

The background of the cover is a photograph of a cobblestone street. In the foreground, there is a vintage metal water fountain. The fountain has a cylindrical body with a decorative top and a curved spout on the side. Water is flowing from the spout onto the cobblestones. The fountain shows signs of age and weathering, with some rust and discoloration. The cobblestones are dark and wet, reflecting the light.

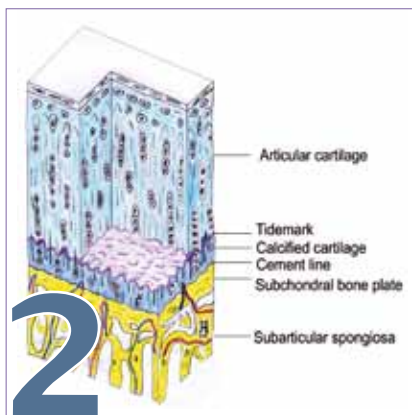
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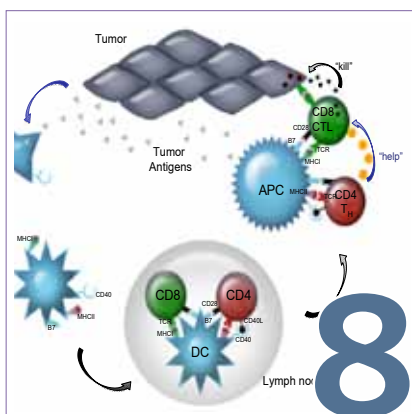
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**Muskuloskeletal Research: Form follows Function | Harnessing
the immune system to treat cancer: from mouse models to
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IMPRESSUM

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EDITORIAL



Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Die Tage werden länger, die Temperaturen steigen, der Frühling kündigt sich an. Zeit für die neueste Ausgabe der DBM Facts. Arbeitsintensive Wochen liegen hinter uns, die Research Days mit dem Besuch des Scientific Advisory Boards im Januar 2011 sind gut verlaufen und haben uns viele neue Impulse gebracht.

Weiteres Erfreuliches gibt es zu berichten: Die Basler Regierung hat Anfang März unseren Antrag zur Umnutzung der Medizinischen Bibliothek zu Forschungslabors positiv beurteilt und mit einer befürwortenden Empfehlung an den Grossen Rat weitergeleitet. Wir hoffen sehr, dass dieses für uns und die Medizinische Fakultät so wichtige Projekt bald realisiert werden kann. Vor kurzem ist Daniel Bodmer zum Ordinarius für Oto-Rhino-Laryngologie ernannt worden. Er wird gleichzeitig Chefarzt der HNO-Klinik. Giandomenica Iezzi wurde vom SNF für eine Förderungsprofessur ausgewählt und wird noch in diesem Jahr ihre eigene Forschungsgruppe am DBM aufbauen. Albert Neutzner wurde von der Departementsleitung zum Forschungsgruppenleiter der «Ocular Pharmacology and Physiology» ernannt. Toni Krebs hat seine Tätigkeit als Facs-Operator aufgenommen und wird Emmauel Traunecker tatkräftig in der Core Facility Flowcytometry am DBM USB unterstützen. Allen herzliche Gratulation und gutes Gelingen bei ihren neuen Aufgaben!

In der nun vorliegenden Ausgabe erfahren wir von Magdalena Müller-Gerbl mehr über Muskuloskeletal Research und weitere Aktivitäten in der Anatomie (ab Seite 2) und Alfred Zippelius führt uns in die Welt der Cancer Immunology ein (ab Seite 8). Die neuesten Publikationen, beginnend mit dem Nature Paper der Forschungsgruppe Primo Schär, finden Sie ab Seite 14 und noch so vieles andere mehr.

Viel Spass bei der Lektüre und Frohe Ostern!

Dear Readers

The days are getting longer, the temperatures rising and spring is making itself known. Time for the latest issue of DBM Facts. Many work intensive weeks are behind us; the Research Days with the visit of the Scientific Advisory Boards in January 2011 went well and brought us many new incentives.

Another piece of pleasing news: at the start of March the Basel administration positively evaluated our application to convert the medical library into research labs and has passed it on to the "Grossen Rat" recommending its acceptance. We hope that this project, which is so important to us and to the medical faculty, will soon be realised. Daniel Bodmer has recently been named as Professor of Oto-Rhino-Laryngology. He will also simultaneously be the head clinician of the HNO Clinic. Giandomenica Iezzi was awarded a Professorship by the SNF and will build her own research group at the DBM over the coming year. Albert Neutzner was named as research group leader of Ocular Pharmacology and Physiology by the departmental administration. Toni Krebs has taken up his position as Facs operator and will actively support Emmauel Traunecker in the flowcytometry core facility at the DBM USB. Congratulations to all and best wishes in your new positions.

In this issue we learn all about musculoskeletal research and other activities in anatomy from Magdalena Müller-Gerbl (from page 2) and Alfred Zippelius introduces us to the world of Cancer immunology (from page 8). The latest publications, starting with the Nature paper from the research group of Primo Schär, can be found from page 14 along with so very much more.

Happy reading and a happy Easter!

Muskuloskeletal Research: Form follows Function

Contrary to the announcement in the last DBM magazine, our research is not concerned with macroscopical anatomy, which is the part of health sciences and which deals with the description of the structure of the body of an organism, to the level of detail which can be reached only by the eye without the use of other equipment, such as microscopes. We, however, are working scientifically in the field of functional anatomy of the musculoskeletal system. At the end of this report I will describe briefly the work involved in my field of duties in gross-anatomy in the Anatomical Institute.

Introduction

In view of a steadily increasing number of persons suffering from degenerative joint disease, it is essential to obtain information on how a joint is loaded. For many years, numerous studies have been published dealing with the loading of joints. On the one hand, you have mathematical models, which can only give general and idealized information. On the other hand, there are a large number of cadaver studies with the great disadvantage that the complex *in vivo* interaction of the various joint structures - above all the muscle action - can never be simulated in an appropriate manner.

We therefore tried another approach, based on the known relationship between the function and morphology of the elements of the locomotor apparatus. The idea that mature tissue can adapt to the functional demands was put forward by Wolff, who suggested that the architecture of a bone is subject to a continuous process of remodeling brought about by mechanical stress. Carter was able to show that the loading history is responsible for the actual shape and mechanical properties of both cortical and cancellous bone.

This relationship between function and morphology is even more evident in the bony lamellae underlying the articular cartilage, the subchondral bone plate (Fig.1).

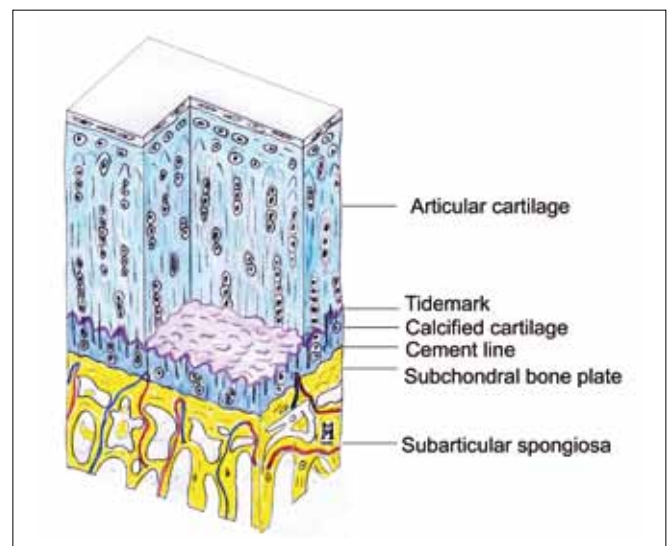


Fig.1: Schematic drawing of the different layers of articular cartilage, subchondral bone plate and subarticular spongiosa (from Madry, Mueller-Gerbl, 2010)

Pauwels stated that the density distribution in the subchondral bone represents a materialised field of stress caused by the time-integrated distribution of load over the joint surfaces. Several cadaver studies revealed that within a joint surface the actual distribution of mineralisation, thickness and structure of subchondral bone can be regarded as a morphological correlate of the loading history. Under pathomechanical conditions, these patterns depart from the normal, and thus reflect abnormal distribution of the load.

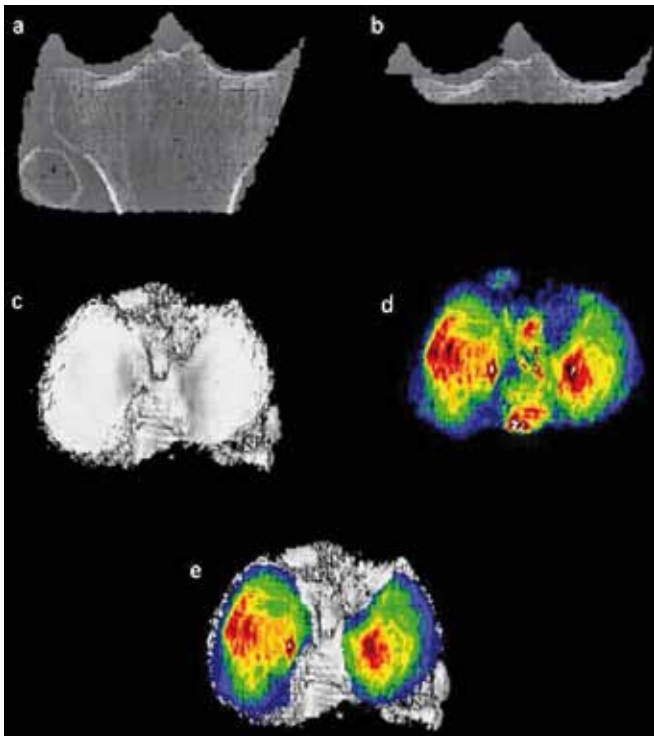


Fig.2: Method of CT-Osteoabsorptiometry (CT-OAM)

- a. Virtual exarticulation**
- b. Segmentation of the subchondral bone plate in single CT-sections**
- c. Reconstruction of the articular surface of the tibial plateau (seen from above)**
- d. Display of the subchondral mineralization distribution by means of a MIP-algorithm**
- e. Construction of the densitogram by superimposition of (c) and (d)**

The challenge now is to analyse the underlying causal mechanisms and the temporal course of the loading history in such a way, that even the change of single factors can be used to estimate, on the one hand predictions of planned adaptation phenomena, and on the other hand the success of operations which have already performed or of other therapies.

We therefore developed the method of CT- Osteoabsorptiometry (CT-OAM), for displaying the subchondral mineralisation patterns in the living and investigated in several studies possible applications of this technique. CT-Osteoabsorptiometry is based upon conventional CT data sets. The images are uploaded into an image analyzing system (ANALYZE, Mayo Clinic, Rochester, MN) for further processing (Fig.2).

In a first step the articular surface is isolated for three-dimensional reconstruction. Then, in a second editing

step, the subchondral plate is isolated in the individual slides and reconstructed three-dimensionally by means of maximum intensity projection. This allows mineralisation distribution to be visualized. For better illustration of mineralisation distribution, a false-colour representation was chosen, where each Hounsfield unit ($<200\text{HU}$ - $>1,200\text{HU}$) was assigned one colour. The final superimposing of the false-colour representation over the reconstructed joint resulted in the densitogram. Density values $>1,200\text{HU}$ are represented in black. Dark red, light red, yellow and light blue are used for the other values (in descending order). The resulting densitogram shows the topographical mineralisation patterns of an articular surface. Greater density is regularly found in the more heavily loaded regions of the joint surface.

It must be stressed that the method described is not primarily thought to calculate absolute values. The primary aim is to illustrate the relative difference in concentration (density) within a joint surface. Contrary to the normal methods using the CT-Densitometry for osteoporosis diagnostics, the CT-Osteoabsorptiometry can only be used to produce good reproducible results in subchondral bone lamellae and compact bones, due to different radiological effects. An objective, quantitative density measurement can be obtained over time using a reference phantom.

Application of CT-Osteoabsorptiometry (CT-OAM) in the human knee-joint

Several studies confirmed that each joint surface has regular reproducible patterns of density distribution, and it can be suggested that these are correlated with the mechanical situation in the joint and reflect the long-term stress acting there.

In healthy subjects the density distribution in the tibial plateau (knee-joint) exhibits a central maximum in the medial and lateral compartment (Fig. 3a). From each of these, the density values decrease concentrically toward the periphery. These findings indicate a more-or-less even stress distribution.

In patients with malalignment of the knee joint such as bow-leg or knock knees, the density patterns devi-

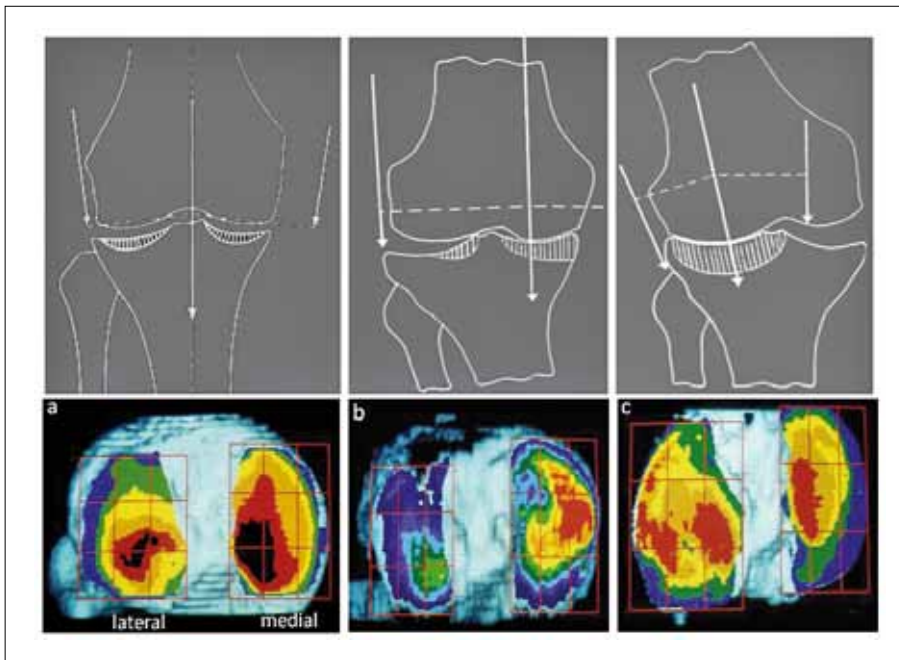


Fig.3: Mineralisation distribution (densitograms) of the tibial plateau (seen from above). In the upper row the corresponding stress diagrams (Maquet, 1976)

- a. 34 year old healthy man: central maximum laterally and medially.**
- b. Female patient with genu varum: displacement of the medial maximum towards the medial edge, reduced mineralization laterally.**
- c. Patient mit genu valgum: additional, marginal maximum laterally, decreased density medially.**

ate from the normal: In cases of genu valgum (fig. 3c), the density was considerably raised in the region of the lateral tibial condyle, where it showed an extended maximum. In the medial condyle, on the other hand, the density was reduced. With genu varum (Fig.3b) the position was reversed: the density was significantly lowered laterally and markedly raised medially. Apart from an increase of the density in the medial condyle the density maximum was displaced towards the medial edge. These patterns probably reflect the overall load distribution in the malaligned knee.

The CT-osteabsorptiometric investigation - a method which can be applied to the living person - showed significant changes in the density pattern compared with the preoperative situation 1 year after a correction osteotomy in patients with genu varum (Fig.4). With this comparative study it has been possible for the first time to establish in human subjects that changes in the subchondral density are an adaptation to an altered mechanical situation based on a change in the local stress.

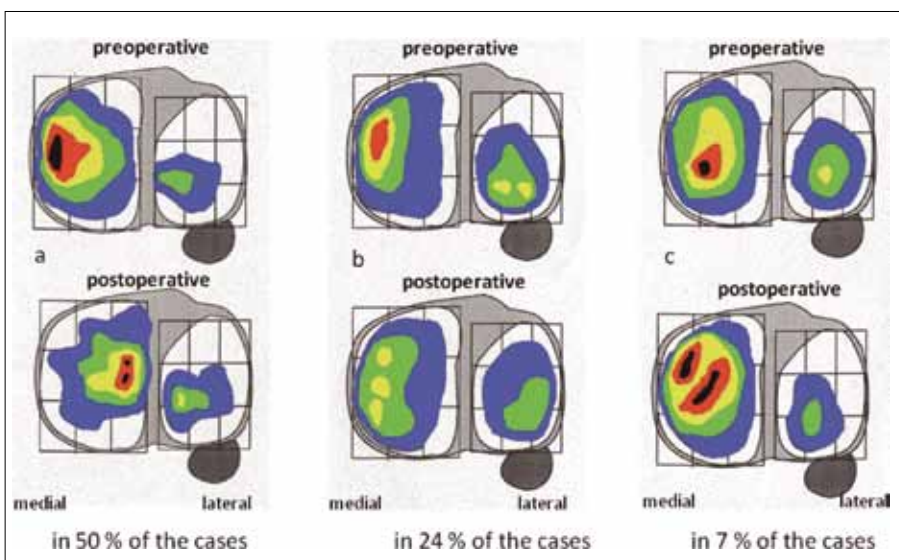


Fig.4: Mineralisation distribution (redrawn from the densitograms) of patients with genu varum, preoperatively and 1 year after operation respectively

- a. Changes of the densitogram in the sense of a return to normal displacement of the medial maximums towards central, increase in density laterally**
- b. Beginning dissolution of the marginal medial maximum**
- c. Appearance of an additional marginal, medial maximum und continuing demineralization laterally in the sense of worsening.**

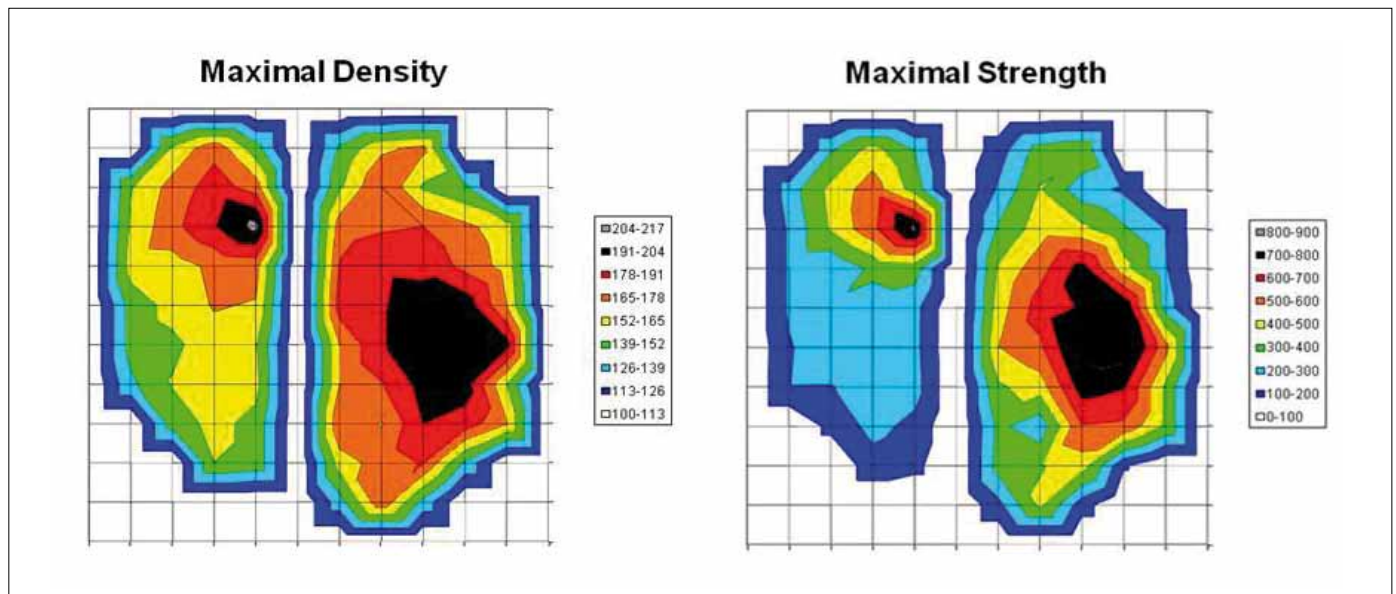


Fig.5: Schematic drawing of density (HU-values converted in gray values) and strength values (N) in the same tibial plateau (seen from above)

In experimental studies in sheep, we could demonstrate that the effects of the removal of the meniscus, implantation of meniscus transplants as well as reconstruction procedures of the anterior cruciate ligaments (ACL) are reflected in altered density patterns.

CT-Osteoabsorptiometry has been proven to provide a new, non-invasive tool, which allows each individual mechanical situation to be assessed *in vivo*. A wide variety of applications in basic research, clinical research and clinical practice are possible.

Correlation between structural parameters and mechanical properties

Another study addressed the question whether these density patterns correlate with mechanical properties of subchondral bone. For this purpose, we measured in the same tibial plateaus both strength (indentation testing) and density values of the subchondral plate at about 72 locations within the joint surfaces. We found a significantly high correlation between the distribution of the strength and that of the mineralization (Fig. 5). This proves that the subchondral mineralization pattern - which can be evaluated *in vivo* - reflects not only the density distribution, but also the distribution of material properties such as strength. In this way the density

values can be used to provide information about the bone quality of individual joints in living patients.

A comparison between the various studies of the thickness and density distribution, the distribution of various mechanical parameters (such as strength, stiffness and hardness) the distribution of the vascular density of the subchondral plate (particularly in the tibial plateau, where they are investigated most of all) shows that these findings are in complete agreement with each other. At places within the joint where the stress is assumed to be greatest, the density is higher, the thickness greater and the vascularization more strongly developed. It can also be assumed that the local expression of all these parameters depends upon the distribution of stress acting on the articular surface.

Outlook

As these differences within a joint surface are not restricted to the subchondral bone plate but extend into the subarticular spongy bone, we are investigating structural and numerical parameters in the depth of a joint by means of micro-CT.

As CT-Osteoabsorptiometry (CT-OAM) is, up to now, a time-consuming procedure, which requires an excel-



Fig.6: Transparent slice of the human foot

Fig.7: Corrosion specimen of the head-neck arteries with a four colour injection technique

lent knowledge of the cross-sectional anatomy of the subchondral bone plate, we are working together with the Department of Informatik (Thomas Vetter, Thomas Albrecht) on a further development of this method, which allows the representation of these mineralisation patterns in a much shorter time and in a less complicated manner to make it suitable for routine clinical applications.

Duties of a macroscopic (gross) anatomist

A so-called macroscopic anatomist has a very varied field of activity, which includes research as well as teaching, which can be very time-consuming. In addition to lectures on macroscopic and microscopic anatomy, which are part of almost every module (Themenblock), there are also courses to be given to medical students in anatomical dissection, histology and the study of the brain. A further activity is the preparation and conservation of cadavers as well as the preparation of demonstration specimens. In addition to the classical process of formalin conservation and preparation, we apply new techniques including plastination (Fig.6) and corrosion technique (Fig.7).

Postdoctoral training and advanced training is also of growing importance at the Anatomical Institute. This

includes courses for surgeons (teaching surgical techniques, testing new operational access paths, new plates and screws etc.), puncture and infiltration courses, as well as anatomical repetition courses for doctors, specialists, physiotherapists and other medical personnel. For these courses, new methods of conservation need to be tested and used, in order to preserve the flexibility and colour of the cadaver. Last year 42 courses, both national and international, took place in our institute.

An additional duty in Basel is the management of the Anatomical Museum, which is a public, university museum welcoming about 20'000 visitors per year. The duties include the maintenance and improvement of the permanent exhibition, as well as the conception and organisation of special exhibitions (the present exhibition is entitled «Die verschiedenen Gesichter des Gesichts»). These exhibitions are set up in close cooperation with clinical colleagues, who have the opportunity to show to the broad public their field of work and the latest research developments in their clinical field. Guided tours (Fig.8) and workshops for children (Fig.9) are also organised, for example, to study the brain, the face or learn about the techniques for macerating bones.

Magdalena Müller-Gerbl



Fig.8: Guided Tour through a special exposition about the brain



Fig.9: Brain workshop for children



Team of Magdalena Müller-Gerbl: Back row (from left to right): Sebastian Hoechel, Valentin Zumstein, Marko Kraljevic, Magdalena Müller-Gerbl, Roger Kurz, Mireille Toranelli, Peter Zimmermann, Piotr Ireneusz Maly. Front row (from left to right): Luminita Göbbel, Jean-Paul Bögl, Rosmarie Jucker, Hanna Pacek.

Harnessing the immune system to treat cancer: from mouse models to patients and vice versa



Group "Cancer Immunology" (from left: Yvonne Fink, Alfred Zippelius, Béatrice Dolder-Schlienger, Philipp Müller, Kea Martin, Grzegorz Terszowski)

Over the past two decades major technical and conceptual advances have led to a refined understanding of the protective immunity against tumors. The release of two large clinical immunotherapy trials showing an improved overall survival benefit in cancer patients has very recently raised hopes in the oncologic community to effectively stimulate therapeutic immunity to cancer. Our group is interested in dissecting the molecular events underlying the cross talk between the immune system and the tumor and hence develops strategies to

augment anti-tumor T cell responses. In particular, we are exploring the emerging concept that future therapeutic benefit will strongly depend on the clinical development of strategies combining different anti-cancer therapies such as chemo-/targeted therapy and immunotherapy. Ideally, combined treatment strategies abrogate specific mechanisms of local immune tolerance and additionally overcome limitations of cytotoxic anti-cancer therapies. In the laboratory, we follow a two-step approach which includes both the immunologic

monitoring of cancer patients, and the development of tumor models; the latter can be utilized to investigate the underlying mechanisms of immuno-modulation exerted by anti-cancer therapies and their potential synergy with immunotherapy. We believe that more detailed mechanistic insights into network interactions between the immune system and the tumor gained from our work with these models will ultimately foster the development of rationally designed therapeutics and translate our insights back into clinical practice.

Tumor Immuno-Surveillance

Using extracts of pyogenic bacteria to induce anti-tumor immune responses, William Coley pioneered cancer immunotherapy over a century ago. In the late 1950s, as immunologists gained an improved knowledge of tumor immunobiology and transplantation, Burnet, Thomas and Medawar proposed the first of several key concepts that corroborate our understanding of immune-surveillance against cancer: the immune system is capable of recognizing cancerous and/or pre-cancerous cells as foreign and eliminates them before they cause harm (Burnet, Brit Med J 1957). While initial experiments performed in partially immunodeficient mice in the 1970s provided arguments against this hypothesis, recent studies have indeed shown that molecularly defined deficiencies in innate and/or adaptive immune components such as the recombinaase activating gene (RAG)-2 and the IFN- γ pathway enhance the susceptibility of the host to both chemically induced and spontaneous tumors (Shankaran, Nature 2001). With this experimental evidence of immune protection against cancer, however, there has been a growing recognition that the immune system may also promote the emergence of tumor cell clones that exhibit reduced immunogenicity and are capable to escape immune recognition. These findings prompted the development of the cancer immuno-editing concept, a dynamic process composed of three phases: an *elimination phase* which includes adaptive tumor immuno-surveillance (Figure 1), followed by an *equilibrium phase* with selection of less immunogenic tumor variants, and an *escape phase* with outgrowth of these tumor variants. Tumor escape is accomplished through a multitude of mechanisms including tumor-intrinsic changes such as altera-

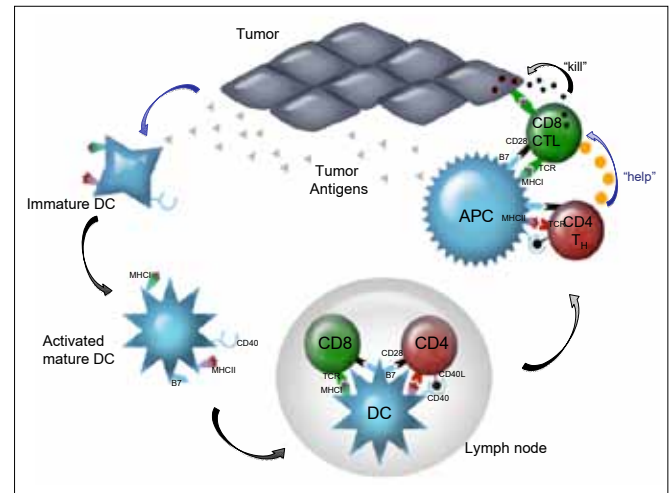


Figure 1: The adaptive immune response to tumor antigens (adapted from Smyth, Nat Immunol 2001).

tions in antigen expression and presentation pathways or potentially immunosuppressive mechanisms in the tumor microenvironment such as extrinsic suppression by regulatory cell populations (Vesely, Ann. Rev. Immunol 2011). In cancer patients all three phases may occur simultaneously at different tumor sites; importantly, most, if not all, tumors that are clinically detectable have evaded immunological control. Clinical evidence supporting the notion of cancer immuno-surveillance in humans is provided by a number of findings. First, tumor-specific response can be detected in a significant proportion of cancer patients and can be induced or boosted by immunization; second, the risk of developing tumors considerably increases in immunocompromised patients such as organ transplant recipients; and third, the presence of effector lymphocytes in a tumor has been correlated with improved clinical outcome in several cancers including melanoma, prostate, renal cell, ovarian and colorectal cancer.

Spontaneous and therapy – induced immune responses in cancer patients

In 1991, the first T-cell defined antigens (MAGE-1, tyrosinase, and Melan-A) were identified from two melanoma patients that had a favourable clinical outcome (van der Bruggen, Science 1991). Today, the list of tumor antigens is long and comprises different categories including differentiation antigens, mutated antigens, viral antigens and cancer testis antigens. The latter antigens represent an important category of antigens, as they are not ex-

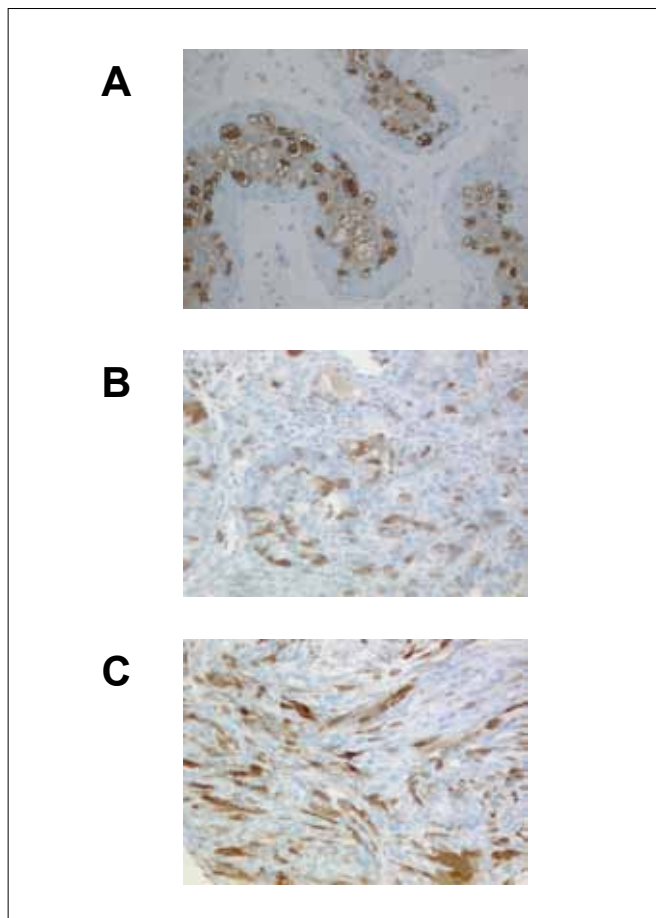


Figure 2: Expression of Cancer Testis (CT) Antigens in normal and tumor tissue. Immunohistochemical staining against the CT antigen CT7/MAGE-C1 in testis (a), squameous cell carcinoma of the skin (b), and malignant melanoma (c).

pressed in non-malignant cells except for gametogenic tissues, but show a broad expression in a large variety of cancer and are highly immunogenic (Figure 2; Simpson, Nature Rev Cancer 2005). NY-ESO-1, initially identified by SEREX in New York from a patient with esophageal cancer, is among the most immunogenic tumor antigens defined to date. Yet, though T cells specifically

directed against those tumor antigens are frequently found at the tumor site (Zippelius, J Exp Med 2002), in most cases they cannot control malignant growth. Several mechanisms of immune tolerance in anti-tumor immunity have been identified. This includes the induction of a state of lymphocyte quiescence which is reflected by the observation that T cells residing in tumor lesions lack robust effector functions and is in contrast to effector functions assessed in circulating T cells (Figure 3; Zippelius, Cancer Res 2004). Tumor escape such as down-regulation of tumor antigen expression has also been observed upon specific immunotherapeutic approaches which is illustrated by a clinical observation we made in a patient with NY-ESO-1 expressing metastatic melanoma. Upon immunization with a recombinant viral construct encoding for NY-ESO-1 which elicited a marked specific humoral and cellular immune response, the metastatic lesions regressed and the patient remained in remission for more than 9 months. Then, a single brain metastasis appeared which upon resection turned out to be NY-ESO-1 negative (Figure 4).

The identification of tumor antigens has given substantial impetus to the immunotherapy of cancer, in particular cancer vaccines. Though many of these vaccines have resulted in the development of humoral and cellular immune responses, only a limited number of treated patients experienced clinical regression in innumerable phase I/II clinical trials. Only recently, sipuleucel, an autologous prostatic acid phosphatase (PAP)-loaded dendritic cell vaccine, has demonstrated a statistically significant improvement in overall survival in patients with metastatic, castration-resistant prostate cancer (Kant-

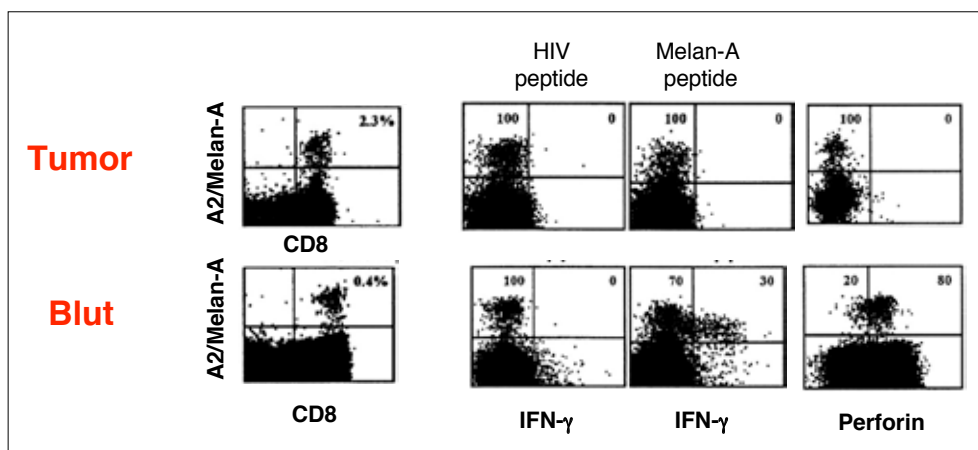


Figure 3: Functional tolerant Melan-A specific T cells at the tumor site compared with circulating T cells exhibiting full effector functions.

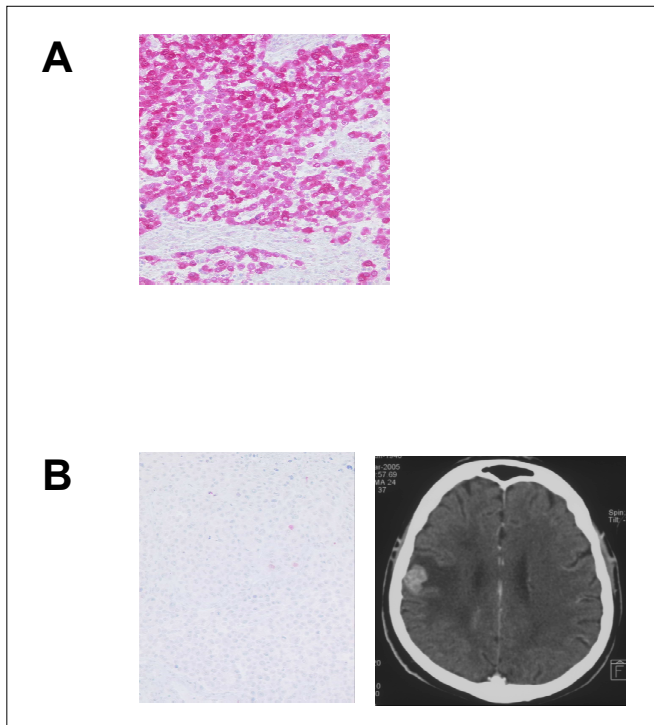


Figure 4: Immunohistochemical staining against the CT antigen NY-ESO-1 in a patient with metastatic melanoma before (a, primary tumor) and after specific vaccination (b, brain met).

off, New Engl J Med 2010). A more profound knowledge of T-cell inhibitory pathways that may significantly hamper successful immunotherapy has led to develop novel immunotherapy approaches. Among these, ipilimumab, a fully human ab against CTLA-4, is a first-in-class T cell activator which has demonstrated superior overall survival in patients with metastatic melanoma receiving ipilimumab compared with a gp100 vaccine (Figure 5; Hodi, New Engl J Med 2010). Of clinical importance, the data provide evidence that a substantial frequency of patients receive durable benefit.

Mouse Tumor Models

Mouse tumor models have been used to gain a deeper understanding of the underlying mechanisms of cancer immunoediting. Transplantation of primary or cultured tumor cells is commonly used (Figure 6). However, these models are limited as large numbers of fully developed, rapidly growing tumor cells are introduced and transplantation may induce a pro-inflammatory response. To overcome these experimental limitations, we are using a genetically engineered mouse model of non-small cell lung cancer that provides spatiotemporal control of tumor onset and mimics the genetic and histopathologi-

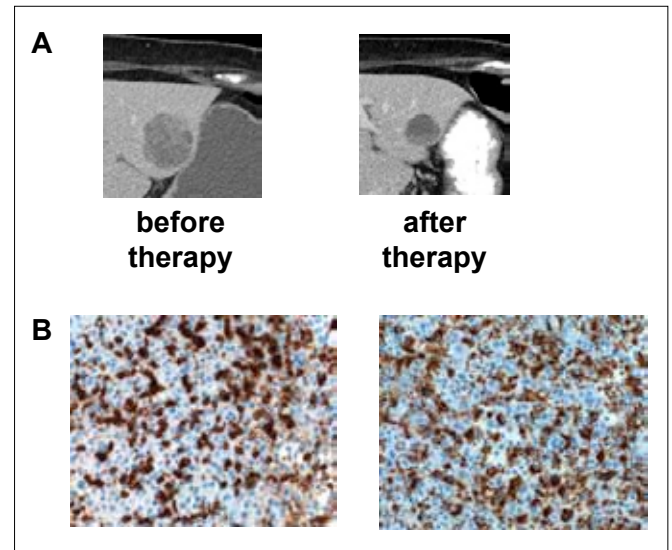


Figure 5: Clinical outcome (a, regression of a lymph node metastasis) and histopathologic analysis (b and c, CD8 and CD68 staining of a subcutaneous metastasis, respectively) of a melanoma patient treated with ipilimumab.

cal features of the human disease. Importantly, it has recently been demonstrated to faithfully model clinical responses upon treatment with cytotoxic and targeted therapies approved for human NSCLC (DuPage, Nat Prot 2009; Singh, Nat Biotech 2010). Tumorigenesis is driven by the conditional expression of oncogenic K-ras^{G12D} in combination with ablation of p53. Tumor formation is initiated in K-ras^{LSL-G12D/+}; p53^{fl/fl} mice by topical application of lentiviral vectors expressing Cre recombinase (Figure 7).

Modulation of specific immunity upon anti-cancer therapy

Owing to their dose-limiting myelosuppressive toxicities, chemotherapy and radiotherapy have been histori-

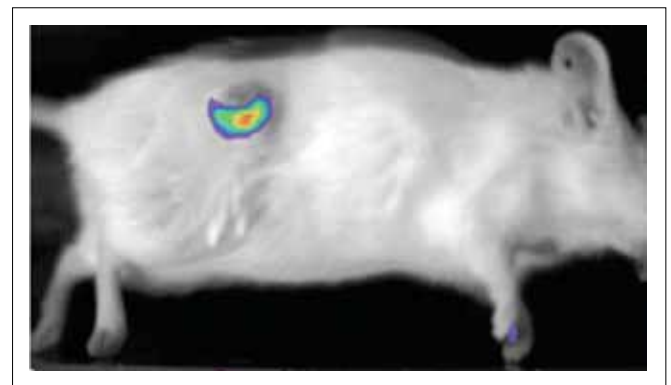


Figure 6: In vivo bioluminescence imaging in an implantable tumor model using NightOWL device.

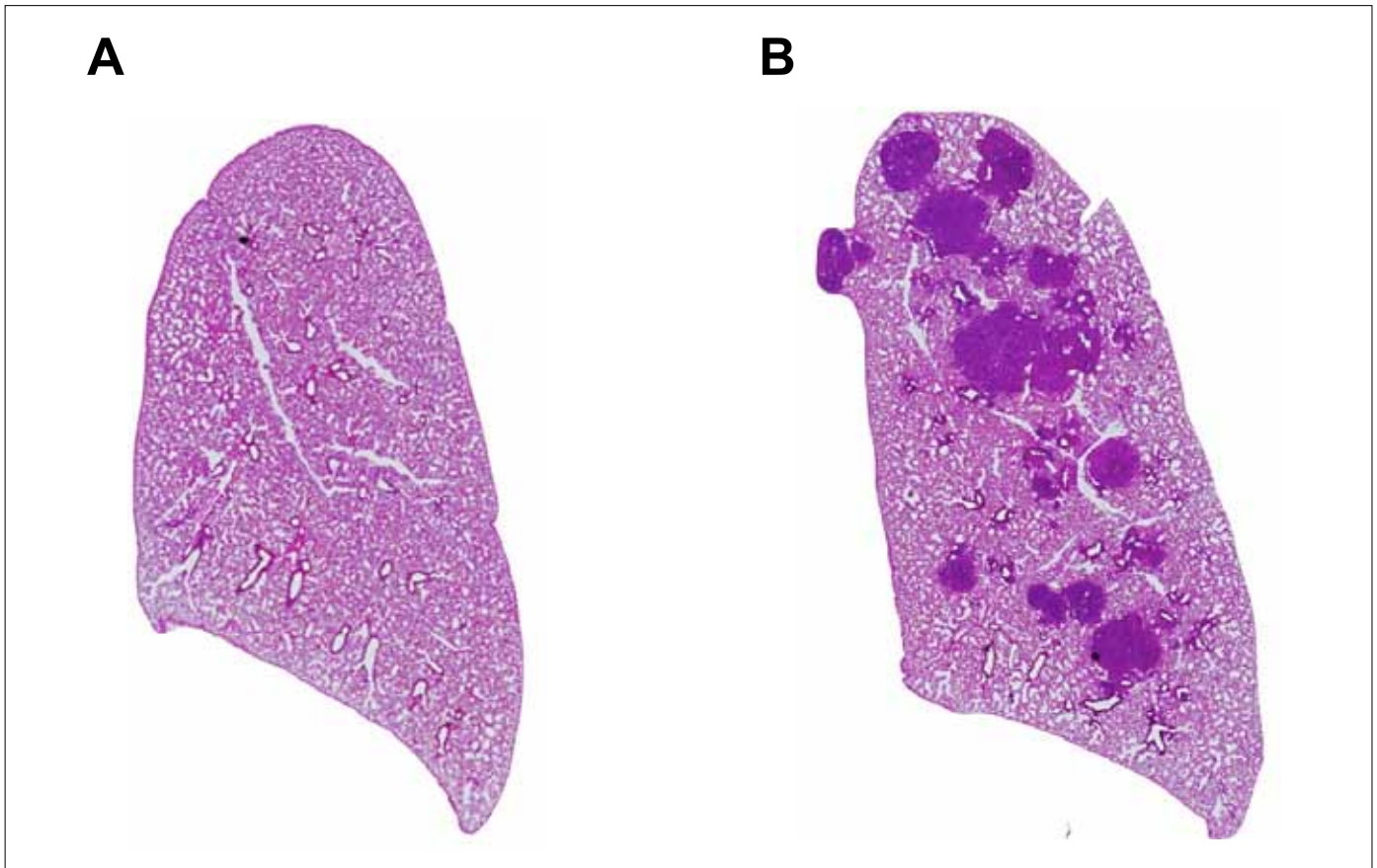


Figure 7: Histologic assessment of lung tissue in tumor bearing *K-ras^{LSL-G12D/+}; p53^{fl/fl}* mice (+AdCre; a) and tumor-free mice (-AdCre; b); in collaboration with M. Pittet, MGH.

cally considered detrimental to anti-tumor immunity. Interestingly, and in contrast to what was previously thought, there is recent evidence that some cytotoxic therapies can enhance anti-tumor immunity. For example, selected agents increase the immunogenicity of dying cancer cells, inhibit the function of regulatory T cells, deplete myeloid derived suppressor cells or trigger DC maturation (Zitvogel, Nat Rev Immunol 2008). Indeed, though the precise mode of action *in vivo*, schedules and doses remain largely unexplored, strategies that combine cytotoxic and immune therapies are increasingly integrated into the therapeutic armamentarium in clinical oncology. We believe that clinical efficacy of novel targeted immuno-modulating compounds such as ipilimumab can be further increased by using rationally designed combination therapies.

Our group is particularly interested to dissect mechanisms implicated in altering the specific anti-tumor immune response and in modifying the local microen-

vironment upon treatment with combinatorial immunotherapy. In addition, we intend to identify immunologic signatures in the tumor micro-environment which may predict therapeutic responses. Our scientific aim is to translate our findings to the clinic to develop novel immuno-based therapies.

Acknowledgements: We would like to thank our collaborators for their great support and fruitful discussions, in particular Ed Palmer (Transplantation Immunology, DBM), Mikael Pittet (MGH, Boston), Lukas Bubendorf and Spasenija Savic (Pathology, UHBS), Silke Potthast and Gregor Sommer (Radiology, UHBS) and our clinical collaborators (Michael Tamm, Pneumology; Didier Lardinois, Thoracic Surgery; Daniel Bodmer, ENT; all UHBS).

Alfred Zippelius

Dissertationen

Seit dem 29. November 2010 darf sich **Daniela Thommen** von der Forschungsgruppe Molecular Nephrology (Departement Biomedizin USB) nach ihrer medizinischen Dissertation nun auch in den Naturwissenschaften Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Endothelial cells as targets for antigen-specific cytotoxic T lymphocytes".

Am 15. Dezember 2010 stellte sich **Peter Mullen** von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "Molecular mechanisms of statin-induced myotoxicity".

Mit der Doktorprüfung am 25. Februar 2011 schloss **Anne-Kathrin John** von der Forschungsgruppe Infection Biology (Departement Biomedizin USB) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "Staphylococcal response to daptomycin in implant-associated infections".

Habilitationen

Venia docendi für **Martin Stern**

Die Regenz der Universität Basel hat in ihrer Sitzung am 9. März 2011 Martin Stern von der Forschungsgruppe Immunotherapy (Departement Biomedizin USB) die Venia docendi für Hämatologie erteilt. Er ist nun befugt, den Titel eines Privatdozenten zu führen.

Beförderungen

Daniel Bodmer wird Ordinarius für Oto-Rhino-Laryngologie

Daniel Bodmer von der Forschungsgruppe Inner Ear Research (Departement Biomedizin USB) wurde vom Universitätsrat zum Ordinarius für Oto-Rhino-Laryngologie an der Medizinischen Fakultät der Universität Basel ernannt. Gleichzeitig wird er Chefarzt der HNO-Klinik am Universitätsspital Basel.

SNF-Förderungsprofessur für **Giandomenica Iezzi**

Giandomenica Iezzi von der Forschungsgruppe Oncology Surgery (ICFS/Departement Biomedizin USB) ist vom Schweizerischen Nationalfonds für eine Förderungsprofessur ausgewählt worden. Sie wird sich dem Thema "Analysis of immune-mediated mechanisms underlying the prognostic effect of T cell infiltration in human colorectal cancer" widmen.

Herzliche Gratulation an alle!

Selected publications by DBM members

Below 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. The DBM affiliation must be mentioned in the authors list as it appeared in 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 primarily concentrating on original articles. 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 April 30, 2011.

Nature

nature

470, 419–423, 2011

IF 34,4

Embryonic lethal phenotype reveals a function of TDG in maintaining epigenetic stability

Daniel Cortázar^{1*}, Christophe Kunz^{1*}, Jim Selfridge², Teresa Lettieri^{3,5}, Yusuke Saito¹, Eilidh MacDougall², Annika Wirz¹, David Schuermann¹, Angelika L. Jacobs¹, Fredy Siegrist⁴, Roland Steinacher^{1,5}, Josef Jiricny³, Adrian Bird² & Primo Schär¹

Abstract:

Thymine DNA glycosylase (TDG) is a member of the uracil DNA glycosylase (UDG) superfamily of DNA repair enzymes. Owing to its ability to excise thymine when mispaired with guanine, it was proposed to act against the mutability of 5-methylcytosine (5-mC) deamination in mammalian DNA¹. However, TDG was also found to interact with transcription factors^{2,3}, histone acetyltransferases⁴ and de novo DNA methyltransferases^{5,6}, and it has been associated with DNA demethylation in gene promoters following activation of transcription^{7,8,9}, altogether implicating an engagement in gene regulation rather than DNA repair. Here we use a mouse genetic approach to determine the biological function of this multifaceted DNA repair enzyme. We find that, unlike other DNA glycosylases, TDG is essential for embryonic development, and that this pheno-

type is associated with epigenetic aberrations affecting the expression of developmental genes. Fibroblasts derived from *Tdg* null embryos (mouse embryonic fibroblasts, MEFs) show impaired gene regulation, coincident with imbalanced histone modification and CpG methylation at promoters of affected genes. TDG associates with the promoters of such genes both in fibroblasts and in embryonic stem cells (ESCs), but epigenetic aberrations only appear upon cell lineage commitment. We show that TDG contributes to the maintenance of active and bivalent chromatin throughout cell differentiation, facilitating a proper assembly of chromatin-modifying complexes and initiating base excision repair to counter aberrant de novo methylation. We thus conclude that TDG-dependent DNA repair has evolved to provide epigenetic stability in lineage committed cells.

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*These authors contributed equally to this work.

Minimal T-cell requirements for triggering haemophagocytosis associated with Epstein–Barr virus-driven B-cell proliferation: a clinical case study

Thomas Daikeler¹, Alexandar Tzankov², Gideon Hoenger³, Olivier Gasser³, Alan Tyndall¹, Alois Gratwohl⁴, Christoph Hess^{3,5}

Abstract:

The pathophysiology of Epstein–Barr virus (EBV)-associated haemophagocytosis remains poorly understood.¹ In EBV-related haemophagocytic lymphohistiocytosis, EBV-infected CD8 T cells and natural killer cells are thought to trigger haemophagocytosis and the associated 'cytokine storm'/systemic inflammatory response syndrome (SIRS) directly.^{2–4}

By contrast, in the context of uncontrolled proliferation of EBV-infected B cells, hyperactively responding EBV-specific T cells are assumed to mediate haemophagocytosis/SIRS.⁵ Both the quantity and quality of such de-regulated EBV-specific T-cell reactivity remain undefined. Unique insight into basic aspects of the postulated T-cell requirements necessary to trigger haemophagocytosis was provided by the case of a 37-year-old woman with mixed connective tissue disease (ribonucleoprotein-Ab positive, severe pulmonary arterial hypertension, polyarthritis, pericarditis and oesophageal sclerosis). Immunosuppression with azathioprine and ciclosporin, as well as a 3-month trial of oral cyclophosphamide due to progressing pulmonary arterial hypertension was ineffective, yet worsened pre-existing lymphopenia. Based on the severe and cyclophosphamide-resistant course of the disease the indication for haematopoietic stem

cell transplantation (HSCT) was established. Before induction-therapy EBV-specific MHC I restricted T-cell reactivity was detectable using ELISpot technology,⁶ and EBV replication (whole-blood PCR) was controlled (figure 1). Subsequent conditioning (cyclophosphamide/ATG) further depleted CD4 and CD8 T cells and EBV-specific T-cell reactivity became undetectable (figure 1). Post-HSCT, the patient developed undulant low-grade fevers. Two months post-HSCT she was admitted with fever and coughing. Within 48 h, pulmonary infiltrations developed, and empiric antimicrobial therapy was initiated. Intriguingly, on the day of hospitalisation, CD8 (and to a lesser extent CD4) T-cell numbers had increased, and strong MHC I and, on this occasion also, MHC II-restricted EBV-specific T-cell responses could be elicited (figure 1).

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Toward modeling the bone marrow niche using scaffold-based 3D culture systems

Nunzia Di Maggio¹, Elia Piccinini¹, Maike Jaworski^{2,3}, Andreas Trumpp^{2,3}, David J. Wendt¹ and Ivan Martin^{1*}

Abstract:

In the bone marrow, specialized microenvironments, called niches, regulate hematopoietic stem cell (HSC) maintenance and function through a complex crosstalk between different cell types. Although *in vivo* studies have been instrumental to elucidate some of the mechanisms by which niches exert their function, the establishment of an *in vitro* model that recapitulates the fundamental interactions of the niche components in a controlled setting would be of great benefit. We have previously shown that freshly harvested bone marrow- or adipose tissue-derived cells can be cultured under perfusion within porous scaffolds, allowing the forma-

tion of an organized 3D stromal tissue, composed by mesenchymal and endothelial progenitors and able to support hematopoiesis. Here we describe 3D scaffold-based perfusion systems as potential models to reconstruct *ex vivo* the bone marrow stem cell niche. We discuss how several culture parameters, including scaffold properties, cellular makeup and molecular signals, can be varied and controlled to investigate the role of specific cues in affecting HSC fate. We then provide a perspective of how the system could be exploited to improve stem cell-based therapies and how the model can be extended toward the engineering of other specialized stromal niches.

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Enhanced excitation-coupled Ca^{2+} entry induces nuclear translocation of NFAT and contributes to IL-6 release from myotubes from patients with central core disease

Susan Treves^{1,2,3,*}, Mirko Vukcevic^{1,2}, Pierre-Yves Jeannet⁴, Soledad Levano^{1,2}, Thierry Girard^{1,2}, Albert Urwyler^{1,2}, Dirk Fischer^{5,6}, Thomas Voit⁷, Heinz Jungbluth^{8,9}, Sue Lillis¹⁰, Francesco Muntoni¹¹, Ros Quinlivan¹², Anna Sarkozy¹³, Kate Bushby¹³ and Francesco Zorzato^{1,2,3}

Abstract:

Prolonged depolarization of skeletal muscle cells induces entry of extracellular calcium into muscle cells, an event referred to as excitation-coupled calcium entry. Skeletal muscle excitation-coupled calcium entry relies on the interaction between the 1,4-dihydropyridine receptor on the sarcolemma and the ryanodine receptor on the sarcoplasmic reticulum membrane. In this study, we directly measured excitation-coupled calcium entry by total internal reflection fluorescence microscopy in human skeletal muscle myotubes harbouring mutations in the *RYR1* gene linked to malignant hyperthermia (MH) and central core disease (CCD). We found that excitation-coupled calcium entry is strongly enhanced in cells from

patients with CCD compared with individuals with MH and controls. Furthermore, excitation-coupled calcium entry induces generation of reactive nitrogen species and enhances nuclear localization of NFATc1, which in turn may be responsible for the increased IL-6 released by myotubes from patients with CCD.

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Oral administration of glucagon-like peptide 1 or peptide YY 3-36 affects food intake in healthy male subjects^{1,2,3}

Robert E Steinert, Birk Poller, M Cristina Castelli, Juergen Drewe, and Christoph Beglinger

Abstract:

Background: Peripheral infusion of glucagon-like peptide 1 (GLP-1) or peptide YY 3-36 (PYY3-36) reduces food intake in healthy, obese, and diabetic subjects. In vivo, both peptides are cosecreted from intestinal L cells; GLP-1 is subject to rapid breakdown by dipeptidyl peptidase IV, and together with PYY3-36 it is likely to be degraded in the liver before entering the systemic circulation. The largest concentrations are observed in the splanchnic blood rather than in the systemic circulation.

Objective: In contrast with peripheral infusion, oral delivery of sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) mimics endogenous secretion. We aimed to investigate how this affects food intake.

Design: Twelve healthy male subjects were studied in a randomized, double-blind, placebo-controlled, 4-way crossover trial. Each subject received in random order 2.0 mg GLP-1, 1.0 mg PYY3-36, or 2.0 mg GLP-1 plus 1.0 mg PYY3-36; the peptides were mixed with SNAC. The placebo treatment was the delivery agent alone. Food intake during an ad libitum test meal was measured.

Results: Both peptides were rapidly absorbed from the gut, leading to plasma concentrations several times higher than those in response to a

normal meal. GLP-1 alone, but not PYY3-36, reduced total energy intake significantly, with marked effects on glucose homeostasis. Coadministration of both peptides reduced total energy intake by 21.5% and fullness at meal onset ($P < 0.05$) but not total 24-h energy intake.

Conclusion: The results show a marked effect of orally administered GLP-1 and PYY3-36 on appetite by showing enhanced fullness at meal onset and reduced energy intake. This trial was registered at clinicaltrials.gov as NCT00822705.

¹ From the Clinical Research Center, Department of Biomedicine (RES, JD, and CB), and the Division of Gastroenterology and Hepatology (RES, JD, and CB), University Hospital, Basel, Switzerland; the Department of Biomedicine, University Hospital, Basel, Switzerland (BP); and Emisphere Technologies, Cedar Knolls, NJ (MCC).

² Supported by a grant from the Swiss National Science Foundation (no. 320000-118330). CB received an unconditional research grant from Emisphere Technologies, Cedar Knolls, NJ, for this study.

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Agonist-activated Ca^{2+} influx occurs at stable plasma membrane and endoplasmic reticulum junctions

Susan Treves^{1,2}, Mirko Vukcevic¹, Johanna Griesser¹, Clara-Franzini Armstrong³, Michael X. Zhu⁴ and Fancesco Zorzato^{1,2,*}

Abstract:

Junctate is a 33 kDa integral protein of sarco(endo)plasmic reticulum membranes that forms a macromolecular complex with inositol 1,4,5-trisphosphate [$\text{Ins}(1,4,5)P_3$] receptors and TRPC3 channels. TIRF microscopy shows that junctate enhances the number of fluorescent puncta on the plasma membrane. The size and distribution of these puncta are not affected by the addition of agonists that mobilize Ca^{2+} from $\text{Ins}(1,4,5)P_3$ -sensitive stores. Puncta are associated with a significantly larger number of peripheral junctions between endoplasmic reticulum and plasma

membrane, which are further enhanced upon stable co-expression of junctate and TRPC3. The gap between the membranes of peripheral junctions is bridged by regularly spaced electron-dense structures of 10 nm. $\text{Ins}(1,4,5)P_3$ inhibits the interaction of the cytoplasmic N-terminus of junctate with the ligand-binding domain of the $\text{Ins}(1,4,5)P_3$ receptor. Furthermore, Ca^{2+} influx evoked by activation of $\text{Ins}(1,4,5)P_3$ receptors is increased where puncta are located. We conclude that stable peripheral junctions between the plasma membrane and endoplasmic reticulum are the anatomical sites of agonist-activated Ca^{2+} entry.

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Kit Ligand and Il7 Differentially Regulate Peyer's Patch and Lymph Node Development

Stéphane Chappaz¹, Claudia Gärtner¹, Hans-Reimer Rodewald² and Daniela Finke¹

Abstract:

Hematopoietic lymphoid tissue inducer (LTi) cells initiate lymph node (LN) and Peyer's patch (PP) development during fetal life by inducing the differentiation of mesenchymal organizer cells. The growth factor signals underlying LTi cell development and LN and PP organogenesis remain poorly understood. LTi cells express the Il7r and the receptor tyrosine kinase Kit, whereas organizer cells express their cognate ligands. To determine the relative significance of Il7 and Kit signaling in LTi cell homeostasis and PP and LN development, we have analyzed mice deficient for Kit ($\text{Kit}^{\text{W/W}^v}$), Il7 ($\text{Il7}^{-/-}$), or both ($\text{Il7}^{-/-} \text{Kit}^{\text{W/W}^v}$). Unlike $\text{Kit}^{\text{W/W}^v}$ and $\text{Il7}^{-/-}$ single mutants, $\text{Il7}^{-/-} \text{Kit}^{\text{W/W}^v}$ mice were almost devoid of LTi cells in their mesenteric LN anlage. This LTi deficiency was associated with a block

in mesenchymal LN organizer cell generation and the absence of almost all LNs. In contrast, intestinal LTi cell numbers, PP organizer cell generation, and PP development were strongly affected by impaired Kit signaling, but were independent of Il7. Hence, Kit and Il7 act synergistically in LN organogenesis, whereas Kit signaling, but not Il7, critically regulates PP organogenesis and LTi cell numbers in the intestine. Consistent with these differential growth factor requirements for PP and LN development, PP organizer cells expressed higher *Kitl* and lower *Il7* levels than did LN organizer cells. Collectively, these results demonstrate that Kit and Il7 differentially control PP and LN organogenesis through the local growth factor-driven regulation of LTi cell numbers.

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An RGD-restricted substrate interface is sufficient for the adhesion, growth and cartilage forming capacity of human chondrocytes

Daniel Vonwil¹, Martin Schuler², Andrea Barbero¹, Simon Ströbel¹, David Wendt¹, Marcus Textor³, Ueli Aebi⁴, Ivan Martin¹

Abstract:

This study aimed at testing whether an RGD-restricted substrate interface is sufficient for adhesion and growth of human articular chondrocytes (HAC), and whether it enhances their post expansion chondrogenic capacity. HAC/substrate interaction was restricted to RGD by modifying tissue culture polystyrene (TCPS) with a poly(ethylene glycol) (PEG) based copolymer system that renders the surface resistant to protein adsorption while at the same time presenting the bioactive RGD-containing peptide GCRGYGRGDS₁₆ (RGD). As compared to TCPS, HAC cultured on RGD spread faster (1.9-fold), maintained higher type II collagen mRNA expression (4.9-fold) and displayed a 19% lower spreading area. On RGD, HAC attachment efficiency (66±10%) and proliferation rate (0.56±0.04 doublings/day), as well as type II collagen mRNA expression in the sub-

sequent chondrogenic differentiation phase, were similar to those of cells cultured on TCPS. In contrast, cartilaginous matrix deposition by HAC expanded on RGD was slightly but consistently higher (15% higher glycosaminoglycan-to-DNA ratio). RGD (bioinactive peptide) and PEG (no peptide ligand) controls yielded drastically reduced attachment efficiency (lower than 11%) and proliferation (lower than 0.20 doublings/day). Collectively, these data indicate that restriction of HAC interaction with a substrate through RGD peptides is sufficient to support their adhesion, growth and maintenance of cartilage forming capacity. The concept could thus be implemented in materials for cartilage repair, whereby in situ recruited/infiltrated chondroprogenitor cells would proliferate while maintaining their ability to differentiate and generate cartilage tissue.

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A bioluminescent mouse model of pancreatic β -cell carcinogenesis

Adrian Zumsteg, Karin Strittmatter, Daniela Klewe-Nebenius¹, Helena Antoniadis and Gerhard Christofori

Abstract:

The Rip1Tag2 transgenic mouse model of pancreatic β -cell carcinogenesis has been instrumental in identifying several hallmarks of cancer, including tumor cell evasion from apoptosis, tumor angiogenesis and tumor invasion. Moreover, Rip1Tag2 mice have been helpful in the development and testing of innovative cancer therapies and tumor imaging protocols. However, based on tumor localization in the mouse, primary tumor growth and metastatic dissemination cannot be easily monitored in a longitudinal axis by non-invasive and low-technology approaches. Here, we report the generation of a new transgenic mouse line as a versatile tool to study β -cell carcinogenesis. Transgenic expression of a bicistronic messenger RNA encoding simian virus large T antigen and firefly luciferase in pancreatic β -cells recapitulates insulinoma development in

a reproducible multistage process. In the mouse line called RipTag-IRES-Luciferase line (RTL) 1, the β -cell-specific expression of luciferase allows the non-invasive monitoring of primary tumor growth over time *in vivo* and the detection and quantification of disseminated tumor cells and micrometastases in distant organs *ex vivo*. When crossed to mouse lines in which the expression of cancer 'modifier' genes has been manipulated, tumor initiation and tumor progression are similarly affected as previously reported for Rip1Tag2 mice, indicating a robust tumor progression pathway shared between the two different transgenic mouse lines. Together, the data indicate that the RTL1 mouse line will be of great value to study anti-tumoral therapeutic approaches as well as to define the functional roles of cancer- and metastasis-related genes when crossed to appropriate transgenic or gene-targeted mouse lines.

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Tissue Engineering

Tissue Engineering

16, 6, 2063, 2010

IF 4,5

A Novel Three-Dimensional Culture System Allows Prolonged Culture of Functional Human Granulosa Cells and Mimics the Ovarian Environment

Katarzyna Kossowska-Tomaszczuk, Ph.D.^{1,2}, Pawel Pelczar, Ph.D.³, Sinan Güven, M.S.², Jacek Kowalski, M.D.⁴, Emanuela Volpi, Ph.D.⁵, Christian De Geyter, M.D.^{1,2}, and Arnaud Scherberich, Ph.D.²

Abstract:

The development of techniques allowing the growth of primordial follicles to mature follicles *in vitro* has much potential for both reproductive medicine and developmental research. However, human primordial and preantral follicles fail to grow after isolation from the surrounding ovarian stroma. Granulosa cells, which normally undergo apoptosis after ovulation, contain a subpopulation of ovarian follicular cells remaining viable *in vitro* over prolonged periods when cultured in the presence of leukemia-inhibiting factor. However, when cultured as monolayers, they progressively lose all their characteristics, such as follicle-stimulating hormone receptor and cytochrome P450-aromatase. Here, we describe

a three-dimensional culture system containing type I collagen, which, together with leukemia-inhibiting factor, allowed the survival and growth of a subpopulation of granulosa cells isolated from mature ovarian follicles and supported them to proliferate into spherical structures exhibiting steroidogenic capacity, as demonstrated by P450-aromatase and 3 β -hydroxysteroid dehydrogenase. After transplantation into the ovaries of immunodeficient mice, these cells became localized preferentially within antral follicles and the prolonged expression of follicle-stimulating hormone receptor was confirmed as well. With this optimization of the culture conditions, an environment was created, which acts as a niche closely mimicking the development of early ovarian follicles *in vitro*.

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Plos One

PLOS one

5, 11, e14109, 2010

IF 4,3

Suppressive Effects of Vascular Endothelial Growth Factor-B on Tumor Growth in a Mouse Model of Pancreatic Neuroendocrine Tumorigenesis

Imke Albrecht¹, Lucie Kopfstein¹, Karin Strittmatter², Tibor Schomber¹, Annelie Falkevall^{4,5}, Carolina E. Hagberg^{4,5}, Pascal Lorentz¹, Michael Jeltsch³, Kari Alitalo³, Ulf Eriksson^{4,5}, Gerhard Christofori¹, Kristian Pietras⁴

Abstract:

Background: The family of vascular endothelial growth factors (VEGF) contains key regulators of blood and lymph vessel development, including VEGF-A, -B, -C, -D, and placental growth factor. The role of VEGF-B during physiological or pathological angiogenesis has not yet been conclusively delineated. Herein, we investigate the function of VEGF-B by the generation of mouse models of cancer with transgenic expression of VEGF-B or homozygous deletion of *Vegfb*.

Methodology/Principal Findings: Ectopic expression of VEGF-B in the insulin-producing β -cells of the pancreas did not alter the abundance or architecture of the islets of Langerhans. The vasculature from transgenic mice exhibited a dilated morphology, but was of similar density as that

of wildtype mice. Unexpectedly, we found that transgenic expression of VEGF-B in the RIP1-Tag2 mouse model of pancreatic neuroendocrine tumorigenesis retarded tumor growth. Conversely, RIP1-Tag2 mice deficient for *Vegfb* presented with larger tumors. No differences in vascular density, perfusion or immune cell infiltration upon altered *Vegfb* gene dosage were noted. However, VEGF-B acted to increase blood vessel diameter both in normal pancreatic islets and in RIP1-Tag2 tumors.

Conclusions/Significance: Taken together, our results illustrate the differences in biological function between members of the VEGF family, and highlight the necessity of in-depth functional studies of VEGF-B to fully understand the effects of VEGFR-1 inhibitors currently used in the clinic.

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⁵ Ludwig Institute for Cancer Research Ltd, Stockholm Branch, Karolinska Institutet, Stockholm, Sweden

Two Distinct Filopodia Populations at the Growth Cone Allow to Sense Nanotopographical Extracellular Matrix Cues to Guide Neurite Outgrowth

Kyung-Jin Jang¹, Min Sung Kim², Daniel Feltrin³, Noo Li Jeon², Kahp-Yang Suh^{1,2}, Olivier Pertz³

Abstract:

Background: The process of neurite outgrowth is the initial step in producing the neuronal processes that wire the brain. Current models about neurite outgrowth have been derived from classic two-dimensional (2D) cell culture systems, which do not recapitulate the topographical cues that are present in the extracellular matrix (ECM) *in vivo*. Here, we explore how ECM nanotopography influences neurite outgrowth.

Methodology/Principal Findings: We show that, when the ECM protein laminin is presented on a line pattern with nanometric size features, it leads to orientation of neurite outgrowth along the line pattern. This is also coupled with a robust increase in neurite length. The sensing mechanism that allows neurite orientation occurs through a highly stereotypical growth cone behavior involving two filopodia populations. Non-aligned filopodia on the distal part of the growth cone scan the pattern in a lateral back and forth motion and are highly unstable. Filopodia at the growth cone tip align with the line substrate, are stabilized by an F-actin rich cytoskeleton and enable steady neurite extension. This stabilization event most likely occurs by integration of signals emanating from non-aligned

and aligned filopodia which sense different extent of adhesion surface on the line pattern. In contrast, on the 2D substrate only unstable filopodia are observed at the growth cone, leading to frequent neurite collapse events and less efficient outgrowth.

Conclusions/Significance: We propose that a constant crosstalk between both filopodia populations allows stochastic sensing of nanotopographical ECM cues, leading to oriented and steady neurite outgrowth. Our work provides insight in how neuronal growth cones can sense geometric ECM cues. This has not been accessible previously using routine 2D culture systems.

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The role of CYP3A4 in amiodarone-associated toxicity on HepG2 cells

Anja Zahno^{1,2,3}, Karin Brecht^{1,2}, Réjane Morand^{1,2}, Swarna Maseneni^{1,2}, Michael Török^{1,2}, Peter W. Lindinger^{1,2,3} and Stephan Krähenbühl^{1,2,3}

Abstract:

Amiodarone is a class III antiarrhythmic drug with potentially life-threatening hepatotoxicity. Recent *in vitro* investigations suggested that the mono-N-desethyl (MDEA) and di-N-desethyl (DDEA) metabolites may cause amiodarone's hepatotoxicity. Since cytochrome P450 (CYP) 3A4 is responsible for amiodarone N-deethylation, CYP3A4 induction may represent a risk factor. Our aim was therefore to investigate the role of CYP3A4 in amiodarone-associated hepatotoxicity. First, we showed that 50 μ M amiodarone is more toxic to primary human hepatocytes after CYP induction with rifampicin. Second, we overexpressed human CYP3A4 in HepG2 cells (HepG2 cells/CYP3A4) for studying the interaction between CYP3A4 and amiodarone in more detail. We also used HepG2 wild type cells (HepG2 cells/wt) co-incubated with human CYP3A4 supersomes for amiodarone activation (HepG2 cells/CYP3A4 supersomes). Amiodarone (10–50 μ M) was cytotoxic for HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4

supersomes, but not for HepG2 cells/wt or less toxic for HepG2 cells/wt incubated with control supersomes without CYP3A4. Co-incubation with ketoconazole, attenuated cytotoxicity of amiodarone incubated with HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4 supersomes. MDEA and DDEA were formed only in incubations containing HepG2 cells/CYP3A4 or HepG2 cells/CYP3A4 supersomes but not by HepG2 cells/wt or HepG2 cells/wt with control supersomes. Metabolized amiodarone triggered the production of reactive oxygen species, induced mitochondrial damage and cytochrome c release, and promoted apoptosis/necrosis in HepG2 cells/CYP3A4, but not HepG2 cells/wt. This study supports the hypothesis that a high CYP3A4 activity is a risk factor for amiodarone's hepatotoxicity. Since CYP3A4 inducers are used frequently and amiodarone-associated hepatotoxicity can be fatal, our observations may be clinically relevant.

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Effect of three-dimensional expansion and cell seeding density on the cartilage-forming capacity of human articular chondrocytes in type II collagen sponges

Silvia E. Francioli^{1,2}, Christian Candrian^{1,3}, Katja Martin⁴, Michael Heberer^{1,2}, Ivan Martin^{1,2}, Andrea Barbero^{1,2}

Abstract:

Chondrocytes for tissue engineering strategies are typically expanded in monolayer (2D), leading to cell dedifferentiation but allowing to generate large cell numbers for seeding into scaffolds. Direct chondrocyte culture in scaffolds, instead, may support better maintenance of the differentiated phenotype but reduce the extent of proliferation and thus the resulting cell density. This study investigates whether the quality of cartilaginous tissues generated *in vitro* by human articular chondrocytes (HAC) on type II collagen sponges is enhanced (1) by direct expansion on the scaffolds (3D), as compared with standard 2D, or (2) by increasing cell seeding density, which in turn requires extensive 2D expansion. Three-dimensional expansion of HAC on the scaffolds, as compared with

2D expansion for the same number of doublings, better maintained the chondrocytic phenotype of the expanded cells (13.7-fold higher levels of *type II collagen* mRNA) but did not enhance their accumulation of glycosaminoglycan (GAG) following chondrogenic culture. Instead, increasing the HAC seeding density in the scaffolds (from $25 \cdot 10^3$ to $66 \cdot 10^3$ cells/mm³) significantly improved chondrogenesis (up to 3.3-fold higher GAG accumulation and up to 9.3-fold higher *type II collagen* mRNA), even if seeded cells had to be expanded and dedifferentiated more extensively in 2D to reach the required cell numbers. This study indicates that, under the specific conditions tested, a high-seeding density of HAC in 3D scaffolds is more critical for the generation of cartilaginous constructs than the stage of cell differentiation reached following expansion.

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Nature Reviews Immunology

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Type 2 diabetes as an inflammatory disease

Marc Y. Donath¹ & Steven E. Shoelson²

Abstract:

Components of the immune system are altered in obesity and type 2 diabetes (T2D), with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes. These immunological changes include altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocyte populations and increased apoptosis and tissue fibrosis. Together, these changes suggest that inflammation participates in the pathogenesis of T2D. Preliminary results from clinical trials with salicylates and interleukin-1 antagonists support this notion and have opened the door for immunomodulatory strategies for the treatment of T2D that simultaneously lower blood glucose levels and potentially reduce the severity and prevalence of the associated complications of this disease.

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HiJAKing the Methylosome in Myeloproliferative Disorders

Radek C. Skoda¹ and Jürg Schwaller¹

Abstract:

JAK2 gain-of-function mutations have been shown to cause myeloproliferative neoplasms. In this issue of *Cancer Cell*, Liu et al. (2011) demonstrate that these *JAK2* mutants, but not wild-type *JAK2*, directly phosphorylate PRMT5 and inhibit its arginine methyltransferase activity, establishing a link between mutant *JAK2* and histone arginine methylation.

Janus kinase 2 (*JAK2*) is a ubiquitously expressed intracellular tyrosine kinase that associates with the cytoplasmic domains of hematopoietic cytokine receptors and becomes activated upon these receptors binding to their cognate ligands. Activating mutations in *JAK2* have been found in the majority of patients with myeloproliferative neoplasms (MPN), which represent clonal hematopoietic stem cell diseases characterized by increased proliferation of the erythroid, megakaryocytic, or myeloid lineages. The vast majority of patients with MPN (about 80%) carry mutations in *JAK2* codon 617 that exchanges a valine with a phenylalanine (*JAK2*-

V617F) (Skoda, 2007). This mutated *JAK2*-V617F is an activated tyrosine kinase that renders hematopoietic cells hypersensitive for signals from upstream cytokine receptors (Epo, Tpo, and G-CSF) and phosphorylates (STAT3 and STAT5), as well as other downstream signaling proteins. In a minority of patients (less than 3% of MPNs), *JAK2* mutations have been found in codon 539 (e.g., *JAK2*-K539L) or in neighboring codons, leading to a variant of MPN with selectively increased numbers of erythroid cells. The mutant *JAK2* proteins were shown to activate proliferation, inhibit apoptosis, and interfere with genome stability. However, all of these effects were also observed when the wild-type *JAK2* was stimulated by cytokine receptor activation. The failure of SOCS3 to inhibit *JAK2*-V617F was so far the only hint that *JAK2*-V617F is not just a constitutively active form of wild-type *JAK2* (Hookham et al., 2007). The work by Liu et al. (2011) describes phosphorylation of the protein arginine methyltransferase 5 (PRMT5) as a novel activity that is unique to the mutant *JAK2*-V617F and *JAK2*-K539L proteins.

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IL-1 β Activation as a Response to Metabolic Disturbances

Marc Y. Donath¹, and Marianne Böni-Schnetzler¹

Abstract:

IL-1 β is a major regulator of islet inflammation in type 2 diabetes. Several factors contribute to the induction of islet-derived IL-1 β , including glucose, free fatty acids, and leptin. A recent report in *Nature Immunology* (Masters et al., 2010) identifies amyloid polypeptide as an additional enhancer of IL-1 β production.

Increasing evidence suggests that an inflammatory process promotes islet dysfunction in type 2 diabetes (Donath et al., 2009). Indeed, islets of patients with type 2 diabetes are characterized by the presence of cytokines, NF- κ B activation, immune cells, β cell apoptosis, amyloid deposits, and fibrosis. This insulinitis is due to a pathological activation of the innate immune system and governed by IL-1 signaling. Supporting the critical role of IL-1 β , specific blockade of IL-1 activity reduces the release of numerous inflammatory cytokines and chemokines from islets exposed to metabolic stress, thereby decreasing islet inflammation, improving insulin secretion and glycaemia. Indeed, several clinical studies have shown that targeting IL-1 β has the potential to improve not only glycated hemo-

globin levels in patients with type 2 diabetes but also to increase insulin production (Larsen et al., 2007). These proof-of-concept studies support a causal role for IL-1 driven islet inflammation in the pathogenesis of the disease.

Unraveling the underlying mechanism of IL-1 β activation in type 2 diabetes, in their recent study in *Nature Immunology*, Masters et al. (2010) discovered that human islet amyloid polypeptide induces IL-1 β in bone-marrow-derived macrophages. This involves activation of the NALP3 (also known as NLPR3) inflammasome resulting in caspase 1 activation and subsequent processing of proIL-1 β and release of mature IL-1 β . In a broader context, metabolic disturbances consistently appear to activate the IL-1 system via the NALP3 inflammasome, for example in amyloid deposits and hyperglycaemia in pancreatic islets, in uric acid crystals in the joint and cholesterol in blood vessels ([Dinarelli, 2009], [Düwell et al., 2010], [Maedler et al., 2002], [Martinon et al., 2006], [Masters et al., 2010] and [Zhou et al., 2010]).

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Das Foto entstand am 17.06.2010 in Madeira Beach, Florida. Es zeigt vier «Braune Pelikane» (*Pelecanus occidentalis*) auf einem ausgedienten hohlen Brückenpfeiler. Foto: Gerry Brunner

FOTO-ART

Zukünftig möchten wir auf dieser Seite die schönsten Fotos von Mitarbeitenden veröffentlichen. Gerry hat den Anfang gemacht. Er wird unter den eingehenden Fotos das nächste aussuchen, der nächste Fotograf das übernächste und so weiter. Alle Fotos, die an die Redaktionsadresse per email gesandt werden, nehmen teil.

From now on we will present the best photos taken by staff on this page. Gerry has made a start. He will choose the next one from the photographs submitted and the next photographer will choose the following one, and so on. All photos submitted by email to the editorial office address will be considered.

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Diabetes Research



Daniel Meier
Diabetes Research



Marianne Böni
Diabetes Research



Carmen Jeger
Adm. ICFS



Deborah Kaiser
Infection Biology



Richard Prazak
Diabetes Research



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Das DBM gratuliert ganz herzlich!



Yann François Oser Duss

Geboren am 29.8.2010



Anagha Hrudaya Sarma

Gundimeda

Geboren am 10.2.2011

***Herzlich
willkommen,
allerseits!***



Johan Melnyk

Geboren 13.1.2011

Toni Krebs neuer Facs-Operator



Am 15. März 2011 hat Toni Krebs seine Tätigkeit als Facs-Operator in der Flowcytometry und Facs-Facility am Departement Biomedizin USB begonnen. Toni wurde 1989 in Neubrandenburg in Mecklenburg-Vorpommern, im Nordosten Deutschlands, geboren. Mecklenburg-Vorpommern ist mit seinen drei Nationalparks, seinen fünf Naturparks und seinen rund 400 Natur- und Landschaftsschutzgebieten berühmt für seine unberührten Naturlandschaften. Nicht nur landschaftlich reizvoll, sondern auch durchaus bekannt ist der Ort, an dem Toni seine Ausbildung zum Biomedizinischen Analytiker und auch schon Erfahrungen in der Flowcytometry gemacht hat: Am Friedrich Loeffler Institut auf der Insel Riems, das zu den ältesten Virusforschungsinstituten weltweit gehört. Von Friedrich Loeffler 1910 zur Erforschung der Maul- und Klauenseuche gegründet, stehen heute neben der Virusforschung alle Aspekte der

Tiergesundheit im Mittelpunkt der Tätigkeit des Instituts. Kurz bevor Toni nach Basel kam, hat er noch seinen Grundwehrdienst beim Panzergrenadierbataillon 411 in der Nähe von Pasewalk absolviert. In seiner Freizeit beschäftigt sich Toni gerne mit der Preussischen Geschichte, die einen guten Ausgleich zum naturwissenschaftlichen Alltag bietet. Toni, wir heissen Dich herzlich bei den Alemannen willkommen und wünschen Dir viel Freude und Erfolg bei Deiner neuen Tätigkeit!

Heidi Hoyer mann

Die Redaktion wünscht allen Leserinnen und Lesern Frohe Ostern!

*The Editorial team of
DBM Facts wishes
all its readers
Happy Easter!*



Spending one day in Rome

If for any reasons, you have only one day to spend in Rome, the first thing you should do is to change your schedule and stay longer. Rome wasn't built in a day so it can't be visited in a day.

The Eternal City is a museum in itself! Italians say that the lifetime is not long enough to visit it, but in only 24 hours you can get a taste to intrigue your senses enough to make you plan to come back as soon as possible.

Barring that, don't waste even a minute of your precious time, put on your most comfortable shoes and organize your day focusing on the main sites. To this end, let us give you a suggestion, do a thematic trip: if you have only one day in Rome make it a food day and use this pretext for enjoying the city that for many centuries has represented the whole world and culture.

Romans love to eat. And they love to eat good food. Despite their easy-going "whatever happens, happens" attitude, they can become really picky when it comes to food. When in Rome, there is one thing you won't have to worry about: being able to find a nice place to eat. Thus, don't be satisfied to enjoy the Eternal City as tourists, but let's do it as real Romans.



Our trip should start in Rome Terminal Station (*Stazione Termini*), the central railway station, properly located to be the starting point of this beautiful day. Freeze immediately for a moment to admire it..."it's only a railway station" can you guess it!... to change your mind we suggest you watch the movie dedicated to "her", *Terminal Station* (1953), written by Truman Capote, directed by Vittorio De Sica and starring Montgomery Clift. Perhaps, just thinking that such prominent people put themselves out for the *Stazione Termini* could be enough to change your outlook.

Thus, let's start with our food trip. Keeping the platforms to your back turn right on Via Marsala (**point A**) and just in front of you there is the *Caffè Trombetta*, a original roman bar. Here, you can taste a cappuccino and a typical roman pastry, the *mari-tozzo*, soft buns with raisins and candied orange peels, plain or filled with fresh cream. We suggest you try the latter version!

After breakfast, the sun is high in the sky, you have to go to *Piazza della Repubblica* (just 10 minutes away from the Terminal Station) (**point B**). The scene is intriguing: rinascimental porticos surrounding the roman *Basilica of Santa Maria degli Angeli e dei Martiri* and in the middle of the square the Fountain of the Naiads will steal your heart with its ornamental water features. Ok, just 5 minutes for taking pictures and let's move to have a look at *Via Nazionale*, where you will find many, many fashionable and very expensive boutiques. The temptation to buy something will be very high, but, guys really, you can just have a look!!!

At the end of the street, you will understand what a breathtaking view is! You are still in 2011, but everything around suggests that you travelled back to 2000 years ago... don't worry, everybody feels the



same the first time they see the *Via de' Fori Imperiali* (**point C**). Now, reconnecting with the Rome of yesterday, you can feel like an ancient Rome emperor, walking down this street after a victorious battle to be glorified by the people. As a fitting end for such a street there is the Colosseum (**point D**), the largest ever built in the Roman Empire, a masterpiece of Roman architecture and engineering and one of the seven wonders of the modern world. Now, please take a moment to daydream what it would have meant for a plebeian to come upon the Colosseum two millennia ago...

... Ah, the amazing ancient Roman age... bip bip... it's half past twelve... lunch time! ... and you should try something typical. We have a place to suggest very close to *Piazza Venezia*, the *Antica Birreria Peroni* (**point E**). For one hundred years, Romans and tourists met here, ate, drank and had fun together. You'll find out how our specialties really do taste, preserved over the years and handed down as family recipes. What about the menu? Of course *spaghetti alla carbonara*, spaghetti served in a sauce whose main ingredients are eggs, *guanciale* (bacon from pig's cheek), black pepper and pecorino cheese, and only because we still have a lot of thing to see some fresh vegetables like *Carciofi alla Giudia*, artichokes, deep fried, simmered in olive oil with garlic and mint.

Now you should feel a little bit better, satisfied and not overburdened, but an Italian meal must end with an *espresso*, so let's move on to try the best example of it in Rome. In this case we would recommend a café located in another unique scenario. To reach this place take the bus n° 87 or 186 direction *Corso del Rinascimento* and ask for the best stop for *Piazza Navona* (**point E**). We don't know how long this could take... yes we know, public transport in Rome is not very efficient! When you reach your stop you are in another wonderful roman square, the *Piazza Navona*. The ancient Romans came here to watch the agones (games), and hence it was known as 'Circus Agonalis' (competition arena). Look at the buildings, the churches, the obelisk and the fountains, focus attention on the one in the middle of the square, *Fontana dei Quattro Fiumi* (Fountain of the Four Rivers), the one that is listed as one of the Altars of Science in the famous movie/book *Angels and Demons*. This fountain was designed by Gianlorenzo Bernini in 1651 and you can see four Gods on the corners of the fountain representing the four major rivers of the world known at the time, the Nile, Danube, Ganges, and Plate.

However, we came here to have a coffee, so let's move on to the nearby *Piazza Sant'Eustachio* (**point G**) in order to taste the best espresso in Rome in the café with the same name. A heaven for all four senses. They offer a varieties of products prepared with a legendary secret blend, and always accompanied by a glass of water as Italian tradition requires. The symbol of *Caffè Sant'Eustachio* is a stag which refers to the conversion to Christianity of the previously pagan Eustace upon seeing an apparition. On top of the basilica of the old church in the same square you will again find this white stag, instead of the traditional cross.

This café is also few steps away from the *Pantheon* (**point H**), one of the main sites in Rome we – the authors – love most. This two millennia-old temple is a jewel, as well as the Roman monument with the greatest number of records: the best preserved, with the biggest brick dome in the history of architecture and it is considered the forerunner of all modern places of worship. It is the most co-pied



The Pantheon

and imitated of all ancient works. Michelangelo felt it was the work of angels, not men. Where it stands was not chosen by chance, but is a legendary place in the city's history. According to Roman legend, it is the place where the founder of Rome, Romulus, was seized by an eagle at his death and taken off into the skies with the Gods.

The Pantheon is a wonder, a dream, but, unfortunately, we have very little time and now I'll probably start to have a craving... an ice-cream craving. Thus, using this excuse we move on to one of the most famous fountains in the world, *Fontana di Trevi* (**point I**), that is, by the way, also very close. You can already hear its presence from the nearby streets. Indeed, as you get closer the sound of its gushing waters grows constantly more intense, reaching a crescendo in the square, where you will find the most breathtaking sight. Suddenly, the space seems to open out and you stand before a symbolic representation of this great force of nature, a tumultuous spring that seems to flow out of the ground. The Trevi Fountain is a triumphant example of Baroque art, a jewel of water and stone that is nestled between the palaces of the historic centre of the city. This masterpiece is so famous that it was the setting for an iconic scene in Federico Fellini's film *La dolce vita* starring Anita Ekberg and Marcello Mastroianni. The fountain was turned off and draped in black in honour of Mastroianni af-

ter the actor's death in 1996. Before going away for the ice-cream don't forget to throw a coin backward into the fountain, this traditional legend could ensure your return to Rome... and you have to!

What about our ice-cream? *Il Gelato di San Crispino*, via della Panetteria 42 (**point J**). "Romans used to argue about which of a dozen or so wonderful gelaterias was the best in town. But, since 1993, the contest has been for second place. Anyone who does not acknowledge that *Il Gelato di San Crispino* is supreme

has not tried it" - *New York Times*. Do you need any other comments? Now, you just have to enjoy it...

We recharged our batteries and now, let's direct to the colourful *Trastevere* (that in Roman dialect means "beyond the Tiber") neighbourhood (**point K**). The best pathway should take around 40 minutes, but we suggest you to spend all of the necessary time completely enjoying this unique scenario. Rome is excellent for walking, because much of the inner core is traffic-free and there are a lot of unknown sites of interest often clustered together, such as old narrow, winding and irregular streets, little, wonderful and sometimes hidden squares, and last but not least, a lot of amazing churches. There are several hundred Roman churches and inside them you can find evidence of every time, culture and historical phase of the Eternal City.

Trastevere is a pearl, one of the most precious in Rome. Thanks to its partial isolation (it was "beyond the Tiber") and to the fact that its population had been multicultural since the ancient Roman period, the inhabitants of Trastevere, called *Trasteverini*, developed a culture of their own. Nowadays, Trastevere maintains its character thanks to its narrow cobbled streets lined by medieval houses. At night, both natives and tourists alike flock to its many bars and restaurants. However, much of the original character of Trastevere remains.

Amongst the thousands restaurants in Trastevere there are many excellent examples of the traditio-

nal Roman cooking. In particular we suggest “*da Augusto*”, an authentic Roman trattoria, situated in an enchanting piazza in Trastevere (*Piazza de’ Renzi*, **point L**). The atmosphere is Roman, informal, cheerful, lively, and sometimes a little bit chaotic. To get in you usually have to expect waiting 30–60 minutes in line, especially during the week-end. Such a long wait is compensated by some of the best typical roman food you could find in the whole of Rome. For the main



Michelangelo's dome of St. Peter Basilica

course you can basically choose among: *rigatoni alla amatriciana*, *alla carbonara* or *cacio e pepe*. Meat is also cooked and served following the traditions of Rome: *pollo alla romana*, *ossobuco*, *straccetti con rucola*, *saltimbocca alla romana*, *trippa*, are only some of the dishes it is possible to eat apart from pasta. Enough?!

Well, now we have to end the day with a bang... a bang, named St. Peter's Basilica! Perhaps, the best solution for reaching the Basilica from Trastevere during the night is to take a taxi: it should not be so expensive. 15 minutes later and 10 euro down you'll find yourselves in front of the evocative *Via della Conciliazione* (**point M**), that symbolizes the moot union between Rome and the Vatican City... regardless of your faith you can only be astonished by *Er Cuppolone* (Michelangelo's dome of St. Peter Basilica).

This central dome dominates the skyline of Rome and it's an experience that will leave impressions on you for the rest of your lives. The American philosopher Ralph Waldo Emerson described St. Peter's as “an ornament of the earththe sublime of the beautiful.” Moreover, “The building of St. Peter's surpasses all powers of description. It appears to me like some great work of nature, a forest, a mass of rocks, or something similar; for I never can realize the idea that it is the work of man. You strive to distinguish the ceiling as little as the canopy of heaven. You lose all sense of measurement with the eye, or proportion; and yet who

does not feel his heart expand when standing under the dome and gazing up at it ? ” (*Mendelssohn's Letters*).

After the time needed to capture this extraordinary and unique image in your mind, we need to end this unforgettable day as we enjoyed it, as real Romans with a night snack! Johnny Food, aka *Lo Zozzone* (“The dirty one”, a name commonly used to identify this kinds of “club”), it's without any doubt the proper place for a sandwich with *porchetta* (baked pork), with sausage, etc...also because it's very close to another breathtaking scene, *Piazza del Popolo*... unfortunately, our day is approaching the end and we have to take a train.

We leave tired, satiated (for sure!), and with the knowledge that if you want to again feel these kinds of emotions you should return here, where the civilization and the culture started, because “*Possis nihil Urbe Roma visere maius*” (You could not see anything bigger than Rome – *Orazio, Carmen Speculare*).

Matteo Centola, Emanuele Trella

The power of Aiki techniques

The concept of Aiki is extremely ancient and is central to both Daitō ryū Aikijujutsu and Aikido, two Japanese martial arts. The Daitō ryū Aikijujutsu is a very old, brutally effective fighting method originating from the samurai tradition of Japan. This martial art has been kept secret and was not taught to the general public throughout centuries (the art was known as "inside-the-clan martial art"). It is only in the nineteenth century that the art became widely known. This was made possible by one man, master Sokaku Takeda who began to accept students from around the country. Sokaku Takeda had many students but the most famous one was Morihei Ueshiba. Ueshiba adopted and simplified the Daitō ryū techniques to create the art of Aikido. In addition, he added to his art under the influence of the Omoto-kyō religion, a prominent spiritual dimension, universal peace and reconciliation.

There are many different definitions of Aiki and the most modern and common interpretation relates to philosophical or sociological meanings as found in most forms of Aikido. The original interpretation found in the Daitō ryū Aikijujutsu is different and much more complex. The term Aiki is composed of the two Chinese characters, "合" (Ai) often used to express adaptation, connection or combination and "気" (Ki), a widely used character to express vital energy, spirit, mind or heart. In the tradition of Aikijujutsu, Aiki is used to describe techniques where the strength of an opponent is used so that unbalance, throw and



submission techniques are applied. The meaning of the Chinese characters highlights the concept of adaptation and combination of one's body to a given attack in order that a quick and effective response can be employed. The principle of Aiki implies the study of combat strategy, distance, perception, body position and movement. The practitioner needs to position the arms, hips and legs so that he can adapt properly to the attack and execute small movements that trigger different reactions in the opponent's body such as unbalance, body stiffness or distraction. In essence, Aiki techniques are used to achieve with minimal efforts a response to an attack, which aims at stimulating the muscles of the opponent. This highlights the idea of adaptation and combination (Ai) to the vital energy (here the strength) of the opponent. Being able to stimulate the muscles opens the door to easily unbalance an opponent with little chance for him to recover. For this purpose Aiki techniques usually target weak points of the human body known as unbalancing points.

Either against a grab or a direct attack, fast and precise movements are used to neutralize an attack as it happens. That means that the opponent should not have time to complete an attack to the point where he would be able to take the advantage. When the Aiki is performed accurately, the opponent does not really know that a technique is being applied against his attack. Once he is able to realize that a counter attack is being developed, he is already unbalanced and neutralized to the ground with no chance to move. As a result, Aiki techniques can be devastating when applied in real combat as it was done in the old Japan. Executed with speed and with the intention of producing serious injuries, Daitō ryu practitioners can unbalance an opponent so that sensitive parts of his body (head, articulations, back) would violently hit the ground. The feeling of having suddenly been thrown to the ground combined with the impact and the subtle submission techniques allow an Aiki master to easily control an oppo-



nent with minimum efforts, even without having to press an articulation. The same principle is also performed to defend against several opponents as they are piled on each other so that the weight of one opponent is used against the others for submission. Finally, Aiki techniques in the tradition of the Daitō ryu Aikijujutsu are combined with atemi (or strikes against vital points of the human body). In contrary to modern boxing, where strikes are applied using a large area for the point of impact, the power originating from the atemi used in Daitō ryu Aikijujutsu is focused into a small region, which yields to vibrations and force penetration much further into the body. Through this striking method it is then possible to reach internal organs with damaging effects, emphasizing the tremendous efficacy of Aiki techniques.



Riad Seddik

Teacher of Daitō ryu Aikijujutsu and Aikido in the martial art association of Dannemarie, France
<http://www.arts-martiaux-dannemarie.com/>

Osterlamm einmal anders

Für den Teig:

- 220 ml Milch
- 100 g Zucker
- 40 g Butter
- 1 Würfel Hefe
- 500 g Mehl (Typ 405)
- ½ TL Salz
- 1 Ei(er)
- evtl. Aprikosen, getrocknete, 100 g

Zum Bestreichen:

- 1 Eigelb

Zum Verzieren:

- 2 Rosinen für die Augen
evtl. Mandelblättchen

Zubereitung:

Aus den Teigzutaten einen süssen Hefeteig herstellen. Wer mag, kann getrocknete Aprikosen ganz fein hacken und unterkneten. Den Hefeteig gehen lassen, bis er sein Volumen etwa verdoppelt hat. Nochmal kurz durchkneten.

Tipp für das Anrichten der Teigstücke: etwas Öl mit der flachen Hand auf der Arbeitsplatte verstreichen und den Hefeteig darauf geben, dann braucht man kein zusätzliches Mehl und der Teig klebt nicht mehr.



Auf dem Blech ordnet man die Teigstücke folgendermassen an: 1 grösseres ovales Stück für den Kopf, 2 längliche Teile

für die Ohren, 4 Beine und evtl. 4 Bällchen für die Füße. 1 Schwanz, ca. 25 kleine Bällchen für den

Körper. Ein paar Mini-Bällchen für das «Pony» – zwischen den Ohren. Zwischen den Teilchen etwas Platz lassen.

Das fertig gelegte Lamm nochmal mindestens 10 Minuten gehen lassen.

Inzwischen den Ofen vorheizen auf 180° Umluft oder 200° Ober-/Unterhitze. Das Lamm grosszügig mit Eigelb bestreichen. Die Rosinen als Augen leicht andrücken (wenn das Lamm nicht mit Ei bestrichen wird, werden die Rosinen bitter, weil sie verbrennen). Das Lamm nach Belieben mit Mandelblättchen bestreuen und 20–25 Minuten backen. Evtl. die letzten 10 Minuten mit Alufolie abdecken, damit es nicht zu dunkel wird.



Durch die kleinen Bällchen kann man später kleine Stückchen abreissen und pur oder mit Marmelade geniessen – der

Hit auf der Osterfeier und bei kleinen und grossen Kindern.

Zubereitungszeit: 40 Min.

Ruhezeit: 1 Std.

Angelika Offinger, Animal Facility

Mein Name ist Angelika Offinger und ich bin seit 2004 als Leiterin der Tierstation in der Mattenstrasse am DBM beschäftigt.

Ich wurde 1971 in einem kleinen Dorf am Rande der schwäbischen Alb als fünftes von sechs Kindern geboren. Aufgrund der ländlichen Umgebung ist es nicht verwunderlich, dass ich von klein an immer Kontakt zu Tieren hatte. Folglich habe ich in meinem ersten Schulaufsatz mit dem klassischen Thema «Was ich später einmal werden will» schon festgehalten, dass ich einmal mit Tieren arbeiten will.



Von links nach rechts: Colette, Angelika Offinger, Manni



Rottweiler-Hündin Ayla

So habe ich nach Grundschule und Gymnasium von 1990 bis 1993 meine Ausbildung zur Tierpflegerin, Fachrichtung Haus- und Versuchstierpflege, an der Universität Ulm/Donau absolviert. Die Ausbildung war sehr abwechslungsreich und deckte nahezu sämtliche Tierarten ab: von diversen, teils exotischen Kleinnagern bis zum Schwein

und Schaf. Dass ich mich beruflich einmal auf Mäuse spezialisieren würde, habe ich zu dem Zeitpunkt selbst nicht erwartet.

Direkt nach der Ausbildung im Februar 1993 wechselte ich aus privaten Gründen an die Universität Freiburg im Breisgau. Dort wurde mir die Möglichkeit gegeben, mich nebenberuflich weiterzubilden, so dass ich dann nach «harten» anderthalb Jahren 2003 die Meisterprüfung vor der Industrie- und Handelskammer Wupper-



Jack Russell-Terrier-Weibchen Biskuit

tal ablegen konnte. Der berufliche Wechsel nach Basel kam dann eher durch Zufall.

Trotz der beruflichen Beschränkung auf nur eine Tierart, könnte ich mir nichts anderes vorstellen – mein Beruf ist für mich immer noch Berufung! Durch die besonderen Arbeitsbedingungen und den direkten Kontakt zu den Wissenschaftlern ist mein Alltag sehr abwechslungsreich.

Tierische Abwechslung habe ich privat: So verbringe ich meine

Freizeit mit Hunden, Schweinen, Pferd (Schweizer Freiberger) und Esel. Die Versorgung der Tiere ist wohl zeitintensiv, aber auch sehr entspannend und ein schöner Ausgleich für die hauptberufliche Tätigkeit im Keller.

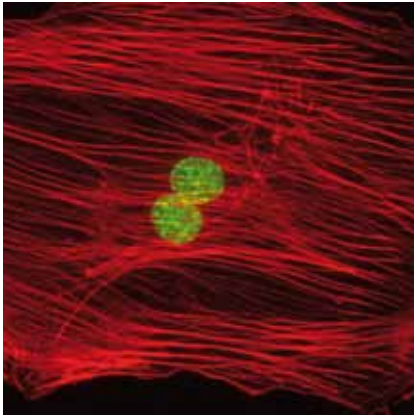
Neben meinen «tierischen» Aktivitäten, gehe ich gerne auf Konzerte oder mache gemeinsam mit meinem Lebensgefährten Ausfahrten auf unseren Oldtimer-Motorrädern. Ein fester Bestandteil im Jahresablauf ist die fünfte Jahreszeit für mich: Fasnet!! Ich liebe es, mich so zu verkleiden, dass es schwer ist, mich zu erkennen, durch Freiburgs Altstadt zu ziehen und einfach Spass zu haben!



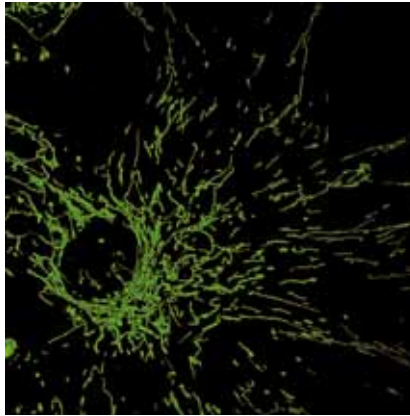
DKW Baujahr 1955

VORSCHAU PREVIEW

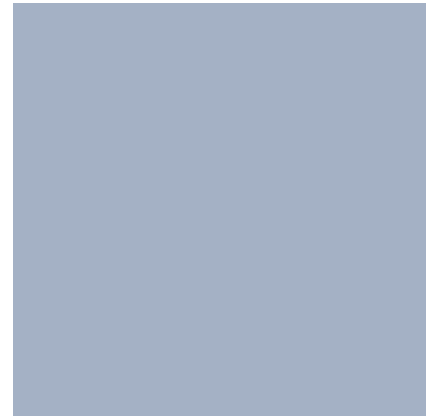
In der nächsten Ausgabe ...



... führt uns Matthias Wymann in die Welt der Cancer- and Immunobiology ein



... erfahren wir von Albert Neutzner mehr über die Herausforderungen in der Ocular Pharmacology and Physiology



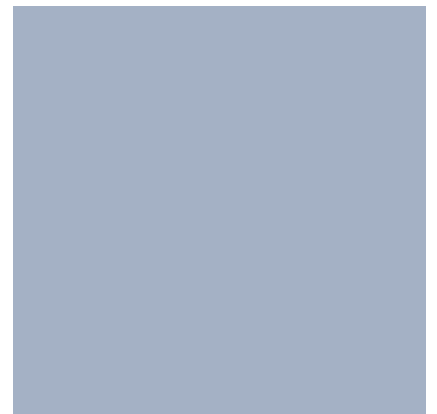
... erzählt uns Frances Kern, wie sie bei einem Leprahilfswerk für die Ärmsten in Kathmandu gearbeitet hat



... erklärt uns Yves Hartmann, was einen sicheren Schützen ausmacht



... stellen wir die schönsten Mitarbeiterfotos vor



Balada de la Amapola

Amapola, sangre de la tierra,
amapola, herida del sol,
boca de la primavera azul,

¡amapola de mi corazón!

Tú te ríes por la viña verde,
por el trigo, por la jara, por
la pradera del arroyo de oro,

¡amapola de mi corazón!

Novia alegre de la boca roja,
mariposa de carmín en flor,
amapola, gala de la vida,

¡amapola de mi corazón!

Juan Ramón Jiménez (1881-1958)

Ballade vom Klatschmohn

O Mohn, Blut der Erde,
Mohn, Wunde der Sonne,
Mund des blauen Frühlings

Du Mohn meines Herzens!

Du lachst über den grünen Weinberg
Über den Weizen, über die Zistrose,
über die Grasweide des Baches in Gold.

Du Mohn meines Herzens!

Fröhliche Braut mit dem roten Mund,
Wangenroter Schmetterling in der Blüte Deiner Jugend!
Mohn, Festkleid des Lebens!

Du Mohn meines Herzens!

Juan Ramón Jiménez (1881-1958)

