DBM FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Tissue Engineering: From 3D culture models to regenerative medicine | Von Ambrustschützen zum Virennachweis: Die Abteilung Infektionsdiagnostik im ehemaligen Stachelschützenhaus | Berlin – creative and dynamic

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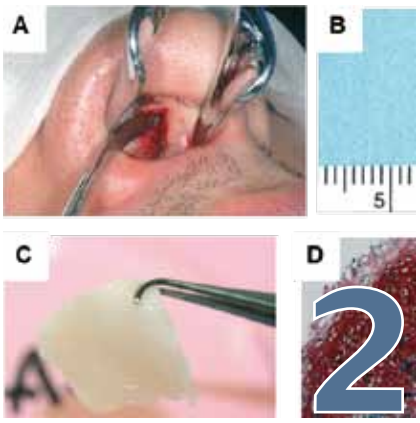

Tissue Engineering: From 3D culture models to regenerative medicine
from Ivan Martin

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UNI BASEL

EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Der Frühling ist die Zeit der Pläne, der Vorsätze. Auch die Mitarbeitenden des DBM haben sich Einiges vorgenommen und so Manches bereits umgesetzt:

Am 9. April fand der Tag der Biomedizin statt. Über 2000 Interessierte aus den umliegenden Kantonen und dem grenznahen Ausland kamen, um sich von den DBM-Forschungsgruppen in die Welt der Wissenschaft entführen zu lassen (siehe Seite 20).

Nicola Aceto und Eline Pecho-Vrieseling haben eine SNF-Förderprofessur erhalten. Nicola widmet sich in seinem Projekt den grundlegenden molekularen Mechanismen, die der Entstehung von Krebsmetastasen zugrunde liegen, mit einem besonderen Schwerpunkt auf der Analyse von zirkulierenden Tumorzell-Clustern beim Menschen. Zusätzlich zur SNF Professur erhielt er letztes Jahr auch einen renommierten ERC Starting Grant. Eline untersucht in ihrem Projekt am Beispiel der Huntington-Krankheit die Rolle von falsch gefalteten Proteinen. Ähnliche Vorgänge kann man auch bei anderen neurodegenerativen Erkrankungen – etwa der Alzheimer-Krankheit – finden. Das DBM wünscht beiden viel Erfolg!

Ivan Martin, Leiter der Forschungsgruppe "Tissue Engineering", koordiniert das EU-Projekt "BIO-CHIP", das vom EU-Förderprogramm Horizon 2020 mit insgesamt 5.1 Millionen Euro unterstützt wird. Sieben Institutionen aus der Schweiz, Deutschland, Italien und Kroatien sind daran beteiligt. Mehr über seine Forschung erfahren Sie ab Seite 2.

Wie vielseitig das DBM ist, zeigt Magdalena Müller-Gerbl in ihrem Artikel über das Anatomische Museum (Seite 16) und Rainer Gosert, der uns an den alltäglichen Herausforderungen im Dienstleistungsbereich der Medizinischen Mikrobiologie teilhaben lässt (Seite 10). Die aktuellsten Publikationen aus dem DBM folgen ab Seite 22.

Mit Zeinab Barekati können wir das iranische Neujahrsfest feiern (Seite 34) und Mathias Schmaler nimmt uns mit in seine Heimatstadt Berlin (Seite 38). Und noch vieles andere mehr erwartet Sie in der neuesten Ausgabe. Viel Spass bei der Lektüre!

Dear Readers

Spring is the time for plans and new resolutions. Even the employees of the DBM have taken this to heart and have started to make many changes:

The "Tag der Biomedizin" took place on the 9th of April. More than 2000 interested individuals from the surrounding cantons and the neighbouring countries came to be introduced to the world of science by the DBM research groups (see page 20).

Nicola Aceto and Eline Pecho-Vrieseling have both received SNF professorships. Nicola has applied himself to his research on the fundamental molecular mechanisms that drive the formation of cancer metastasis, with particular focus on the analysis of circulating tumor cell clusters in humans. In addition to his SNF professorship he also received a renowned ERC Starting Grant. Eline's research investigates the role of misfolded proteins in Huntington's Disease. Similar findings have also been made in respect of other neurodegenerative diseases such as Alzheimer's. We at the DBM wish them both every success!

Ivan Martin, leader of the research group "Tissue Engineering", is coordinating the EU-Project BIO-CHIP which is being funded by the EU Framework Programme Horizon 2020 for a total of 5.1 Million Euro. Seven institutions from Switzerland, Germany, Italy and Croatia are taking part in the project. You can read more about Ivan's research from page 2.

The versatility of the DBM is highlighted by Magdalena Müller-Gerbl in her article on the Anatomical Museum (page 16) and by Rainer Gosert who lets us take a look at the daily challenges incurred by the services sector of medical microbiology (page 10). The latest publications from the DBM can be found from page 22 onward.

We celebrate the Iranian new year with Zeinab Barekati (page 34) and Mathias Schmaler introduces us to his hometown, Berlin (page 38). All that and more awaits you in this latest edition.
Happy reading!

Tissue Engineering:From 3D culture models to regenerative medicine

The Tissue Engineering group was started in 1999 as an initiative of the surgical units at the University Hospital Basel, coordinated by the recently retired Prof. Michael Heberer and with the goal to develop biological cartilage implants based on adult human cells. The program was initially strictly focused, as required by fact that only 4 working hands were available in the lab, namely those of a young assistant surgeon (now Prof. Marcel Jakob, head of trauma and orthopaedic surgery) and mine (yes, I could indeed handle a pipetboy). The first successful SNF and European grant applications, the collaboration with newly established surgical professorships with strong interest in regenerative medicine (Prof. Dirk Schaefer, Prof. Hans-Florian Zeilhofer, Prof. Stefan Schären) and the embedding in the positively developing DBM, enabled a progressive consolidation of the group and extension to new research areas. This short and hopefully "light" article will describe the current scientific and translational programs of the Tissue Engineering group, and provide a few hints on the structural and functional organization of a team now including approximately 30 people (Figure 1).

Figure 1: The Tissue Engineering group in February 2016

Objectives and organization of the group

The common denominator of the research projects in the group is related to the establishment of 3D cell culture systems, combining interdisciplinary efforts in cell biology, engineering technologies and materials science. These systems are used as models to investigate fundamental aspects of tissue development, and as grafts to induce tissue regeneration. Several collaborative programs have been established within the DBM to employ the developed tools for 3D culture of tumor cells (Prof. Giulio Spagnoli, Prof. Gandomenica Iezzi), endothelial cells (PD Dr. Andrea Banfi), thymic epithelial cells (Prof. Georg Holländer), glial cells (Prof. Raphael Guzman), pluripotent stem cells (Prof. Christian De Geyter) and cardiac cells (PD Dr. Anna Marsano). However, our main focus has been maintained around the development of cartilage and bone tissues, including bone marrow. Figure 2 illustrates in a simplified way the priority research programs, the areas embedding our scientific questions and translational targets, and the horizontal platforms, necessary to provide the engineering background to the different fields and the regulatory perspective for clinical translation. The latter platforms are those linking the group with its secondary affiliations within the Medical

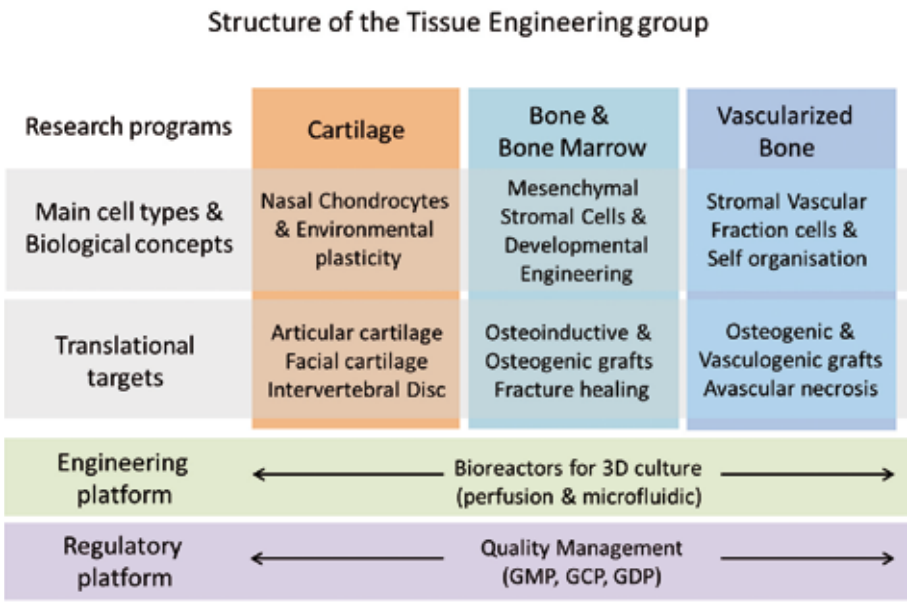

Figure 2: Schematic representation of the research programs of the group and of their structural organization

Faculty, namely the Department of Biomedical Engineering (DBE) and the Department of Clinical Research (DKF), respectively. A tight interaction with the clinic has been pivotal for the development of the group; more than 20 trained surgeons (Figure 3) have worked in the past years full time in the lab. Thanks to their professional development after their time in research, they have enabled clinical translation of our concepts and strategies. The variety of topics and the size of the group can now only be managed thanks to the professional help of staff scientists employed in the group on a stable basis, coordinating the cartilage-related projects (PD Dr. Andrea Barbero), the bone-related projects (PD Dr. Arnaud Scherberich), the engineering technologies (Dr. David Wendt) and the regulatory aspects (Dr. Sylvie Miot and Anke Wixmerten). The following sections have been sketched by these "scientific pillars" and are meant to provide a flavor of the different targets / questions currently addressed.

Nasal chondrocytes and environmental plasticity (A. Barbero)

The reproducible and durable repair of articular cartilage following traumatic injuries is still an unmet clinical need. The most advanced cell-based therapies are based on the use of autologous chondrocytes harvested from the damaged joint, which display a large and uncontrollable inter- and intra-donor variability. We have been first to identify that chondrocytes from the nasal septum, as compared to those from articular cartilage, have a superior and more reproducible chondrogenic capacity following in vitro expansion, in addition to being available in an autologous setting, under minimally invasive conditions. The possibility of generating cartilage tissues from nasal chondrocytes (Figure 4) has inspired plastic surgeons to use the materials as autologous grafts for the reconstruction of the alar lobule of the nose after skin tumor resection, a procedure for which normally cartilage from ears, ribs or large parts of the nasal septum from the same patient would be used. The results of a first-in-man clinical trial (Clinical-trials.gov NCT 01242618, Swissmedic TpP-I-2010-002) have demonstrated that the engineered grafts could satisfy structural, functional and aesthetic needs, bypassing additional morbidity of native cartilage tissue harvest (1). These results are now opening the way to implementation into more challenging and larger facial defects.

But going back to the original clinical target, are nasal chondrocyte-derived grafts compatible with implantation in a joint? After demonstrating that nasal chondrocytes can respond to physical forces resembling joint loading and can recover after exposure to the inflammatory factors typical of joint injury, we addressed their genetic compatibility with an articular cartilage environment. We found that nasal chondrocytes – of neural crest origin – display a distinct profile of HOX gene expression from articular chondrocytes – of mesoderm origin –, independently of their in vitro manipulation. However, upon implantation in a joint, they can be reprogrammed by the recipient site and acquire the HOX "signature" typical of articular chondrocytes (2). These results have led to pre-clinical goat studies and ultimately to the treatment of 17 patients with traumatic cartilage injuries in the knee (Clinical-trials.gov NCT01605201, Swissmedic TpP-I-2012-001). Clinical

Figure 3: The clinical partners of the Tissue Engineering group in February 2016

outcomes still need to be consolidated at longer terms, but assessments by MRI (stability, integrity and quality of the grafts and repair tissue) and improvements in the clinical scores assessed by the patient are highly promising. These studies have also been instrumental to receive funding within the Horizon2020 program of a phase II clinical study, which is coordinated by our team and will include treatment of a total of 108 patients (Project BIO-CHIP, http://biochip-h2020.eu). In parallel, pre-clinical studies are ongoing to test the feasibility of the procedure for the treatment of more challenging indications, with features typically associated with osteoarthritic degeneration.

Bone, Bone marrow and Vascularized bone (A. Scherberich with A. Todorov)

The golden standard for the treatment of critical bone defects is the use of autologous bone, typically harvested from the iliac crest, which is associated with large morbidity at the donor site. Mesenchymal stromal/stem cells from the bone marrow have previously been proposed to generate osteogenic grafts as a surrogate of autologous bone, but the efficiency and reproducibility of the procedure has not yet been convincing. The working hypothesis of the group is that the robustness of bone formation by engineered tissues could be increased if these could mimic processes typical of bone embryonic development. The strategy has brought, in collaboration with the team of Prof. Rolf Zeller, to the generation of intermediate templates consisting of hypertrophic cartilage that – upon in vivo implantation – have the capacity to autonomously remodel into bone tissue and thereby recapitulate the events occurring during endochondral ossification (3). Remarkably, the same processes can be triggered by the same tissues if suitably decellularized, thus highlighting a pivotal role of extracellular matrices embedding the cocktail of factors necessary and sufficient to prime regenerative processes (4). Moreover, the bone organ developed by this approach is capable to host fully functional hematopoietic stem cells (5) and is thus being investigated in collaboration with the groups of Prof. Radek Skoda and Prof. Claudia Lengerke as a humanized environment to study the interaction of leukemic cells with a 3D stromal niche (6).

Mesenchymal stromal cells are also found within the Stromal Vascular Fraction (SVF) of adipose tissue, in conjunction with endothelial lineage cells. The demonstrated capacity of these different cell types to self-assemble into osteogenic and vasculogenic structures upon ectopic or orthotopic implantation (7) represents an opportunity for the engineering of osteogenic and simultaneously vasculogenic grafts to enhance fracture healing. Given the abundance of this cellular material, these grafts can be manufactured without cell expansion or in vitro culture, thus in a mode which is compatible with intra-operative procedures. This concept has led to the clinical treatment of 8 elderly individuals with osteoporotic fractures in the humerus (ClinicalTrials.gov NCT01532076), where the standard procedure of plate fixation has been augmented by the implantation of SVF-based grafts generated during the operation (Figure 5). Despite the limited number of patients, biopsies taken at the repair site upon plate removal indicate the formation of de novo bone tissue throughout the implant site, as opposed to osteoconduction from the

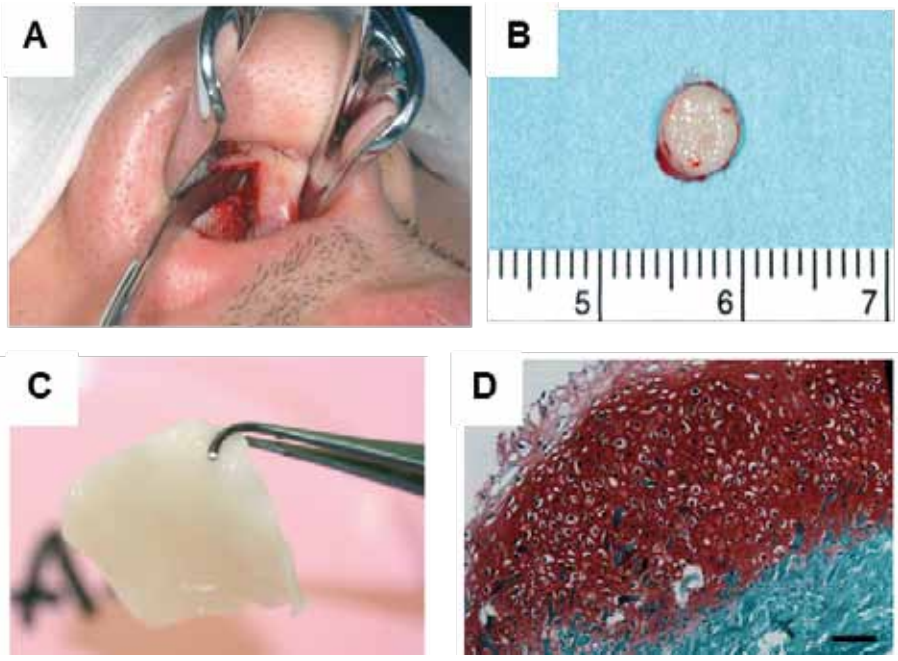

Figure 4: Engineering of autologous nasal cartilage grafts. (A) Collection of a nasal cartilage biopsy from a patient, this procedure is performed under local anaesthesia and results in minimal donor site morbidity. (B) Biopsy of nasal cartilage septum. (C-D) Tissue engineered cartilage graft: macroscopic (C) and histological appearance (Safranin-O staining specific for sulfated glycosaminoglycans (D).

existing bone, thus strongly suggesting osteogenesis by the grafted cells. Studies are ongoing to combine the strategy of engineered and decellularized matrices presented in the previous section with the use of SVF cells to intraoperatively "re-activate" such constructs in order to enhance bone and vascular development.

Engineering platforms (D. Wendt)

Conventional 2D culture systems (Petri dishes, culture flasks) cannot adequately recapitulate the complex microenvironment experienced by cells in vivo. 3D model systems, which mimic specific aspects of this microenvironment, are vital to gain a greater understanding of basic cell and tissue functions within the native milieu. However, challenges in biology and engineering have to be overcome to establish and maintain cells in 3D, predominantly because – unable to vascularize – tissues in vitro have to be supplied with oxygen and nutrients in a different way. We have pioneered the use of direct perfusion of fluid through the matrix of engineered tissues to mimic interstitial fluid flow within custom-designed bioreactor systems in order to generate uniform tissue structures (Figure 6A). More recently, we have also validated a microfluidic system allowing the spontaneous formation of 3D cellular structures and their exposure to different combinations and concentrations of regulatory molecules. The system is in use to investigate in a relatively higher throughput the signals supporting the growth and differentiation of mesenchymal progenitors (8) (Figure 6B).

Despite the compelling clinical need, advances in the field of tissue engineering have yet to result in viable products with widespread therapeutic adoption. Among the challenges to be addressed, overcoming manufacturing-related limitations will be key for a successful translation. Since the production of tissue grafts is typically based on conventional manual cell and tissue culture techniques, these labor-intensive processes are challenging to standardize, difficult to scale-up, and incur high costs in the long-term. While the clinical trials conducted by our laboratory have demonstrated the safety, feasibility, and preliminary evidence of the efficacy of functional cartilage tissue grafts, the manufacturing processes used to produce the engineered tissues will ultimately pose significant regulatory and economic challenges for routine clinical practice. Bioreactors have the potential to overcome the limitations of manual

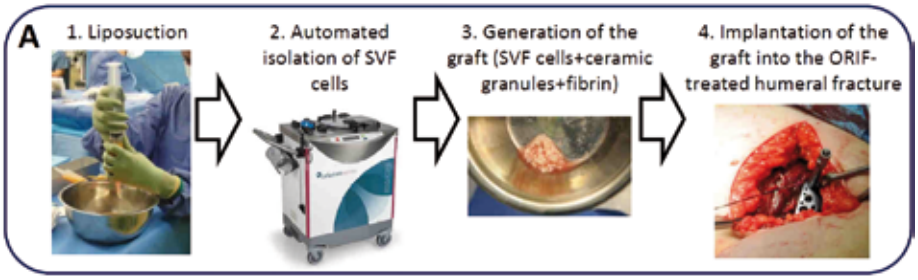

Figure 5: Intraoperative engineering of autologous Stromal Vascular Fraction-based grafts for the clinical treatment of humerus fractures in osteoporotic individuals

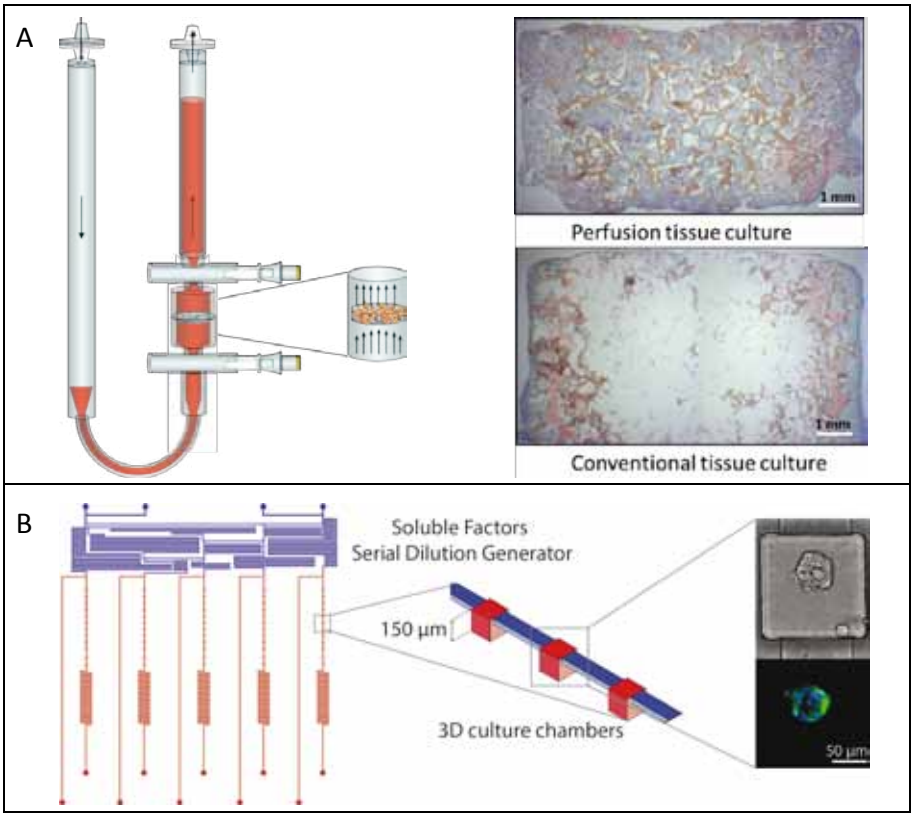

Figure 6: (A) Direct perfusion system to support efficient cell seeding into 3D porous scaffolds and uniform in vitro tissue development. (B) Microfluidic-based system to allow high-throughput test of compounds within culture chambers, where cells can organize into microtissues and monitored by fluorescence microscopy online.

manufacturing methods by: i.) providing a controlled physico-chemical culture environment that tightly regulates the bioprocesses, minimizing process and product variability, ii.) including non-invasive sensor-based monitoring which offer a high level of traceability and facilitate compliance to regulatory guidelines, and iii.) automating the various bioprocesses to standardize production methods and maximize prospective scale-up and cost-effectiveness in the long-term (9). Based on the solid foundation established by the past work in the group, we now aim to conduct a Phase I clinical trial based on cartilage grafts produced in a streamlined bioreactor system within the DBM GMP facility. This clinical trial will provide an unprecedented proof-of-concept of bioreactor-based, fully streamlined manufacturing of an engineered tissue for clinical use.

A crucial step to industrialize the 3D perfusion culture model described above, as well as to develop a clinical-grade system for the engineering of implantable cellular grafts, was the founding of the lab's spin-off company Cellec Biotek AG (www.cellecbiotek.com).

Regulatory platform
(S. Miot, A. Wixmerten)

From a regulatory standpoint, Tissue Engineered Products belong to a recently developed, new category of medicinal products, the Advanced Therapy Medicinal Products (ATMPs). Manufacturing and use of these products require the establishment of a Quality Management System, regulating processes in compliance with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and Good Distribution Practice (GDP). For us as experienced basic and pre-clinical researchers, entering the new field of clinical trials and subsequent regulatory aspects was comparable to a jump in at the deep end. Fortunately we could benefit from the knowledge of the colleagues at the Hospital Pharmacy to establish a quality management system, including a document management system and several folders of SOPs (Standard operating procedures) for the GMP-compliant production of grafts. We quickly discovered that the translation from lab protocol to SOP includes not only a change in format and addition of detail, but also the need to use different reagents (GMP-grade, for human use and not derived from animals) and to document every procedural step in manufacturing protocols. Furthermore, the personnel had to adapt to working in a clean room, which requires extensive protective clothing and monitoring of the environmental conditions. Following further efforts to formally document the design and course of the trial (study protocol), manufacturing and characteristics of the medicinal product (Investigator's brochure, Investigational medicinal product dossier) as well as data collection (Case Report Form, database) and Patient documents (Patient information and informed consent), we received approval by the ethical committee (EKNZ) and Swissmedic to carry out clinical studies and manufac-

ture cell-based transplant products in the established infrastructure (now managed in tight cooperation with PD Dr. Werner Krenger, head of the DBM-GMP facility).

A conclusive, personal note from a PhD student (S. Pigeot)

How is life in the Tissue Engineering Group? How can I capture the main impressions of being part of this team? The management of the group is obviously challenging, due to the large size and diversity of topics investigated. But the established structure and coordinated efforts by Ivan and the senior scientists allow efficient and frequent interactions, such that I feel well supervised while maintaining my independence and responsibilities. What I find of high value are the daily "after lunch meetings" which in rotation Ivan has with each of the group members, and which give us the opportunity to periodically assess our progress and ensure a general cohesion between the different project lines. The scientific interactions within the lab are stimulated in our "Progress report" series, where every week a member of the group presents the own results and/or plans to the rest of the team, and in the "Regenerative medicine journal club", which is organized every two weeks with the goal to get inspired by outstanding achievements by other groups. On a more practical standpoint, the working organization also needs to be well orchestrated and all the lab members obviously need to help out. In addition to the work carried out by Francine Wolf and Sandra Feliciano, our technical assistants, each group member is responsible for a few tasks in the lab such as general ordering, preparing general aliquots, buffers, etc. Teams are generated to clean the cell culture rooms weekly and the incubators monthly. It goes without saying that such an organization sometimes incurs into implementation challenges, but overall the spirit of mutual assistance prevails and the daily life in the lab carries on in a friendly and enjoyable atmosphere.

Ivan Martin

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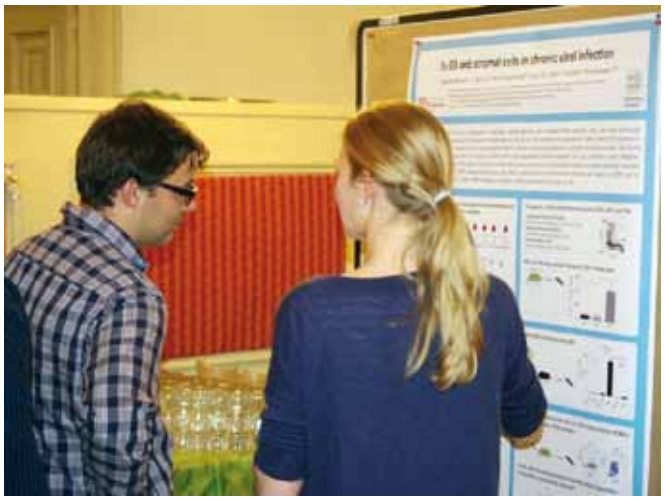
UniBasel immunologists retreat to the mountains



The immunologists at the University of Basel have organized themselves into a community, which fosters scientific exchange and collaborations. The UniBasel Immunology Community (UBICO) was formed in the spring of 2014 and is comprised of basic scientists and clinicians with a research focus in Immunology. The UBICO grew out of the Immunology Schwerpunkt at the DBM, but additionally includes scientists at the Biocenter, UKBB and the BSSE. The UBICO is generously supported by the DBM and the Departments of Internal Medicine and Surgery at the USB. Major activities include a well-attended weekly research seminar and a seminar series where distinguished immunologists from around the world are invited to Basel to present their work and interact with UBICO Faculty members. Immunology PhD students organize a Journal Club where a paper from the visiting immunologist's lab is informally discussed. Discussions between the PhD students and the visiting immunologists have been very lively.

Additionally, the UBICO sponsors a research meeting exclusively for PhD students where they present and discuss their work. The "Basler Studienstiftung" also sponsors UBICO activities for promoting the education of young MD and PhD students in Immunology.

We had our first retreat in Engelberg on November 2-3, 2015. On an early Monday morning 100 students, postdocs and faculty began their journey to the conference site – Hotel Edelweiss, a very cozy and charming ho-

tel in Engelberg built in 1901 in the middle of "Angel Mountains". Susanne and Peter Kuhn, the owners of the hotel, welcomed us with an extraordinarily warm and personal hospitality. Everything was perfectly organized and the hotel was technically well equipped. Our scientific program with oral presentations started shortly after our arrival and ended the next day in the afternoon. The program covered basic concepts, models and technologies, recent news from genes to proteins regulating development and effect functions of immune cells and translation into therapies. After an UBICO group leader meeting on the first day, we had a poster session with an apero until late in the night. Twenty-four research

groups presented their work and the atmosphere was very interactive and friendly.

Daniela Finke

Feedback from the students:

"I found it extremely useful both in terms of getting myself in-depth information about novel technical approaches in immunology and as well in interacting with experienced clinical and non-clinical immunologist."

"I learned the main topics of each group in Basel, which gave me the opportunity to think about possible collaborations or even the available equipment we have in the city. I also could train my networking with not only other PhD students but also Postdocs and PIs (which I find useful for future career). As I was presenting the poster I got many useful comments and advices on how to proceed my project not only from scientific point of view but also tips on my protocols which I'm trying to improve."

"The presentations and poster session were full of unbiased interaction between all participants, regardless whether they are students or professors. Definitely the retreat enhanced the cohesion of our growing Uni Basel Immunology Community and I think it would be a great success to enforce such kind of retreat once a year."

Auszeichnungen

Bürgi-Preis an Anna Rickli

Anna Rickli von der Forchungsgruppe Psychopharmacology Research (Departement Biomedizin Hebelstrasse) wurde während der Tagung der Schweizerischen Gesellschaft für Pharmakologie und Toxikologie mit dem Bürgi-Preis ausgezeichnet. Der Bürgi-Preis wird alle zwei Jahre für die beste Dissertation mit pharmakologischem Inhalt innerhalb der Schweiz verliehen.

Anouk Blatter hat für ihre Diplomarbeit "Kritisches Hinterfragen des aktuellen Immunflureszenztests für Flaviviren" in der Forschungsgruppe "Molecular Virology" (Departement Biomedizin Petersplatz) von der Schweizerischen Union für Labormedizin die Auszeichnung für die beste Arbeit erhalten.

Das DBM gratuliert ganz herzlich!

Von Armbrustschützen zum Virennachweis: Die Abteilung Infektionsdiagnostik im ehemaligen Stachelschützenhaus

Im 16. Jahrhundert beherbergte das Stachelschützenhaus mit den städtischen Armbrustschützen, deren Aufgabe es war, die Stadt zu verteidigen, wenig akademisches Personal. Dies änderte sich Anfang des 18. Jahrhunderts, als Bernoulli im neugebauten Südflügel, dem „physikalischen laboratorio", seine Experimente durchführte. Schließlich fand im 20. Jahrhundert die neugegründete Hygienische Anstalt ihr Zuhause am Petersplatz.

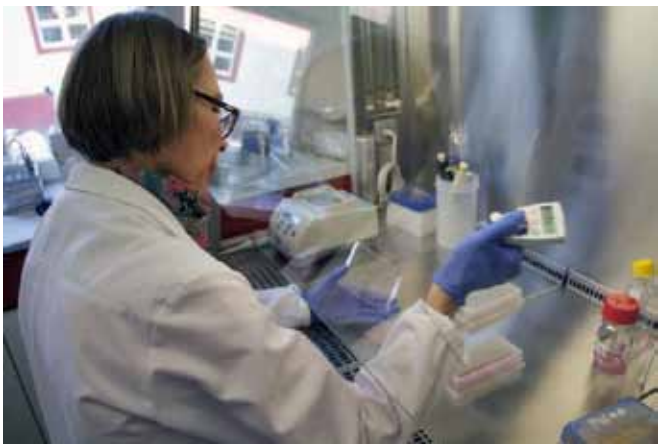
Heute bietet das Haus Petersplatz Raum für mehrere Forschungsgruppen des Departements Biomedizin (DBM) der Universität Basel sowie für die Abteilung Infektionsdiagnostik (AbtID). Die AbtID besteht aus vier Labors, der Molekularen Diagnostik, Serologie, Genotypisierung und Resistenz sowie dem Labor Virusisolierung, welche für das Universitätsspital Basel (USB), das Universitätskinderspital beider Basel (UKBB) und weitere Spitäler und Arztpraxen in der Nordwestschweiz Analysen durchführen. Die AbtID ist gemäß QM (Qualitätsmanagement) nach ISO/IEC 17025 zertifiziert und dies seit 1999, daher gilt sie als eines der ersten Diagnostiklabors der Schweiz. Darüber hinaus beherbergt die AbtID das Bestätigungslabor für HIV/AIDS Diagnosen und das Nationale WHO-Referenzlabor für Poliomyelitis. Das Leitbild der AbtID sieht den Patienten im Mittelpunkt ihrer Tätigkeiten. Dies wird durch eine breite Angebotspalette, dem Einsatz neuester Untersuchungsmethoden, einer schnellen Resultatübermittlung und qualitativ hochstehender Beratung erreicht. In der AbtID werden jährlich ca. 35'000 Analysen durchgeführt, wovon etwa knapp zwei Drittel aus dem USB eingehen. Im vorliegenden Beitrag möchte ich Sie zu einer kurzen Reise durch die verschiedenen Labors der AbtID einladen.

Ein nicht ganz alltäglicher Fall der AbtID

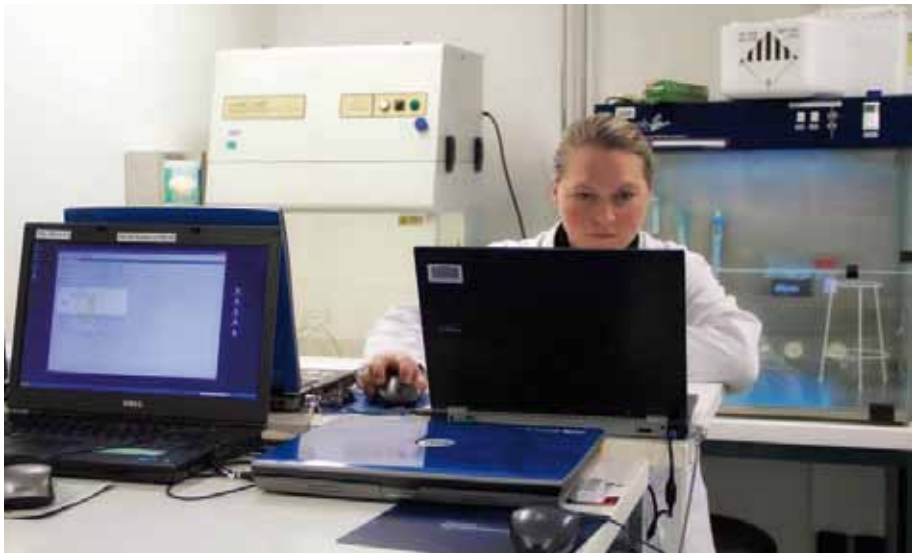
David stellt sich im Notfall des USB mit Kopfschmerzen, Müdigkeit, Schwindel, trockenem Mund und Diarrhoe (Durchfall) vor. Er verneint Antibiotikaeinnahme und extensiven Alkoholkonsum, welche zu einer Diarrhoe führen können. Da er im Moment seinen Militärdienst ableistet und somit engem menschlichen Kontakt ausgesetzt ist, kommen Adenoviren als Auslöser der Diarrhoe in Frage und eine Stuhlprobe geht zur Abklärung ins Labor Virusisolierung (LabVI) am Haus Petersplatz.

Stuhlproben sind aufgrund enthaltener Inhibitoren und unterschiedlicher Konsistenz ein eher problematisches Material. Davids Stuhlprobe wird aufgeschwemmt, d. h. eine definierte Menge wird in einen Puffer überführt, suspendiert und zur Abtrennung der festen Bestandteile zentrifugiert. Nach der Aufarbeitung wird im LabVI innerhalb von 15 min ein Schnelltest auf Adeno- und Rotaviren durchgeführt, der negativ ausfällt.

Da mit dem Schnelltest kein Erreger in Davids Probe identifiziert werden konnte, wird die Suche auf weitere gastroenteritische Erreger ausgedehnt. Dazu verwendet das LabVI das xTAG Gastrointestinal Pathogen Panel (GPP), eine Next-Generation Multiplex Analyse basierend auf Bead-Technologie, die gleichzeitig 15 der wichtigsten Pathogene (Viren, Bakterien und Parasiten) nachweist und das Resultat innerhalb 4 Stunden nach Extraktion der Probe liefert. Damit ist der Laborleiter



Beatrice Hess, Labor Virusisolierung, beim Pipettieren der Zellen für einen Neutralisationstest.



Rita Reuter, Labor Molekulare Diagnostik, bei der Auswertung einer Real-Time PCR.

in der Lage gleichentags den behandelnden Arzt telefonisch über ein positives Resultat zu informieren. Das LabVI kann in Davids Stuhlprobe keinen gastroenteritischen Erreger nachweisen.

Neben den beschriebenen Techniken führt das LabVI Virusisolierungen durch. Diese sind geeignet, wenn es sich um relativ rasch wachsende, lytische Viren handelt. Das Probenmaterial wird auf Zellkulturen gegeben und die im Material enthaltenen Viren infizieren die Zellen und vermehren sich. Die massenhafte Vermehrung verursacht einen sogenannten cytopathischen Effekt (CPE), ein Abrunden und Absterben der infizierten Wirtszellen, der mikroskopisch beobachtet werden kann. Die Virusisolierung hat den Vorteil, dass infektiöse Partikel nachgewiesen werden und gilt deshalb als Goldstandard. Allerdings ist eine nachgeschaltete Analyse, z. B. in Form einer Immunfluoreszenz mit spezifischen, markierten Antikörpern (AK), zur genauen Identifizierung des Virusisolats nötig. Auf diese Weise werden im LabVI Herpes-Simplex-Virus 1/2 (HSV 1/2), Cytomegalievirus (CMV), Varizella-Zoster-Virus (VZV), Adenovirus, Enteroviren, Influenzaviren und Respiratory Syncytial Virus (RSV) identifiziert.

Aktuell läuft auch ein Projekt zur routinemäßigen HSV 1/2 Resistenztestung für antivirale Substanzen wie Aciclovir mittels automatisierter Interpretation des CPE. Diese Innovation zeigt, dass trotz des Schwerpunkts auf molekulare Verfahren, bestimmte phänotypische Tests weiterhin sinnvoll sein können.

Im LabVI ist außerdem das Nationale WHO-Referenzlabor für Poliomyelitis beheimatet. Entsprechend werden Stuhlproben aus der gesamten Schweiz auf Polioviren (PV) untersucht. Obwohl im Jahr 2015 mit bisher weltweit 74 Fällen an akuter schlaffer Lähmung (engl. Acute Flaccid Paralysis, AFP), verursacht durch Wild PV, ein Allzeittief erreicht wurde, hat die weltweite Überwachung der Poliomyelitis, durch die Flüchtlingskrise in Syrien, nichts an Brisanz eingebüßt. Noch im Jahr 2013 wurde Wild PV aus Pakistan nach Syrien eingeschleppt und es kam zu 23 Poliomyelitis Fällen. Bereits ein einzelner bestätigter Poliomyelitis-Fall in der Schweiz wäre wie ein Ausbruchsereignis einzustufen, da weniger als 1% der Infektionen unter dem Bild der AFP verlaufen.

Nach Rücksprache mit dem behandelnden Arzt wird nun eine Blutprobe von David ans Labor Molekulare Diagnostik (LabMD) zur weiteren Abklärung geschickt. Im LabMD wird Probenmaterial auf pathogene Erreger mittels Nukleinsäure-Amplifikations-Testung (NAT) oder auch Polymerase-Ketten-Reaktion (PCR) analysiert. Dazu wird DNA und RNA aus Vollblut, Plasma, Serum, Körperflüssigkeiten, Biopsien, Punktaten oder Liquor (Rückenmarks-Flüssigkeit) gewonnen und teilweise die direkt anschließende PCR-Reaktion pipettiert. Dieses Labor ist am meisten automatisiert und liefert die quantitativen Viruslast-Resultate für Humanes Immundefizienz Virus (HIV), Hepatitis B, Hepatitis C und CMV täglich mit Hilfe eines Vollautomaten. Analysen für andere Erreger (z. B. Epstein-Barr-Virus oder HSV 1/2) erfolgen auf Real-Time PCR Cyclern, welche in Echtzeit die Menge an vervielfältigter Nukleinsäure mittels Fluoreszenzsignal messen. Durch die parallele Analyse international definierter WHO-Quantifizierungs-Standards erlaubt das Verfahren eine Quantifizierung der Nukleinsäure in der Probe. Die einzelnen Schritte der Analyse sind räumlich getrennt um das Kontaminationsrisiko zu minimieren.

Das LabMD bietet neben Dengue- und Chikungunya- seit kurzem einen Zikavirus Nukleinsäurenachweis an.

Christine Bauer, Labor Genotypisierung/Resistenz, beim Ansetzen einer Sequenzier-PCR.

Zikavirus gehört zur Gattung der Flaviviren, deren Vertreter, durch Stechmücken übertragen, schwere Erkrankungen, wie hämorrhagische Fieber oder Infektionen des ZNS verursachen. Zikavirus, erstmals 1952 beim Menschen beschrieben, wurde bisher mit eher milden Krankheitsverläufen in Verbindung gebracht. Seit Ende 2015 besteht im Zusammenhang mit der aktuell in Lateinamerika laufenden Epidemie der Verdacht auf einen Zusammenhang zwischen Zikavirus-Infektionen bei Schwangeren und Mikrozephalie (signifikant verminderter Kopfumfang) bei Föten und Neugeborenen. Allerdings gibt es noch keine verlässlichen Daten über die Häufigkeit von Mikrozephalie in Lateinamerika vor der Zikavirus-Epidemie. Zudem wurde für andere virale Erreger, wie Rubellavirus (Erreger der Röteln) und CMV oder das Protozoon Toxoplasma gondii, ein Zusammenhang zwischen Mikrozephalie und Infektionen während der frühen Phase der Schwangerschaft erbracht. In der ersten Woche nach Symptombeginn, in der virämischen Phase, kann die RNA des Virus durch eine Zikavirus-spezifische Reverse-Transkriptase PCR (RT-PCR) im Blut nachgewiesen werden. Analysen auf andere Flaviviren, wie Dengue- oder das Alphavirus Chikungunyavirus, welche ähnliche Symptome verursachen können, sowie die Reiseanamnese, sollten in die Gesamtbeurteilung eingehen.

Um eine hohe analytische Sensitivität zu erreichen, muss vom Auftraggeber ausreichend Probenmaterial eingesandt werden. Dies ist öfter nicht der Fall bei Materialien, welche von Natur aus in geringen Mengen vorliegen, wie Vorderkammerpunktat oder Liquor. In solchen Fällen kontaktiert die LabortechnikerIn den Auftraggeber und klärt ab, ob zusätzliches Probenmaterial vorhanden ist. Wenn nicht, nimmt der Laborleiter Kontakt mit dem behandelnden Arzt auf. Er klärt im direkten Gespräch, ob eine Priorisierung der Analysen sinnvoll und machbar ist oder das Material verdünnt werden soll, was die analytische Sensitivität der Nachweismethode herabsetzt.

Bei respiratorischen Proben ist die Qualität des Materials von entscheidender Bedeutung. Respiratorische Erreger der unteren Atemwege lassen sich am besten aus broncheoalveolärer Lavage nachweisen, Erreger der oberen Atemwege hingegen werden in Nasen-, Rachenabstrich, Sputum oder Bronchialsekret detektiert. Neben Schnelltesten für Influenzaviren und RSV mit einer Bearbeitungszeit von nur 15–60 min, verwendet das LabMD für eine breitere Suche nach respiratorischen Erregern eine Next-Generation Multiplex Analyse, die auf Fluoreszenz-Bead-Technologie basiert und 96 Proben auf einmal analysieren kann. Der RPP detektiert gleichzeitig 22 respiratorische Erreger und liefert das Resultat innerhalb 3 Stunden nach Extraktion der Probe. Dies erlaubt dem Laborleiter den behandelnden Arzt gleichentags telefonisch über ein positives Resultat zu informieren und somit eine schnelle Isolierung des Patienten zu ermöglichen. Während der Influenza-Saison werden vom LabMD täglich bis zu 30 RPP-Analysen durchgeführt. Die wöchentlich aktualisierte Statistik für respiratorische Erreger ist unter www.zid.ch > Infektionsstatistik einsehbar.

Das LabMD findet in Davids Blutprobe 350'000 Kopien HIV pro mL. Die hohe Viruslast deutet auf eine HIV-Neuinfektion hin und muss mit Hilfe einer zweiten, unabhängigen Blutprobe bestätigt werden. Ein Bestätigungstest ist vom Gesetzgeber vorgeschrieben um eine falsch-positive Diagnose auszuschließen. Dazu wird vom USB eine neue Blutprobe Davids ans Labor Serologie (LabS) geschickt. Das LabS fungiert als HIV-Referenzlabor und erhält Aufträge zur HIV-Testung und -bestätigung aus der ganzen Schweiz.

Der Nachweis von Antigenen (Ag) erlaubt einerseits die Identifizierung von Ag-tragenden Krankheitserregern,

andererseits können durch den Nachweis bestimmter Antikörper (AK) im Blut Krankheiten diagnostiziert werden. Beim HIV-Bestätigungstest sind auf einer Trägermembran die unterschiedlichen HIV-Proteine (Ag) nebeneinander aufgebracht. Von der LabortechnikerIn wird Davids Serumprobe auf die Membran pipettiert. Sind AK gegen HIV vorhanden, heften sich diese an die Virusproteine auf dem Streifen. Nach weiteren Arbeitsschritten werden dunkle Striche auf dem Teststreifen sichtbar. Damit ist der Bestätigungstest positiv ausgefallen. Jetzt muss David darüber informiert werden, dass er HIV-1-positiv ist.

In der Schweiz nehmen die Fälle sexual übertragener Krankheiten seit einigen Jahren zu. Als Folge erhält das LabS viele Untersuchungen zum Nachweis von Treponema pallidum, dem Erreger der Lues (Syphilis). Da T. pallidum nur mit Spezialmethoden gezüchtet werden kann, kommt der Serologie eine besondere Bedeutung zu. Als Suchtest dient die Treponema-pallidum-Partikel-Agglutination (TPPA). Als Ag werden Lysate von T. pallidum verwendet, die an Gelatinepartikel gekoppelt sind. Sind AK im Serum vorhanden, reagieren sie mit den Ag der «beladenen» Gelatinepartikel und es kommt zur Verklumpung (Agglutination) der Partikel. Ein positives TPPA Resultat wird mit einem Bestätigungstest überprüft. Zur Beurteilung des Krankheitsverlaufs, bzw. Behandlungserfolges, wird die Reaktion des Serums mit unspezifischen Lipoid-Ak durch den RPR-Test (Rapid-Plasma-Reagin) benutzt.

In der Schweiz erkranken jährlich ca. 550 Menschen an Tuberkulose, wobei eine Verschiebung von älteren Schweizern zu jungen Migranten zu beobachten ist. Zum spezifischen Nachweis einer Infektion mit Mycobacterium tuberculosis verwendet die Serologie das Interferon-Gamma-Release Assay (IGRA). T-Lymphozyten des Patienten werden mit Ag von M. tuberculosis über Nacht stimuliert. Ist eine Infektion vorhanden, kann die Sekretion von Interferon-Gamma nachgewiesen werden. Als Testformate werden das Immunoassay (QuantiFERON-TB) oder der ELISPOT (T SPOT.TB) angeboten. Bei beiden Tests kann das Ergebnis bereits nach 1 Tag abgelesen und der behandelnde Arzt informiert werden, damit der Patient isoliert und eine Therapie eingeleitet werden kann.

Angelika Aebli, Labor Serologie, bei der Validierung der Masern / Mumps Serologie.

Im Jahr 2013 wurden schweizweit mehr als 22 Millionen Auslandsreisen unternommen. Entsprechend hoch ist die Zahl an Reiserückkehrern mit Verdacht auf tropische Erkrankungen. Von den Ärzten werden deshalb vermehrt Aufträge erteilt, Flavivirus-Serologien (Dengue-, West-Nil- und Zikavirus) durchzuführen. Seit März bietet das Haus Petersplatz eine Zikavirus-Serologie an.

David wird vom Arzt im USB darüber informiert, dass er eine HIV-Erkrankung hat. Der Arzt erklärt ihm, dass die von David beschriebenen Symptome und die Diarrhoe kompatibel mit einer HIV-1 Infektion sind. HIV-1 ist die Ursache für die Entstehung des Acquired Immune Deficiency Syndrome (AIDS). Das Virus schädigt das Immunsystem, da CD4 T-Helfer-Lymphozyten zerstört werden. Der Arzt wird David die Therapiemöglichkeiten erläutern. Bei einer wirksamen kombinierten antiretroviralen Therapie (cART) wird die Vermehrung von HIV-1 durch Medikamente unterdrückt und es ist kein Virus im Blut des Patienten nachweisbar. Steigt die Virusmenge im Verlauf der cART trotz Einhaltung der Medikation an, kann dies ein Hinweis auf eine Mutation des HIV-1 und damit auf eine Resistenz sein. Um zu klären, ob David sich bereits mit einem resistenten HIV-Stamm infiziert hat oder das Virus gegen die verschiedenen Medikamentenklassen empfindlich ist, wird der Arzt eine Resistenzbestimmung veranlassen. Dazu wird Davids Blut ans Labor Genotypisierung/Resistenz (LabGR) geschickt.

Im LabGR werden die Genabschnitte Protease, Reverse Transkriptase und Integrase der viralen RNA mit Hilfe der RT-PCR vermehrt und sequenziert. Die Nukleotidabfolge von Davids HIV-1 wird mit der Referenzsequenz in der SmartGene Datenbank abgeglichen, es erfolgt eine genotypische Resistenzbestimmung. Das HIV-1 in Davids Blut weist keine relevanten Punktmutationen auf und somit ist klar, dass kein resistentes HIV-1 übertragen wurde. In Davids Fall sollten alle Medikamentenklassen die Vermehrung von HIV-1 effizient unterdrücken. Als Spezialuntersuchung gilt die Bestimmung des HIV-1 Tropismus gegenüber der zellulären Rezeptoren CCR5 und CXCR4. Die Untersuchungen werden innerhalb weniger Tage vom LabGR durchgeführt und der Arzt erhält einen Bericht, der die Resistenz gegen die unterschiedlichen Medikamentenklassen übersichtlich graphisch darstellt.

CMV führt wie alle Herpesviren zu einer persistierenden Infektion. Unter Immunsuppression kann es zur Reaktivierung kommen und es können unterschiedliche Organmanifestationen auftreten. Bei Reaktivierung stehen dem Arzt effektive Medikamente zur Verfügung, deren Wirksamkeit durch das Auftreten von Resistenzen stark herabgesetzt werden kann. Die Mitarbeiter des LabGR suchen in so einem Fall nach Mutationen im UL97 (Phosphotransferase) und UL54 (DNA-Polymerase) Gen. Die Genotypisierung deckt Resistenzen gegen die Medikamente Ganciclovir, Foscarnet und Cidofovir ab, was dem Arzt erlaubt auf eine Alternativtherapie zu wechseln.

Fazit

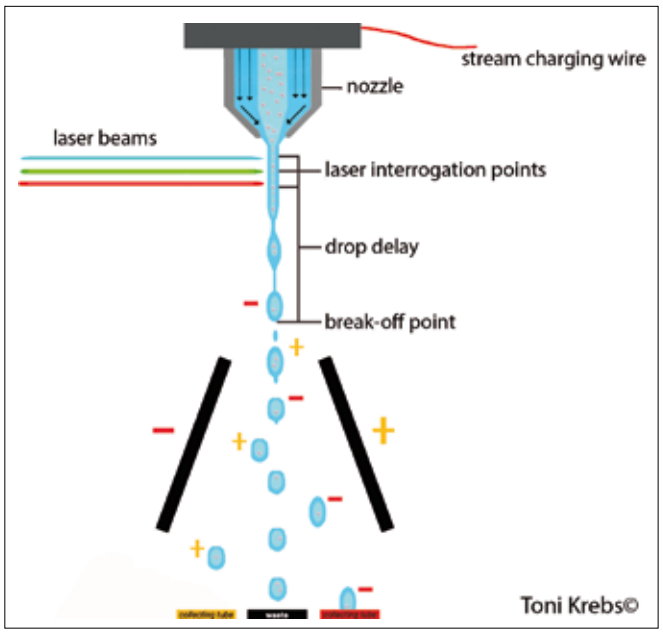
Die Arbeit in der AbtID ist spannend und dank der sich täglich mit der Klinik ändernden Herausforderungen durch die Auftraggeber sehr anspruchsvoll. Die Kombination von Routinediagnostik und Forschung, Entwicklung sowie Einführung neuer diagnostischer Tests erfordert flexible und interessierte Mitarbeiter, die in einem hochmotivierten Team gute Entfaltungsmöglichkeiten erhalten.

Rainer Gosert

Mitarbeiter der Abteilung Infektionsdiagnostik. Vordere Reihe (links nach rechts): Christel Widia, Anna Sophie Bahlmann (Assistentin), Klaudia Bagienski (Leiterin LabGR), Bettina Oettli, Zeliha Özkan, Hülya Atici, Sibylle Stauffer, Aline Weber, Frauke Mekolli; hintere Reihe (links nach rechts): Angelika Aebli, Christine Bauer, Rita Reuter, Sylvie Goepfert, Sasa Maksimovic, Rainer Gosert (Leiter LabVI und WHO Nationales Referenzlabor für Poliomyelitis), Hans H. Hirsch (Leiter AbtID), Thomas Klimkait (Stv Leiter AbtID, Leiter LabS)

SweetySpot-Software development in the DBM Flow Cytometry Facility for droplet based Cell Sorters

For years, BD Influx users have jealously been watching the user friendly BD Aria Diva Software with Sweet Spot software. Now my new software development for droplet-based cell sorters closes the gap because it can do the same as Sweet Spot but is now available for the BD Influx and BD FACS Jazz. In theory it could be used for every droplet-based cell sorter with a camera watching the break-off point and an accessible communication protocol. My software observes and automatically readjusts the break-off point by setting new values for the amplitude. Droplet based cell sorters work with liquid which is pressed through a nozzle with a specific diameter. Because of a transducer with a piezoelectric crystal that vibrates in a specific frequency, the pressed stream is broken up into single drops. This break-off point is very important and has to be stable through the whole time of sorting. Before sorting this break-off point has to be defined and the cell sorter calibrated. The operator has to calculate the time a particle needs from the measurement point to this break-off point, the so-called drop delay. Obviously this point needs to be stable during the sort because it defines which drop with your particle inside will be deflected and collected in a tube. But only if the drop delay was calculated correctly. Otherwise the charged drop is empty or a particle is inside you don't want to be sorted. You can see this process of building the break off point in picture 101.



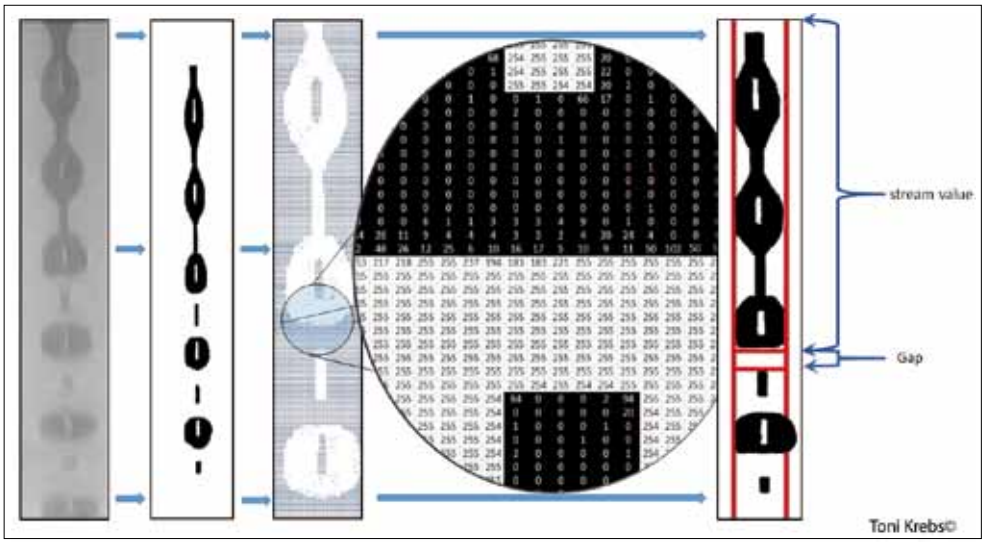
picture 101

How it works

A camera is used to observe the break off point. The images are captured as a so called array. (picture 102 from left first image). In the next step, the array image is transformed to an 8-bit greyscale image. The standard camera on the machine has a resolution about 640x480 pixels, so we have 307 200 pixels. Each pixel is represented in our greyscale image by an integer value in the range of 0 to 255 (8-bit deep greyscale image -->2^8=256 possible values, but we use only values between 0 to 255). Now we set a threshold to our grey image, so that we can more easily calculate where the break off point is. The library I use for thresholding has different methods and types for setting a threshold. To get the best result and an almost noise free image, I use adaptive thresholding but I implemented every type of the thresholding method so that the user can decide what is the best for their needs. You can see the threshold image in picture 102 (from left the second image). Thereby the values in the range of 0 to 255 are replaced with almost two possible values around 0 (black) and around 255 (white). In figure 102 (from left picture 3 and 4), I extracted the pixel intensity values from our threshold image and exported them to Microsoft Excel (picture 3) to make it more clear. Picture 4 shows a cut-out of the excel sheet after all values close to zero were marked black (picture 4). With the pixel intensity values of 0 and 255 from the threshold image it is easier to calculate where the break off point is. With my own search algorithmic with simple math, I can calculate the stream position and the gap between the stream position and the first satellite drop, which are the necessary values to keep the break-off point stable. You can see the final processed image in picture 102 from left, image 5. These two parameters are calculated for every camera frame (around 25–30 frames per second).

The advantages of SweetySpot

My Software is 100% written in Python. Python is one of the most powerful Programming languages because it is relative easy to read. Like Java, Python is an interpreter language which means that you don't have to compile your software for a specific operating system. The Python interpreter translates it to machine code. The interpreter is available for almost every operating system (Windows, Mac, Linux). SweetySpot is written completely in python for maximum flexibility and fast update. The key functions like image processing and calculation are written in C with python bindings for maximum perfor-



picture 102

mance. It is very comfortable because it works out of the box (possible in one folder or one file), meaning no software installation is necessary. Another great advantage is that my software is completely independent from the company operating software (for example the BD Sortware Software for the BD Influx Sorter). The purpose of this software is to keep the break off point stable and to protect your sample and collection tubes.

How to bring the Influx closer to state of the art?

Generally, the fluidics system of almost all Cell-Sorters can be operated through software. Unfortunately, with Influx it isn't possible. I did a little hardware modification to make it possible on our influx one. I installed a simple relay, connected it to the fluidic operating circuits of the influx and to a network (also allows connecting through Ethernet, w-lan, microcontroller, computer etc.). Now we have an influx with software which observes the break off point and automatically readjusts it by setting new values if the break-off point changes and with the hardware modification, we can additionally operate the fluidic system with SweetySpot. With the access to the fluidic system of the Influx it was also possible to program a "secure mode" in SweetySpot. My software recognizes a partial or full nozzle clock and tries to protect your sample and collection tubes. It automatically stops the fluidic main stream of the machine and changes the position of the WDU (robotic arm with holder of the collecting tubes) to avoid contamination of your collection tubes. At the same time, it stops the sample run to avoid losing any microliter of your sample. At the last step it could send an email or give a sms or a call to inform the operator that something went wrong. The future plan for it is to change two magnetic valves on the Influx, so that I can program an automatic fluidics system, such as automatic start-up, automatic debubbling, automatic washing steps and so on. But don't be afraid. Everything on the influx will stay original and untouched. For downgrading just disconnect the two tubing's and reconnect them to the originally installed valve.

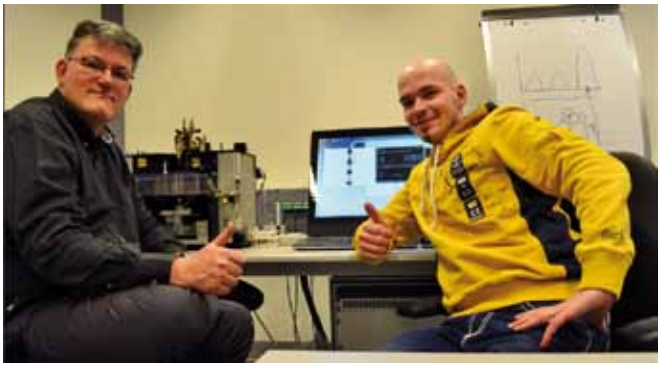
Don't forget, "In theory it could be used for every droplet-based cell sorter, not just the BD influx."

This year I was invited by BD to the European Technology Center in Heidelberg Germany. They gave me the possibility to test SweetySpot on the BD FACS Jazz cell sorter. It has been rumoured that BD produces software with this purpose for the Influx, but in Europe nobody has seen this software, even in Heidelberg. For me it would be very interesting to compare my Software with the Software from BD. But it's sure that the version from BD won't have a kind of "secure mode" that mine has and it's also sure that for the BD FACS Jazz cell sorter no software with this purpose exists from BD at the time of writing. (picture 103 from left to right) Dr Jens Fleischer and Toni Krebs after successfully testing SweetySpot on the FACS Jazz Cell Sorter from BD in Heidelberg.

To look ahead

In my opinion SweetySpot is a great development but there is no market for selling or licensing it. BD will come with his own version for the Influx. I hope I will get the ok to start an open source project under, probably the General Public Licence (GPL) or Berkeley Software Distribution (BDS) license and make it available for free, for everyone who wants to use it under the terms of the GPL/BDS. As long as I get the ok from the University Hospital, I will create a website with the source code, instruction to build the dependencies for SweetySpot and user manuals. There will also be information available about other projects in flow cytometry.

Toni Krebs



picture 103

The Anatomical Museum Basel

The Anatomical Museum of the University of Basel is one of the oldest museums specializing in human anatomy and enjoys international recognition for its historical and modern exhibits from experts and the general public alike. Valuable, unique anatomical preparations from the early days of modern natural sciences have survived until the present day.

Right through to the 19th century, anatomists and their collections made significant contributions to the advancement of medical science. Their preparations were similarly valuable for teaching and research, and their collections became key to acquiring new insights. Yet the collected items are not only significant historical monuments to the development of medical and natural sciences. As the German medical historian Thomas Schnalke so aptly stated, they are also among "the original objects of medical documentation and the practices of scientific observation, reflection, contestation, and publication derived thereof" and are thus "means of publication with their own merits and quality".

A journey beneath the skin

As part of the Faculty of Medicine, the Anatomical Museum – one of the official museums of the University of Basel – opens up a window onto the world of medicine. As a public museum, its numerous exhibitions depict the structure of the human body. In an age of increasing health awareness, it therefore provides factual information to all interested parties. In addition to the permanent exhibition, a journey beneath the skin before "coming back to life", special exhibitions are offered in collaboration with various clinics or other university institutions.

The alternating special exhibitions provide extra information on specific areas of the body in an easily accessible format. The latest findings on the structure and function of different organs and organ systems, such as the face, brain and back, stand side-by-side with developments in diagnosing and treating specific illness-

Entrance of the Anatomical Museum

es. Guided tours by experts allow the public to learn straight from the horse's mouth, and the museum offers workshops for children and young people, too. The Anatomical Museum also provides an extensive teaching collection that – divided into organ systems – is used for the training and further education of medical students and personnel.

Vesalius and the beginnings of the museum

The establishment of the museum and its further development are closely connected with the history of the Faculty of Medicine at the University of Basel and the field of anatomy. One milestone in the history of the anatomical collection was the time spent in Basel by the Flemish anatomist Andreas Vesalius (1514–1564). Many

Historical section: the oldest anatomical preparation of a skeleton, made by Andreas Vesalius

foreign scholars were drawn to the city in the 16th century by the flourishing art of printing, including Vesalius, who is considered to be the true founder of modern anatomy. By working on human corpses, he freed himself from ancient anatomy and studied the entire human body in minute detail. These findings formed the basis for his epochal work "De humani corporis fabrica", which was printed in Basel in 1543 by the renowned publisher and printer Johannes Oporinus. An original copy is displayed in the museum.

In order to oversee the printing of his work, Vesalius spent quite some time in Basel. On May 12, 1543, he held a "public anatomy", that is, the dissection of the corpse of an executed criminal. This lasted several days. With the help of the surgeon Franz Jeckelmann, Vesalius then joined the bones back together with wire and donated the preparation to the university. Today, this skeleton is considered to be the world's oldest anatomical preparation; it is preserved and displayed in the Anatomical Museum.

Platter, Jung, His

The Faculty of Medicine was further expanded by Felix Platter (1536–1614) who in 1571 was awarded a professorship in practical medicine and became a city physician. He prepared several skeletons, which he also bequeathed to the university. Unfortunately, these skeletons were damaged during the French Revolution and some parts were actually removed. The remaining pieces are displayed in the Anatomical Museum and are among the most valuable anatomical preparations in the entire world. Public anatomies had been taking place in Basel since 1570, with each audience member paying an entrance fee. These public dissections then stopped in the 18th century, and anatomy retreated back behind its walls.

In 1822, Carl Gustav Jung (1794–1864) came to Basel as Professor of Surgery, Anatomy, and Obstetrics. Two years after he arrived, the city council provided him with a loan, among other things, and granted him permission to set up an Anatomical Cabinet – the precursor to today's Anatomical Museum – in the "Unteres Kollegium" on the Rheinsprung. Under Jung's leadership, a variety of preparations and wax models were produced and a few years later, the Anatomical Cabinet became an actual museum, which even then was open for public viewings on Sundays.

The university's annual report for 1844 contains the following entry on visitor numbers to the Cabinet: "(…) and it was only with great effort that the curious onlookers could be held back during the time in which the establishment was closed". The Anatomical Museum still has in its possession valuable wax models from the period around 1850, including models demonstrating the nerves between the neck and head, the vegetative nerve supply to the internal organs, and a greatly enlarged model of the ear.

Look into the permanent exhibition

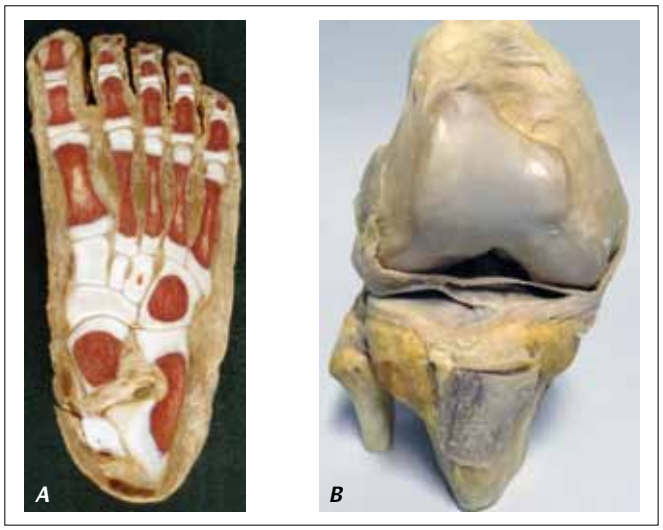
Kid's workshop «Brain»

Jung's predecessors also appreciated the museum as a valuable resource; they introduced new preparation methods and continually extended the collection. Wilhelm His (1831–1904), Professor of Anatomy and Physiology from 1857, significantly advanced understanding of antenatal morphogenesis and function development through his fundamental work in the field of embryology. The museum still possesses many valuable wax models of embryos in various stages of development, as well as some instruments and devices for producing wax plate reconstructions. His developed a process for producing a series of sectional views so that entire embryos could be reconstructed in plastic down to the very last detail.

Expansion and relocation

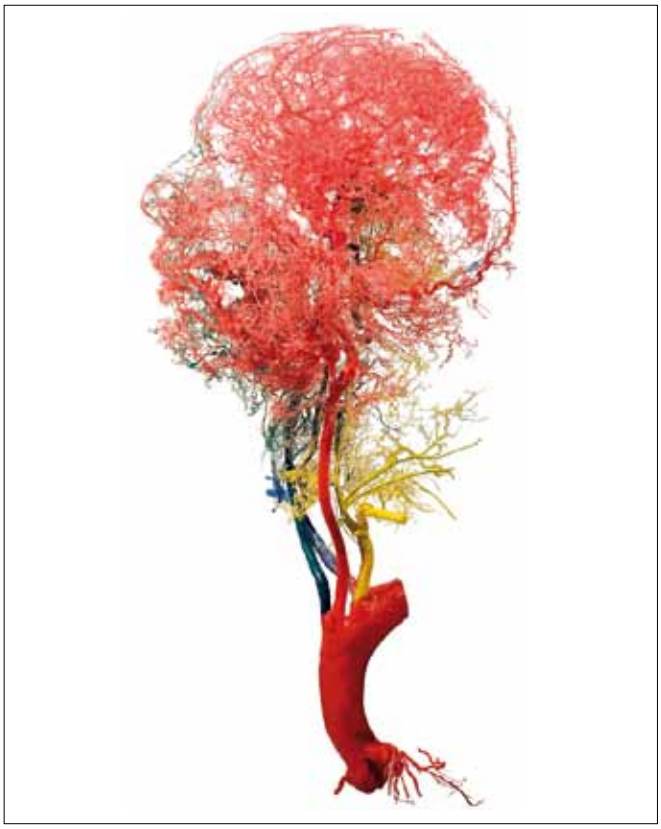
With space becoming ever scarcer and no further scope to expand the "Unteres Kollegium" on the Rheinsprung, the only option left was to relocate the anatomy department. From 1885 to 1921, the Anatomical Institute – together with the Physiological Institute in the Vesalianum building – was housed between the Petersplatz and Spalenvorstadt. The Anatomical Collection was stored partly in the basement and partly on the first floor. However, this building was soon bursting at the seams, as well.

It was under the direction of Professor Hanson Kelly Corning (1860–1951) that a new, separate building to house the Anatomical Collection was erected on Pestalozzi street and opened in 1921. In moving the collection to the new institute, Corning adhered to a principle in Austrian anatomical studies that differentiates between two types of collection: An "exhibition", which is open to the public on Sundays, and a "hands-on collection", which contains preparations primarily intended for use in lectures and courses. The Anatomical Museum was initially more of an archive, which is why a number of



A) Longitudinal section of the foot of a 4 year old child stained with alizarine red (white cartilage, red bone) .
B) Knee-joint from ventral (plastinated).

Skull of a six year old child with two sets of teeth. The outlines of the permanent teeth and the roots of the primary teeth are clearly visible

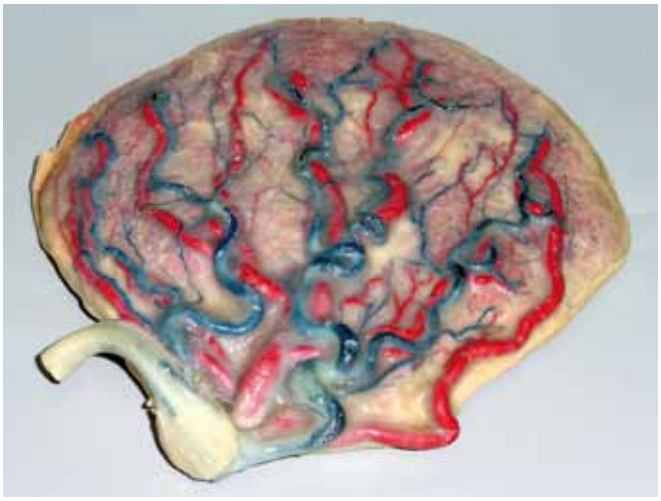


Corrosion preparation of the head: presentation of the arteries with coloured plastic, removal of any other structures by means of maceration.

preparations were stored in the previous style. This presentation style remained unchanged until 1978: The most valuable exhibits were displayed amid a range of less interesting preparations.

An educational redesign

In 1980, those responsible for the museum redesigned some sections of the exhibition by presenting individual exhibits and preparations of the musculoskeletal system in a new way. In 1985, the museum was opened for the second time once the internal organ, nervous system and embryology preparations had been arranged systematically in accordance with the latest museum and educational theories. Educational presentation was one of the most important aims of the redesign process. In addition to new display cases and exhibition walls, this also included systematic arrangement and informative preparations produced using modern techniques. As well as comprehensible and standardized labeling, it was important to provide additional captions, drawings, photographs, X-rays, and anything else that would significantly improve the informative value of the exhibits.



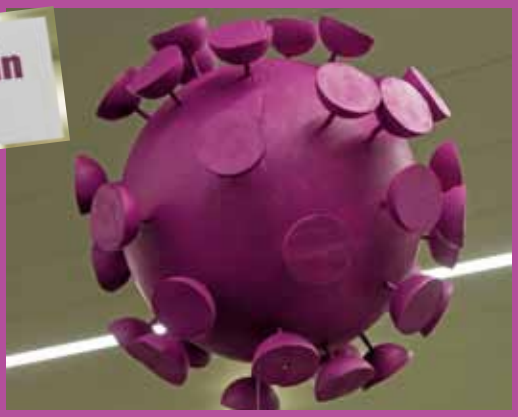
Placenta (vessels are injected with coloured plastic).

The new museum concept, the latest installation techniques, and the bold decision to bring in some color and make things more relaxed have reduced the grisly image often attributed to the Anatomical Collection. This is undoubtedly one of the reasons why increasing numbers of schools are bringing their pupils here to increase their understanding of biology. In 1995, an event was held to mark the opening of the renovated museum in the new educational facility of the Anatomical Institute and to celebrate the fact that it was once again open to the general public; its format remains more or less the same to this day. Exhibits concentrate predominantly on original preparations of human body parts, organs and tissue that are arranged systematically and topographically, as well as on antenatal human development. Valuable historical exhibits, for example key pieces of medical educational history, also form part of the museum and it continues to document the evolution of model production providing an historical overview of preparation techniques.

Magdalena Müller-Gerbl

Tag der Biomedizin

Samstag, 9. April 2016



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Modular composition and dynamics of native $GABA_B$ receptors identified by high-resolution proteomics

Jochen Schwenk[1,2,7], Enrique Pérez-Garci[3,7], Andy Schneider[1], Astrid Kollewe[1], Anne Gauthier-Kemper[4], Thorsten Fritzius[3], Adi Raveh[3], Margarita C Dinamarca[3], Alexander Hanuschkin[5], Wolfgang Bildl[1], Jürgen Klingauf[4], Martin Gassmann[3], Uwe Schulte[1,2,6], Bernhard Bettler[3] & Bernd Fakler[1,2]

$GABA_B$ receptors, the most abundant inhibitory G protein–coupled receptors in the mammalian brain, display pronounced diversity in functional properties, cellular signaling and subcellular distribution. We used high-resolution functional proteomics to identify the building blocks of these receptors in the rodent brain. Our analyses revealed that native $GABA_B$ receptors are macromolecular complexes with defined architecture, but marked diversity in subunit composition: the receptor core is assembled from $GABA_{B1a/b}$, $GABA_{B2}$, four KCTD proteins and a distinct set of G-protein subunits, whereas the receptor's periphery is mostly formed by transmembrane proteins of different classes. In particular, the periphery-forming constituents include signaling effectors, such as Cav2 and HCN channels, and the proteins AJAP1 and amyloid-β A4, both of which tightly associate with the sushi domains of $GABA_{B1a}$. Our results unravel the molecular diversity of $GABA_B$ receptors and their postnatal assembly dynamics and provide a roadmap for studying the cellular signaling of this inhibitory neurotransmitter receptor.

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Bidirectional GABAergic control of action potential firing in newborn hippocampal granule cells

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Newly generated young neurons in the adult hippocampus receive GABAergic synaptic inputs, which are crucial for activity-dependent survival and functional maturation between 1–3 weeks after mitosis. We found synaptically driven action potential (AP) firing in these newborn young cells in adult mice. Although glutamatergic synaptic inputs remained subthreshold, activation of GABAergic synaptic inputs depolarized young neurons and reliably evoked APs. Furthermore, pairing of subthreshold excitatory postsynaptic potentials or somatic current injection with brief bursts of GABAergic inputs revealed efficient GABAergic excitation at conductances of ~1.5 nS, corresponding to the activity of only three or four interneurons. Stronger GABAergic inputs (>4 nS) effectively blocked AP firing via shunting inhibition, which might be important to dynamically control spiking output in both directions. Taken together, GABAergic interneurons differentially recruit newborn young granule cells by supporting either AP generation or shunting inhibition dependent on hippocampal network activity.

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Trastuzumab emtansine (T-DM1) renders HER2$^+$ breast cancer highly susceptible to CTLA-4/PD-1 blockade

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Targeted drug delivery with antibody-drug conjugates such as the HER2-directed ado-trastuzumab emtansine (T-DM1) has emerged as a powerful strategy for cancer therapy. We show that T-DM1 is particularly effective in eliciting antitumor immunity in patients with early breast cancer (WSG-ADAPT trial) and in a HER2-expressing orthotopic tumor model. In the latter, despite primary resistance to immunotherapy, combined treatment with T-DM1 and anti–CTLA-4/PD-1 (cytotoxic T lymphocyte–associated protein-4/programmed cell death protein-1) was curative because it triggered innate and adaptive immunity. Tumor rejection was accompanied by massive T cell infiltration, T_H1 (T helper 1) cell polarization, and, notably, a substantial increase in regulatory T cells. Depletion of regulatory T cells resulted in inflammation and tissue damage, implying their essential role in protecting the host during therapy. This study provides insights into the mechanisms of T-DM1's therapeutic activity and a rationale for potential therapeutic combination strategies with immunotherapy.

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Small RNA profiling reveals deregulated phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3K)/Akt pathway in bronchial smooth muscle cells from asthmatic patients

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Background: Aberrant expression of small noncoding RNAs (sncRNAs), microRNAs (miRNAs) and PIWI-interacting RNAs (piRNAs) in particular, define several pathologic processes. Asthma is characterized by airway hyperreactivity, chronic inflammation, and airway wall remodeling. Asthma-specific miRNA profiles were reported for bronchial epithelial cells, whereas sncRNA expression in asthmatic bronchial smooth muscle (BSM) cells is almost completely unexplored.

Objective: We sought to determine whether the primary BSM sncRNA expression profile is altered in asthmatic patients and identify targets of differentially expressed sncRNAs. Methods: Small RNA sequencing was used for sncRNA profiling in BSM cells (from 8 asthmatic and 6 nonasthmatic subjects). sncRNA identification and differential expression analysis was performed with iMir software. Experimentally validated miRNA targets were identified by using Ingenuity Pathway Analysis, and putative piRNA targets were identified by using miRanda software.

Results: BSM cells from asthmatic patients showed abnormal expression of 32 sncRNAs (26 miRNAs, 5 piRNAs, and 1 small nucleolar RNA). Target prediction for deregulated miRNAs and piRNAs revealed experimentally validated and predicted mRNA targets expressed in the BSM cells. Thirty-eight of these mRNAs represent major targets for deregulated miRNAs and might play important roles in the pathophysiology of asthma. Interestingly, 6 of these mRNAs were previously associated with asthma, considered as novel therapeutic targets for treatment of this disease, or both. Signaling pathway analysis revealed involvement of 38 miRNA-targeted mRNAs in increased cell proliferation through phosphatase and tensin homolog and phosphoinositide 3-kinase/Akt signaling pathways.

Conclusions: BSM cells of asthmatic patients are characterized by aberrant sncRNA expression that recapitulates multiple pathologic phenotypes of these cells.

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IL-7R signaling in regulatory T cells maintains peripheral and allograft tolerance in mice

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Foxp3$^+$CD4$^+$ regulatory T cells (T_{reg}) have a crucial role in controlling CD4+ T-cell activation, proliferation, and effector function. However, the molecular mechanisms regulating T_{reg} function remain poorly understood. Here we assessed the role of IL-7, a key cytokine regulating T-cell homeostasis, in suppressor capacity of T_{reg}. Using a skin allograft model in which transplant acceptance is controlled by the number of transferred T_{reg}, we find that T_{reg} impair the proliferation of allogeneic CD4$^+$ T cells, decrease production of IFNγ by effector T cells, and prevent early and increase late IL-7 induction by lymph node stromal cells. Increased IL-7 availability enhanced T_{reg} survival, stabilized T_{reg} molecular signature, enhanced surface IL-2Rα expression, and improved IL-2 binding of T_{reg}, which diminished proliferation of alloreactive CD4$^+$ T cells. Sequestration of IL-7 or impairment of IL-7R signaling after allograft transplantation abolished T_{reg}-mediated tolerance by limiting their suppressive capacity. Aged *Il7rα*-ΔT_{reg} mice displayed mild symptoms of autoimmunity correlating with impaired expansion of effector T_{reg} in response to IL-2. Thus, IL-7R signaling on T_{reg} supports the functional activity of effector T_{reg} by increasing their IL-2 sensitivity in the lymph node during peripheral and allograft tolerance.

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Generation of a Selective Small Molecule Inhibitor of the CBP/p300 Bromodomain for Leukemia Therapy

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Abstract

The histone acetyltransferases CBP/p300 are involved in recurrent leukemia-associated chromosomal translocations and are key regulators of cell growth. Therefore, efforts to generate inhibitors of CBP/p300 are of clinical value. We developed a specific and potent acetyl-lysine competitive protein–protein interaction inhibitor, I-CBP112, that targets the CBP/p300 bromodomains. Exposure of human and mouse leukemic cell lines to I-CBP112 resulted in substantially impaired colony formation and induced cellular differentiation without significant cytotoxicity. I-CBP112 significantly reduced the leukemia-initiating potential of MLL-AF9$^+$ acute myeloid leukemia cells in a dose-dependent manner *in vitro* and *in vivo*. Interestingly, I-CBP112 increased the cytotoxic activity of BET bromodomain inhibitor JQ1 as well as doxorubicin. Collectively, we report the development and preclinical evaluation of a novel, potent inhibitor targeting CBP/p300 bromodomains that impairs aberrant self-renewal of leukemic cells. The synergistic effects of I-CBP112 and current standard therapy (doxorubicin) as well as emerging treatment strategies (BET inhibition) provide new opportunities for combinatorial treatment of leukemia and potentially other cancers.

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Arenavirus Glycan Shield Promotes Neutralizing Antibody Evasion and Protracted Infection

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Abstract

Arenaviruses such as Lassa virus (LASV) can cause severe hemorrhagic fever in humans. As a major impediment to vaccine development, delayed and weak neutralizing antibody (nAb) responses represent a unifying characteristic of both natural infection and all vaccine candidates tested to date. To investigate the mechanisms underlying arenavirus nAb evasion we engineered several arenavirus envelope-chimeric viruses and glycan-deficient variants thereof. We performed neutralization tests with sera from experimentally infected mice and from LASV-convalescent human patients. NAb response kinetics in mice correlated inversely with the N-linked glycan density in the arenavirus envelope protein's globular head. Additionally and most intriguingly, infection with fully glycosylated viruses elicited antibodies, which neutralized predominantly their glycan-deficient variants, both in mice and humans. Binding studies with monoclonal antibodies indicated that envelope glycans reduced nAb on-rate, occupancy and thereby counteracted virus neutralization. In infected mice, the envelope glycan shield promoted protracted viral infection by preventing its timely elimination by the ensuing antibody response.

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Antioxidants & Redox Signaling Antioxidants & Redox Signaling Vol. 24, Nr 2, 2016 IF 7.407

Statins Trigger Mitochondrial Reactive Oxygen Species-Induced Apoptosis in Glycolytic Skeletal Muscle

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Abstract

Aims: Although statins are the most widely used cholesterol-lowering agents, they are associated with a variety of muscle complaints. The goal of this study was to characterize the effects of statins on the mitochondrial apoptosis pathway induced by mitochondrial oxidative stress in skeletal muscle using human muscle biopsies as well as *in vivo* and *in vitro* models.

Results: Statins increased mitochondrial H_2O_2 production, the Bax/Bcl-2 ratio, and TUNEL staining in deltoid biopsies of patients with statin-associated myopathy. Furthermore, atorvastatin treatment for 2 weeks at 10 mg/kg/day in rats increased H_2O_2 accumulation and mRNA levels and immunostaining of the Bax/Bcl-2 ratio, as well as TUNEL staining and caspase 3 cleavage in glycolytic (plantaris) skeletal muscle, but not in oxidative (soleus) skeletal muscle, which has a high antioxidative capacity. Atorvastatin also decreased the GSH/GSSG ratio, but only in glycolytic skeletal muscle. Cotreatment with the antioxidant, quercetin, at 25 mg/kg/day abolished these effects in plantaris. An *in vitro* study with L_6 myoblasts directly demonstrated the link between mitochondrial oxidative stress following atorvastatin exposure and activation of the mitochondrial apoptosis signaling pathway.

Innovation: Treatment with atorvastatin is associated with mitochondrial oxidative stress, which activates apoptosis and contributes to myopathy. Glycolytic muscles are more sensitive to atorvastatin than oxidative muscles, which may be due to the higher antioxidative capacity in oxidative muscles.

Conclusion: There is a link between statin-induced mitochondrial oxidative stress and activation of the mitochondrial apoptosis signaling pathway in glycolytic skeletal muscle, which may be associated with statin-associated myopathy.

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Molecular and functional interactions between AKT and SOX2 in breast carcinoma

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Abstract

The transcription factor SOX2 is a key regulator of pluripotency in embryonic stem cells and plays important roles in early organogenesis. Recently, SOX2 expression was documented in various cancers and suggested as a cancer stem cell (CSC) marker. Here we identify the Ser/Thr-kinase AKT as an upstream regulator of SOX2 protein turnover in breast carcinoma (BC). SOX2 and pAKT are co-expressed and co-regulated in breast CSCs and depletion of either reduces clonogenicity. Ectopic SOX2 expression restores clonogenicity and *in vivo* tumorigenicity of AKT-inhibited cells, suggesting that SOX2 acts as a functional downstream AKT target. Mechanistically, we show that AKT physically interacts with the SOX2 protein to modulate its subcellular distribution. AKT kinase inhibition results in enhanced cytoplasmic retention of SOX2, presumably via impaired nuclear import, and in successive cytoplasmic proteasomal degradation of the protein. In line, blockade of either nuclear transport or proteasomal degradation rescues SOX2 expression in AKT-inhibited BC cells. Finally, AKT inhibitors efficientlysuppress the growth of SOX2-expressing putative cancer stem cells, whereas conventional chemotherapeutics select for this population. Together, our results suggest the AKT/SOX2 molecular axis as a regulator of BC clonogenicity and AKT inhibitors as promising drugs for the treatment of SOX2-positive BC.

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Beating heart on a chip: a novel microfluidic platform to generate functional 3D cardiac microtissues

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In the past few years, microfluidic-based technology has developed microscale models recapitulating key physical and biological cues typical of the native myocardium. However, the application of controlled physiological uniaxial cyclic strains on a defined three-dimension cellular environment is not yet possible. Two-dimension mechanical stimulation was particularly investigated, neglecting the complex three-dimensional cell–cell and cell–matrix interactions. For this purpose, we developed a heart-on-a-chip platform, which recapitulates the physiologic mechanical environment experienced by cells in the native myocardium. The device includes an array of hanging posts to confine cell-laden gels, and a pneumatic actuation system to induce homogeneous uniaxial cyclic strains to the 3D cell constructs during culture. The device was used to generate mature and highly functional micro-engineered cardiac tissues (μECTs), from both neonatal rat and human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM), strongly suggesting the robustness of our engineered cardiac micro-niche. Our results demonstrated that the cyclic strain was effectively highly uniaxial and uniformly transferred to cells in culture. As compared to control, stimulated μECTs showed superior cardiac differentiation, as well as electrical and mechanical coupling, owing to a remarkable increase in junction complexes. Mechanical stimulation also promoted early spontaneous synchronous beating and better contractile capability in response to electric pacing. Pacing analyses of hiPSC-CM constructs upon controlled administration of isoprenaline showed further promising applications of our platform in drug discovery, delivery and toxicology fields. The proposed heart-on-a-chip device represents a relevant step forward in the field, providing a standard functional three-dimensional cardiac model to possibly predict signs of hypertrophic changes in cardiac phenotype by mechanical and biochemical costimulation.

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Cardiac mTOR complex 2 preserves ventricular function in pressure-overload hypertrophy

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Aims

Mammalian target of rapamycin (mTOR), a central regulator of growth and metabolism, has tissue-specificfunctions depending on whether it is part of mTOR complex 1 (mTORC1) or mTORC2. We have previously shown that mTORC1 is required for adaptive cardiac hypertrophy and maintenance of function under basal and pressure-overload conditions. In the present study, we aimed to identify functions of mTORC2 in the heart.

Methods and results

Using tamoxifen-inducible cardiomyocyte-specific gene deletion, we generated mice deficient for cardiac rapamycininsensitive companion of mTOR (rictor), an essential and specific component of mTORC2. Under basal conditions, rictor deficiency did not affect cardiac growth and function in young mice and also had no effects in adult mice. However, transverse aortic constriction caused dysfunction in the rictor-deficient hearts,whereas function was maintained in controls after 1 week of pressure overload. Adaptive increases in cardiac weight and cardiomyocyte cross-sectional area, fibrosis, and hypertrophic and metabolic gene expression were not different between the rictor-deficient and control mice. In control mice, maintained function was associated with increased protein levels of rictor, protein kinase C(PKC)βII, and PKCδ,whereas *rictor* ablation abolished these increases. *Rictor* deletion also significantly decreased PKCε at baseline and after pressure overload. Our data suggest that reduced PKCε and the inability to increase PKCβII and PKCδ abundance are, inaccordance with their known function, responsible for decreased contractile performance of the rictor-deficient hearts.

Conclusion

Our study demonstrates that mTORC2 is implicated in maintaining contractile function of the pressure-overloaded male mouse heart.

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Complexity of Host Micro-RNA Response to Cytomegalovirus Reactivation After Organ Transplantation

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Human *(Homo sapiens)* micro-RNAs (hsa-miRNAs)regulate virus and host-gene translation, but the biological impact in patients with human cytomegalovirus (hCMV) infection is not well defined in a clinically relevant model. First, we compared hsa-miRNA expression profiles in peripheral blood mononuclear cells from 35 transplant recipients with and without CMV viremia by using a microarray chip covering 847 hsa-miRNAs. This approach demonstrated a set of 142 differentially expressed hsa•miRNAs. Next, we examined the effect of each of these miRNAs on viral growth by using human fibroblasts (human foreskin fibroblast-1) infected with the hCMV Towne strain, identifying a subset of proviral and antiviral hsa-miRNAs. miRNA-target prediction software indicated potential binding sites within the hCMV genome (e.g., hCMV-UL52 and -UL100 [UL = unique long]) and host-genes (e.g., *interleukin-1 receptor, IRF1*). Luciferase-expressing plasmid constructs and immunoblotting confirmed several predicted miRNA targets. Finally, we determined the expression of selected proviral and antiviral hsa-miRNAs in 242 transplant recipients with hCMV-viremia. We measured hsa-miRNAs before and after antiviral therapy and correlated hsa-miRNA expression levels to hCMV-replication dynamics. One of six antiviral hsa-miRNAs showed a significant increase during treatment, concurrent with viral decline. In contrast, six of eight proviral hsa-miRNAs showed a decrease during viral decline. Our results indicate that a complex and multitargeted hsa-miRNA response occurs during CMV replication in immunosuppressed patients. This study provides mechanistic insight and potential novel biomarkers for CMV replication.

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Cartilage graft engineering by co-culturing primary human articular chondrocytes with human bone marrow stromal cells

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Abstract

Co-culture of mesenchymal stromal cells (MSCs) with articular chondrocytes (ACs) has been reported to improve the efficiency of utilization of a small number of ACs for the engineering of implantable cartilaginous tissues. However, the use of cells of animal origin and the generation of small-scale micromass tissues limit the clinical relevance of previous studies. Here we investigated the *in vitro* and *in vivo* chondrogenic capacities of scaffold-based constructs generated by combining primary human ACs with human bone marrow MSCs (BM-MSCs). The two cell types were cultured in collagen sponges (2 x 6 mm disks) at the BM-MSCs:ACs ratios: 100:0, 95:5, 75:25 and 0:100 for 3 weeks. Scaffolds freshly seeded or further precultured *in vitro* for 2 weeks were also implanted subcutaneously in nude mice and harvested after 8 or 6 weeks, respectively. Static co-culture of ACs (25%) with BM-MSCs (75%) in scaffolds resulted in up to 1.4-fold higher glycosaminoglycan (GAG) content than what would be expected based on the relative percentages of the different cell types. *In vivo* GAG induction was drastically enhanced by the *in vitro* preculture and maximal at the ratio 95:5 (3.8-fold higher). Immunostaining analyses revealed enhanced accumulation of type II collagen and reduced accumulation of type X collagen with increasing ACs percentage. Constructs generated in the perfusion bioreactor system were homogeneously cellularized. In summary, human cartilage grafts were successfully generated, culturing BM-MSCs with a relatively low fraction of non-expanded ACs in porous scaffolds. The proposed co-culture strategy is directly relevant towards a single-stage surgical procedure for cartilage repair.

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Simvastatin induces mitochondrial dysfunction and increased atrogin-1 expression in H9c2 cardiomyocytes and mice in vivo

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Abstract

Simvastatin is effective and well tolerated, with adverse reactions mainly affecting skeletal muscle. Important mechanisms for skeletal muscle toxicity include mitochondrial impairment and increased expression of atrogin-1. The aim was to study the mechanisms of toxicity of simvastatin on H9c2 cells (a rodent cardiomyocyte cell line) and on the heart of male C57BL/6 mice. After, exposure to 10 μmol/L simvastatin for 24 h, H9c2 cells showed impaired oxygen consumption, a reduction in the mitochondrial membrane potential and a decreased activity of several enzyme complexes of the mitochondrial electron transport chain (ETC). The cellular ATP level was also decreased, which was associated with phosphorylation of AMPK, dephosphorylation and nuclear translocation of FoxO3a as well as increased mRNA expression of atrogin-1. Markers of apoptosis were increased in simvastatin-treated H9c2 cells. Treatment of mice with 5 mg/kg/day simvastatin for 21 days was associated with a 5 % drop in heart weight as well as impaired activity of several enzyme complexes of the ETC and increased mRNA expression of atrogin-1 and of markers of apoptosis in cardiac tissue. Cardiomyocytes exposed to simvastatin in vitro or in vivo sustain mitochondrial damage, which causes AMPK activation, dephosphorylation and nuclear transformation of FoxO3a as well as increased expression of atrogin-1. Mitochondrial damage and increased atrogin-1 expression are associated with apoptosis and increased protein breakdown, which may cause myocardial atrophy.

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Effects of Cytochrome P450 Inhibition and Induction on the Phenotyping Metrics of the Basel Cocktail: A Randomized Crossover Study

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Abstract

Background and Objective Activity of human cytochrome P450 enzymes (CYPs) shows high inter-and intraindividual variability, which is determined by genetic and non-genetic factors. Using a combination of CYP-specific probe drugs, phenotyping cocktails allow simultaneous assessment of the activity of different CYP isoforms. The objective of this study was to characterize the phenotyping metrics of the Basel cocktail in healthy male subjects with induced and inhibited CYP activity.

Methods In a randomized crossover study, the probe drugs for simultaneous phenotyping of CYP1A2 (caffeine), CYP2B6 (efavirenz), CYP2C9 (losartan), 2C19 (omeprazole), CYP2D6 (metoprolol), and CYP3A4 (midazolam) were administered to 16 subjects without pretreatment (baseline), after pretreatment with a combination of CYP inhibitors (ciprofloxacin, ketoconazole, and paroxetine), and after CYP induction with rifampicin. All subjects were genotyped. Pharmacokinetic profiles of the probe drugs and their main metabolites and metabolic ratios 2, 4, 6, and 8 h after probe drug application were determined in plasma and compared with the corresponding area under the plasma concentration-time curve (AUC) ratios.

Results The Basel phenotyping cocktail was well tolerated by all subjects independent of pretreatment. Good correlations of metabolic ratios with AUC ratios of the corresponding probe drugs and their metabolites for all three conditions (baseline, CYP inhibition, and CYP induction) were found at 2 h after probe drug administration for CYP3A4, at4hfor CYP1A2and CYP2C19, and at 6 h for CYP2B6 and CYP2D6. While CYP inhibition significantly changed AUC ratios and metabolic ratios at these time points for all six CYP isoforms, CYP induction did not significantly change AUC ratios for CYP2C9. For CYP3A4, total 10-hydroxymidazolam concentrations after pretreatment of samples with β-glucuronidase were needed to obtain adequate reflection of CYP induction by the metabolic ratio.

Conclusions Inhibition of CYP activity can be detected with the Basel phenotyping cocktail for all six tested CYP isoforms at the proposed time points. The AUC ratio of losartan:losartan carboxylic acid in plasma does not seem suitable to detect induction of CYP2C9. The observed metabolic ratios for inhibited and induced CYP activity need to be confirmed for extensive metabolizers, and typical ratios for subjects with genetically altered CYP activity will need to be established in subsequent studies.

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Loss of STAT1 protects hair cells from ototoxicity through modulation of STAT3, c- Jun, Akt, and autophagy factors

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Hair cell damage is a side effect of cisplatin and aminoglycoside use. The inhibition or attenuation of this process is a target of many investigations. There is growing evidence that STAT1 deficiency decreases cisplatin-mediated ototoxicity; however, the role of STAT function and the molecules that act in gentamicin-mediated toxicity have not been fully elucidated. We used mice lacking STAT1 to investigate the effect of STAT1 ablation in cultured organs treated with cisplatin and gentamicin. Here we show that ablation of STAT1 decreased cisplatin toxicity and attenuated gentamicin-mediated hair cell damage. More TUNEL-positive hair cells were observed in explants of wild-type mice than that of STAT1$^{-/-}$ mice. Although cisplatin increased serine phosphorylation of STAT1 in wild-type mice and diminished STAT3 expression in wild-type and STAT1$^{-/-}$ mice, gentamicin increased tyrosine phosphorylation of STAT3 in STAT1$^{-/-}$ mice. The early inflammatory response was manifested in the upregulation of TNF-α and IL-6 in cisplatin-treated explants of wild-type and STAT1$^{-/-}$ mice. Expression of the anti-inflammatory cytokine IL-10 was altered in cisplatin-treated explants, upregulated in wild-type explants, and downregulated in STAT1$^{-/-}$ explants. Cisplatin and gentamicin triggered the activation of c-Jun. Activation of Akt was observed in gentamicin-treated explants from STAT1$^{-/-}$ mice. Increased levels of the autophagy proteins Beclin-1 and LC3-II were observed in STAT1$^{-/-}$ explants. These data suggest that STAT1 is a central player in mediating ototoxicity. Gentamicin and cisplatin activate different downstream factors to trigger ototoxicity. Although cisplatin and gentamicin triggered inflammation and activated apoptotic factors, the absence of STAT1 allowed the cells to overcome the effects of these drugs.

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The Survey on Cellular and Engineered Tissue Therapies in Europe in 2013

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Following the coordinated efforts of five established scientific organizations, this report, the sixth of its kind, describes activity in Europe for the year 2013 in the area of *cellular and engineered tissue therapies,* excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. Three hundred eighteen teams from 31 countries responded to the cellular and engineered tissue therapy survey; 145 teams from 25 countries reported treating 2187 patients, while a further 173 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (45%; 89% autologous), cardiovascular disorders (20%; 99% au-tologous), hematology/oncology, predominantly prevention or treatment of graft versus host disease (GvHD) and HSC graft enhancement, (19%; <1% autologous), neurological disorders (3%; 100% autologous), gastro-intestinal disorders (2%; 32% autologous), and other indications (11%; 67% autologous). The majority of autologous cells (88%) were used to treat musculoskeletal/rheumatological (57%) and cardiovascular (27%) disorders, whereas allogeneic cells were used mainly for hematology/oncology (64%). The reported cell types were mesenchymal stem/stromal cells (MSC) (49%), HSC (28%), chondrocytes (11%), dendritic cells (2%), keratinocytes (1%), and others (9%). In 46% of the grafts, cells were delivered following *ex vivo* expansion, sorted in 17% of the reported cases and transduced in only 3%. Thirty three percent of treatments were delivered intravenously or intra-arterially, and of the remaining 67%, 37% used a membrane/scaffold, 28% a suspension, and 2% a gel. The data are compared to those previously collected to identify trends in a still unpredictably evolving field.

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Three Dimensional Multi-Cellular Muscle-Like Tissue Engineering in Perfusion-Based Bioreactors

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Abstract:
Conventional tissue engineering strategies often rely on the use of a single progenitor cell source to engineer in vitro biological models; however, multi-cellular environments can better resemble the complexity of native tissues. Previous described co-culture models used skeletal myoblasts, as parenchymal cell source, and mesenchymal or endothelial cells, as stromal component. Here, we propose instead the use of adipose tissue-derived stromal vascular fraction cells, which include both mesenchymal and endothelial cells, to better resemble the native stroma. Percentage of serum supplementation is one of the crucial parameters to steer skeletal myoblasts toward either proliferation (20%) or differentiation (5%) in two-dimensional culture conditions. On the contrary, three-dimensional (3D) skeletal myoblast culture often simply adopts the serum content used in monolayer, without taking into account the new cell environment. When considering 3D cultures of mm-thick engineered tissues, homogeneous and sufficient oxygen supply is paramount to avoid formation of necrotic cores. Perfusion-based bioreactor culture can significantly improve the oxygen access to the cells, enhancing the viability and the contractility of the engineered tissues. In this study, we first investigated the influence of different serum supplementations on the skeletal myoblast ability to proliferate and differentiate during 3D perfusion-based culture. We tested percentages of serum promoting monolayer skeletal myoblast-proliferation (20%) and differentiation (5%) and suitable for stromal cell culture (10%) with a view to identify the most suitable condition for the subsequent co-culture. The 10% serum medium composition resulted in the highest number of mature myotubes and construct functionality. Co-culture with stromal vascular fraction cells at 10% serum also supported the skeletal myoblast differentiation and maturation, hence providing a functional engineered 3D muscle model that resembles the native multi-cellular environment.

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Pharmacokinetics and Concentration-Effect Relationship of Oral LSD in Humans

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Abstract

Background: The pharmacokinetics of oral lysergic acid diethylamide are unknown despite its common recreational use and renewed interest in its use in psychiatric research and practice.

Methods: We characterized the pharmacokinetic profile, pharmacokinetic-pharmacodynamic relationship, and urine recovery of lysergic acid diethylamide and its main metabolite after administration of a single oral dose of lysergic acid diethylamide (200 μg) in 8 male and 8 female healthy subjects.

Results: Plasma lysergic acid diethylamide concentrations were quantifiable (>0.1ng/mL) in all the subjects up to 12 hours after administration. Maximal concentrations of lysergic acid diethylamide (mean±SD: 4.5±1.4ng/mL) were reached (median, range) 1.5 (0.5–4) hours after administration. Concentrations then decreased following first-order kinetics with a half-life of 3.6±0.9 hours up to 12 hours and slower elimination thereafter with a terminal half-life of 8.9±5.9 hours. One percent of the orally administered lysergic acid diethylamide was eliminated in urine as lysergic acid diethylamide, and 13% was eliminated as 2-oxo-3-hydroxy-lysergic acid diethylamide within 24 hours. No sex differences were observed in the pharmacokinetic profiles of lysergic acid diethylamide. The acute subjective and sympathomimetic responses to lysergic acid diethylamide lasted up to 12 hours and were closely associated with the concentrations in plasma over time and exhibited no acute tolerance.

Conclusions: These first data on the pharmacokinetics and concentration-effect relationship of oral lysergic acid diethylamide are relevant for further clinical studies and serve as a reference for the assessment of intoxication with lysergic acid diethylamide.

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Metastatic spread in patients with non-small cell lung cancer is associated with a reduced density of tumor-infiltrating T cells

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Abstract

Tumor-infiltrating lymphocytes play an important role in cell-mediated immune destruction of cancer cells and tumor growth control. We investigated the heterogeneity of immune cell infiltrates between primary nonsmall cell lung carcinomas (NSCLC) and corresponding metastases. Formalin-fixed, paraffin-embedded primary tumors and corresponding metastases from 34 NSCLC patients were analyzed by immunohistochemistry for CD4, CD8, CD11c, CD68, CD163 and PD-L1. The percentage of positively stained cells within the stroma and tumor cell clusters was recorded and compared between primary tumors and metastases. We found significantly fewer $CD4^+$ and $CD8^+$ T cells within tumor cell clusters as compared with the stromal compartment, both in primary tumors and corresponding metastases. $CD8^+$ T cell counts were significantly lower in metastatic lesions than in the corresponding primary tumors, both in the stroma and the tumor cell islets. Of note, the CD8/CD4 ratio was significantly reduced in metastatic lesions compared with the corresponding primary tumors in tumor cell islets, but not in the stroma. We noted significantly fewer $CD11c^+$ cells and $CD68^+$ as well as $CD163^+$ macrophages in tumor cell islets compared with the tumor stroma, but no difference between primary and metastatic lesions. Furthermore, the CD8/CD68 ratio was higher in primary tumors than in the corresponding metastases. We demonstrate a differential pattern of immune cell infiltration in matched primary and metastatic NSCLC lesions, with a significantly lower density of $CD8^+$ T cells in metastatic lesions compared with the primary tumors. The lower CD8/CD4 and CD8/CD68 ratios observed in metastases indicate a rather tolerogenic and tumor-promoting microenvironment at the metastatic site.

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Progression of Lung Cancer Is Associated with Increased Dysfunction of T Cells Defined by Coexpression of Multiple Inhibitory Receptors

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Abstract

Dysfunctional T cells present in malignant lesions are characterized by a sustained and highly diverse expression of inhibitory receptors, also referred to as immune checkpoints. Yet, their relative functional significance in different cancer types remains incompletely understood. In this study, we provide a comprehensive characterization of the diversity and expression patterns of inhibitory receptors on tumor-infiltrating T cells from patients with non–small cell lung cancer. In spite of the large heterogeneity observed in the amount of PD-1, Tim-3, CTLA-4, LAG-3, and BTLA expressed on intratumoral $CD8^+$ T cells from 32 patients, a clear correlation was established between increased expression of these inhibitory coreceptors and progression of the disease. Notably, the latter was accompanied by a progressively impaired capacity of T cells to respond to polyclonal activation. Coexpression of several inhibitory receptors was gradually acquired, with early PD-1 and late LAG-3/BTLA expression. PD-1 blockade was able to restore T-cell function only in a subset of patients. A high percentage of $PD\text{-}1^{hi}$ Tcells was correlated with poor restoration of T-cell function upon PD-1 blockade. Of note, $PD\text{-}1^{hi}$ expression marked a particularly dysfunctional T-cell subset characterized by coexpression of multiple inhibitory receptors and thus may assist in identifying patients likely to respond to inhibitory receptor–specificantibodies. Overall, these data may provide a framework for future personalized T-cell–based therapies aiming at restoration of tumor-infiltrating lymphocyte effector functions.

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Impaired mitochondrial function in HepG2 cells treated with hydroxy-cobalamin[c-lactam]: A cell model for idiosyncratic toxicity

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Abstract

The vitamin B12 analog hydroxy-cobalamin[c-lactam] (HCCL) impairs mitochondrial protein synthesis and the function of the electron transport chain. Our goal was to establish an in vitro model for mitochondrial dysfunction in human hepatoma cells (HepG2), which can be used to investigate hepatotoxicity of idiosyncratic mitochondrial toxicants.

For that, HepG2 cells were treated with HCCL, which inhibits the function of methylmalonyl-CoA mutase and impairs mitochondrial protein synthesis. Secondary, cells were incubated with propionate that served as source of propionyl-CoA, a percursor of methylmalonyl-CoA. Dose-finding experiments were conducted to evaluate the optimal dose and treatment time of HCCL and propionate for experiments on mitochondrial function.

50 μM HCCL was cytotoxic after exposure of HepG2 cells for 2 d and 10 and 50 μM HCCL enhanced the cytotoxicity of 100 or 1000 μM propionate. Co-treatment with HCCL (10 μM) and propionate (1000 μM) dissipated the mitochondrial membrane potential and impaired the activity of enzyme complex IV of the electron transport chain. Treatment with HCCL decreased the mRNA content of mitochondrially encoded proteins, whereas the mtDNA content remained unchanged. We observed mitochondrial ROS accumulation and decreased mitochondrial SOD2 expression. Moreover, electron microscopy showed mitochondrial swelling. Finally, HepG2 cells pretreated with a non-cytotoxic combination of HCCL (10 μM) and propionate (100 μM) were more sensitive to the mitochondrial toxicants dronedarone, benzbromarone, and ketoconazole than untreated cells.

In conclusion, we established and characterized a cell model, which could be used for testing drugs with idiosyncratic mitochondrial toxicity.

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Stress-Induced *In Vivo* Recruitment of Human Cytotoxic Natural Killer Cells Favors Subsets with Distinct Receptor Profiles and Associates with Increased Epinephrine Levels

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Abstract

Background

Acute stress drives a 'high-alert' response in the immune system. Psychoactive drugs induce distinct stress hormone profiles, offering a sought-after opportunity to dissect the *in vivo* immunological effects of acute stress in humans.

Methods

3,4-methylenedioxymethamphetamine (MDMA), methylphenidate (MPH), or both, were administered to healthy volunteers in a randomized, double-blind, placebo-controlled cross-over-study. Lymphocyte subset frequencies, natural killer (NK) cell immune-phenotypes, and changes in effector function were assessed, and linked to stress hormone levels and expression of CD62L, CX3CR1, CD18, and stress hormone receptors on NK cells.

Results

MDMA/MPH > MDMA > MPH robustly induced an epinephrine-dominant stress response. Immunologically, rapid redistribution of peripheral blood lymphocyte-subsets towards phenotypically mature NK cells occurred. NK cytotoxicity was unaltered, but they expressed slightly reduced levels of the activating receptor NKG2D. Preferential circulation of mature NK cells was associated with high epinephrine receptor expression among this subset, as well as expression of integrin ligands previously linked to epinephrine-induced endothelial detachment.

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Presynaptic $GABA_B$ Receptors Regulate Hippocampal Synapses during Associative Learning in Behaving Mice

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Abstract

$GABA_B$ receptors are the G-protein-coupled receptors for GABA, the main inhibitory neurotransmitter in the central nervous system. Pharmacological activation of GABAB receptors regulates neurotransmission and neuronal excitability at pre-and postsynaptic sites. Electrophysiological activation of $GABA_B$ receptors in brain slices generally requires strong stimulus intensities. This raises the question as to whether behavioral stimuli are strong enough to activate $GABA_B$ receptors. Here we show that $GABA_{B1a}^{-/-}$ mice, which constitutively lack presynaptic $GABA_B$ receptors at glutamatergic synapses, are impaired in their ability to acquire an operant learning task. *In vivo* recordings during the operant conditioning reveal a deficit in learning-dependent increases in synaptic strength at CA3-CA1 synapses. Moreover, $GABA_{B1a}^{-/-}$ mice fail to synchronize neuronal activity in the CA1 area during the acquisition process. Our results support that activation of presynaptic hippocampal $GABA_B$ receptors is important for acquisition of a learning task and for learning-associated synaptic changes and network dynamics.

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A Case Series of Acquired Drug Resistance-Associated Mutations in Human Immunodeficiency Virus-Infected Children: An Emerging Public Health Concern in Rural Africa

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The acquisition of drug-resistance mutations among African children living with in human immunodeficiency virus on antiretroviral treatment has been scarcely reported. This threatens the overall success of antiretroviral programs and the clinical outcomes of children in care. We present a well characterized series of children from rural Tanzania with acquired drug-resistance mutations to contribute to the better understanding of this emerging public health concern.

There are few data on the acquisition of drug-resistance mutations among African children living with human immunodeficiency virus (HIV) on antiretroviral treatment (ART). Overall, in resource-limited settings, HIV-1 treatment failure in children is estimated to be 40% [1]. Virologic suppression and long-term treatment success are harder to achieve in children than in adults [2]. This is mostly due to high pre-ART viral loads (VLs), poorer virologic response, and risk of subtherapeutic drug concentrations caused by limited pediatric drug formulations, variable pharmacokinetics, and rapid changes in body weight [1, 3–7]. These factors, often associated with suboptimal adherence, may promote the emergence of drug-resistancemutations. Only 1 study from Kenya has described the pattern of acquired drug-resistance mutations in African children presenting ART failure [5, 8]. In Tanzania, a small study found a virologic failure (VF) rate of 58%, 100% with drug-resistance mutations [9].

The emergence of acquired drug-resistance mutations in children threatens ART programs in sub-Saharan Africa and needs to be studied further. We present a well characterized series of children from a rural Tanzanian setting with treatment failure due to the acquisition of drug-resistance mutations.

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Selected publications by DBM members

Above you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. Department of Biomedicine and University of Basel affiliation must be mentioned in authors list as published by the journal.
3. The final version of the article must be available (online pre-publications will be included when the correct volume, page numbers etc. becomes available).

We are focussing on original publications. Due to page constraints, abstracts of publications that appeared in lower ranked journals may not be able to be included. Review articles are generally not considered, unless they appeared in the very top journals (e.g. Cell, Science, Nature, NEJM, etc.). The final decision concerning inclusion of an abstract will be made by the chair of the Department of Biomedicine.

If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is May 31, 2016.

Mascarpone-Torte zum Muttertag

Für den Teig:
- 250 g Butter
- 100 g Zucker
- 1 Prise Salz
- 6 Eidotter
- 100 g Kuvertüre (weiß)
- 250 g Mehl
- 2 TL Backpulver
- 50 g Raspelschokolade
- 6 Stück Eiweiss
- Fett (für die Form)

Für die Füllung:
- 2 Becher Mascarpone (à 250g)
- 4 Eidotter
- 150 g Zucker
- 4 EL Kirschwasser
- 150 g Kirschgelee
- 1 Glas Sauerkirschen (720ml)

Für die Verzierung:
- 1 Becher Schlagsahne
- 1 EL Vanillezucker
- 200 g Marzipanrosen (und -herzen)
- 80 g Pistazien

Elektro-Backofen auf 180°C vorheizen. Butter, Zucker und Salz verrühren bis sich der Zucker gelöst hat. Eidotter hinzufügen und alles schaumig schlagen. Weiße Kuvertüre im heißen Wasserbad schmelzen. Mehl und Backpulver mischen, sieben, zu der Butter-Ei-Mischung geben und unterrühren. Geschmolzene Kuvertüre und Raspelschokolade unterheben. Eiweiß steif schlagen und unterziehen.

Den Teig in eine gefettete Springform füllen, ca. 50 Minuten backen (Elektro- und Gasbackofen 180°C/Stufe 3, Umluft 160°C), auf einem Kuchengitter auskühlen lassen und zweimal quer durchschneiden. Mascarpone, Eidotter, Zucker und Kirschwasser cremig rühren. Gelee erhitzen, mit der Hälfte den unteren Boden bestreichen und die Mascarponecreme darauf verteilen. Kirschen abtropfen lassen und auf der Creme verteilen.

Den zweiten Boden auflegen, mit der restlichen Marmelade bestreichen und mit dem dritten Boden abdecken. Schlagsahne mit Vanillezucker steif schlagen, Torte damit bestreichen und mit Marzipanherzen und -rosen sowie gehackten Pistazien verzieren und bis zum Servieren kalt stellen.

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Clinical Pharmacology

Hansen Nils
Experimental Hematology

Chen Qian
Hepatology

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Molecular Neurobiology Synaptic Plasticity
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In Memoriam: Paolo Bianco

The community of scientists, politicians, and regulators around the field of stem cell biology has been shocked by the sudden death of Paolo Bianco by the loss of a passionate, rigorous, deeply honest, inspiring man. We would like to remember Paolo with the eyes of students, as we were when we met him for the first time. The features of his personality that impressed us from the beginning, which we could only confirm in the subsequent years, were his profound knowledge, vigorous critical attitude, and genuine interest to engage in scientific discussions, embedding his strong opinions within a respectful dialogue.

Paolo was more than a scientist; he was a philosopher in its etymological sense of "lover of wisdom". Behind his drive for discovery was a search for the truth, which he pursued by integrating unstructured creativity with logical reasoning. In his quest for knowledge, he was opposed to any possible compromise to moral integrity, which he taught to generations of scientists not only with fine words but also with a model of personal conduct. Paolo was active at all levels, including public debates and policy making, to battle ideological positions and commercial interests that were not based on solid experimental data and the principles of good scientific practice.

The soul of Paolo, beyond any religious belief, continues to live in those students or professionals, who have been inspired by his curiosity, dedication, insightful thinking, and behavior. With his life, he has demonstrated aversion to science as a source of power or as a way to merely receive recognition and visibility; to us, he leaves the challenge to carry on these ethical principles as well as his timeless passion for science.

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Dissertationen

Am 9. Dezember 2015 konnte **Atanas Todorov** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Endochondral Ossification – Towards a Clinical Translation".

Am 10. Dezember 2015 stellte sich **Marco Fischer** von der Forschungsgruppe "Immunobiology" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: "Mitochondria and effector functions of human CD8+ T cells".

Seit dem 14. Dezember 2015 darf sich **Ralph Dühr** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) Herr Dr. nennen. Er befasste sich in seiner Doktorarbeit mit dem Thema: "Modulation of Growth and Differentiation of Mesenchymal Cells for Cartilage and Bone Tissue Engineering".

Mit der Doktorprüfung am 15. Dezember 2015 schloss **Ori Rokach** von der Forschungsgruppe "Perioperative Patient Safety" (Departement Biomedizin Hebelstrasse) erfolgreich eine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: "The molecular dysregulation of Excitation contraction coupling in patients with congenital muscle disorders".

Am 17. Dezember 2015 stellte sich **Marijana Sekulic** von der Forschungsgruppe "Perioperative Patient Safety" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel ihrer Dissertation hiess: "Characterization of the excitation-contraction coupling in extraocular muscles".

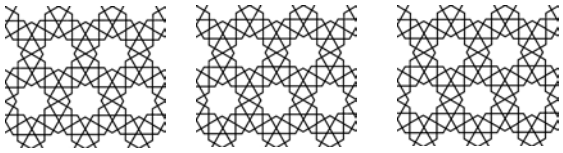
Am 10. März 2016 konnte **Thierry Nordmann** von der Forschungsgruppe "Diabetes Research" (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Pancreatic ß-cell identity and inflammation in type 2 diabetes".

Das DBM gratuliert ganz herzlich!

Persian New Year (Norouz)

I have been almost seven years in Basel and have had the pleasure of studying and working in the DBM. There was always great interest from people who worked with me about my culture. It came as a surprise to me when Heidi asked me to write about Norouz for the DBM magazine. In spite of all the bad images created by media about my country, I am delighted to use this opportunity to show a part of great Iranian culture to my friends and colleagues.

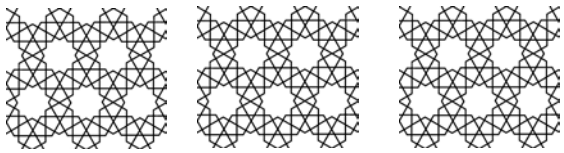
Here, I will try to introduce the cultural root of this celebration as well as traditions that come from my little search into Persian history and what we do today, I hope I can deliver them correctly.



The first day of spring, 20 or 21 March, is Persian New Year called "Norouz" (it also written Now-Ruz, Nowruz, No Roz, No-Rooz, Norouz, or Navroz in English). Norouz is the biggest festival in Iran and has been celebrated for over 3,000 years by over 300 million people. This celebration originated from an ancient Iranian religion (Zoroastrian) however people from different ethnic communities and with different religious backgrounds have celebrated it for thousands of years. The reason that different countries celebrate Norouz goes back to the time of the Persian Empire that included various civilizations and when it was the largest empire in ancient history. The Persian Empire spanned, at its maximum extent, from the Balkans (west) to the Indus Valley (east) and from Eurasian Steppe in the north to the Persian Gulf and the Gulf of Oman in the south (Fig.1). This entire region was under Iranian influence and therefore they share some similar traditions today.

Fig1. The extent of the Iranian empire 3000 years ago.*

This celebration is in accordance with the Zoroastrian Religious Calendar "Avestan". The Avestan calendar is synchronized with the solar year (539BC) and Noroz starts at the exact vernal equinox and is called "Sale Tahvil". An Equinox occurs when the sun is vertically above the point of the equator meaning this is the time that the length of day and night is equal. In theory this is the day that the cold of winter turns into the warmth of spring. The time of the Sale Tahvil depends on the exact time of the Equinox and is calculated to the exact hour, minute and second as this changes each year. People celebrate Noroz immediately after Sale Tahvil, no matter if it is during the day or the night.



The Norouz ceremony is a symbolic representation of an ancient concept; the end and rebirth. There is also evidence showing that Persepolis was built in Iran for Norouz celebrations. The walls of this

Fig2. Haji Firoz cheering up people in the streets a few days before Norouz.*

royal palace depict the signs of this celebration. After Islam came to Persia, Norouz was still the most honoured tradition by the main leaders of Muslims. Thus the fest remained as the main celebration of the land in Iranian culture.

The fest starts with Khone Tekoni (shaking house) or in the other word spring-cleaning. A few weeks before New Year, Iranians clean and rearrange their homes. They make or buy new clothes to wear during Norouz.

The traditional fictional character of the Noroz season is called Haji Firoz (Fig.2). His face is darkened with make-up and he wears red clothes and a hat. A few days before Norouz, he sings and dances with trombones in the streets and makes a happy atmosphere and symbolizes rebirth and good cheer.

On the day of Norouz , families wear their new clothes and gather around the Haftseen (7S) table and wait for Sale Tahvil (Fig.3). The table is prepared with seven symbolic items beginning with a letter "S" in Persian and some other items. The items symbolically correspond to seven creations and have a holy immortal protecting theme.

HaftSeen (7S Items):

1) Sabzeh; wheat or lentil sprouts prepared in a dish which symbolizes rebirth.
2) Samanu, a sweet pudding cooked out of wheat bud, symbolizing affluence
3) Somaq, especial berries which symbolizes sunrise because of its colour
4) Senjed , dried fruit from sea-buckthorn symbolizing love
5) Sir (Garlic) reprehensive of medicine
6) Sib (Apple) symbolizing beauty and health
7) Serke (Vinegar) symbolizing age and patience

Sometimes a missing item could be replaced with another item starts with S letter. For example Sonbol (Hyacinth) symbolizing spring or Sekke (coins) symbolizing prosperity and wealth.

Other Items:

- Water and gold fish symbolizing life within life
- A mirror reflecting the past and showing the future
- Candles represent light, energy and giving warmth to others

Fig3. Haftseen table with all items starting with letter S and other required items.*

Fig 4. Traditional New Year dish for dinner, Sabzipolo ba Mahi (herbed rice and fish).*

- Painted eggs symbolizing fertility
- Holy book or a book of poetry from Hafiz, khaiam or roomi
- Pastries are also commonly displayed on the table because according to legend king Jamshid discovered sugar during Norouz

Immediately after Sale Tahvile the family embrace each other and exchange gifts. Gifts are usually some given from an older person to the younger ones. And usually the first thing people eat after Sale Tahvil is sweets or pastries to start the year sweetly. The traditional New Year dinner is Sabzipolo ba Mahi (herbed rice and Fish). Here in Switzerland there are some small Iranian communities who celebrate Norouz mainly in Geneva, Lausanne and Zurich. A group of friends and I also celebrate Norouz every year here. It is not easy to find the items (especially in Basel) but I try to set my table as well and have a small celebration (Fig5).

Over the next 12 days of holidays people are expected to pay house visits to each other. Friends

Fig5. My own Haftseen Table, 5 years ago (1390).

and family visit each other, drink tea and have sweets and nuts. These visits are meant to show that we are remembering and supporting beloved ones. Usually these are short visits so that we can visit everyone on our lists. Typically the younger first visit the older member of the family and on later days the older family members visit the younger ones.

The 13th day of Norouz called "Sizdah bedar" meaning 13 outdoors. People go out in groups and spend all day outdoors in nature, like family picnics, where children play and music and happy things are around. On this day people throw out their Sabzeh to dispose of bad luck. It is also a custom for young single ladies to bunch up the leaves of the Sabzeh prior to disposing of it with the wish of getting married before next year is over. After the 13th bedar, the Norouz holiday is finished and everybody is back to work or to school.

Nouroz was proclaimed as an international day by the United Nations General Assembly in 2010 to promote values of peace and solidarity between people and different communities. The time of the vernal equinox for the Norouz this year was on Sunday March 20, 2016 at 5:30:12 a.m (Zurich time) and in the Persian calendar it was on Sunday 1st Farvardin, 1395 (new Persian calendar adopted after Islam) at 8:00:12 a.m (Tehran). Every year one can count down the time left to Norouz celebration, simply by using " "http://www.7seen.com".

Nouroz Mobarak!
Happy Persian New Year!

Zeinab Barekati

**; Pictures are selected from Google search*

Hafez – Song of Spring

The gentle breeze will blow a new
Vitality to the barren earth.
The old will become young.

Persian Lilacs will offer the white lily
Their fragrant red cup.
The narcissus eye will glimpse the anemone.

Because of the tyranny of separation endured
The nightingale shall speed
Into the rose garden bursting with song.

If I've left the mosque for the tavern,
Don't complain: the ceremonies stretch on f a r t o o l o n g
And time is short.

Heart, if you deposit today's joy for tomorrow
You may be left with nothing.
For who will guarantee it?

In the month before the fast
Drink your fill of wine
For this sun, too, will set
In Ramazan
These will be out of sight.

The rose's beauty is very dear.
Enjoy its petals when it is here.
As soon as it comes it is gone.

Ministrel, for this Feast of Love sing your melody!
No more chatter of the past
Nor of the future, now.

Hafez has made the journey to Life
For you.
Bid him fond adieu for soon in death his passing he—*shall be*.

Berlin – creative and dynamic

The other day I flew back to Berlin. Going there I picked up the orange flight magazine and saw an article about 10 things that you must do in Berlin. A new and hip Caravan hotel opened in Berlin. I probably would have expected to happen it in Amsterdam rather than in Berlin. That made me smile and I thought: Berlin is really never boring.

(picture 1)

After the opening of the borders separating both German counties, Berlin has developed into a modern metropolis. Berlin was first made up from the small settlements Berlin and Cölln. Later several small villages and cities like Spandau, Köpenick, Charlottenburg and Hellersdorf, after which the different boroughs were named, were incorporated into Berlin. Also because of the individual charm of each borough, Berlin is one of the most interesting and dynamic cities in Europe. Berlin is attractive to residents and tourist, a hot melting pot of different cultures with young and old of 180 different nations, which make it open for innovations and creativity.

While politicians of Berlin are often slow in making decisions for new innovative projects (comment: I was supposed to arrive at the new airport in October 2014), the Berlin residents themselves shape and influence their city by accomplishing interesting projects.


(picture 2)

In the years after the "Fall of the Wall" (picture 1) leading to the reunification of Germany, Berlin was once again chosen as the capital of Germany. As a consequence of this big construction sites arouse in city center. New buildings were designed for the government and industry and changed the Berlin sky-

(picture 3)

line. The German Chancellery was build, which Berlin residents call the "Washing machine" and indeed there are similarities (picture 2). Almost all old buildings including the "Berlin Dom" (my favourite view point, picture 3), the "Rote Rathaus" (seat of Berlin mayor, picture 4), the "Nikolaiviertel" (area of the settlement Cölln, right of the Rote Rathaus), the "Brandenburger Tor" (picture 5) and the "Reichstag" (picture 6) were reconstructed and renovated. Due to the renovation, it was possible for Jeanne-Claude and Christo to wrap the Reichstag in aluminium-covered material. At the same time, Bunkers and hidden rooms were discovered in the underground and were converted to clubs, bars and exhibition rooms. Many free areas along the Wall and the river Spree were used for beach bars and offered afterwork drinks in relaxing atmosphere (picture 7). Rooms and halls became available after closing industrial factories and warehouses in both East and West of Berlin. Many of these facilities like the "Kulturbrauerei" (picture 8) were temporally used for public events

(picture 4)

(picture 5)

(picture 6)

(picture 7)

and entertainments. Sometimes we even went into a metro station and there all of the sudden behind a simple door appeared a club or a bar. Berlin's music scene benefited very much from this attractive possibility so that all kind of music styles were made available to us. Especially techno, dance and hiphop influenced the multifaced club culture in Berlin. In 2007, the city was recommended by Billboard as one of the leading dance centers in Europe, with the "Love Parade" as one of the main events.

The growing city was not only attracting musicians but also creative people working in other businesses. Designer, painters, writers and actors moved to Berlin, and supported the change from an industrial based economy city to a more service and management-oriented one. Guerilla-kitchen chefs opened small illegal restaurants in private apartments working without licenses. We had to solve riddles to find the way to the restaurant or to get a drink. It was a fantastic adventure for everyone participating. Today, Berlin has developed to a cultural city with 3 opera houses, 1500 theaters and stages, more than 170 museums and collections, and 300 galleries.

Since my days in Berlin, many places that I liked and often visited have closed or are used otherwise in a different way. The Berlin scene is still moving and constantly changing the face of the city. Famous clubs were converted into into restaurants; other clubs, bars or shops kept their names but moved within the city. Some locations closed permanently or have been replaced by new buildings. In this respect, I wanted to show my family the borough Hellersdorf, in which I was growing up and going to school. My old Gymnasium (High school) and its buildings were dismantled because of changing needs. I was standing next to the old fence, which is the only physical thing that

(picture 8)

(picture 9)

has remained from the old school (picture 9). But I still have my memories! I meet my friends regularly and school mates at least every five years. Despite the fact that I have seen many changes in Berlin, it is a strange feeling for us to have no old school anymore. The next time we will probably meet in a new fancy club. Yes, I know that all this is part of a very dynamic city like Berlin and the basis for creativity and innovations. But is it necessary that the city changes that fast? Sometimes I have the impression, I walk through Berlin as a tourist searching for cool locations and interesting innovative things. However, some things are not changing that fast. Our previous appartment block "Marke Plattenbau" still looked exactly the some like before (picture 10). Only a playground was build and the wall of our old powerhouse was nicely decorated for children (picture 11).

The day after I left Berlin, in spite of my many new impressions, I was happy to be back in Basel. I am going to meet my friends and colleagues in the Cargo Bar, tomorrow. This bar was opened before I started working in the DBM and might be still at the same place in a couple of years, despite the fact that the Cargo is located in a dynamic city; however a little bit smaller than Berlin.

Mathias Schmaler

(picture 10)

(picture 11)

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Ergonomie am Arbeitsplatz

Die Ergonomie an einem Arbeitsplatz, speziell mit einem Bildschirm darauf, ist ein wichtiges Thema und wird gerne vernachlässigt. Dieser Beitrag soll darauf aufmerksam machen, wie wichtig einem selbst dieses Thema sein sollte.

Mit einem richtig eingestellten Arbeitsplatz können mitunter Schmerzen in den verschiedensten Teilen des Körpers verhindert werden. Keiner sitzt gerne mit Rücken- oder Nackenschmerzen an seinem Schreibtisch. Speziell dann nicht, wenn man den lieben langen Tag sitzenderweise verbringt.

Dabei kann bereits mit ein paar einfachen Einstellungen des Schreibtischstuhles und des Schreibtischs die Ergonomie erheblich verbessert werden.

Der Schreibtischstuhl zum Beispiel wird am besten wie folgt eingestellt:
Die Sitzhöhe des Stuhles sollte so hoch sein, dass die Oberschenkel ganz auf der Sitzfläche aufliegen. Dabei sollten aber die Füsse nicht in der Luft hängen, sondern auf dem Boden stehen. Hierfür muss eventuell die Höhe des Stuhles verändert werden.

Sobald der Stuhl auf die eigene Körpergrösse angepasst ist, sollte der Schreibtisch sowie der Bildschirm und die Tastatur darauf ausgerichtet werden. Sitzt man nun auf dem Schreibtischstuhl, sollten die Unterarme im rechten Winkel auf dem Tisch aufliegen. Hier müsste sonst eventuell die Höhe des Schreibtischs an den Stuhl angepasst werden. Ist das nicht möglich, was sicher häufig der Fall sein wird, muss eventuell noch etwas mit der Höhe des Stuhls gespielt werden.

Sind diese zwei Punkte erledigt, sollte der Bildschirm auf dem Schreibtisch noch auf die neue Sitzposition angepasst werden. Der Bildschirm sollte so eingerichtet sein, dass zwischen der Höhe der Augen und oberhalb der Oberkante des Bildschirms ca. 10 cm Unterschied ist. Damit wäre die richtige Höhe eingestellt, was wiederum Nacken- und Augenschmerzen vorbeugt.

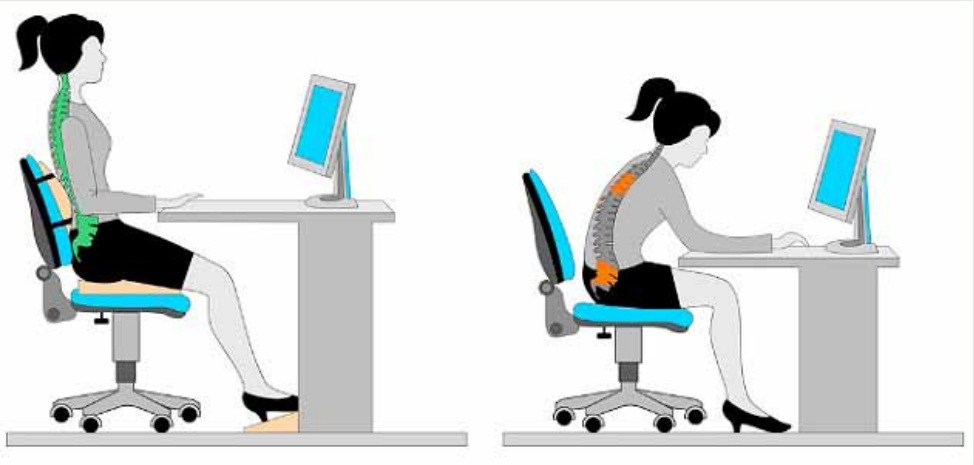
Auch die Tastatur kann auf dem Schreibtisch falsch positioniert sein. Wenn die Tastatur nur mit gestreckten Armen erreicht werden kann, dient das nicht der Ergonomie. Richtig wäre, wenn die Unterarme im rechten Winkel locker aufliegen, um so dann die Tastatur zu bedienen.

All das schlägt die SUVA auf ihrer Homepage vor, um die Ergonomie am Arbeitsplatz zu fördern. Sicherlich kann eine richtig umgesetzte Ergonomie am Arbeitsplatz diversen Schmerzen vorbeugen, doch auch die perfekte ergonomische Einstellung am Arbeitsplatz ist auf Dauer nicht förderlich.

Das Rezept zum schmerzfreien Arbeiten liegt also in der Mischung von allem. Keiner kann 8 Stunden am Stück so dasitzen, wie oben beschrieben. Das Beste, was man also machen kann, ist die oben beschriebenen Einstellungen bei sich umzusetzen, aber ruhig zwischen durch mal die Beine auszustrecken. Ein bisschen Bewegung dazwischen tut auf jeden Fall gut. So schadet es auch nicht, mal aufzustehen und dem Büro-Nachbarn die Nachricht persönlich vorbei zu bringen oder einfach mal „Hallo“ zu sagen, statt eine E-Mail zu verfassen.

Es ist also nicht allzu schwer, sich sein Leben am Arbeitsplatz erheblich zu erleichtern, auch wenn die oben genannten Punkte nur einen Überblick geben. Wenn es um einen ergonomischen Arbeitsplatz geht, kann noch viel mehr beachtet werden. Doch auch bereits mit diesen einfachen Einstellungen kann man schon viel bewirken.

Timo Dörflinger



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Today: Qingzhu Sun, Pneumology

It is a great honour to be invited to introduce myself and my hometown Xi'an to all the members of the Department of Biomedicine, University Hospital of Basel. My name is Qingzhu Sun and I am from China. Qingzhu is my Chinese name, which means green bamboo and it represents the hope of courage and the health of my parents.

When I learned that I would write an article to introduce my home country China, I had no idea where to start. Since China is such a big country (nearly the size of the whole of Europe), even as a Chinese, I have only been to 10 out of the 31 provinces. I think the better idea is to share some interesting information, scenery, features and portrayals of the ancient city of Xi'an where I come from.

Xi'an is located in the central-northwest part of China. In addition to being well known as the origin of the Terracotta Warriors from the Qin Dynasty and the eastern terminal of the Silk Road, Xi'an is one of the four ancient cities of China with over 3,000 years of history and has been the capital city of 13 dynasties over the period of 1,100 years. It is also one of the origins of the ancient Chinese civilization in the Yellow River region. Xi'an was known as Chang'an (the eternal and peaceful city) in the past and has recorded the great changes of the country just like a living history book. Therefore, you can marvel at numerous historical sites and cultural relics in and around the city.

Since the 1990s, Xi'an has been known as the leading city of China's Western Development Drive Program, and it is an important economic, cultural, industrial and educational center of the central-northwest region of China, providing visitors with modern and convenient facilities. Wandering through the Xi'an old city at night, you will see the glory of her past matching with the dynamism of the present. Moreover, Xi'an is a big city. The population of Xi'an is 8 million, yes, you're right, equivalent to the population of the whole of Switzerland.

There are so many attractions in Xi'an, the most famous is the Terracotta Army, which is listed under UNESCO's World Culture Heritage. The Terracotta Army or the "Terracotta Warriors and Horses" is a collection of terracotta sculptures depicting the armies of Qin Shi Huang, the first Emperor of China. It is a form of funerary art buried with the emperor in 210-209 BC with the aim to protect the emperor in his afterlife.

One should never get bored in Xi'an. The ancient Xi'an City Wall, Bell Tower, Big Wild Goose Pagoda, Qinshihuang Mausoleum, Famen Temple are just a few major historical sites for those who are interested in history to explore. If you prefer the nature, then you may visit the Huashan Mountain, Qinling Mountain or national wetland park.

When someone asks me what do I miss the most living in Switzerland? Without doubt, my answer is the Chinese foods. Xi'an cuisine has a good, hearty style that will never let you leave the table hungry. Noodles and dumplings are the staples of the local food and they are always filling and satisfying.

If you come to Xi'an for the first time, you will most probably be shocked by the various night fares. Even the simplest restaurant at the furthest end of the lane attracts foodies from everywhere in and around the city. A bowl of Crumbled Bread in Mutton Stew (Yangrou Paomo), a few bunches of mutton shashlik and a bottle of beer are the most authentic supper dishes of Xi'an.

If there is a place in Xi'an you have to go, it must be the Muslim food street. The Muslim street is the gathering place of the delicious food vendors in Xi'an. You can find various tasty, unique and traditional foods here. My favourite one is "Yangrou Paomo", a tasty

The night views of Xi'an.

Xi'an views

Xi'an specialty that consists of a mutton soup served with wheat flour flat bread. The hard bread is broken up and added to the soup. If you want to show you are a local gastronome, try to break the hard bread with your hands, as small as possible. After several minutes' concoction and boiling, the bowl of delicious Yangrou Paomo will be served to your table for you to enjoy. Then the mixture is eaten along with pickled garlic cloves.

Another dish the Xi'an locals like very much is "Liang Pi", the Xi'an cold noodles. The most famous so far is called Qinzhen Cold Noodle, and it's recipe dates back to the Qin Dynasty (221–206 BC). It is said that the residents of the city of Qin could not afford to pay the tax, so instead they paid the emperor with cold noodles. The emperor liked the noodles and reduced the tax for that town. Since then, the cold noodle has become famous and welcomed by locals. The cold noodle is made from steaming rice milk. It's a combination of slices of the steamed rice milk with variable spices and vegetables such as cucumber and bean sprout. The sauce dressing the cold noodle determines the taste of the noodle. Though each restaurant has its own secret recipe, the important compositions of the sauce are hot chili oil, Chinese rice vinegar and sesame seed paste.

The sweet desserts in Xi'an.

"Chinese hamburger" is another wonderful dish, that's what we call it in English, but this hamburger is totally different from the one you eat in western countries. If you are in Xi'an, you can see some small restaurants along the streets which sell this local specialty. When you take a closer look, you will find each restaurant is equipped with a typical stove with a big pot next to it. The cook will put the hand-made pancake in the fire heated stove heated to bake. But what is in the pot? The answer is pork stew, which cooked over 4 hours with over 30 ingredients, including spring onion, ginger, aniseed etc. The well-done pork is then put into the pancake and served.

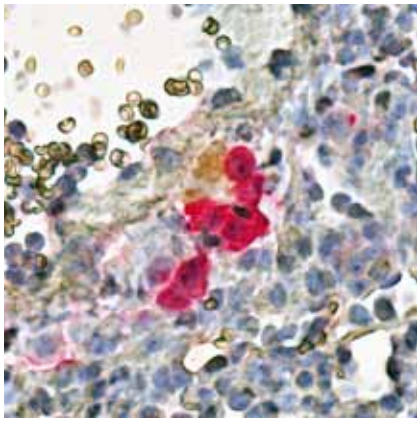
The 4 typical traditional foods in Xi'an: Rou jia mo (Chinese hamburger), Liang Pi (cold noodles), Kao youmo (baked bread with cumin) and Yangrou Paomo (Pancake in mutton soup)

How many different types of food are there in Xi'an? Nobody knows. From the Xi'an Muslim street alone, there are more than 200 types of snacks and special dishes, including: Sour Soup Dumplings (Suantang Jiaozi), Steamed dumplings with Stuffed Hot Gravy (Guantang Bao), Chinese lamb kebabs (Yangrou Chuan), steamed sticky rice with a rose flavored jam (Jing Gao), Stir-fried Starch Rice Tofu (Chao Liangfen), Persimmon Osmanthus Pancake (Shizi Bing) ….

Want to lose weight when you are in Xi'an? It is too difficult.

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



. . . führt uns Nicola Aceto in sein Forschungsgebiet Cancer Metastasis ein

. . . erfahren wir von Frances Kern, wie das Projekt Caredor Waisenkinder in Kamerun unterstützt

. . . gehen wir mit Mike Abanto auf Hummerfang in Florida

. . . geben erfahrene Fussballfans Tipps, wie man am besten die EM geniesst

. . . starten wir das grosse Urlaubspostkartenspiel

Die Sonne scheint für dich – deinetwegen; und wenn sie müde wird, beginnt der Mond, und dann werden die Sterne angezündet.

Es wird Winter, die ganze Schöpfung verkleidet sich, spielt Verstecken, um dich zu vergnügen.

Es wird Frühling; Vögel schwärmen herbei, dich zu erfreuen; das Grün sprießt, der Wald wächst schön und steht da wie eine Braut, um dir Freude zu schenken.

Es wird Herbst, die Vögel ziehn fort, nicht weil sie sich rar machen wollen, nein, nur damit du ihrer nicht überdrüssig würdest.

Der Wald legt seinen Schmuck ab, nur um im nächsten Jahr neu zu erstehen, dich zu erfreuen....

All das sollte nichts sein, worüber du dich freuen kannst?

Lerne von der Lilie und lerne vom Vogel, deinen Lehrern: zu sein heißt: für heute dasein – das ist Freude.

Lilie und Vogel sind unsere Lehrer der Freude.

Søren Aabye Kierkegaard
(1813 – 1855), dänischer Philosoph,
Theologe und Schriftsteller