DBM FACTS

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

Mechanisms controlling tumor Heterogeneity, metastasis and resistance | The DBM Postdoc Club – a unique networking opportunity | St. Patrick's Day

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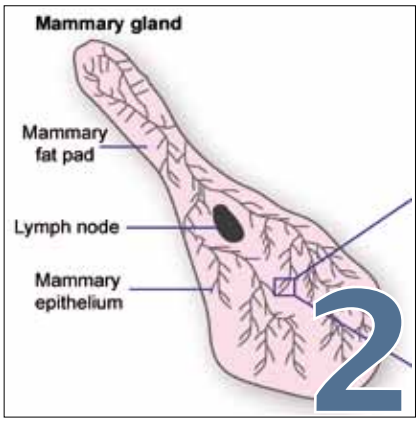
Departement Biomedizin Basel



Mechanisms controlling tumor Heterogeneity, metastasis and resistance
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Auch das ist Sport

IMPRESSUM

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Layout
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IT-Unterstützung
Niklaus Vogt

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Fotos
Titelfoto: Jinhae Gunhangje Festival in Korea (shutterstock)

Druck
Morf Bimo Print AG, Binningen

Anschrift
Redaktion DBM Facts
Departement Biomedizin
Hebelstrasse 20
4031 Basel
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UKBB Universitäts-Kinderspital beider Basel

Universitätsspital Basel

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Das DBM ist gut in das Jahr 2017 gestartet. Vom Advisory Board haben wir im Rahmen der Research Days viele positive Rückmeldungen und gleichzeitig wertvolle Anregungen erhalten. Bei den Publikationen sind wir ebenfalls auf sehr gutem Weg. In grossem Umfang konnten Wissenschaftler des DBM in ausgewiesenen Journalen publizieren (Seite 13).
Wir freuen uns, Christophe Kunz in einer neuen Funktion zu begrüssen. Er kümmert sich ab sofort als Betriebskoordinator um den Neubau des DBM. Julien Roux verstärkt seit Anfang März die Bioinformatics Core Facility. Wir wünschen beiden viel Freude und Erfolg bei ihrer neuen Tätigkeit!
Mit Momo Bentires-Alj beginnt der wissenschaftliche Teil der nun vorliegenden Ausgabe. Momo, der vor einem halben Jahr vom FMI kommend mit seiner Gruppe THMR am DBM seine neue Heimat gefunden hat, stellt uns seine Forschungsschwerpunkte vor (ab Seite 2). Ab Seite 8 berichtet der DBM Postdoc Club über seine Aktivitäten. Doch das Leben sollte nicht nur aus Arbeit bestehen, schauen Sie doch auch einmal auf die Seiten 32 und 34 …

Viel Spass bei der Lektüre und schöne Ostertage

Dear Readers

The DBM has had a good start to 2017. We have had lots of positive feedback from the Advisory Board in relation to the Research Days as well as valuable suggestions. We are also doing well in terms of publications. Scientists from the DBM have published widely in selected Journals (page 13).
We are delighted to welcome Christophe Kunz to his new position. Effective immediately, he will take over as service coordinator of the construction of the new DBM. Since the start of March Julien Roux has strengthened the Bioinformatics Core Facility. We wish them every success in their new positions.
Momo Bentires-Alj starts the scientific section of this edition. Momo, who found his new home at the DBM six months ago, when he moved here from FMI with his group THMR, introduces us to the focus of his research (from page 2). From page 8 onward the DBM Postdoc Club tell us about their activities. However, life should not just be focussed on work, so have a look at pages 32 and 34 …

Enjoy the read and wishing you all a happy Easter

Mechanisms controlling tumor Heterogeneity, metastasis and resistance

INTRODUCTION

Breast cancer is diagnosed in ~1.6 million women worldwide and ~600,000 lives are lost to the disease annually. Patients may do well after surgery and adjuvant treatment but drug-resistant, fatal metastases often develop. Critical to the phenomenon of resistant metastases is tumor heterogeneity, which is the thread connecting the research in our lab. We perform both open-ended exploratory studies and translational biomedical research.

Tumor heterogeneity impinges on prognosis, response to therapy, and metastasis and is one of the most important and clinically relevant areas of cancer research (Koren and Bentires-Alj 2015). Heterogeneity results from genetic and epigenetic alterations that enhance the plasticity and fitness of cancer cells in the face of hurdles such as the metastatic cascade and anticancer therapies. At the molecular, cellular, and whole organism levels, we assess mechanisms that influence normal and neoplastic breast stem cells, metastasis, and resistance to therapy. We explore both cell autonomous (genetic, epigenetic, and proteomic) and non-cell autonomous mechanisms (immune cells, adipcoytes, etc.). These interdisciplinary projects seek to elucidate the integrated effects of signaling pathways and epigenetics on breast cell fate and tumor heterogeneity, and to leverage this mechanistic understanding into personalized therapy (Figure 1).

M. Bentires-Alj is a founder and president of the European Network for Breast Development and Cancer (ENBDC, www.enbdc.org), which fosters global interactions between labs in these areas, and co-founder with Profs. Walter Paul Weber, Gerhard Christofori and Christoph Rochlitz of the Basel Breast Consortium (www.BaselBC.org), which is committed to promoting basic, clinical, and translational interdisciplinary research projects within Switzerland and neighbouring cities. This provides our research team with national and international collaborations. In addition, we are part of the MetastasiX group, the Basel Stem Cell Network, the Basel Signaling Alliance, and the Basel personalized Health cancer cluster.

1. MOLECULAR MECHANISMS CONTROLLING NORMAL AND NEOPLASTIC BREAST CELL STATES

R. Amante, D. De Silva, S. Koren, A. Musch, M. Salvador, F. Zilli

The mammary gland epithelium is surrounded by a basement membrane and stromal cells and is composed of hierarchically organized cell types that contribute to tissue homeostasis. Two major cell lineages organized in a bi-layered structure constitute the mammary gland: the luminal layer lining the ducts and the alveoli and the myoepithelial layer with a basal location (Figure 2). A key issue in breast cancer biology is the effect of genomic lesions in specific mammary cell lineages on tumor heterogeneity and progression. The impact of transforming events on fate conversion in cancer cells-of-origin, their contribution to tumor heterogeneity, and the underlying mechanism remain largely elusive and are major areas of research in our group. We use in situ genetic lineage tracing, unbiased pooled shRNA, CRISPR or transposon-based screens, and hypothesis-driven approaches. Our studies include:

PIK3CA^{H1047R} induces multipotency and multi-lineage mammary tumors. Using *in situ* genetic lineage tracing and limiting dilution transplantation, we have unraveled the potential of *PIK3CA*^{H1047R}, one of the most frequent mutations occurring in human breast cancer, to induce

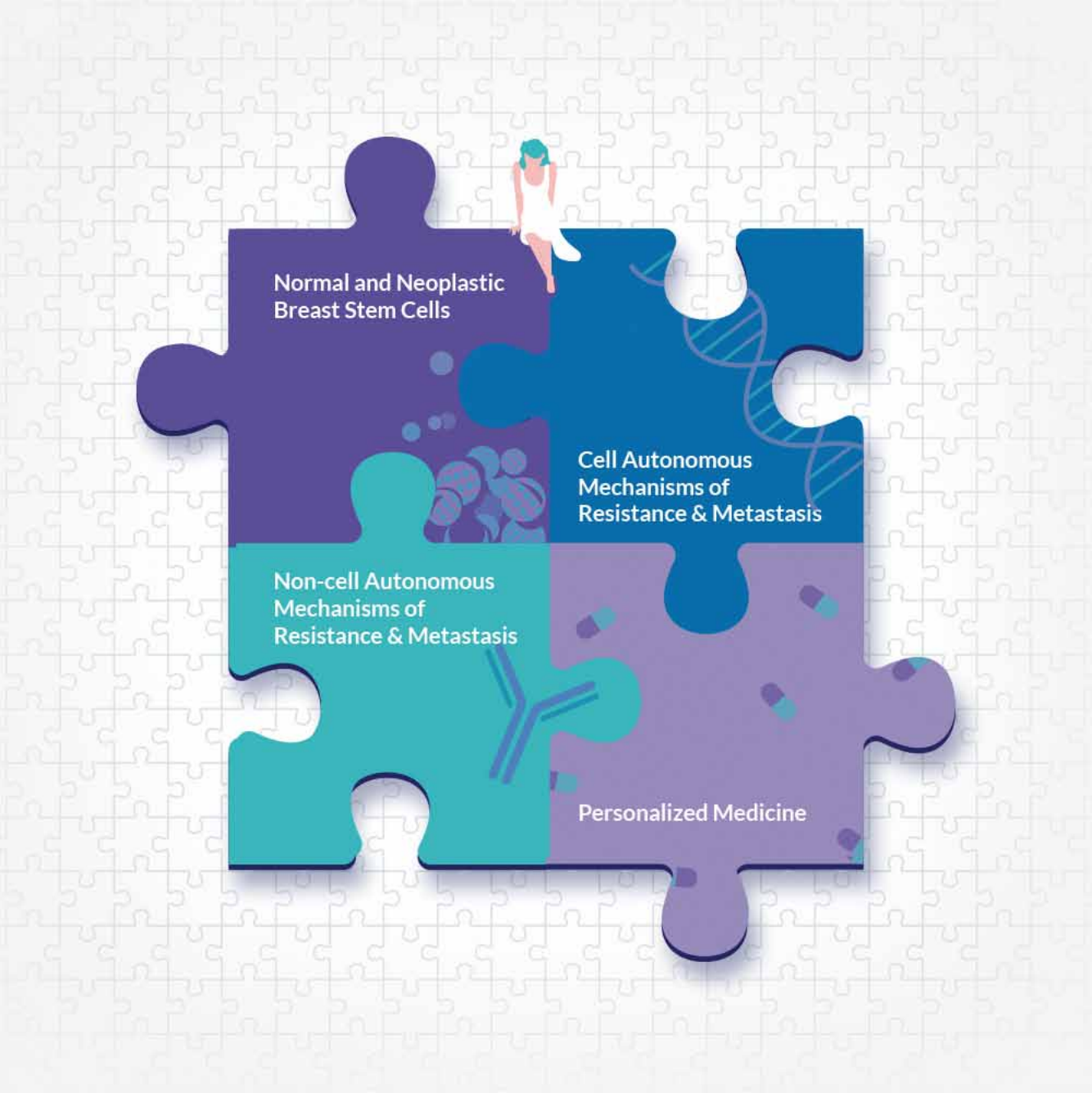

Fig. 1. Research areas in the Bentires-Alj lab

multipotency during tumorigenesis in the mammary gland. Our results define a key effect of *PIK3CA*^{H1047R} on mammary cell fate in the pre-neoplastic mammary gland and show that the cell-of-origin of *PIK3CA*^{H1047R} tumors dictates their malignancy, thus revealing a mechanism underlying tumor heterogeneity and aggressiveness (Koren, Reavie et al. 2015).

Hippo kinases LATS1/2 control human breast cell fate via crosstalk with ERα. Using a high-content confocal image-based shRNA screen for tumor suppressors regulating human breast cell fate, we have discovered that ablation of the Hippo kinases large tumor suppressors (LATS) 1 and 2 promotes luminal fate and increases the number of bipotent and luminal progenitors, the proposed cell-of-origin of most human breast cancers. Mechanistically, we revealed a crosstalk between Hippo and ERα signaling. In the presence of LATS, ERα was targeted for ubiquitination and Ddb1–cullin 4-associated-factor 1 (DCAF1)-dependent proteasomal degradation.

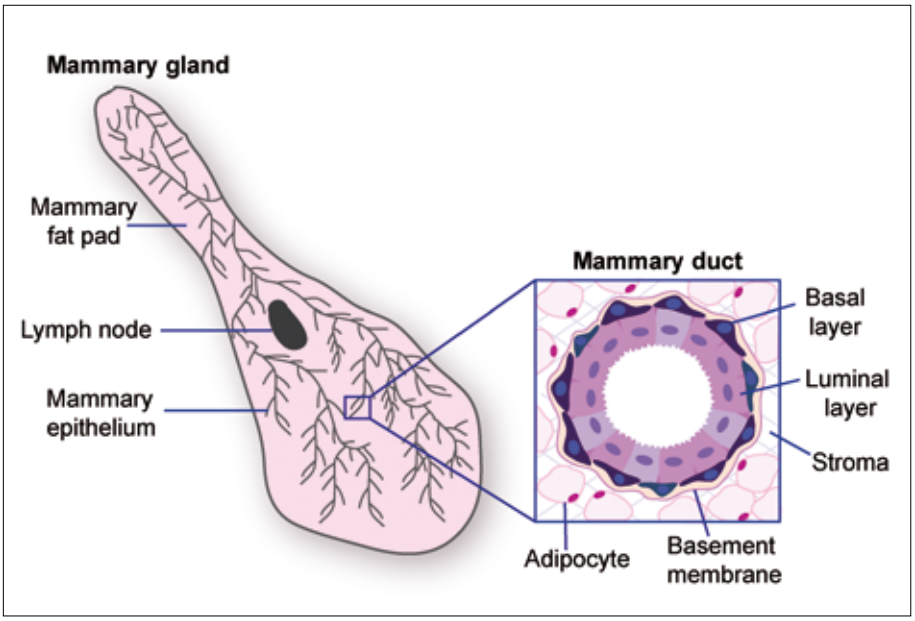

Fig.2. Schematic of the mouse mammary gland.

Our findings reveal a non-canonical (i.e., YAP/TAZ-independent) effect of LATS in the regulation of human breast cell fate (Britschgi, Duss et al. 2017).

2. CELL AUTONOMOUS MECHANISMS CONTROLLING METASTASIS AND RESISTANCE

P. Auf der Maur, M. Obradovic, J. Pinto Couto, A. Sethi, M. Vulin

The vast majority of breast cancer death is due to metastasis. Curing metastatic breast cancer clearly represents an unmet medical need. Understanding the mechanisms underlying drug resistant metastases is a large focus of our team (Ramos and Bentires-Alj 2015). We use systems medicine quantitative methods, single cell analysis, multiphoton intravital imaging, synthetic lethal screens, unbiased pooled shRNA, CRISPR or transposon-based screens, and hypothesis-driven approaches. Our studies include:

Tyrosine phosphatase SHP2 promotes breast cancer progression, maintains the tumor-initiating cell population and increases cell motility. We demonstrated a fundamental effect for the tyrosine phosphatase SHP2 in tumor maintenance and progression in HER2-positive and triple-negative breast cancers (TNBCs). Our data show that SHP2 is important for self-renewal of breast tumor-initiating cells and for tumor maintenance and progression. Using mouse models and multiphoton intravital imaging, we have identified a crucial effect of SHP2 on TNBC cell motility *in vivo*. Unbiased phosphoproteomics and biochemical analyses showed that SHP2 activates several SRC-family kinases and downstream targets, most of which are inducers of migration and invasion. These studies provide new insights into signaling cascades that regulate neoplastic breast stem cells and metastasis and a rationale for targeting SHP2 in breast cancer (Aceto, Sausgruber et al. 2012, Sausgruber, Coissieux et al. 2015).

Molecular mechanisms controlling breast cancer resistance to PI3K inhibition. The PI3K pathway is hyperactivated in many cancers, including 70% of breast cancers. The clinical response to PI3K inhibitors is not as efficient as expected. In order to anticipate potential molecular mechanisms of resistance to the p110α isoform-selective inhibitor BYL719, we developed resistant breast cancer cell lines, assessed the concomitant changes in cellular signaling pathways using unbiased phosphotyrosine proteomics and characterized the mechanism of resistance using pharmacological inhibitors. Our study demonstrates that the IGF1R/p110β/AKT/mTOR axis confers resistance to BYL719 in PIK3CA mutant breast cancers. This provides a rationale for the combined targeting of p110α with IGF1R or p110β in pa-

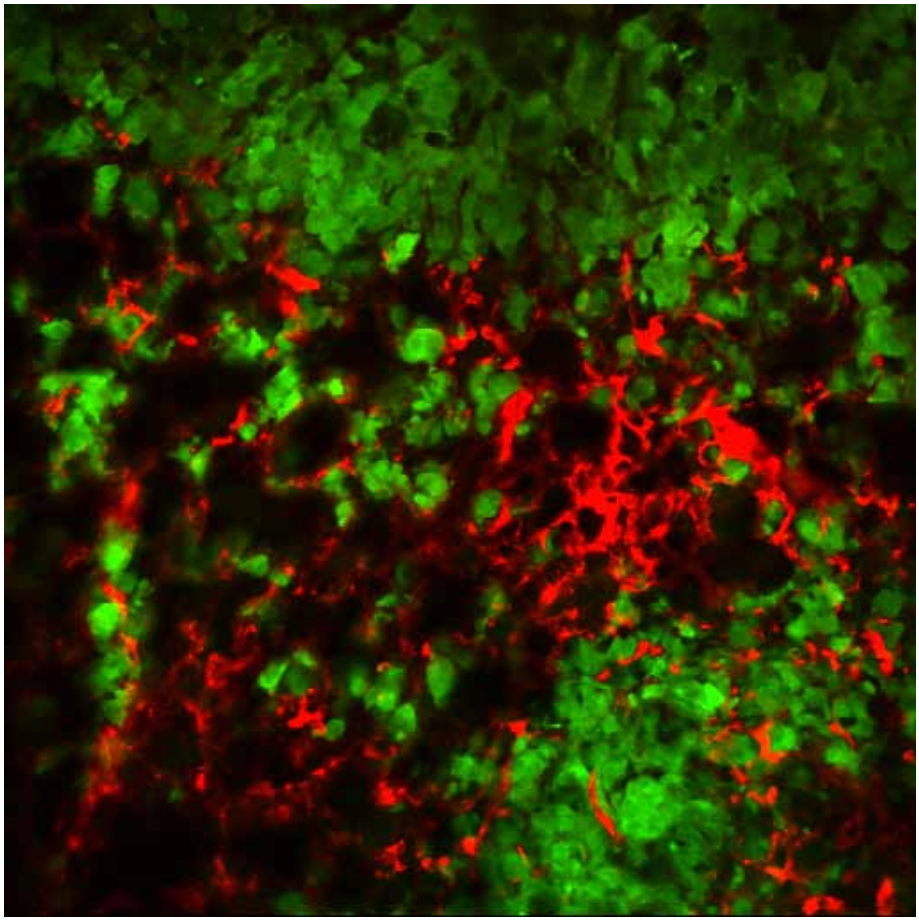

Fig. 3. Intravital multiphoton image of metastatic cells (GFP, green) in the lungs, 50 µm below the surface, 10 min after i.v. injection of 70-kDa Texas Red Dextran, allowing the visualization of the vasculature in the metastatic niche.

tients with breast tumors harboring *PIK3CA* mutations (Leroy, Ramos et al. 2016).

Mathematical modeling of tumor heterogeneity during progression to metastases and clinical validation. We use a systems biology/medicine approach to unravel, integrate, and mathematically model the cellular and molecular determinants of breast cancer metastasis. With collaborators from the USB, FMI, UNIBAS, UNIZ and IBM, we are part of an interdisciplinary SystemsX funded project (MetastasiX) that aims at single cell analysis during progression to metastases and clinical validation.

3. NON-CELL AUTONOMOUS MECHANISMS CONTROLLING METASTASIS AND RESISTANCE

M. Ackerknecht, M. M. Coissieux, A. Correia, R. Okamoto, V. Richina

We study the effects of the tumor microenvironment focusing on immune cells and adipocytes. We use *ex vivo* 3D cultures, immunocompetent mouse models and multiphoton intravital imaging. Our studies include:

Discontinuation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. We have discovered a paradoxical effect of the CC chemokine ligand 2 (CCL2) in metastatic breast cancer. Secretion of CCL2 by mammary tumors recruits CCR2-expressing inflammatory monocytes to primary tumors and metastatic sites, and CCL2 neutralization in mice inhibits metastasis by retaining monocytes in the bone marrow. Surprisingly, interruption of CCL2 inhibition leads to an overshoot of metastases and accelerates death. This is the result of monocyte release from the bone marrow, enhancement of cancer cell mobilization from the primary tumor, as well as blood vessel formation and increased proliferation of metastatic cells in the lungs in an IL-6/VEGF-A-dependent manner (Figure 3) (Bonapace, Coissieux et al. 2014).

4. PERSONALIZED MEDICINE: BRIDGING THE GAP BETWEEN EXPLORATORY RESEARCH AND CLINICAL APPLICATIONS

R. Okamoto, B. Hamelin, M. Obradovic, R. Mechera, B.T. Preca

With colleagues from the USB (Surgery, Gynecology, Pathology and Oncology), FMI, UNIBAS, UNIZ, ETH and IBM, we are building a breast cancer personalized medicine team which should ultimately improve treatment for patients. We will use genomics, proteomics, and immunomics, combined with drug response profiling and computational analysis for assessing and modeling cancer and tumor microenvironment heterogeneity in a longitudinal way. We apply a personalized systems medicine interdisciplinary approach to discover predictive biomarkers and mechanisms of resistance, identify novel targets and rationally design combination therapy.

Mohamed Bentires-Alj and team

Back row (from left to right) : Marie-May Coissieux, Romain Amante, Milica Vulin, Priska Auf der Maur, Baptiste Hamelin, Atul Sethi.
Front row (from left to right) : Markus Ackerknecht, Marion Salvador, Veronica Richina, Shany Koren-Hauer, Alexandra Musch, Mohamed Bentires-Alj.
Missing on the foto : Robert Mechera, Duvini De Silva, Ryoko Okamoto, Federica Zilli, Joana Pinto do Couto Silva, Ana Pinto Correia, Milan Obradovic, Bogdan-Tiberius Preca.

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The DBM Postdoc Club – a unique networking opportunity

Being a postdoc can be tough. After surviving the challenges of being a PhD student, young scientists often face completely new issues such as developing scientific projects on their own, obtaining independent funding, mentoring PhD students and at the same time thinking about future perspectives in- and outside academia. During this time, postdocs often start families, which brings a whole new set of challenges. Simultaneously, postdocs are supposed to pursue ground-breaking research in competitive top notch labs and publish with high impact to stay in academia. Sounds a bit like juggling, doesn't it?!

As a professional networking platform the DBM Postdoc Club was founded as an association by and for postdoctoral scientists at the Department of Biomedicine in Basel. Our steering committee consists of 4 – 6 postdoctoral volunteers, representing the different DBM locations at Hebelstrasse, Mattenstrasse, Petersplatz, and both Pestalozzi and Klingelbergstrasse. Importantly, the DBM Postdoc Club is officially supported by the DBM administration as part of the education and career program and is granted financial support for our events throughout the year. The cultural diversity of our department is reflected in the representatives of the Postdoc Club who currently come from Finland, Italy, Germany and New Zealand. By the way, we are always looking for new members to support our postdoc club! If you are interested, just get in touch with us by mail or pass by at one of our events.

"Happy hour": Monthly DBM Postdoc Happy Hour at KaBar.

DBM Postdoctoral Career Day 2016

As our founding aim is to support the professional development of young scientists the committee organises annual career-orientated events for DBM postdocs. In September 2016, we arranged a DBM Postdoctoral Career Day for the first time, which included invited speakers who shared their career development with us, providing insight in their current profession. Radek Skoda and Primo Schär from the DBM talked about their experiences in academia and shared information on the path to gaining a professorship as well as funding possibilities in Switzerland. In addition, we learned about non-research professions from a market access specialist (Jean-Francois Ricci; Wellmera), European patent attorney (Andreas Schöllhorn; Latscha Schöllhorn Partner), scientific journalist (Ulrike Brandt-Bohne) and start-up CEO (Ulf Grawunder, NBE Therapeutics). Furthermore, Susanne Matuschek from Matuschek Consulting instructed us on how to network at conferences and meetings and to develop the right skills to boost your career development. The workshop took place at the company Actelion in Allschwil and we were pleased that almost 40 DBM postdocs joined our invitation and made our workshop a resounding success.

Upcoming events in 2017

Following the tradition of a yearly event for all DBM postdocs, organisation and planning of such happening for 2017 is in full swing. We are currently preparing a hands-on workshop on a specific but omnipresent aspect of career development, the job interview. At certain points in our career, no matter whether changing to a new postdoc position, moving to industry or taking

"Retreat": Basel Postdoc Network Retreat, June 2016, in Saas-Fee.

the next step in your academic career, we will be confronted by a situation in which we have to convincingly "sell" ourselves and our qualities – one which many of us are not always sufficiently prepared for. In order to overcome this lack of practical experience in such a demanding and exciting situation, we would like to offer interested postdocs the opportunity to actively train for interviews in small groups with the help and guidance of professional coaches. More detailed information on this event will follow.

Additionally, since we aim to provide a platform for networking, both within and without the institute, we would also like to draw your attention to the annual Basel Postdoc Network Retreat, taking place in Zermatt from June 21st-23rd. This event provides a great occasion to meet and discuss scientific achievements with colleagues from various disciplines, institutes and research areas from academia and industry. Besides the opportunity to connect and discuss with invited internationally renowned researchers, there will also be sessions on alternative career opportunities in science and beyond. More information can be found on the homepage:

http://postdocretreat.biozentrum.unibas.ch/

Last but not least

In times where you may seem chained to the bench, you may not be able to afford spending entire days to join some of the aforementioned events. But you may still want to escape the bench for at least a few hours – which is the perfect occasion to join us at our monthly "Happy Hour" at KaBar to network with other postdocs from the department. Watch your inbox for the flyer - we would be very happy to see you there!

The DBM Postdoc Club representatives:

Oliver Gorka, Giuseppe Isu, Karoliina Pelttari, Julian Spagnuolo, Franziska Uhlenbrock https://biomedizin.unibas.ch/en/education/post-doc/

DBM Postdoc Club Basel

Congress 26–27 January 2017, Bern

In January I had the pleasure of attending the congress hosted by the Swiss Academy of Sciences (SCNAT) entitled "We Scientists Shape Science". Also in attendance from the DBM were Professor Ed Palmer and Nivedya Swarnalekha. The premise of the congress was that it isn't enough for science to move faster - the endeavor should also improve qualitatively. According to the call for participants, the organizers "want science to be creative, solid, open, helpful for society and a good career opportunity for talented youth." And as the title indicates, if we want to see changes in how science is done, then we have to do it ourselves. The intended results of the congress were concrete actions that can begin to address some of the challenges. Institutional stakeholders were also present to observe, offer their feedback, and hopefully, commit to taking relevant action.

In his opening statements, SCNAT President, Professor Marcel Tanner, admitted that even in Switzerland, science has problems. However, he cautioned against jumping too quickly to the conclusion that all the problems lie with the funding agencies or publishing houses. Throughout the event, he returned to this call to action: what are we as individuals willing to do? He emboldened the participants to make the two-day conference a "space for creative ideas" where the variety of perspectives from different disciplines would be a strength rather than a hurdle.

Dr. Karim Bschir, a philosopher of science, challenged the audience with three interrelated theses: How much room for improvement is there in Swiss science, actually, and what are we willing to do to achieve these perhaps marginal gains? Secondly, he asked us to always consider the aspect of risk - what are the risks (and to whom) of changing the status quo? Finally he pointed out that practically speaking, we must ultimately determine which individual or institutional actors are willing to take these risks.

On the first day of the congress, we were tasked with determining the challenges in our respective areas of focus: Time for Research, Space for Creativity, Scientific Career, Scientific Practice, Open Science, and Science in Society. These topics reveal the areas where the Academy sees the need and potential for improvement. The second day saw participants seeking concrete proposals to begin to address these challenges.

Although the conclusions reached by the six groups have been published (http://www.naturalsciences.ch/wescientists/, http://we-scientists.blogspot.ch/), a brief description of each follows.

Time for Research focused on the observation that many scientists spend too much time on non-research activities, such as administration and fund-raising.

Space for Creativity was a search for ways to enable scientists to explore riskier, less "safe" lines of investigation and to recharge and derive inspiration from other areas of life.

Scientific Career dealt with the challenges of hiring metrics (the assumption being that there may be too much reliance on publication-based factors) as well as the problems with the idea that the only successful outcome of a PhD is a professorship.

Scientific Practice primarily handled the topics of integrity in science and reproducibility of results, particularly in light of the increasing risk of public skepticism (at least in some political circles) about science.

The **Open Science** group discussed not only increased access to semantically enriched publications and data (including citable but otherwise unpublished data), but also the consideration of such contributions in both hiring and institutional assessments.

Finally, **Science in Society** tackled the interface between scientists, the public, and policy makers. Professor Tanner's experience here, seconded by Professor René Schwarzenbach, President of SCNAT's Science and Policy Platform, was that the model of scientist as counselor or provider of policy prescriptions was wrong, and that a real dialogue, time consuming as it may be, was needed instead.

Noteworthy Stakeholder Reactions

Representation: Professor Janet Hering of EAWAG found it a shame that the fields of engineering, social science and humanities were poorly represented at the congress, since

they operate precisely at the interface of science and society. Others noted the relative absence of scientists in the midst of their careers: students, post-docs and retirees seemed to predominate.

Interpersonal contact: Professor Tanner cautioned, while discussing mentorship, against a trend he sees: people preferring to communicate electronically rather than face-to-face. Is this just a rift between generations or a serious warning that our ability to effect change is only as strong as our genuine interpersonal connections?

Privilege, not entitlement: Professor Hering also warned academic scientists, even at the highest level of accomplishment, never to forget that their job is a privilege funded by society, not an entitlement. When scientists act and speak from a posture of entitlement, it is guaranteed to increase public skepticism and perceptions of elitism. She said that, given this financing arrangement, it is completely reasonable to ask what the return to society is of scientists' work.

System-level change: It is commonly observed that Swiss institutions and the organizations that instantiate them change slowly, if at all. However, one reason for this is the relative lack of bottom-up pressure - scholars who train in other countries often find there a much more vigorous pool of activism. Maybe scientists in Switzerland think everything is perfect already (a symptom of relatively high compensation?), or maybe they have reason to fear possible repercussions of rocking the boat in their departments. Whatever the reasons, we ought not complain about closed doors at research institutions or funding agencies if no one is doing any knocking. Without action from concerned scientists, institutional inertia is a self-fulfilling prophecy.

Discussion – openness as end and means

I would like to make the claim that openness is the perfect metaphor for this conference's mission. On the one hand, this is not a particularly original or amazing insight, considering one of the workshop topics was "Open Science". However, I would submit that openness is not only a goal but also, in a broader sense, an instrument for meeting the challenges.

It's fairly intuitive to interpret the challenges presented at the conference using the concept of openness, and this interpretation leads naturally to some avenues for concrete action.

Time (for Research) and Space (for Creativity) are about creating temporal and spatial potential - nothing at all can happen without this open, empty state.

Openness to other career paths is a sensible response if the percentage of PhD candidates who go on to find stable professorships is too low. On the part of mentors and administrators, initiating an open and honest dialogue about the issue is a crucial first step.

Several challenges that spanned multiple topics revolved around risk, particularly the risk to young scientists of moving into a new field or making, as an individual or a research institution, a principled decision to publish in and support open access journals. How can this kind of openness to risk be acknowledged and rewarded?

Another important manifestation of openness is generosity - how can the ever more competitive character of science be tempered by a collegial culture based on sharing one's time, data and ideas in the service of a public good?

Finally, the practice of science itself is based on openness: science is about observing what happens. But creative science also flows from the inner child, a sense of joy and wonder at the world, an open "beginner's mind" rather than one blinded by presuppositions.

In my view, science itself needs to be cracked open and shared, not only through easier access to publicly funded data and publications and better communication between scientists and society, but also as a fundamental aspect of humanity. Scientific thought is not something achievable only by a few; it is a part of being human. But the natu-

ral scientific mind that finds wonder in the world must be nurtured throughout the whole education process, the flame of curiosity carefully fed.
Expanding the participation in science in this way is clearly a long-term goal, but it may be a helpful way to develop a healthy dialogue between scientists and the public. No question: researchers absolutely need to be able to communicate their work to non-scientists - one stakeholder wished never again to hear from a scientist who's asked to explain their work that "it's too complicated". Effectively reaching all different kinds of audience is part of a scientist's job. But by showing everyone from a young age that they too are in some sense naturally scientists, a science-society bridge can be built from both sides.

A rational approach to finding practical solutions to these challenges would be to apply scientific ways of thinking more often to the "non-scientific" hurdles we see on our path. If iterative processes of observation and creative criticism were applied by individuals at all relevant levels of action, we would likely go a long way toward addressing the challenges raised at the congress. The more that individual scientists and institutional actors are willing to observe and assess their own presuppositions and conduct, the sooner we will open together the space in which science, in the service of society, can flourish.

David Schreiner

Dissertationen

Am 18. November 2016 konnte **Riccardo Mancuso** von der Forschungsgruppe "Clinical Pharmacology" (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Identification and characterisation of novel αLβ2 inhibitors and their differentiation from known inhibitors".

Am 28. März 2017 stellte sich **Ronny Nienhold** von der Forschungsgruppe „Experimental Hematology" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: "Genetic lesions and clinical implications in myeloproliferative neoplasms".

Auszeichnungen

Venia docendi verliehen

In ihren Sitzungen im Dezember 2016, Januar 2017 und März 2017 hat die Regenz der Universität Basel **Lukas Jeker** von der Forschungsgruppe "Molecular Immune Regulation" (Departement Biomedizin Hebelstrasse) die Venia docendi für Experimentelle Medizin verliehen. **Yves Brand** von der Forschungsgruppe "Inner Ear Research" (Departement Biomedizin Hebelstrasse) erhielt die Venia docendi für Otorhinolaryngologie und **Michael Osthoff** von der Forschungsgruppe "Clinical Immunology" (Departement Biomedizin Hebelstrasse) die Venia docendi für Innere Medizin/Infektiologie. Sie sind damit befugt, den Titel eines Privatdozenten zu führen. **Frank Stenner-Liewen** von der Forschungsgruppe "Cancer Immunology" (Departement Biomedizin Hebelstrasse) wurde zum Titularprofessor für Medizinische Onkologie befördert.

Das DBM gratuliert ganz herzlich!

Nature nature doi:10.1038/nature20829 IF 38,138

The Hippo kinases LATS1 and 2 control human breast cell fate via crosstalk with ERα

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Cell fate perturbations underlie many human diseases, including breast cancer1,2. Unfortunately, the mechanisms by which breast cell fate are regulated are largely unknown. The mammary gland epithelium consists of differentiated luminal epithelial and basal myoepithelial cells, as well as undifferentiated stem cells and more restricted progenitors3,4. Breast cancer originates from this epithelium, but the molecular mechanisms that underlie breast epithelial hierarchy remain ill-defined. Here, we use a highcontent confocal image-based short hairpin RNA screen to identify tumour suppressors that regulate breast cell fate in primary human breast epithelial cells. We show that ablation of the large tumour suppressor kinases (LATS) 1 and 2 (refs 5, 6), which are part of the Hippo pathway, promotes the luminal phenotype and increases the number of bipotent and luminal progenitors, the proposed cells-of-origin of most human breast cancers. Mechanistically, we have identified a direct interaction between Hippo and oestrogen receptor-α (ERα) signalling. In the presence of LATS, ERα was targeted for ubiquitination and Ddb1–cullin4-associated-factor 1 (DCAF1)-dependent proteasomal degradation. Absence of LATS stabilized ERα and the Hippo effectors YAP and TAZ (hereafter YAP/TAZ), which together control breast cell fate through intrinsic and paracrine mechanisms. Our findings reveal a non-canonical (that is, YAP/TAZ-independent) effect of LATS in the regulation of human breast cell fate.

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Nature Immunology nature immunology doi:10.1038/ni.3659 IF 19,381

Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation

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The deleterious effect of chronic activation of the IL-1β system on type 2 diabetes and other metabolic diseases is well documented. However, a possible physiological role for IL-1β in glucose metabolism has remained unexplored. Here we found that feeding induced a physiological increase in the number of peritoneal macrophages that secreted IL-1β, in a glucose-dependent manner. Subsequently, IL-1β contributed to the postprandial stimulation of insulin secretion. Accordingly, lack of endogenous IL-1β signaling in mice during refeeding and obesity diminished the concentration of insulin in plasma. IL-1β and insulin increased the uptake of glucose into macrophages, and insulin reinforced a pro-inflammatory pattern via the insulin receptor, glucose metabolism, production of reactive oxygen species, and secretion of IL-1β mediated by the NLRP3 inflammasome. Postprandial inflammation might be limited by normalization of glycemia, since it was prevented by inhibition of the sodium–glucose cotransporter SGLT2. Our findings identify a physiological role for IL-1β and insulin in the regulation of both metabolism and immunity.

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The Journal of Clinical Investigation JCI 2017;127(2):549–563 IF 12,575

Targeting deregulated AMPK/mTORC1 pathways improves muscle function in myotonic dystrophy type I

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Myotonic dystrophy type I (DM1) is a disabling multisystemic disease that predominantly affects skeletal muscle. It is caused by expanded CTG repeats in the 3′-UTR of the dystrophia myotonica protein kinase (DMPK) gene. RNA hairpins formed by elongated DMPK transcripts sequester RNA-binding proteins, leading to mis-splicing of numerous pre-mRNAs. Here, we have investigated whether DM1-associated muscle pathology is related to deregulation of central metabolic pathways, which may identify potential therapeutic targets for the disease. In a well-characterized mouse model for DM1 (HSA^{LR} mice), activation of AMPK signaling in muscle was impaired under starved conditions, while mTORC1 signaling remained active. In parallel, autophagic flux was perturbed in HSA^{LR} muscle and in cultured human DM1 myotubes. Pharmacological approaches targeting AMPK/mTORC1 signaling greatly ameliorated muscle function in HSA^{LR} mice. AICAR, an AMPK activator, led to a strong reduction of myotonia, which was accompanied by partial correction of misregulated alternative splicing. Rapamycin, an mTORC1 inhibitor, improved muscle relaxation and increased muscle force in HSA^{LR} mice without affecting splicing. These findings highlight the involvement of AMPK/mTORC1 deregulation in DM1 muscle pathophysiology and may open potential avenues for the treatment of this disease.

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Journal of Allergy and Clinical Immunology (Letter to the Editor) IF 12,485

Vedolizumab as a successful treatment of CTLA-4–associated autoimmune enterocolitis

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To the Editor: In 2007, a 39-year-old white male (unique patient identifier [UPI]: CTLA-4_AAA.II.1) presented with chronic, noninfectious diarrhea. The patient's history was noticeable for adrenal insufficiency diagnosed in 1991.

In 2013, his diarrhea worsened, resulting in weight loss of more than 20 kg and severe dehydration. Prednisolone (1 mg/kg of body weight given for several weeks) was entirely ineffective. Macroscopic enterocolitis was seen, corresponding histologically to extensive infiltration with $CD3^+$ T cells in cryptal areas (Fig E1, A, in this article's Online Repository at www.jacionline.org). Enterocytes showed enhanced positivity for Ki-67, indicating augmented proliferation (Fig E1, B). Complete absence of mucus-producing goblet cells was observed in colon and small intestine (data not shown). At that time, hypogammaglobulinemia (IgG, 4.4 g/L [normal, 7-16 g/L]; IgA, 0.53 g/L [normal, 0.7-4 g/L]) was first noticed, whereas serum IgM level was within normal range. On a computed tomography scan, no evidence for malignancy or lymphoproliferation was found and lung morphology was normal. Intravenous immunoglobulin (IVIG) substitution (0.5 g/kg body weight per month, given for 4 months) had no effect on diarrhea and the patient required intravenous fluids repeatedly.

In 2014, the patient developed severe hyporegenerative anemia. Bone marrow biopsy revealed isolated yet almost complete absence of erythropoietic cells (data not shown), and the diagnosis of pure red cell aplasia was established. Parvovirus was tested negative by PCR.

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The EMBO Journal (2016) 35: 2315–2331 IF 9,643

Evi1 regulates Notch activation to induce zebrafish hematopoietic stem cell emergence

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Abstract

During development, hematopoietic stem cells (HSCs) emerge from aortic endothelial cells (ECs) through an intermediate stage called hemogenic endothelium by a process known as endothelial-to-hematopoietic transition (EHT). While *Notch* signaling, including its upstream regulator *Vegf*, is known to regulate this process, the precise molecular control and temporal specificity of Notch activity remain unclear. Here, we identify the zebrafish transcriptional regulator *evi1* as critically required for Notch-mediated EHT. *In vivo* live imaging studies indicate that *evi1* suppression impairs EC progression to hematopoietic fate and therefore HSC emergence. *evi1* is expressed in ECs and induces these effects cell autonomously by activating Notch via pAKT. Global or endothelial-specific induction of *notch, vegf*, or pAKT can restore endothelial Notch and HSC formations in *evi1* morphants. Significantly, evi1 overexpression induces Notch independently of Vegf and rescues HSC numbers in embryos treated with a Vegf inhibitor. In sum, our results unravel *evi1*–pAKT as a novel molecular pathway that, in conjunction with the *shh–vegf* axis, is essential for activation of Notch signaling in VDA endothelial cells and their subsequent conversion to HSCs.

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PNAS 734–739 | January 24, 2017 | vol. 114 | no. 4 IF 9,423

Cocapture of cognate and bystander antigens can activate autoreactive B cells

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Autoantibodies againstmyelin oligodendrocyteglycoprotein(MOG) are associated with autoimmune central nervous system diseases like acute disseminated encephalomyelitis (ADEM). For ADEM, it is speculated that a preceding infection is the trigger of the autoimmune response, but the mechanism connecting the infection to the production of MOG antibodies remains amystery. Wereasoned that the ability of B cells to capture cognate antigen from cell membranes, along with small quantities of coexpressed "bystander" antigens, might enable B-cell escape from tolerance. We tested this hypothesis using influenza hemagglutinin as a model viral antigen and transgenic, MOG-specific B cells. Using flow cytometry and live and fixed cell microscopy, we show that MOG-specific B cells take up large amounts of MOG from cell membranes. Uptake of the antigen from the membrane leads to a strong activation ofthe capturing B cell. When influenza hemagglutinin is also present inthe membrane of the target cell, it can be cocaptured with MOG by MOG-specific B cells via the B-cell receptor. Hemagglutinin and MOG are both presented to T cells, which in turn are activated and proliferate. As a consequence, MOG-specific B cells get help from hemagglutinin-specific T cells to produce anti-MOG antibodies. In vivo, the transfer of MOG-specific B cells into recipient mice after the cocapture of MOG and hemagglutinin leads to the production of class-switched anti-MOG antibodies, dependent on the presence of hemagglutinin-specific T cells. This mechanism offers a link between infection and autoimmunity.

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PNAS PNAS E8122–E8130 | November 29, 2016 IF 9,423

Permissive roles of cytokines interleukin-7 and Flt3 ligand in mouse B-cell lineage commitment

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Hematopoietic cells are continuously generated throughout life from hematopoietic stem cells, thus making hematopoiesis a favorable system to study developmental cell lineage commitment. The main factors incorporating environmental signals to developing hematopoietic cells are cytokines, which regulate commitment of hematopoietic progenitors to the different blood lineages by acting either in an instructive or a permissive manner. Fms-like tyrosine kinase-3 (Flt3) ligand (FL) and Interleukin-7 (IL-7) are cytokines pivotal for B-cell development, as manifested by the severely compromised B-cell development in their absence. However, their precise role in regulating B-cell commitment has been the subject of debate. In the present study we assessed the rescue of B-cell commitment in mice lacking IL-7 but simultaneously overexpressing FL. Results obtained demonstrate that FL overexpression in IL-7–deficient mice rescues B-cell commitment, resulting in significant Ebf1 and Pax5 expression in Ly6D$^+$CD135$^+$CD127$^+$CD19$^-$ precursors and subsequent generation of normal numbers of CD19$^+$ B-cell progenitors, therefore indicating that IL-7 can be dispensable for commitment to the B-cell lineage. Further analysis of Ly6D$^+$CD135$^+$CD127$^+$CD19$^-$ progenitors in IL-7– or FL-deficient mice overexpressing Bcl2,aswellasinIL-7transgenicmicesuggests that both FL and IL-7 regulate B-cell commitment in a permissive manner: FL by inducing proliferation of Ly6D$^+$CD135$^+$CD127$^+$CD19$^-$ progenitors and IL-7 by providing survival signals to these progenitors.

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Clinical Infectious Diseases Clinical Infectious Diseases 2017;64(3):295–300 IF 8,736

Therapeutic Immune Recovery and Reduction of CXCR4-Tropic HIV-1

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Background. In the absence of therapy, CXCR4 (X4)–tropic human immunodeficiency virus type 1 (HIV-1) increases over time, associated with accelerated disease progression. In contrast, the majority of patients receiving long-term combination antiretroviral therapy (cART) present with CCR5 (R5)-tropic HIV-1 variants. It is unclear whether cART itself mediates the reduction of X4-tropic HIV-1. The current study aimed at assessing the tropism of viral integrates in patients' blood during fully suppressive cART.

Methods. The relative frequencies of X4-tropic proviral HIV-1 variants were determined by means of next-generation sequencing (False Positive Rate (FPR), 3.5%; R5- or X4 tropic variants occurring at less than 2% of the total virus population) for 35 treated patients in the Swiss HIV Cohort Study and followed longitudinally over time. Full viral suppression and a continuous CD4 T-cell recovery during cART were documented for all patients. Viral phylogenetic changes and sequence evolution were analyzed.

Results. The majority of patients (80%) experienced no frequency increase in X4-tropic proviruses during therapy. Although some proviral sequence evolution was demonstrable in >50% of these patients during therapy, this growing viral diversity was in no case paralleled by the emergence or expansion of X4-tropic provirus variants. In the remaining 20% of patients, the documented expansion of X4-tropic provirus was based on the outgrowth of single viral variants from minority populations already present before therapy initiation.

Conclusion. Our study demonstrates that X4-tropic HIV sharply declines in most patients during successful therapy, which indicates a preferential tropism-dependent provirus elimination in the immunocompetent host. The recently implemented World Health Organization strategies of immediate therapy initiation are fully in line with this gradual loss of X4 tropism during therapy. Moreover, the early use of coreceptor antagonists against the remaining CCR5-tropic viruses may be indicated.

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The Journal of Pathology: Clinical Research | The Journal of Pathology | January 2017; 3: 44–57 IF 7,381

T-cadherin in prostate cancer: relationship with cancer progression, differentiation and drug resistance

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Abstract

Prostate cancer represents the second leading cause of cancer-related death in men. T-cadherin (CDH13) is an atypical GPI-anchored member of the cadherin family of adhesion molecules. Its gene was reported to be downregulated in a small series of prostate tumours. T-cadherin protein expression/localisation in prostate tissue has never been investigated. The purpose of our study was to analyse CDH13 gene and protein levels in large sets of healthy and cancer prostate tissue specimens and evaluate CDH13 effects on the sensitivity of prostate cancer cells to chemotherapy. Analysis of CDH13 gene expression in the TCGA RNAseq dataset for prostate adenocarcinoma (N = 550) and in tissue samples (N = 101) by qPCR revealed weak positive correlation with the Gleason score in cancer and no difference between benign and malignant specimens. Immunohistochemical analysis of tissue sections (N = 12) and microarrays (N = 128 specimens) demonstrated the presence of CDH13 on the apical surface and at intercellular contacts of cytokeratin 8-positive luminal cells and cells double-positive for cytokeratin 8 and basal marker p63. T-cadherin protein expression was markedly upregulated in cancer as compared to benign prostate hyperplasia, the increase being more prominent in organ-confined than in advanced hormone-resistant tumours, and correlated negatively with the Gleason pattern. T-cadherin protein level correlated strongly with cytokeratin 8 and with an abnormal diffuse/membrane localisation pattern of p63. Ectopic expression of CDH13 in metastatic prostate cancer cell line DU145 reduced cell growth in the presence of doxorubicin. We conclude that CDH13 protein, but not its gene expression, is strongly upregulated in early prostate cancer, correlates with changes in luminal/basal differentiation and p63 localisation, and promotes sensitivity of cancer cells to doxorubicin. These data identify CDH13 as a novel molecule relevant for prostate cancer progression and response to therapy.

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The Journal of Neuroscience | The Journal of Neuroscience | Feb. 1, 2017 • 37(5):1162–1175 IF 5,924

KCTD Hetero-oligomers Confer Unique Kinetic Properties on Hippocampal $GABA_B$ Receptor-Induced K^+ Currents

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$GABA_B$ receptors are the G-protein coupled receptors for the main inhibitory neurotransmitter in the brain, GABA. $GABA_B$ receptors were shown to associate with homo-oligomers of auxiliary KCTD8, KCTD12, KCTD12b, and KCTD16 subunits (named after their T1 K^+-channel tetramerization domain) that regulate G-protein signaling of the receptor. Here we provide evidence that $GABA_B$ receptors also associate with hetero-oligomers of KCTD subunits. Coimmunoprecipitation experiments indicate that two-thirds of the KCTD16 proteins in the hippocampus of adult mice associate with KCTD12. We show that the KCTD proteins hetero-oligomerize through self-interacting T1 and H1 homology domains. Bioluminescence resonance energy transfer measurements in live cells reveal that KCTD12/ KCTD16 hetero-oligomers associate with both the receptor and the G-protein. Electrophysiological experiments demonstrate that KCTD12/KCTD16 hetero-oligomers impart unique kinetic properties on G-protein-activated Kir3 currents. During prolonged receptor activation (one min) KCTD12/KCTD16 hetero-oligomers produce moderately desensitizing fast deactivating K^+ currents, whereas KCTD12 and KCTD16 homo-oligomers produce strongly desensitizing fast deactivating currents and nondesensitizing slowly deactivating currents, respectively. During short activation (2s) KCTD12/KCTD16 hetero-oligomers produce nondesensitizing slowly deactivating currents. Electrophysiological recordings from hippocampal neurons of KCTD knock-out mice are consistent with these findings and indicate that KCTD12/KCTD16 hetero-oligomers increase the duration of slow IPSCs. In summary, our data demonstrate that simultaneous assembly of distinct KCTDs at the receptor increases the molecular and functional repertoire of native $GABA_B$ receptors and modulates physiologically induced K^+ current responses in the hippocampus.

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Stem Cells STEM CELLS 2016;34:2956–2966 IF 5,902

Implantation of Stromal Vascular Fraction Progenitors at Bone Fracture Sites: From a Rat Model to a First-in-Man Study

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Abstract

Stromal Vascular Fraction (SVF) cells freshly isolated from adipose tissue include osteogenic-and vascular-progenitors, yet their relevance in bone fracture healing is currently unknown. Here, we investigated whether human SVF cells directly contribute to the repair of experimental fractures in nude rats, explored the feasibility/safety of their clinical use for augmentation of upper arm fractures in elderly individuals. Human SVF cells were loaded onto ceramic granules within fibrin geland implanted in critical nude rat femoralfractures after locking-plate osteosynthesis, with cell-free grafts as control. After 8 weeks, only SVF-treated fractures did not fail mechanically and displayed formation of ossicles at the repair site, with vascular andbone structures formed by human cells. The same materials combined with autologous SVF cells were then used to treat low-energy proximal humeral fractures in 8 patients (64-84 years old) along with standard open reduction and internal fixation. Graft manufacturing and implantation were compatible with intraoperative settings and led to no adverse reactions, thereby verifying feasibility/safety. Biopsies of the repair tissue after up to 12 months, upon plate revision or removal, demonstrated formation of bone ossicles, structurally disconnected and morphologically distinct from osteoconducted bone, suggesting the osteogenic nature of implanted SVF cells. We demonstrate that SVF cells, without expansion or exogenous priming, can spontaneously form bone tissue and vessel structures within a fracture-microenvironment.The gained clinical insights into the biological functionality of the grafts, combined with their facile, intra-operative manufacturing modality, warrant further tests of effectiveness in larger, controlled trials.

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Frontiers in Immunology frontiers in Immunology December 2016 | Volume 7 | Article 565 IF 5,695

Multimodal Regulation of NET Formation in Pregnancy: Progesterone Antagonizes the Pro-NETotic Effect of Estrogen and G-CSF

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Human pregnancy is associated with a mild pro-inflammatory state, characterized by circulatory neutrophil activation. In order to explore the mechanism underlying this alteration, we examined NETosis during normal gestation. Our data indicate that neutrophils exhibit a pro-NETotic state, modulated in a multimodal manner during pregnancy. In general, circulatory granulocyte colony-stimulating factor, the levels of which increase during gestation, promotes neutrophil extracellular trap (NET) formation. Early in pregnancy, NETosis is enhanced by chorionic gonadotropin, whereas toward term is stimulated by estrogen. A complex interaction between estrogen and progesterone arises, wherein progesterone restrains the NETotic process. In this state, extensive histone citrullination is evident, yet full NETosis is inhibited. This coincides with the inability of neutrophil elastase to translocate from the cytoplasm to the nucleus and is regulated by progesterone. Our findings provide new insight concerning gestational and hormone-driven pathologies, since neutrophil recruitment, activation, and NET release could be associated with excessive endothelial and placental injury.

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Scientific Reports SCIENTIFIC REPORTS 6:36440 | DOI: 10.1038/srep36440 1 IF 5,228

A microfluidic device for measuring cell migration towards substratebound and soluble chemokine gradients

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Cellular locomotion is a central hallmark of eukaryotic life. It is governed by cell-extrinsic molecular factors, which can either emerge in the soluble phase or as immobilized, often adhesive ligands. To encode for direction, every cue must be present as a spatial or temporal gradient. Here, we developed a microfluidic chamber that allows measurement of cell migration in combined response to surface immobilized and soluble molecular gradients. As a proof of principle we study the response of dendritic cells to their major guidance cues, chemokines. The majority of data on chemokine gradient sensing is based on *in vitro* studies employing soluble gradients. Despite evidence suggesting that in vivo chemokines are often immobilized to sugar residues, limited information is available how cells respond to immobilized chemokines. We tracked migration of dendritic cells towards immobilized gradients of the chemokine CCL21 and varying superimposed soluble gradients of CCL19. Differential migratory patterns illustrate the potential of our setup to quantitatively study the competitive response to both types of gradients. Beyond chemokines our approach is broadly applicable to alternative systems of chemo- and haptotaxis such as cells migrating along gradients of adhesion receptor ligands vs. any soluble cue.

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Oncotarget Oncotarget December 10, 2016 IF 5,008

Induction of hypoxia and necrosis in multicellular tumor spheroids is associated with resistance to chemotherapy treatment

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Abstract
Culture of cancerous cells in standard monolayer conditions poorly mirrors growth in three-dimensional architectures typically observed in a wide majority of cancers of different histological origin. Multicellular tumor spheroid (MCTS) culture models were developed to mimic these features. However, *in vivo* tumor growth is also characterized by the presence of ischemic and necrotic areas generated by oxygenation gradients and differential access to nutrients. Hypoxia and necrosis play key roles in tumor progression and resistance to treatment. To provide in vitro models recapitulating these events in highly controlled and standardized conditions, we have generated colorectal cancer (CRC) cell spheroids of different sizes and analyzed their gene expression profiles and sensitivity to treatment with 5FU, currently used in therapeutic protocols. Here we identify three MCTS stages, corresponding to defined spheroid sizes, characterized by normoxia, hypoxia, and hypoxia plus necrosis, respectively. Importantly, we show that MCTS including both hypoxic and necrotic areas most closely mimic gene expression profiles of *in vivo*-developing tumors and display the highest resistance to 5FU. Taken together, our data indicate that MCTS may mimic *in vitro* generation of ischemic and necrotic areas in highly standardized and controlled conditions, thereby qualifying as relevant models for drug screening purposes.

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The Journal of Immunology | The Journal of Immunology | 2016; 197:3669–3679 | IF 4,985

Von Willebrand Factor Interacts with Surface-Bound C1q and Induces Platelet Rolling

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Premature atherosclerosis and thrombotic complications are major causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). However, the high incidence of these complications cannot be explained by traditional risk factors alone, suggesting direct effects of an activated immune system on hemostasis. The unexpected nucleotide sequence homology between SLE patient–derived autoantibodies against complement C1q (Fab anti-C1q) and von Willebrand factor (VWF) led us to investigate a potential interaction between the complement and hemostatic systems on the level of initiating molecules. VWF was found to bind to surface-bound C1q under static conditions. The binding could specifically be inhibited by Fab anti-C1q and C1q–derived peptides. Under shear stress the C1q–VWF interaction was enhanced, resembling the binding of VWF to collagen I. Additionally, we could show that C1q–VWF complexes induced platelet rolling and firm adhesion. Furthermore, we observed VWF binding to C1q-positive apoptotic microparticles and cholesterol crystals, as well as increased VWF deposition in C1q–positive glomeruli of SLE patients compared with control nephropathy. We show, to our knowledge for the first time, binding of VWF to C1q and thus a direct interaction between starter molecules of hemostasis and the classical pathway of complement. This direct interaction might contribute to the pathogenic mechanisms in complement-mediated, inflammatory diseases.

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Journal of Antimicrobial Chemotherapy | Journal of Antimicrobial Chemotherapy | December 20, 2016 | IF 4,919

Role of Gag mutations in PI resistance in the Swiss HIV cohort study: bystanders or contributors?

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Background: HIV Gag mutations have been reported to confer PI drug resistance. However, clinical implications are still controversial and most current genotyping algorithms consider solely the protease gene for assessing PI resistance.
Objectives: Our goal was to describe for HIV infections in Switzerland the potential role of the C-terminus of Gag (NC–p6) in PI resistance. We aimed to characterize resistance-relevant mutational patterns in Gag and protease and their possible interactions.
Methods: Resistance information on plasma samples from 2004–12 was collected for patients treated by two diagnostic centres of the Swiss HIV Cohort Study. Sequence information on protease and the C-terminal Gag region was paired with the corresponding patient treatment history. The prevalence of Gag and protease mutations was analysed for PI treatment-experienced patients versus PI treatment-naive patients. In addition, we modelled multiple paths of an assumed ordered accumulation of genetic changes using random tree mixture models.
Results: More than half of all PI treatment-experienced patients in our sample set carried HIV variants with at least one of the known Gag mutations, and 17.9% (66/369) carried at least one Gag mutation for which a phenotypic proof of PI resistance by *in vitro* mutagenesis has been reported. We were able to identify several novel Gag mutations that are associated with PI exposure and therapy failure.
Conclusions: Our analysis confirmed the association of Gag mutations, well known and new, with PI exposure. This could have clinical implications, since the level of potential PI drug resistance might be underestimated.

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Clin Pharmacokinet Clinical Pharmacokinetics DOI 10.1007/s40262-017-0513-9 IF 4,829

Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects

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Abstract

Background and Objective Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. The aim of the present study was to characterize the pharmacokinetics and exposure–response relationship of oral LSD.

Methods We analyzed pharmacokinetic data from two published placebo-controlled, double-blind, cross-over studies using oral administration of LSD 100 and 200 μg in 24 and 16 subjects, respectively. The pharmacokinetics of the 100-μg dose is shown for the first time and data for the 200-lg dose were reanalyzed and included. Plasma concentrations of LSD, subjective effects, and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.

Results Geometric mean (95% confidence interval) maximum plasma concentration values of 1.3 (1.2–1.9) and 3.1 (2.6–4.0) ng/mL were reached 1.4 and 1.5 h after administration of 100 and 200 lg LSD, respectively. The plasma half-life was 2.6 h (2.2–3.4 h). The subjective effects lasted (mean ± standard deviation) 8.2 ± 2.1 and 11.6 ± 1.7 h for the 100-and 200-μg LSD doses, respectively. Subjective peak effects were reached 2.8 and 2.5 h after administration of LSD 100 and 200 μg, respectively. A close relationship was observed between the LSD concentration and subjective response within subjects, with moderate counterclockwise hysteresis. Half-maximal effective concentration values were in the range of 1 ng/mL. No correlations were found between plasma LSD concentrations and the effects of LSD across subjects at or near maximum plasma concentration and within dose groups.

Conclusions The present pharmacokinetic data are important for the evaluation of clinical study findings (e.g., functional magnetic resonance imaging studies) and the interpretation of LSD intoxication. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination up to 12 h. The effects of LSD were related to changes in plasma concentrations over time, with no evidence of acute tolerance.

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International Journal of Cardiology CARDIOLOGY 221 (2016) 539–545 IF 4,638

Prognostic value of an abnormal response to acetylcholine in patients with angina and non-obstructive coronary artery disease: Long-term follow-up of the Heart Quest cohort

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Abstract

Background: This study aims to determine whether small vessel disease (SVD) or vasospastic disease (VSD) has an impact on prognosis.

Methods: The prospective cohort embraced 718 patients with angina equivalent symptoms and no coronary stenosis ≥50% recruited between 1997 and 2008. At baseline, patients were classified as having SVD, VSD, other cardiac disease or non-cardiac problem based on intracoronary acetylcholine application and fast atrial pacing during coronary angiography. Patients underwent follow-up between 2007 and 2015. Prognostic significance of the diagnosis on cardiovascular events (cardiovascular death or non-fatal myocardial infarction) was evaluated using Cox proportional hazards models adjusted for age and sex.

Results: The mean follow-up duration was 11.3 ± 2.7 years. Only 11 patients (1.5%) were lost to follow-up, resulting in an analyzed population of 707 patients. Patients with SVD (HR: 4.9, 95% CI: 1.1–22.4, P = 0.040) and VSD (HR: 4.8, 95% CI: 1.0–23.4, P = 0.050) had an increased risk of suffering cardiovascular events compared to patients with non-cardiac problems. Among SVD patients, those with the presence of endothelial dysfunction had a particularly high risk (HR: 7.3, 95% CI: 1.5–35.5, P = 0.015). Among patients with SVD or VSD, those having persisting or worsening angina during follow-up had a higher risk than patients in whom angina improved (HR: 4.8, 95% CI: 1.9–12.3, P = 0.001).

Conclusions: Our study shows that patients with SVD or VSD have an increased risk of cardiovascular events. This particularly applies to SVD patients with endothelial dysfunction. Symptoms should be taken seriously in SVD and VSD patients.

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Frontiers in Pharmacology | frontiers in Pharmacology | November 2016 | Volume 7 | Article 443 IF 4,418

Comparison of Liver Cell Models Using the Basel Phenotyping Cocktail

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Currently used hepatocyte cell systems for *in vitro* assessment of drug metabolism include hepatoma cell lines and primary human hepatocyte (PHH) cultures. We investigated the suitability of the validated *in vivo* Basel phenotyping cocktail (caffeine [CYP1A2], efavirenz [CYP2B6], losartan [CYP2C9], omeprazole [CYP2C19], metoprolol [CYP2D6], midazolam [CYP3A4]) *in vitro* and characterized four hepatocyte cell systems (HepG2 cells, HepaRG cells, and primary cryopreserved human hepatocytes in 2-dimensional [2D] culture or in 3D-spheroid co-culture) regarding basal metabolism and CYP inducibility. Under non-induced conditions, all CYP activities could be determined in 3D-PHH, CYP2B6, CYP2C19, CYP2D6, and CYP3A4 in 2D-PHH and HepaRG, and CYP2C19 and CYP3A4 in HepG2 cells. The highest non-induced CYP activities were observed in 3D-PHH and HepaRG cells. mRNA expression was at least four-fold higher for all CYPs in 3D-PHH compared to the other cell systems. After treatment with 20 μM rifampicin, mRNA increased 3-to 50-fold for all CYPs except CYP1A2 and 2D6 for HepaRG and 3D-PHH, 4-fold (CYP2B6) and 17-fold (CYP3A4) for 2D-PHH and four-fold (CYP3A4) for HepG2. In 3D-PHH at least a two-fold increase in CYP activity was observed for all inducible CYP isoforms while CYP1A2 and CYP2C9 activity did not increase in 2D-PHH and HepaRG. CYP inducibility assessed in vivo using the same phenotyping probes was also best reflected by the 3D-PHH model. Our studies show that 3D-PHH and (with some limitations) HepaRG are suitable cell systems for assessing drug metabolism and CYP induction *in vitro*. HepG2 cells are less suited to assess CYP induction of the 2C and 3A family. The Basel phenotyping cocktail is suitable for the assessment of CYP activity and induction also *in vitro.*

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Stem Cells Translational Medicine | Stem Cells Translational Medicine | 2016;5:1–9 IF 4,247

Spontaneous In Vivo Chondrogenesis of Bone Marrow-Derived Mesenchymal Progenitor Cells by Blocking Vascular Endothelial Growth Factor Signaling

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Abstract

Chondrogenic differentiation of bone marrow-derived mesenchymal stromal/stem cells (MSCs) can be induced by presenting morphogenetic factors or soluble signals but typically suffers from limited efficiency, reproducibility across primary batches, and maintenance of phenotypic stability. Considering the avascular and hypoxic milieu of articular cartilage, we hypothesized that sole inhibition of angiogenesis can provide physiological cues to direct in vivo differentiation of uncommitted MSCs to stable cartilage formation. Human MSCs were retrovirally transduced to express a decoy soluble vascular endothelial growth factor (VEGF) receptor-2 (sFlk1), which efficiently sequesters endogenous VEGF in vivo, seeded on collagen sponges and immediately implanted ectopically in nude mice. Although naïve cells formed vascularized fibrous tissue, sFlk1-MSCs abolished vascular ingrowth into engineered constructs, which efficiently and reproducibly developed into hyaline cartilage. The generated cartilage was phenotypically stable and showed no sign of hypertrophic evolution up to 12 weeks. In vitro analyses indicated that spontaneous chondrogenic differentiation by blockade of angiogenesis was related to the generation of a hypoxic environment, in turn activating the transforming growth factor-β pathway. These findings suggest that VEGF blockade is a robust strategy to enhance cartilage repair by endogenous or grafted mesenchymal progenitors. This article outlines the general paradigm of controlling the fate of implanted stem/progenitor cells by engineering their ability to establish specific microenvironmental conditions rather than directly providing individual morphogenic cues.

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Stem Cells Translational Medicine | STEM CELLS TRANSLATIONAL MEDICINE | 2016;5:1–11 IF 4,247

Fat-Derived Stromal Vascular Fraction Cells Enhance the Bone-Forming Capacity of Devitalized Engineered Hypertrophic Cartilage Matrix

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Abstract

Engineered and devitalized hypertrophic cartilage (HC) has been proposed as bone substitute material, potentially combining the features of osteoinductivity, resistance to hypoxia, capacity to attract blood vessels, and customization potential for specific indications. However, in comparison with vital tissues, devitalized HC grafts have reduced efficiency of bone formation and longer remodeling times. We tested the hypothesis that freshly harvested stromal vascular fraction (SVF) cells from human adipose tissue—which include mesenchymal, endothelial, and osteoclastic progenitors—enhance devitalized HC remodeling into bone tissue. Human SVF cells isolated from abdominal lipoaspirates were characterized cytofluorimetrically. HC pellets, previously generated by human bone marrow-derived stromal cells and devitalized by freeze/thaw, were embedded in fibrin gel with or without different amounts of SVF cells and implanted either ectopically in nude mice or in 4-mm-diameter calvarial defects in nude rats. In the ectopic model, SVF cells added to devitalized HC directly contributed to endothelial, osteoblastic, and osteoclastic populations. After 12 weeks, the extent of graft vascularization and amount of bone formation increased in a cell-number-dependent fashion (up to, respectively, 2.0-fold and 2.9-fold using 12 million cells per milliliter of gel). Mineralized tissue volume correlated with the number of implanted, SVF-derived endothelial cells (CD31+ CD34+ CD146+). In the calvarial model, SVF activation of HC using 12 million cells per milliliter of gel induced efficient merging among implanted pellets and strongly enhanced (7.3-fold) de novo bone tissue formation within the defects. Our findings outline a bone augmentation strategy based on off-the-shelf devitalized allogeneic HC, intraoperatively activated with autologous SVF cells.

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Eur. J. Immunology | European Journal of Immunology | 2017. 47: 394–405 IF 4,179

Pro-B cells propagated in stromal cell-free cultures reconstitute functional B-cell compartments in immunodeficient mice

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Up to now long-term in vitro growth of pro-B cells was thought to require stromal cells. However, here we show that fetal liver (FL) and bone marrow (BM) derived pro-B cells can be propagated long-term in stromal cell-free cultures supplemented with IL-7, stem cell factor and FLT3 ligand. Within a week, most cells expressed surface CD19, CD79A, λ5, and VpreB antigens and had rearranged immunoglobulin D-J heavy chain genes. Both FL and BM pro-B cells reconstituted the B-cell compartments of immuno-incompetent Rag2-deficient mice, with FL pro-B cells generating follicular, marginal zone (MZB) and B1a B cells, and BM pro-B cells giving rise mainly to MZB cells. Reconstituted Rag2-deficient mice generated significant levels of IgM and IgG antibodies to a type II T-independent antigen; mice reconstituted with FL pro-B cells generated surprisingly high IgG_1 titers. Finally, we show for the first time that mice reconstituted with mixtures of pro-B and pro-T cells propagated in stromal cell-free in vitro cultures mounted a T-cell-dependent antibody response. This novel stromal cell-free culture system facilitates our understanding of B-cell development and might be applied clinically.

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Tissue Engineering termis® Vol. 22, Numbers 21 and 22, 2016 IF 3,892

Regenerative Potential of Tissue-Engineered Nasal Chondrocytes in Goat Articular Cartilage Defects

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Nasal chondrocytes (NC) were previously demonstrated to remain viable and to participate in the repair of articular cartilage defects in goats. Here, we investigated critical features of tissue-engineered grafts generated by NC in this large animal model, namely cell retention at the implantation site, architecture and integration with adjacent tissues, and effects on subchondral bone changes. In this study, isolated autologous goat NC (gNC) and goat articular chondrocytes (gAC, as control) were expanded, green fluorescent protein-labelled and seeded on a type I/III collagen membrane. After chondrogenic differentiation, tissue-engineered grafts were implanted into chondral defects (6 mm in diameter) in the stifle joint for 3 or 6 months. At the time of explantation, surrounding tissues showed no or very low (only in the infrapatellar fat pad <0.32%) migration of the grafted cells. In repair tissue, gNC formed typical structures of articular cartilage, such as flattened cells at the surface and column-like clusters in the middle layers. Semi-quantitative histological evaluation revealed efficient integration of the grafted tissues with the adjacent native cartilage and underlying subchondral bone. A significantly increased subchondral bone area, as a sign for the onset of osteoarthritis, was observed following treatment of cartilage defects with gAC-, but not with gNC-grafts. Our results reinforce the use of NC-based engineered tissue for articular cartilage repair and preliminarily indicate their potential for the treatment of early osteoarthritic defects.

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Journal of Neurochemistry Journal of Neurochemistry (2016) 139, 1113–1123 IF 3,842

Pasireotide prevents nuclear factor of activited T cells nuclear translocation and acts as a protective agent in aminoglycoside-induced auritory hair cell loss

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Abstract

Hearing impairment is a global health problem with a high socioeconomic impact. Damage to auditory hair cells (HCs) in the inner ear as a result of aging, disease, trauma, or toxicity, underlies the majority of cases of sensorineural hearing loss. Previously we demonstrated that the Ca^{2+}-sensitive neuropeptide, somatostatin (SST), and an analog, octreotide, protect HCs from gentamicin-induced cell death *in vitro*. Aminoglycosides such as gentamicin trigger a calcium ion influx (Ca^{2+}) that activates pro-apoptotic signaling cascades in HCs. SST binding to the G-protein-coupled receptors (SSTR1-SSTR5) that are directly linked to voltage-dependent Ca^{2+} channels inhibits Ca^{2+} channel activity and associated downstream events. Here, we report that the SST analog pasireotide, a high affinity ligand to SSTRs 1–3, and 5, with a longer half-life than octreotide, prevents gentamicin-induced HC death in the mouse organ of Corti (OC). Explant experiments using OCs derived from SSTR1 and SSTR1and 2 knockout mice, revealed that SSTR2 mediates pasireotide's antiapoptotic effects. Mechanistically, pasireotide prevented a nuclear translocation of the Ca^{2+}-sensitive transcription factor, nuclear factor of activated T cells (NFAT), which is ordinarily provoked by gentamicin in OC explants. Direct inhibition of NFAT with 11R-VIVIT also prevented the gentamicin-dependent nuclear translocation of NFAT and apoptosis. Both pasireotide and 11R-VIVIT partially reversed the effects of gentamicin on the expression of downstream survival targets (NMDA receptor and the regulatory subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase, PI3K). These data suggest that SST analogs antagonize aminoglycoside-induced cell death in an NFAT-dependent fashion. SST analogs and NFAT inhibitors may therefore offer new therapeutic possibilities for the treatment of hearing loss.

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Nature Microbiology | nature microbiology | 2, 16268 (2017)

Myeloperoxidase targets oxidative host attacks to *Salmonella* and prevents collateral tissue damage

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Host control of infections crucially depends on the capability to kill pathogens with reactive oxygen species (ROS). However, these toxic molecules can also readily damage host components and cause severe immunopathology. Here, we show that neutrophils use their most abundant granule protein, myeloperoxidase, to target ROS specifically to pathogens while minimizing collateral tissue damage. A computational model predicted that myeloperoxidase efficiently scavenges diffusible H_2O_2 at the surface of phagosomal *Salmonella* and converts it into highly reactive HOCl (bleach), which rapidly damages biomolecules within a radius of less than 0.1 μm. Myeloperoxidase-deficient neutrophils were predicted to accumulate large quantities of H_2O_2 that still effectively kill *Salmonella*, but most H_2O_2 would leak from the phagosome. *Salmonella* stimulation of neutrophils from normal and myeloperoxidase-deficient human donors experimentally confirmed an inverse relationship between myeloperoxidase activity and extracellular H_2O_2 release. Myeloperoxidase-deficient mice infected with *Salmonella* had elevated hydrogen peroxide tissue levels and exacerbated oxidative damage of host lipids and DNA, despite almost normal *Salmonella* control. These data show that myeloperoxidase has a major function in mitigating collateral tissue damage during antimicrobial oxidative bursts, by converting diffusible long-lived H2O2 into highly reactive, microbicidal and locally confined HOCl at pathogen surfaces.

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REVIEWS

Nature | nature REVIEWS | Vol 540 | 1 December 2016 IF 38,138

Organization and functions of mGlu and $GABA_B$ receptor complexes

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The neurotransmitters glutamate and γ-aminobutyric acid (GABA) transmit synaptic signals by activating fast-acting ligand-gated ion channels and more slowly acting G-protein-coupled receptors (GPCRs). The GPCRs for these neurotransmitters, metabotropic glutamate (mGlu) and $GABA_B$ receptors, are atypical GPCRs with a large extracellular domain and a mandatory dimeric structure. Recent studies have revealed how these receptors are activated through multiple allosteric interactions between subunit domains. It emerges that the molecular complexity of these receptors is further increased through association with trafficking, effector and regulatory proteins. The structure and composition of these receptors present opportunities for therapeutic intervention in mental health and neurological disorders.

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REVIEWS

Annu. Rev. Immunol. Annual Review of Immunology 2016. 34:479–510 IF 35,543

The Immunology of CD1- and MR1-Restricted T Cells

Lucia Mori[1,2], Marco Lepore[1] and Gennaro De Libero[1,2]

Abstract

CD1- and MHC-related molecule-1 (MR1)-restricted T lymphocytes recognize nonpeptidic antigens, such as lipids and small metabolites, and account for a major fraction of circulating and tissue-resident T cells. They represent a readily activated, long-lasting population of effector cells and contribute to the early phases of immune response, orchestrating the function of other cells. This review addresses the main aspects of their immunological functions, including antigen and T cell receptor repertoires, mechanisms of nonpeptidic antigen presentation, and the current evidence for their participation in human and experimental diseases.

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Selected publications by DBM members

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

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

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

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

Deadline for the next issue is June 30, 2017.


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Ostern

Vom Münster Trauerglocken klingen.
Vom Tal ein Jauchzen schallt herauf.
Zur Ruh sie dort dem Toten singen,
Die Lerchen jubeln: Wache auf!
Mit Erde sie ihn still bedecken,
Das Grün aus allen Gräbern bricht,
Die Ströme hell durch Land sich strecken,
Der Wald ernst wie in Träumen spricht,
Und bei den Klängen, Jauchzen, Trauern,
Soweit ins Land man schauen mag,
Es ist ein tiefes Frühlingsschauern
Als wie ein Auferstehungstag.

Joseph von Eichendorff

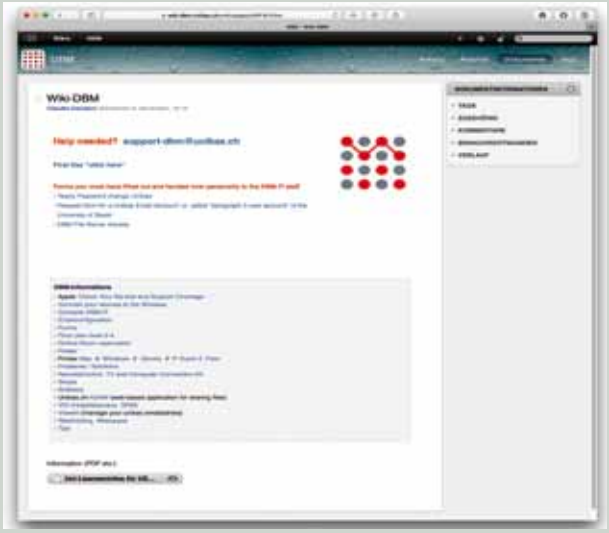
Congratulations

Das DBM gratuliert ganz herzlich!

Alice Mereau
Geboren am 24.02.2017

Herzlich willkommen, allerseits!

+ IT News +++ IT News +++ IT News ++



Das DBM-IT Wiki bietet vieles für jeden…

Infos für alle, die neu am DBM sind. Aber auch viele Anleitungen für diejenigen, welche schon lange dabei sind, aber noch nie etwas davon gehört haben.

Einige IT-Aufgaben, wie z.B. das Wechseln von Passwörtern und die damit verbundenen Anpassungen beim Drucken, findet man auf dem Wiki.

Haben Sie Tipps, Anregungen und Wünsche, so schreiben Sie uns ein Email an support-dbm@unibas.ch

Wir können für Sie und Ihre Forschungsgruppe ein eigenes Wiki erstellen. So können Sie Informationen einfach für die ganze Gruppe verwalten.
Schauen Sie doch einmal in das Wiki hinein. Es lohnt sich…

The DBM-IT wiki has something for everyone…

There is information for those who are new to the DBM. There is also a lot of information for those who have been here for some time but have not heard of it before.

Some IT- tasks such as how to change passwords and make the relevant changes for password linked printing can be found on the wiki.

Do you have tips, proposals or questions? If so then please email us at support-dbm@unibas.ch

We can set up a wiki for you and your research group. It is a great way to easily share information with the whole group.

If you haven't already then do check out the wiki. It's worth it…

GraphicConverter 10 – ein Photoshop Ersatz

Ab sofort bieten wir den GrapicConverter 10 als Alternative zu Photoshop an. Sie können das Programm bei der DBM-iT gratis beziehen.

GrapicConverter ist ein schlankes, aber sehr mächtiges Bildbearbeitungsprogramm, das sich auch noch programmieren lässt.

So können im "Batch"-Verfahren unzählige Bilder auf einmal verändert werden. Sei es, dass man diese skaliert haben will – z.B. auf eine maximale Höhe oder Breite unter Beibehaltung des Seitenverhältnisses oder/ und auch noch einige Filter anwenden will.

GraphicConverter 10 – a Photoshop replacement

We are now offering GrapicConverter 10 as an alternative to Photoshop. You can obtain the program free from DBM-IT. GraphicCovnverter is a small but powerful image editing program that can also be programmed. It can be used to edit numerous images at one time using batch processing. Perhaps you want them scaled, to a maximum height or width to fit a page size, and/or altered with a specific filter.

St. Patrick's Day – The Irish National Holiday

National holidays are celebrated in most countries around the world and in many cases these are celebrations of an historic political achievement, such as independence. In Ireland, however, the national day commemorates Saint Patrick, the foremost patron saint of Ireland. St. Patrick's Day falls on March 17th, which is traditionally believed to be the death date of Saint Patrick. Patrick was a 5th century Romano-British Christian missionary and bishop and among other things is credited with bringing Christianity to Ireland and banishing snakes from the country, although the latter can be accepted as legend rather than fact as there never were any snakes in Ireland.

St.Patrick's Day, Lá Fhéile Pádraig in Irish, has been celebrated since the 17th century although it is really only in more recent times that the celebrations have moved beyond the church and now include festivals, céilithe (Irish dancing sessions), public parades, the wearing of the green and of course the wetting of the shamrock.

All things green

Green has long been associated with Ireland and the wearing of the green has become a common part of the St. Patrick's Day celebrations. At the very least celebrants will wear some shamrock. Legend has it that St. Patrick used the three leaves of the shamrock to teach the pagan Irish about the Holy Trinity and, as a result, this plant has become the symbol of Saint Patrick and is commonly worn on Saint Patrick's Day. For many however, the wearing of the green also means donning some green attire and it is not uncommon nowadays to see people dressed head to toe in bright green clothing, often with comic oversized hats and/or other fun costumes/decoration.

The drowning of the shamrock

Saint Patrick's Day generally falls during Lent, a time when there would have been traditional restrictions on eating and drinking alcohol. Because these Lenten restrictions were lifted for the day, this encouraged the holiday's tradition of imbibing in alcohol. Beer, whiskey or cider would generally have been considered the drink of choice for the day. The shamrock, that had been worn on the lapel or hat on the day, would be put in the last drink of the day in the tradition known as the drowning of the shamrock.

The wearing of the green has moved well beyond just pinning some shamrock to your lapel or hat.

Celebrations in Ireland

The St. Patrick's Day celebrations in Ireland are widespread and while they are a celebration of all things that are Irish. Most county towns will have parades that feature local marching bands, dancers, street theatre, performers, schools, sports clubs and lots more. While the majority of these parades will take place on March 17th itself, it is not uncommon for some to be held early to allow for some of the major local participants to travel to take part in bigger national or indeed international parades and events. In the mid 1990s an official Saint Patrick's Day Festival in Dublin was set up by the government of Ireland. The aim of this festival was "to de-

The Rhine Falls are lit in green as part of the Global Greening celebrations of St. Patrick's Day.

velop a major annual international festival around the national holiday over which the 'owners' of the festival, the Irish people, would stand proud. It sets out to reflect the talents and achievements of Irish people on many national and world stages, and it acts as an exciting showcase for the manifold skills of the people of Ireland, of every age and social background." This festival has grown into a multi-day event and does indeed live up to expectations.

As part of the celebrations Seachtain na Gaeilge (Irish language week) also takes place at the start of March in the period leading up to St. Patrick's Day and encourages all Irish speakers to embrace their inner Gaelgoir (Irish speaker) and to use their cúpla focail (few words) as often as they can.

Another firm fixture on the St. Patrick's Day calendar are the GAA (Gaelic Athletic Association) All-Ireland Club Championship Finals in both hurling and Gaelic football. Unlike most major sporting events which usually take place on the weekends these Club Championship Finals are traditionally held at the main GAA stadium, Croke Park, in Dublin on St. Patrick's Day. This year, for the first time ever, our local hurling team won the county championships and made it all the way through to this final. Although they did not win on the day they more than did themselves and all of their supporters more than proud with their efforts and achievements.

Celebrations around the world and beyond!

St. Patricks Day is not just celebrated in Ireland itself but has very much become a global celebration and is celebrated by millions around the world. It is said to be the one national festival that is celebrated in more countries around the world than any other.

In North America parades, the wearing of green

Greetings to those at home and abroad.

and the overindulgence of alcohol are all commonplace celebrations on the day and their origins date back to the 18th century. Since the 1950s the shamrock ceremony has taken place at the White House. During this ceremony, the US president is presented with a bowl of shamrock from the Irish people and the presentation is often made by the Irish Taoiseach (prime minister).

Parades, street parties or celebrations can be found in many other cities and countries around the world including Moscow, Buenos Aires, Sydney, Tokyo, Singapore and Montserrat.

Another recent tradition is the Global Greening where major monuments, buildings and landmarks around the world are lit/turned green for the day. These include the Rhine Falls here in Switzerland as well as other major landmarks such as One World Trade Center, the London Eye, Niagra Falls, the Colosseum in Rome, the Leaning Tower of Pisa, Burj al Arab in Dubai, Table Top Mountain in Cape Town, Matsue Castle in Japan, Gwangandaegyo (Diamond Bridge) in South Korea and even the Great Wall of China. In Chicago they go as far as to dye the river green for the celebrations and the famous red carpet in Cannes will become the 'green carpet' on 17 March.

Further afield the date has even been marked in space by some of the astronauts in the ISS through the wearing of green and/or the playing of Irish music.

Paula Cullen

Auch das ist Sport

Der Frühling ist schon da, der Sommer kommt auch bald. Es wird Zeit nach draussen zu gehen und dies im wahrsten Sinne des Wortes. Es muss nicht immer Leistungssport sein, wie der folgende Artikel eines Ex-Fussballers zeigt.

Spazierengehen

Aktiver Sport, das war einmal. Meine beiden Knie haben eine mittlere Amateurfussballkarriere nicht überstanden, Knorpelschaden links und rechts. Kein Fußball, Tennis oder Beachvolleyball mehr, nicht mal Joggen. Mir bleibt nur die süsse Erinnerung an lang vergangene Flanken und Freistösse. Und das Gehen, das stramme Spazierengehen.

> Von einem, der spazieren geht,
> kann man niemals behaupten,
> er mache einen Umweg.
> (Arthur Schopenhauer)

Wann immer es meine Zeit zulässt, streue ich auf dem Heimweg von der Arbeit einen Fussmarsch ein. Die Variable ist die U-Bahnfahrt, mein Zuhause ist vier Stationen vom Büro entfernt. Manchmal fahre ich drei oder zwei und laufe den Rest, ein anderes Mal gehe ich den kompletten Weg. Das sind immerhin vier Kilometer. Auf dem Hinweg bleibt weniger Zeit. Aber auch morgens wähle ich aus zwei gleichschnellen Routen fast immer diejenige, bei der der Gehanteil höher ist. Auch am Wochenende erschliesse ich Eimsbüttel, St. Pauli und Eppendorf per pedes. Das Fahrrad benutze ich selten, weil ich fürchte, von der gleichen schlecht gelaunten Rücksichtslosigkeit befallen zu werden wie die meisten Hamburger Radfahrer.

Hamburg ist begehbar, diese Stadt kann ich auch nach Jahren noch wie ein Tourist erleben, ergehen. Grosse und kleine Parks, Wasser in verschiedenen Umrahmungen, Anmutungen und Fliessgeschwindigkeiten, schöne Häuser, alte Häuser, reiche Häuser, kaputte Häuser, Sehenswürdigkeiten wie Landungsbrücken, Jungfernstieg, Planten und Blomen, der Bunker am Heiligengeistfeld. Wie sagte einst ein Philosoph: Ambulo ergo sum. Ich gehe, also bin ich. Es ist gesund, man ist an der frischen Luft, es belebt den Geist. Aber als Sport ist Spazierengehen nicht so hart wie es klingen mag, nicht so sexy wie Flanken und Freistösse. Doch haben sich durch das stete Training im Extremstadtwandern meine Schrittlänge und -frequenz erhöht. Wenn Google Maps 15 Minuten Weg anzeigt, schaffe ich es schon mal in 10. Andere kommen bei meinem Tempo ins Schnaufen. Gehe ich nicht alleine, sagen meine Begleitungen, nicht nur die weiblichen: Mach mal langsam! Sie nennen mich Speedy.

Kosten: keine

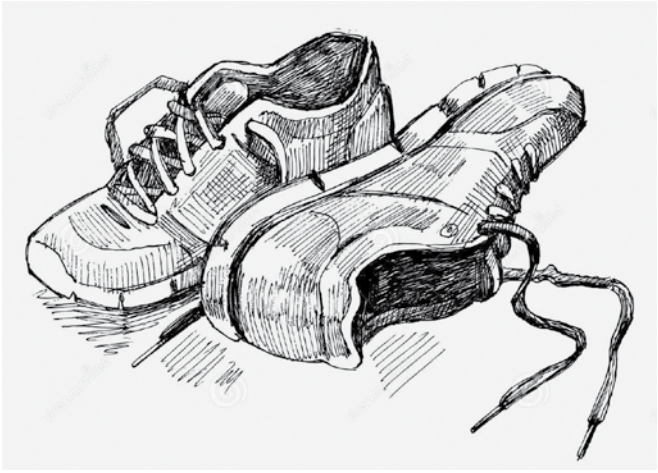
Regeln: Eigentlich nur eine: «Wettkampfmässiges Gehen ist eine Abfolge von Schritten, die so gesetzt werden, dass der Geher dabei Kontakt mit dem Boden hat und ein mit menschlichem Auge sichtbarer Kontaktverlust nicht vorkommt. Das ausschreitende Bein muss vom Moment des Aufsetzens auf den Boden bis zur senkrechten Stellung gestreckt, das heisst am Knie nicht gebeugt sein.» Quelle: Seite 135 des Leichtathletik-Regelwerks

Dachverband: Deutscher Leichtathletik Verband, mehr Infos gibt es beim Förderverein Geher-Team. In der Schweiz: www.swiss-athletics.ch, www.swisswalking.org

Herkunft: Erstmals praktiziert vor mindestens 3,2 Millionen Jahren

Oliver Fritsch arbeitet für die Sportredaktion von ZEIT ONLINE und ist Trainer der SV Blankenese in der Landesliga Hammonia Hamburg. Nach Spielen der deutschen Mannschaft bewertet der Inhaber der C-Lizenz die Taktik und die Spieler. Quelle: ZEIT ONLINE

Nichts kann einem die Tür zu sich selbst besser öffnen als ein Spaziergang durch schlechtes Wetter.
(Mark Twain)



DBM-Quiz

Ein fiktiver Hund rennt von Bern (CH) nach Paris. Die Distanz beträgt Luftlinie 500 km. Am Hinterbein ist eine Blechbüchse angebunden. Er macht Schritte von einem Meter Länge und bei jedem Schritt schlägt die Büchse einmal auf. Seine Startgeschwindigkeit ist 1 m/s. Jedes Mal, wenn er die Büchse aufschlagen hört, verdoppelt er seine Geschwindigkeit.

Mit welcher Geschwindigkeit kommt er in Paris an?

Unter den richtigen Einsendern wird der Gewinn von einem Centro-Essensbon ausgelost. Bon appetit!
Einsendeschluss: 30. Juni 2017

Save the date

DBM Summer Symposium

Thursday August 31, 2017

8:00 – 13:15
Kleiner Hörsaal, ZLF, Hebelstrasse 20

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

Thursday, August 31, 2017

16:30 – 21:30
Kraftwerkinsel Birsfelden

For DBM members only

Mach' deine Pläne fürs Jahr im Frühling
und die für den Tag frühmorgens.
(Chin. Weisheit)