline cartilage in the case of osteoarthritis and/or primary cartilage defects. Although attempts to achieve this are numerous all over the world, long-term success has remained elusive. As of today, neither biomaterials alone nor the combination of biomaterials and tissue engineering cell constructs have led to the regeneration of normal hyaline cartilage.

One of these classic examples would be the production of cartilage scaffolds; many forms and structures are available in research, yet none of them properly mimics the natural morphology of hyaline cartilage. In this instance, the collagen structure is quite clear, and is such that fibrils are parallel to each other in the deep and middle zone. Indeed, it is only in the superficial zone that they change size and direction to a more radial structure.

Nevertheless, most of the scaffolds used for cartilage resurfacing are porous and resemble more trabecular bone than original cartilage structure (see Fig. 1). The reason for this incompatibility is unknown and may be due to difficulties to produce structures that are alike to one another.

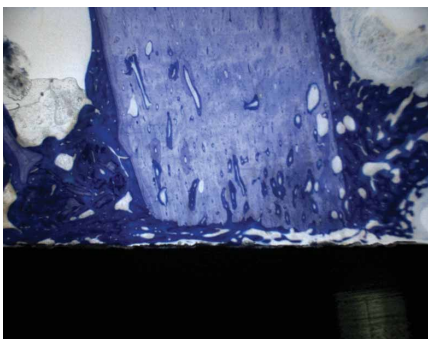

Fig. 3 A metallic implant *in situ* is shown in this histology picture (ground section, surface staining with toluidine blue). Note that the newly formed bone (dark blue) can be easily distinguished from the old lamellar (light blue) bone. The bone-interface-contact (BIC) can be calculated on these pictures

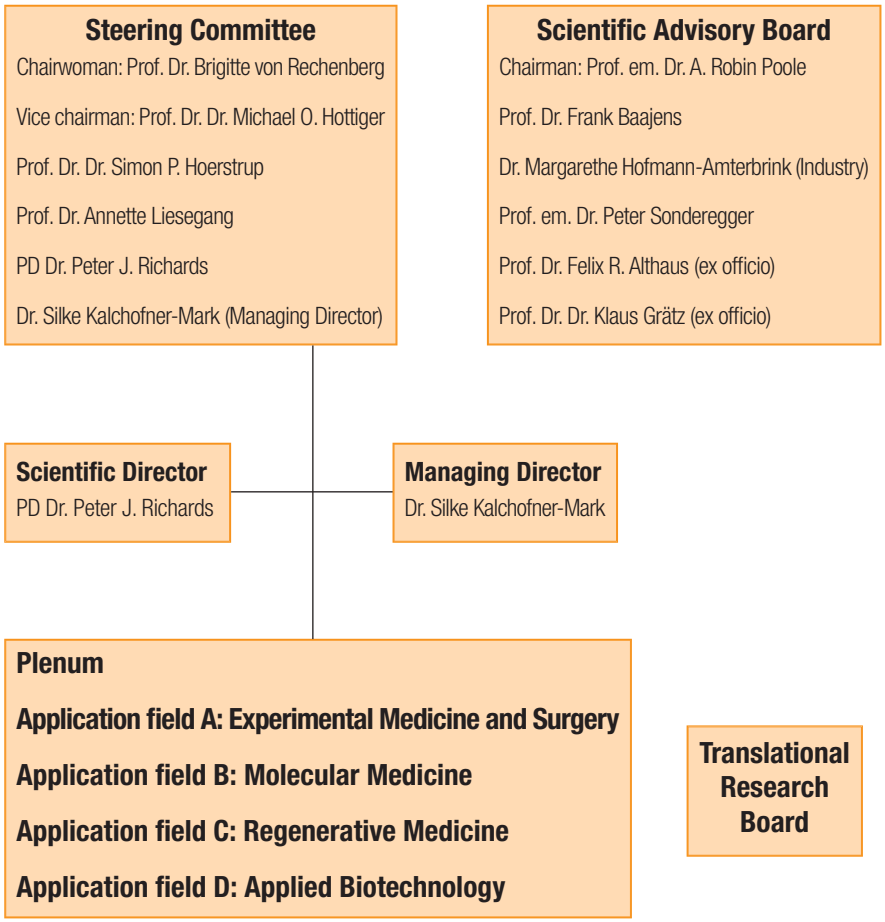

Fig. 2 The organigram of the CABMM with the application fields

With the advent of new technologies such as electrospinning and other similar sophisticated methodologies, however, this reason is being called into question, and it is now believed that the most likely cause is simply related to the fact that material scientists and clinicians do not communicate sufficiently for the optimisation of scaffold structures to be a success. It is therefore essential that cell biologists, material scientists, biomechanical engineers and clinicians are involved in such a project.

Similar scenarios are true for many other biotechnology products that are synthetised *in vitro* but fail once they have been implanted *in vivo* because clinical aspects were not sufficiently respected.

The CABMM was therefore formed with groups from basic, preclinical and clinical research, and so allows for a product to be monitored from the 'bench to bedside…and back'. Although the mixture of groups seems colourful, it makes a lot of sense if viewed from the more holistic approach.

Application fields

There are four major application fields within the CABMM: a) experimental surgery and medicine, b) molecular medicine, c) regenerative medicine, and d) applied biotechnology (see Fig. 2).

Members are selected according to their CVs and expertise, including their capacity for generating competitive research grants. Their track

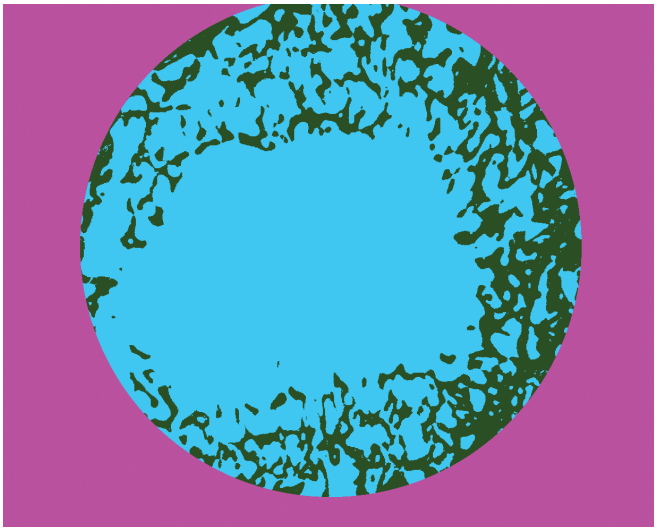

Fig. 4 Preparation of a drill hole for histomorphometrical measurements. The background is coloured pink, the newly formed bone green, and the granulation tissue turquoise

record is also reviewed with regard to their collaboration with other CABMM members.

Cardiovascular and musculoskeletal problems are within the focus of the CABMM in the various application fields, but groups that offer sophisticated technology applying for various research fields are also valuable members of the network. The latter include synthesis of scaffolds and their decoration with biomimetics including (protracted) release according to their requirements *in situ.*

Due to the nature of the various application fields, the network consists of members from the University of Zurich (UZH), mainly from the medical or veterinary faculty (Vetsuisse). Associate members belong to the ETHZ (Swiss Federal Institute of Technology) or to other national or international universities, where members are longstanding collaborators and project partners of the UZH or ETHZ, such as clinicians from the University of Innsbruck (Austria), University of Basel, Bern (Inselspital) and Lausanne (CHUV).

Committee

A central steering committee that is elected by the membership and composed of three members and the scientific director (Pete Richards) representing all application fields, is responsible for the administration of the CABMM, and is supported by the managing director (Silke Kalchofen-Mark).

The scientific director is also head of the CABMM platform, where laboratory space can be hired for small groups to conduct their *in vitro* experiments. This is especially attractive for smaller groups due to the fact that, in addition to a modern laboratory infrastructure, expertise in basic scientific technologies (biochemistry, molecular medicine, cell cultures facilities, etc.) is also available and helps to reach goals more efficiently than working alone and trying to establish things that other groups have already established.

In particular, this structure facilitates clinical projects where clinical materials from human or animal sources have to be analysed. Furthermore, a reference histology laboratory has also been built, where expert routine histology with paraffin or cryosections are offered, as well as sophisticated immunohistology and embedding in methylmetacrylate (plastic sections). The latter is especially important if (metal) implants need to be cut *in situ* in order to study their osseointegration, biocompatibility or function over time (see Fig. 3).

The histology laboratory differs from routine laboratories in that individual research needs can be addressed and expertise in specific research questions is available. In addition to the technological aspects, support for interpretation or histomorphometrical measurements is also provided (see Fig. 4). Highly skilled laboratory technicians work in the laboratory supporting both the members and external researchers in all aspects of their research.

Enhancing collaborations

Collaborations between basic and clinical researchers are impressive within the CABMM network (see Fig. 5) and are steadily increasing. A spring and autumn symposium, where members present not only their research focus but also their technological skills, ensures that members are aware of each other's expertise.

Symposiums differ from each other such that lectures which are presented in many different medical fields. Apart from widening the scientific horizon of each individual member, this helps people to interact and get in touch with other scientists that, under normal conditions, they would never meet. These meetings are also important for the doctoral students, which account for 130-140 of all CABMM members.

Translational research projects

Projects of translational research where the slogan 'from bench to bedside…and back' is a reality, are numerous at the CABMM. Among them include projects dealing with osteoporosis, the regeneration of heart valves, the degeneration of skeletal muscles, and studies of vascular flow in conjunction with aneurisms. In the area of osteoporosis (P Richards/M Blauth), the function of mesenchymal stem cells from bone marrow and adipose tissue from humans are compared to those of osteoporotic knock-out mice for their potential of osteogenic differentiation.

From this, it was discovered that mechanisms seem to be similar in humans and mice, which enables a much better translation of results for future therapeutic approaches. Very similar to this are preclinical studies in sheep for the replacement of heart valves (S Hoerstrup).

Sheep have a similar heart size to humans, which means that devices can easily be adapted to the experimental conditions. At the same time,

anaesthesia and post-operative management are instrumental for overall success and, as sheep are quite sensitive for anti-coagulation therapy and post-operative lung affections, the professional veterinary care of animals during and after surgery can make all the difference.

The combination of highly specialised human cardiology, a veterinary laboratory and anaesthesia specialists is optimal for successful results. The same is true for studies dealing with the degeneration of skeletal muscle in conjunction with tears of the rotator cuff in humans (C Gerber/D Meyer, B von Rechenberg).

Here, the sheep provide a very valuable animal model showing similar signs of degeneration as human muscles. What is more, their size also allows the testing of sophisticated medical tension devices for muscle regeneration. Intensive post-operative care and daily careful device management is essential, and professional veterinary care decreases complication rates significantly.

In addition to sheep, rabbits are accepted animal models for the study of the mechanisms involved in the development of aneurisms. Their size is also such that they can be used in the testing of stent devices for modern therapy with coils or clips with or without an appropriate coating to enhance thrombus formation.

Furthermore, the combination of highly specialised neurosurgeons and veterinary professionals make it possible to achieve optimal results. For all of these collaborations, histologic evaluations in the special reference laboratory of the CABMM or evaluations of radiographs, computer tomography or magnetic resonance imaging (MRI) at the Department of Veterinary Diagnostic Imaging can be conducted. Subsequent interpretation can be made with veterinary and human pathologists and radiologists to assure the translation to human diseases and patients.

Regulatory affairs

For biotechnological products, many requirements have to be fulfilled to pass registration at the Food and Drug Administration (FDA:www.fda.gov/). The manufacturing of products must be performed under the guidelines of Good Manufacturing Practice (GMP), preclinical animal studies must be conducted under Good Laboratory Practice (GLP) and clinical trials in humans under Good Clinical Practice (GCP) conditions.

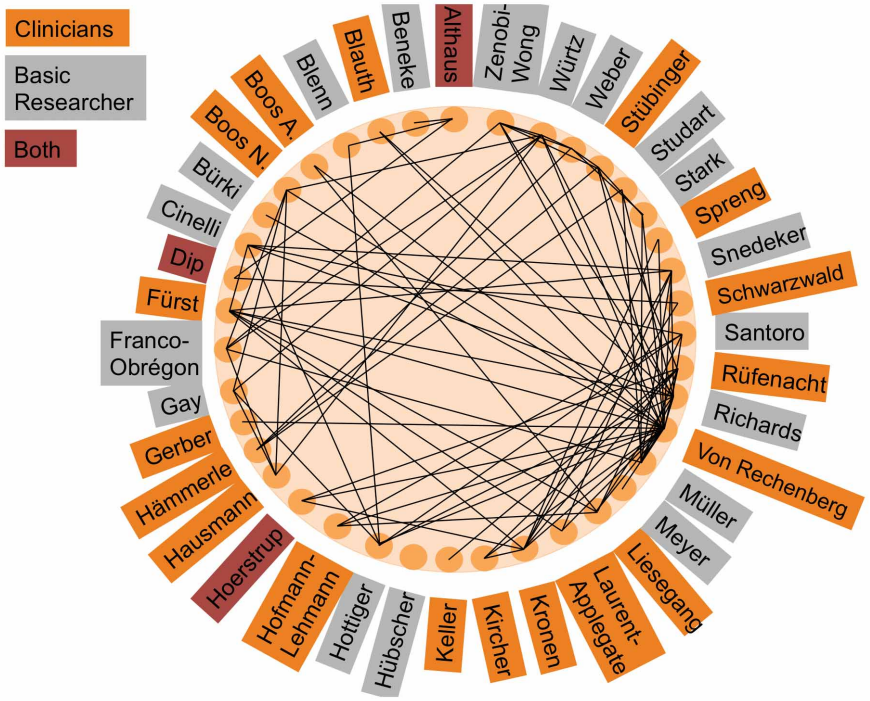

Fig. 5 Visualisation of collaborative network between basic scientists and clinicians at the CABMM

Within the CABMM, the Swiss Center of Regenerative Medicine (S Hoerstrup) is accredited for GMP, the Musculoskeletal Research Unit (MSRU, B von Rechenberg) has applied for GLP at the Swissmedic (soon to be accredited), and the University Hospital is accredited to conduct GCP trials.

The combination makes the University of Zurich a unique place for translational medicine, and the only university in Europe where a product and its development can be taken from 'bench to bedside…and back' under official regulatory conditions.

Advantages

The advantages over commercial GLP or GMP facilities include the availability of ultramodern infrastructure at the various academic institutions, including the high expertise of the staff at the various clinical, pre and paraclinical departments. Modern equipment and facilities for surgery and diagnostic imaging are available and, in the case of the Vetsuisse Faculty, are fit for all kinds of animal species. Furthermore, a modern hybrid operation unit for animals is available at the medical faculty.

To have all of this together within walking distance is a tremendous advantage for experimental animals and people alike, as well as for industrial partners that can continue working with a well known team from 'bench to bedside...and back'.

The CABMM will continue to grow and assemble a unique network of competence in translational medicine.

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browse www.cabmm.uzh.ch