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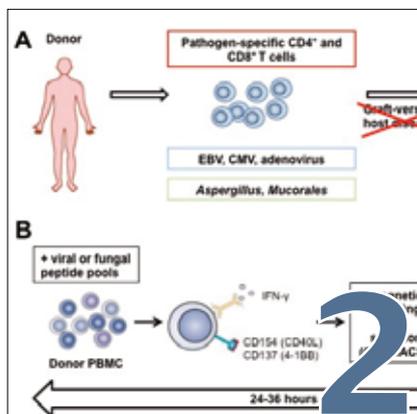
DBM

FACTS

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



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IMPRESSUM

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EDITORIAL



Radek Skoda
Leiter DBM

Der Herbst ist da und damit auch die Zeit des Erntens. Auch wir dürfen uns freuen: Das DBM hat sehr gute Publikationen hervorgebracht, auf die sich mehr als nur ein Blick lohnt (ab Seite 11).

Noch mehr Positives gibt es zu berichten: Tania Rinaldi Barkat wurde als Professorin für Neurophysiologie gewählt (Assistenzprofessur mit Tenure Track) und wird ihre Tätigkeit am DBM Klingelbergstrasse aufnehmen. Wir freuen uns über diese Berufung und wünschen ihr einen guten Start und viel Erfolg. Ganz herzlich gratulieren wir Marc Donath zum Cloëtta Preis 2014 und Adrian Egli und Matthias Mehling, die beide ein Ambizione-SCORE erhalten haben.

In der neuesten Ausgabe der DBM Facts werden Sie von Nina Khanna und ihrem Team auf Entdeckungsreise in die Forschung der Infection Biology mitgenommen (ab Seite 2) und ab Seite 7 stellt Ihnen Robert Ivanek die Bioinformatik am DBM vor. Wunderschöne Impressionen erreichen Sie aus Chile (Seite 29), auf kulinarische Entdeckungsreise geht es durch das Elsass (Seite 35). Einen Rückblick auf die Fussball-WM mit den Augen einer Frau können Sie mit Martina Konantz ab Seite 33 erleben und dass das DBM auch feiern kann, zeigt es ab Seite 39.

Schöne Herbsttage und viel Spass bei der Lektüre!

It's autumn and harvest time – also for the DBM. Convince yourself on the many exciting 2014 DBM publications (from page 11 onwards).

More good news to report: Tania Rinaldi Barkat was elected tenure track assistant professor in neurophysiology and will have her laboratory at DBM Klingelbergstrasse. We are looking forward to her appointment and wishing her a successful start. We also congratulate Marc Donath on the winning of the Cloëtta prize 2014 and Adrian Egli and Matthias Mehling, who both have received an Ambizione-SCORE.

In the current issue of DBM Facts Nina Khanna and her team will let us discover the research of infection biology (page 2) and Robert Ivanek presents the DBM Bioinformatics core facility (page 7). We will get wonderful impressions from Chile (page 29) and go on a culinary journey through the region of Alsace (page 35). With the eyes of a woman Martina Konantz will look back to the soccer world championship (page 33) and the DBM demonstrates once again that it can celebrate (page 39).

Enjoy the harvest season and the newest issue of DBM Facts!

Improving treatment of infectious diseases

The Infection Biology research group explores host- and pathogen-specific aspects of infectious diseases in a translational setting together with the Division of Infectious Diseases and Hospital Epidemiology, the Laboratory of Clinical Microbiology, the Division of Hematology at the University Hospital Basel, the Biozentrum, ETH Zürich and Basel and the University of Fribourg. Our laboratory has two main topics: First, we aim at understanding and improving the host immune response towards viruses and fungi in immunocompromised patients. This also includes vaccine responses¹⁻⁵. The second goal is to explore novel anti-infective approaches against foreign-body/implant-associated infections caused by staphylococci^{6,7}.

In this report, we focus on infections in immunocompromised patients, the host immune response to fungal infections, as well as pre-clinical and clinical studies of adoptive T-cell therapy for fungal and viral infections.

Infections in immunocompromised patients are common

Chemotherapies to treat leukemia and solid tumors and immunosuppressive treatments to reduce graft versus host diseases (GVHD) and rejection in transplant recipients have overall increased the short and mid-term survival of these patients. However, the loss of pathogen-specific immunity associated with these treatments increases the risk for infectious complications. Invasive fungal and viral infections belong to the most serious complications in these patients and are still associated with an exuberant mortality. Although antifungal and antiviral drugs are available for some infections, their therapeutic efficacy is often limited and depends on several factors including the immune status of the host and the extent of infection at the time of diagnosis. Due to the disease severity in these patients and the problem of accurate diagnosis, efforts have been made to implement prophylactic and preemptive drugs. Application of these drugs is however associated with toxicity, high



Foto: From left to right, front row: Claudia Bernardini, Anne-Kathrin Woischnig, Nina Khanna; middle row: Adrian Egli, Claudia Stühler, Justyna Nowakowska; back row: Richard Kühn, Fabrizia Ferracin, Pascal Forrer. Missing people are David Burckhardt and Mohammedyaseen Syedbasha.

costs and the emergence of resistant or less susceptible pathogens. Therefore, efforts to improve diagnosis, development of novel immunological biomarkers to guide treatment duration and to decrease host immunosuppression while enhancing the reconstitution of immune defenses are crucial. Immunotherapeutic strategies such as adoptive transfer of virus- and fungus-specific T-cells could boost long-term immunity and thereby reduce toxicity and costs induced by preemptive and prophylactic drug regimens.

Opportunistic fungal infections are associated with high mortality

The most common opportunistic fungal pathogens causing disease in immunocompromised patients are the yeasts *Candida species* (spp.) and the molds *Aspergillus spp.*^{2,8}. *Aspergillus fumigatus* is a saprophytic, filamentous mold that is mainly found in the soil. In humans it predominantly affects the lungs and is characterised by hyphal invasion and destruction of pulmonary tissue (Figure 1). In patients undergoing myeloablative chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT), the incidence of pulmonary invasive aspergillosis is between 10 and 20% and is associated with an attributable mortality of 20-50%. In recent years, due to the wide use of antifungal prophylaxis, rare molds such as *Fusarium spp.* and *Mucorales spp.* have emerged⁸.

Host immune responses to fungi are not well understood

Neutrophils belong to the first line of defence and are key players to control fungal infections. In many patients at risk for fungal infection the total number of

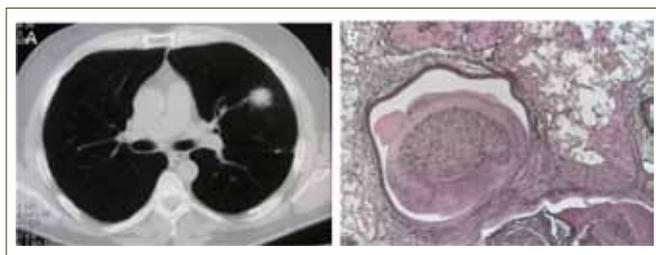


Figure 1. (A) Computed tomography of the chest with invasive pulmonary aspergillosis (Radiology, University Hospital of Basel). (B) Histological sections of invasive pulmonary aspergillosis stained with Grocott with a magnification of 2,5x (Pathology, University Hospital of Basel).

neutrophils is in a normal range, but little is known about the effector functions including migration, oxidative burst and degranulation. Moreover, the interaction with lymphocytes remains unclear. Distinct fungus-specific CD4⁺ T-helper (T_H) subsets such as T_H1 and probably T_H17 cells, CD8⁺ T cells and natural killer (NK) cells are important for pathogen control in mice, whereas activation of T_H2 cells often exacerbates disease (Figure 2)². T_H1 cytokines interferon-gamma (IFN- γ) and/or GM-CSF are able to enhance the oxidative burst of neutrophils in response to fungi as well as increase the hyphal damage. We are currently establishing the mechanism by which T_H1 cytokines are able to boost the effector functions of neutrophils and are elucidating specific signaling pathways of these cytokines in neutrophils and their role in apoptosis.

As the recovery of the antifungal immunity in patients after HSCT is largely unknown, we have studied the quantitative and qualitative impairments in these patients.

Antifungal immune response is impaired after HSCT

Within a prospective study from 2011-2013 at the stem cell transplant unit at the University Hospital of Basel, we investigated the immune reconstitution of neutrophils, NK cells and T lymphocytes in 60 patients after HSCT with or without invasive aspergillosis over one year. Overall post-transplant patients developing fungal in-

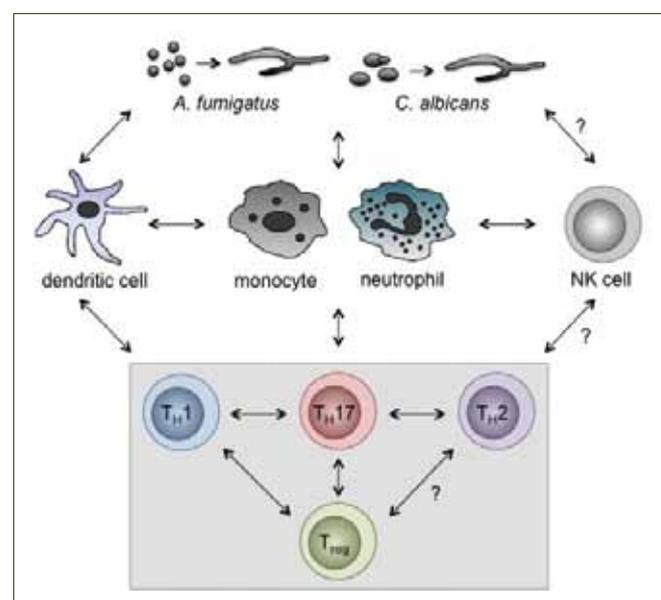


Figure 2. Crosstalk of the key players in anti-fungal immunity

fections showed low lymphocyte and NK cell counts whereas the numbers of neutrophils remained normal. Interestingly, the production of reactive oxygen species of the neutrophils was comparable to patients without fungal infections and to healthy individuals. In contrast, fungus-specific T-cell immunity showed significantly lower IFN- γ responses and almost no detectable IL-17 production up to 12 months post-transplantation when compared to healthy donors, indicating a dominant impairment of adaptive immunity after HSCT. These findings support the generation of T-cell therapy to boost long-term immunity and to control the devastating fungal infections.

T-cell Immunotherapy for viral and fungal infections

Previous studies have demonstrated that virus-specific T-cells are efficacious and safe with respect to prevention of GVHD⁹ (Figure 3) but limited data for antifungal T-cell transfer are available in humans.

The generation of virus-specific T-cells is currently limited due to its elaborate production requiring *in-vitro* expansion over at least 14 days under good manufacturing practice (GMP) conditions. Therefore, more rapid approaches without the need of long-term *in vitro* expansion would be desirable. The selection of IFN- γ -producing T cells following stimulation with viral antigens by the GMP-approved Miltenyi® IFN- γ Capture System for direct infusion into patients is rapid (< 48 hours)

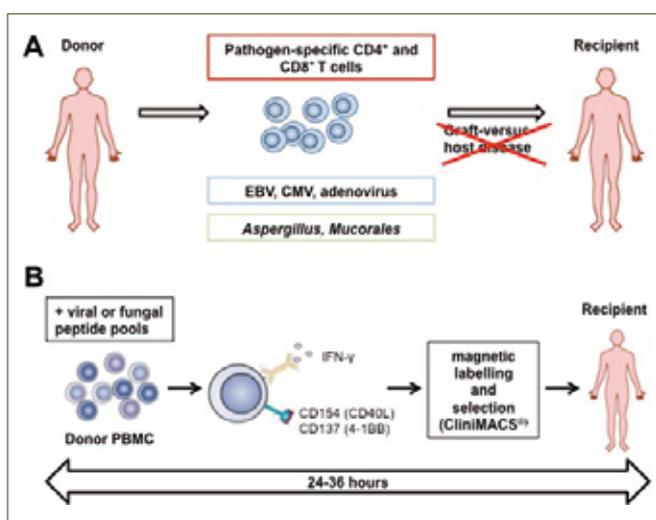


Figure 3. Adoptive T-cell transfer for viral and fungal infections. (A) Pathogen-specific T cells reduce the risk of graft-versus-host disease. (B) Pathogen-specific T cells can be selected based on IFN- γ secretion or activation-dependent expression of CD154 and CD137 within 36 hours for direct infusion into recipients.

and promising for cytomegalovirus (CMV), adenovirus and Epstein-Barr virus (EBV)¹⁰. The IFN- γ Capture System is however restricted to antigens with moderate to high memory T-cell frequencies in peripheral blood and can therefore not be used for the isolation of fungus-specific T cells. To increase the sensitivity for isolation of these rare pathogen-specific memory cells, other T-cell activation markers may be more suitable which enable capture of a greater number of antigen-specific T cells irrespective of cytokine production. Different T-cell surface molecules that are selectively expressed or strongly upregulated after T-cell activation such as CD25, CD69, CD71, CD134, CD137 and CD154 could be similarly useful for selection of antigen-specific T cells (Figure 4). CD154 and CD137 for example are transiently expressed on activated CD4⁺ and CD8⁺ T cells following antigen stimulation. We recently were able to show that CD154 is a promising candidate for selection of pathogen-specific T cells due to its high specificity and sensitivity¹.

We are currently performing pre-clinical adoptive T-cell transfer studies for EBV using the IFN- γ Capture System and are comparing different isolation methods for fungal pathogens. Furthermore, we are establishing a clinical protocol and have already used the ClinMACS[®] Cytokine Capture System in two patients suffering from treatment-refractory CMV infection at the University Hospital of Basel.

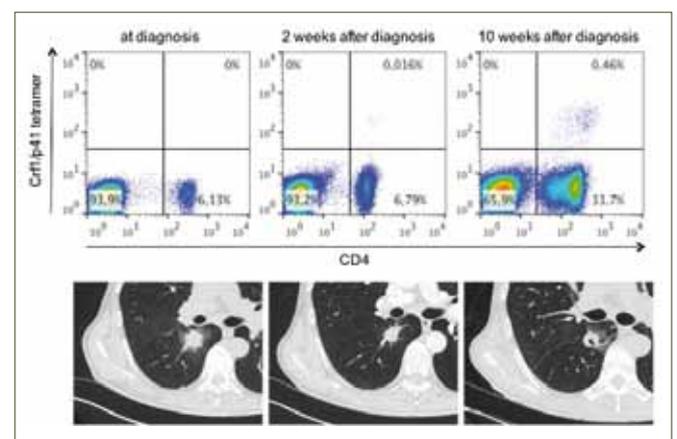


Figure 4. Peripheral blood mononuclear cells of a HLA-DRB1*04-positive HSCT recipient at different time points after diagnosis of IA were pre-stimulated with *A. fumigatus* Crf1/p41 peptide for 7 days and the frequency of Crf1/p41-specific T cells determined by MHC class II tetramer staining. Computed tomography of the chest at the respective time points is shown in the panels below.

Pre-clinical studies

T-cells specific for fifteen EBV proteins for clinical application

EBV-associated post-transplant lymphoproliferative disorders (PTLDs) belong to the most serious complications of immunosuppression occurring in approximately 5% of all HSCT recipients. In these patients the immunosuppression reduces the number and/or the function of the EBV-specific T cells leading to uncontrolled proliferation of EBV-infected B cells and tumor formation. Thus, reconstitution of antigen-specific T cells has the potency to provide immediate and also long-term protection against PTLDs. Since the T-cell response to EBV is directed against a set of viral proteins and strongly depends on the human leukocyte antigen (HLA) types, determination of protective EBV-derived antigens poses a great challenge. We therefore aimed at identifying immunogenic antigens most suitable for generation of a T-cell product using the CliniMACS® Cytokine Capture System. We are especially interested in designing an EBV-specific T-cell product consisting of both CD4⁺ and CD8⁺ cells covering a broad range of HLA types and in investigating its role in controlling PTLDs. We demonstrated that a mix of CD8⁺ and CD4⁺ T-cell epitopes with known HLA restrictions derived from 15 EBV latent and lytic proteins induced significantly higher T-cell responses and allowed better IFN- γ -based selection than peptide pools of single EBV proteins including EBV nuclear antigen (EBNA)1, EBNA3c, latent membrane protein (LMP)2a and BZLF1 – all known to be expressed in PTLDs. Additionally, the EBV_{mix}-specific T cells recognized endogenously processed viral antigens, were devoid of alloreactive potential and controlled better the EBV-infected B cells in vitro. These findings indicate a clear advantage of combining defined T-cell epitopes derived from different EBV proteins over using single viral antigens for the generation of EBV-specific T cells for adoptive transfer.

Aspergillus-specific T cells for immunotherapy

As T cells, in particular CD4⁺ T_H1 cells, appear to control invasive fungal infections in humans and mice, induction of fungus-specific CD4⁺ T_H1 immunity is an appealing strategy to combat these infections. However, immunotherapeutic strategies are so far limited due to

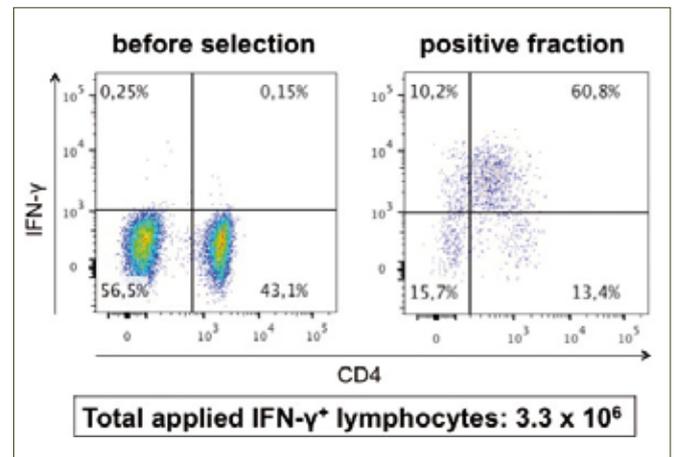


Figure 5. (A) IFN- γ positive enrichment for CMV pp65. IFN- γ positivity before selection (left). Positive lymphocyte fraction shows 71% purity (CD4⁺ and CD8⁺) after stimulation with CMV pp65 peptide pool (right). This experiment has been performed with 1×10^9 PBMC of a CMV⁺ leukapheresis of a healthy stem cell donor for the treatment of a patient with multi-resistant treatment refractory CMV retinitis at the Diagnostic Hematology at the University Hospital of Basel after approval by the Ethical Committee EKNZ (10/2014 "Zulassung für eine Einzelbehandlung"). Total cell yield was 3.3×10^6 .

lack of antigens inducing protective T-cell responses in HSCT recipients and targeting a broad spectrum of pathogenic fungi and their elaborate production.

We identified three *A. fumigatus* proteins Crf1, Gel1 and Pmp20 that are strongly inducing T_H1 responses in healthy individuals and HSCT recipients. T cells specific for these antigens expanded in patients with well-controlled invasive aspergillosis after HSCT and this corresponded with a reduction of the fungal lesion in computed tomography indicating that these cells contribute to control the infection (Figure 5). We were also able to demonstrate that T_H1 cells specific for the three proteins can be selected within 24 hours based on activation-dependent expression of CD137 or CD154 with similar efficiency and specificity. These cells recognize endogenously processed *A. fumigatus* and the multi-specific T-cell lines, especially those selected by CD154, additionally cross-react to different *Aspergillus* and *Mucorales* spp.

First patient experience using CMV-specific T cells to treat multi-resistant CMV infection and retinitis

In October 2013 we treated a 52-year-old CMV-seropositive patient that suffered after allogeneic HSCT from a multi-resistant CMV infection with retinitis with CMV-

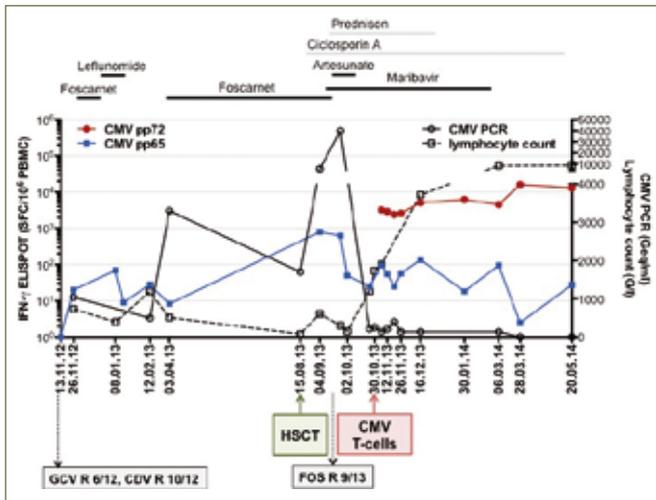


Figure 5. (B) Course of the patient

specific T cells. Using the CliniMACS® Cytokine Capture System after stimulation with CMV pp65 peptide pool 3.3×10^6 total CD3⁺ cells with a purity of 70% of IFN- γ ⁺ CD3⁺ were selected and applied to the patient.

The follow-up was favorable: the patient recovered from the CMV retinitis and cleared the virus in peripheral blood two months after adoptive T-cell transfer and concomitantly CMV pp65-specific but also pp72-specific T cells expanded in peripheral blood. Antiviral drug treatment with maribavir could be stopped after 3 months and no relapse occurred. This case illustrates for the first time in Switzerland that adoptive T-cell therapy for a viral infection is safe and feasible using the CliniMACS® Cytokine Capture System and might also lead to the control of the viral infection. A phase I/II study in recipients of HSCT with treatment refractory post-transplant viral infections to foster adoptive T-cell transfer is currently planned.

Nina Khanna and team

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Bioinformatics: from algorithmics and nerdhood to every-day skills

For a PhD student of 2014 it almost sounds like a fairytale: Once upon a time, scientists would pipette with their mouth, and draw sketches of their findings by hand. They would draft their research manuscripts on a typewriter, send copies to a journal as a pile of paper and receive editorial decisions by fax. Nobody suspected that email would be a daily part of your life, let alone a way to transport confidential scientific findings. This isn't a fairytale of Watson and Crick and the discovery of the DNA in the 50s; this was the reality of PhD students 20 year ago. *"To email"* is a verb of everyday life now and for every molecular biologist, *"to sequence"*, *"to align"* and *"to blast"* is too.

Bioinformatics is recognized as a key component of biology – nevertheless it is a young scientific discipline, in which biology, computer science, mathematics, statistics and information technology merge. Since its beginnings bioinformatics has gone through many transformations driven initially by theoretical informatics in the 70s [ref1], and later by technologic advances in computer science and biological research.

Bioinformatics is a field that, unlike most classical natural sciences, was pioneered by a woman: Dutch researcher Paulien Hogeweg, now in her 70s, coined the word bioinformatics to refer to the study of information processes in biotic systems [ref 2]. She studied and developed computational models to study the social structure of animals and devised an algorithm, which is the basis for today's phylogenetic trees based on genome sequences.

It was only in 1976 that scientists established the first full genome sequence: a genome of MS2-RNA-phage [ref3]. It took another two decades until the first bacterial (influenza) [ref4] and eukaryotic (yeast) genomes [ref5] were added and 'to sequence' became a common verb in molecular biology – and with length of genomes and increasing amount of sequence and later protein-data - bioinformatics gained its place amongst the other "grown up" science fields.

Whole genome shotgun sequencing allowed the number of genomes sequences to be quickly increased, and from 1982 to the present, the number of bases in GenBank has doubled approximately every 18 months. The new kid on the block focused on the development of tools, which allow for alignment and comparison (Basic Local Alignment Search Tool, BLAST [ref6]) of the newly discovered sequences and on creating databases, to which scientists could upload their data – the protein data base (PDB, [ref7]) was established in 1971 and GenBank for storing DNA sequences followed in 1982 [ref8]. Today's NCBI genome database contains more than 4000 virus, over 27,000 bacterial and 1600 eukaryote genomes [ref9,10].

Another important point, necessary to address at this early stage was development of guidelines and standards for data submission into the public repositories and issues related to data release and accessibility policies. The explosion of the sheer amount of data called for a new vocabulary in linking datasets to each other – ontology and database cross-referencing (Gene Ontology Database founded in 1998) were born out of these needs [ref11].

These rapid developments and the challenges that come with them created a huge demand on the job



Core Facility Bioinformatics DBM (from left to right): Florian Geier and Robert Ivanek

market and many graduate programs in bioinformatics were established under the guidance of the International Society for Computational Biology (ISCB), founded in 1996.

From viruses to bacteria, the ultimate goal was of course to gain insight into the genome of man. The human genome project, biology's largest collaborative effort ever, started in 1990 and took more than 10 years to complete [ref12]. Having one human genome as a reference immediately posed new questions: How do we differ from each other, what makes the difference between sick and healthy?

Technological improvements, this time in the synthesis of oligonucleotides allowed that step to be taken by designing oligonucleotide microarrays (for example genotyping arrays) – which in a lock-and-key principle can reveal the presence of a certain nucleotide sequence. These new genotyping arrays were first used in linkage studies to identify the disease causing genes in Mendelian disorders, and later in genome wide association studies (GWAS) to find genes responsible for more complex traits [ref13].

The microarray method can of course not only be applied to analysis of DNA but can also be used to measure RNA levels, the “ever changing transcriptome”, and this moved biology and bioinformatics from whole genome sequencing to whole genome expression profiling [ref14].



Computer infrastructure at SciCORE.

Analysis of microarray and sequencing data became a fundamental in bioinformatics and provided not only a lot of new insights in biology – but the rapid expansion and drop in prices equally opened new legal and ethical issues regarding privacy of genomic data, commercialization and patenting – many of which haven't reach a global consensus yet.

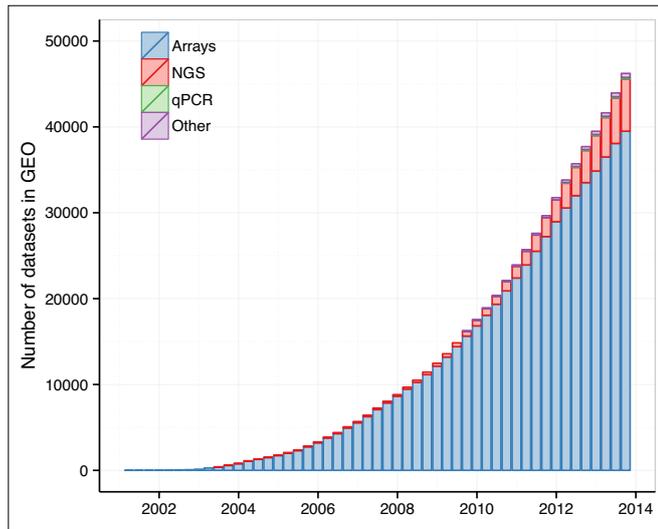
Along with companies taking interest in genomic sequences, a new method evolved in recent years, which changed the landscape of bioinformatics once more: “next generation sequencing” (NGS). The first human genome was a decade's effort, today with NGS, a single scientist could obtain a whole genome sequence in a day.

Again, this advance expanded to the world of RNA, expression profiling stopped to be dependent on genome annotation and scientist can now study the full variety of transcripts present in a given cell. NGS furthermore allows for looking at DNA modifications, like methylation, on a genome wide scale through bi-sulfite sequencing.

Data, now amassed in units of genome size, create challenges, they required better computer infrastructures for their storage and processing, their different nature required tools and new standards for their deposition in public repositories and annotation. Today we can clearly see that sequencing is representing a growing fraction of all data deposited in Gene Expression Omnibus, the most commonly used public repository for high-throughput data [ref15].

For many research questions, NGS is replacing microarrays and the availability of “bench-top” high-throughput sequencers moved the sequencing technology from large sequencing centers and core facilities to individual labs. Sequencing is becoming a daily tool in molecular biology, just as PCR and western blotting. At the same time of course, researchers need and do gain the skill-set for data analysis, hundreds number of bioinformatics courses are offered online and many curriculums of molecular biology demand the proficiency in analysis tools or even a bit of coding skill.

The everyday need for bioinformatics in classical 'wet-lab' research groups, the transition to new vocabulary and ways of experiment planning cannot be done over-



Number of experiments in GEO database.

night. Many institutions, including the DBM, set-up the bioinformatics core facilities not only as a facility to execute analysis but also to support this adaptation process.

We, the Bioinformatics Core Facility at the DBM [ref16] aim to provide a centralized resource of expertise in computational biology and statistics. Bioinformatics isn't a service "after the experiment is done" – solid and reliable data analysis already starts during experiment design! We are here to help you from a bioinformatics perspective to guide and support from 'How many repeats will I need?' to analysis, data management and visualization. Standardization is important in computational biology but no project in basic research is standard and we are here to work with you on specific workflows for your project.

The rapid technological advances and the growing number of bioinformatics approaches and tools make it difficult to keep track of with limited resources at the facility. Therefore we closely interact with the Swiss Institute of Bioinformatics [ref17] and with other bioinformatics units in the Basel area in order to implement the latest bioinformatics approaches, namely with the group of Dr. Michael Stadler from Friedrich Miescher Institute for Biomedical Research [ref18] and the group of Prof. Torsten Schwede, who is running Scientific Computing Core Facility – SciCORE [ref19].

We believe that we will achieve the best results when core skills in bioinformatics will become common

knowledge, therefore we provide regular training sessions. Together with bioinformatics group from the Friedrich-Miescher Institute we organize basic courses in the statistical software "R". This five-day practical course provides beginners with training on how to explore and visualize the data and perform wide range of statistical tests. You don't need to become a "nerd" quite yet, but "thinking bioinformatically" will help you plan your experiment thoughtfully and will make our work together efficient and fun. We are looking forward to explore the future of bioinformatics together with the researchers of the DBM and push each other to new horizons in this process!

Robert Ivanek

(with a contribution of Sylvia Tippmann)

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<http://www.isb-sib.ch/>
<http://www.fmi.ch>
<http://www.scicore.ch>

Dissertationen

Seit dem 25. Juni 2014 darf sich **Justyna Nowakowska** von der Forschungsgruppe Infection Biology (Departement Biomedizin Hebelstrasse) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Different treatment approaches to infectious diseases: from novel antimicrobials to T-cell therapy".

Ebenfalls am 25. Juni 2014 wurde es ernst für **Francesca Amicarella** von der Forschungsgruppe Cancer Immunotherapy (ICFS/Departement Biomedizin Hebelstrasse). Das Thema ihrer Dissertation, die sie

erfolgreich abschloss, lautete: "Immunobiology of IL-17A in human colorectal cancer".

Am 2. Juli 2014 konnte **Carolina Medeiros da Cunha** von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie widmete sich in ihrer Arbeit dem Thema "Mesenchymal stromal cell-based regulation of angiogenesis and inflammation in cartilage formation."

Auszeichnungen

Cloëtta-Preis 2014 geht an Marc Donath

Marc Donath von der Forschungsgruppe Diabetes Research (Departement Biomedizin Hebelstrasse) erhält gemeinsam mit Henrik Kaessmann von der Universität Lausanne den diesjährigen Cloëtta-Preis. Beide erhalten je eine Preissumme von 50'000 CHF. Marc Donath erhält die Auszeichnung für seine Erforschung des Entstehungsmechanismus des Typ-2-Diabetes. Die Preisverleihung findet am 14. November 2014 am Universitätsspital Zürich statt. Der Cloëtta-Preis fördert und unterstützt die medizinische Forschung und mit ihr verbundene naturwissenschaftliche Disziplinen in der Schweiz.

Ilija Lujic Informatiker mit eidgenössischen Diplom

Ilija Lujic von der DBM IT hat im Mai 2014 erfolgreich die Prüfung zum Informatiker mit eidgenössischem Diplom Fachrichtung Business Solutions abgelegt.

Radek Skoda erhält 450'000 Dollar für Studie zur chronischen Leukämie

Radek Skoda von der Forschungsgruppe Experimental Hematology (Departement Biomedizin Hebelstrasse) hat im Juni 2014 den Gateway/RT F-CCR/SAKK Forschungspreis der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) erhalten. Ausgezeichnet wurde sein Projekt, da es Aussicht auf eine neuartige Behandlungsmöglichkeit von Patientinnen und Patienten mit einer bestimmten Form von chronischer Leukämie bietet. Der Gateway/RT F-CCR/SAKK Forschungspreis in der klinischen Krebsforschung ist mit 450.000 US-Dollar dotiert und wird gemeinsam von Gateway for Cancer Research, einer in den USA ansässigen gemeinnützigen Organisation, und der Rising Tide Foundation for Clinical Cancer Research finanziert.

Das DBM gratuliert ganz herzlich!

Attenuated sensing of SHH by *Ptch1* underlies evolution of bovine limbs

Javier Lopez-Rios^{1,*}, Amandine Duchesne^{1,2,*}, Dario Speziale¹, Guillaume Andrey³, Kevin A. Peterson⁴, Philipp Germann⁵, Erkan Ünal^{1,5}, Jing Liu⁴, Sandrine Floriot², Sarah Barbey⁶, Yves Gallard⁶, Magdalena Müller-Gerbl⁷, Andrew D. Courtney⁸, Christophe Klopp⁹, Sabrina Rodriguez^{2,†}, Robert Ivanek^{1,10}, Christian Beisel⁵, Carol Wicking⁸, Dagmar Iber⁵, Benoit Robert¹¹, Andrew P. McMahon⁴, Denis Duboule^{3,12} & Rolf Zeller¹

The large spectrum of limb morphologies reflects the wide evolutionary diversification of the basic pentadactyl pattern in tetrapods. In even-toed ungulates (artiodactyls, including cattle), limbs are adapted for running as a consequence of progressive reduction of their distal skeleton to symmetrical and elongated middle digits with hoofed phalanges. Here we analyse bovine embryos to establish that polarized gene expression is progressively lost during limb development in comparison to the mouse. Notably, the transcriptional upregulation of the *Ptch1* gene, which encodes a Sonic hedgehog (SHH) receptor, is disrupted specifically in the bovine limb bud mesenchyme. This is due to evolutionary alteration of a *Ptch1* cis-regulatory module, which no longer responds to graded SHH signalling during bovine handplate development. Our study provides a molecular explanation for the loss of digit asymmetry in bovine limb buds and suggests that modifications affecting the *Ptch1* cis-regulatory landscape have contributed to evolutionary diversification of artiodactyl limbs.

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³ School of Life Sciences, Federal Institute of Technology Lausanne, CH-1015 Lausanne, Switzerland.

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¹¹ Institut Pasteur, Génétique Moléculaire de la Morphogénèse and Centre National de la Recherche Scientifique URA-2578, F-75015 Paris, France.

¹² Department of Genetics and Evolution, University of Geneva, CH-1211 Geneva, Switzerland.

* Present address: Institut National de la Recherche Agronomique, Laboratoire d'Ingénierie des Systèmes Biologiques et des Procédés, F-31077 Toulouse, France.

† These authors contributed equally to this work.

Engineered autologous cartilage tissue for nasal reconstruction after tumour resection: an observational first-in-human trial

Ilario Fulco^{1,*}, Sylvie Miot^{1,*}, Martin D Haug¹, Andrea Barbero¹, Anke Wixmerten¹, Sandra Feliciano¹, Francine Wolf¹, Gernot Jundt², Anna Marsano¹, Jian Farhadi³, Michael Heberer¹, Marcel Jakob¹, Dirk J Schaefer¹, Ivan Martin¹

Summary

Background Autologous native cartilage from the nasal septum, ear, or rib is the standard material for surgical reconstruction of the nasal alar lobule after two-layer excision of non-melanoma skin cancer. We assessed whether engineered autologous cartilage grafts allow safe and functional alar lobule restoration.

Methods In a first-in-human trial, we recruited five patients at the University Hospital Basel (Basel, Switzerland). To be eligible, patients had to be aged at least 18 years and have a two-layer defect ($\geq 50\%$ size of alar subunit) after excision of non-melanoma skin cancer on the alar lobule. Chondrocytes (isolated from a 6 mm cartilage biopsy sample from the nasal septum harvested under local anaesthesia during collection of tumour biopsy sample) were expanded, seeded, and cultured with autologous serum onto collagen type I and type III membranes in the course of 4 weeks. The resulting engineered cartilage grafts (25 mm x 25 mm x 2 mm) were shaped intra-operatively and implanted after tumour excision under paramedian forehead or nasolabial flaps, as in standard reconstruction with native cartilage. During flap refinement after 6 months, we took biopsy samples of repair tissues and histologically analysed them. The primary outcomes were safety and feasibility of the procedure,

assessed 12 months after reconstruction. At least 1 year after implantation, when reconstruction is typically stabilised, we assessed patient satisfaction and functional outcomes (alar cutaneous sensibility, structural stability, and respiratory flow rate).

Findings Between Dec 13, 2010, and Feb 6, 2012, we enrolled two women and three men aged 76–88 years. All engineered grafts contained a mixed hyaline and fibrous cartilage matrix. 6 months after implantation, reconstructed tissues displayed fibromuscular fatty structures typical of the alar lobule. After 1 year, all patients were satisfied with the aesthetic and functional outcomes and no adverse events had been recorded. Cutaneous sensibility and structural stability of the reconstructed area were clinically satisfactory, with adequate respiratory function.

Interpretation Autologous nasal cartilage tissues can be engineered and clinically used for functional restoration of alar lobules. Engineered cartilage should now be assessed for other challenging facial reconstructions.

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* Contributed equally

Modulation of Age- and Cancer-Associated DNA Methylation Change in the Healthy Colon by Aspirin and Lifestyle

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Background

Aberrant DNA methylation in gene promoters is associated with aging and cancer, but the circumstances determining methylation change are unknown. We investigated the impact of lifestyle modulators of colorectal cancer (CRC) risk on the stability of gene promoter methylation in the colonic mucosa.

Methods

We measured genome-wide promoter CpG methylation in normal colon biopsies (n = 1092) from a female screening cohort, investigated the interaction of lifestyle factors with age-dependent increase in methylation with log-linear multivariable regression, and related their modifying effect to hypermethylation in CRC. All statistical tests were two-sided.

Results

Of 20 025 promoter-associated CpGs analyzed, 1713 showed statistically significant age-dependent methylation gains. Fewer CpGs acquired methylation in users of aspirin (≥ 2 years) and hormonal replacement therapy (HRT age ≥ 50 years) compared with nonusers (43 vs 1355; 1 vs 1377, respectively), whereas more CpGs were affected in smokers (≥ 20 years) and individuals with a body mass index (BMI) of 25 kg/m² and greater

compared with control groups (180 vs 39; 554 vs 144, respectively). Fifty percent of the CpGs showing age-dependent methylation were found hypermethylated in CRC (odds ratio [OR] = 20; 95% confidence interval [CI] = 18 to 23; $P < 2 \times 10^{-16}$). These loci gained methylation with a higher median rate compared with age-only methylated sites ($P = 2 \times 10^{-76}$) and were enriched for polycomb regions (OR = 3.67). Importantly, aspirin ($P < .001$) and HRT use ($P < .001$) reduced the methylation rate at these cancer-related genes, whereas smoking ($P < .001$) and high BMI ($P = .004$) increased it.

Conclusions

Lifestyle, including aspirin use, modulates age-associated DNA methylation change in the colonic epithelium and thereby impacts the evolution of cancer methylomes.

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A novel self-lipid antigen targets human T cells against CD1c⁺ leukemias

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T cells that recognize self-lipids presented by CD1c are frequent in the peripheral blood of healthy individuals and kill transformed hematopoietic cells, but little is known about their antigen specificity and potential antileukemia effects. We report that CD1c self-reactive T cells recognize a novel class of self-lipids, identified as methyl-lysophosphatidic acids (mLPAs), which are accumulated in leukemia cells. Primary acute myeloid and B cell acute leukemia blasts express CD1 molecules. mLPA-specific T cells

efficiently kill CD1c⁺ acute leukemia cells, poorly recognize nontransformed CD1c-expressing cells, and protect immunodeficient mice against CD1c⁺ human leukemia cells. The identification of immunogenic selflipid antigens accumulated in leukemia cells and the observed leukemia control by lipid-specific T cells in vivo provide a new conceptual framework for leukemia immune surveillance and possible immunotherapy.

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¹⁰ Singapore Immunology Network (SIgN), Agency for Science, Technology, and Research, Singapore 138648

Simultaneous Detection of Hepatitis C Virus and Interferon Stimulated Gene Expression in Infected Human Liver

Stefan Wieland¹, Zuzanna Makowska², Benedetta Campana^{2,3}, Diego Calabrese², Michael T. Dill^{2,3}, Josan Chung¹, Francis V. Chisari¹ and Markus H. Heim^{1,2,3}

Approximately 50% of patients with chronic hepatitis C (CHC) have ongoing expression of interferon stimulated genes (ISGs) in the liver. It is unclear why this endogenous antiviral response is inefficient in eradicating the infection. Several viral escape strategies have been identified in vitro, including inhibition of interferon (IFN) induction and ISG messenger RNA (mRNA) translation. The in vivo relevance of these mechanisms is unknown, because reliable methods to identify hepatitis C virus (HCV)-infected cells in human liver are lacking. We developed a highly sensitive in situ hybridization (ISH) system capable of HCV RNA and ISG mRNA detection in human liver biopsies and applied it to study the interaction of HCV with the endogenous IFN system. We simultaneously monitored HCV RNA and ISG mRNA using HCV isolate- and ISG mRNA-specific probes in liver biopsy sections from 18 CHC patients. The signals were quantified

at the single-cell resolution in a series of random high-power fields. The proportion of infected hepatocytes ranged from 1%-54% and correlated with viral load, but not with HCV genotype or ISG expression. Infected cells occurred in clusters, pointing to cell-to-cell spread as the predominant mode of HCV transmission. ISG mRNAs were readily detected in HCV-infected cells, challenging previously proposed mechanisms of viral interference with the immune system. Conversely, infected cells and neighboring cells showed increased ISG mRNA levels, demonstrating that the stimulus driving ISG expression originates from HCV-infected hepatocytes. Conclusion: HCV infection in human hepatocytes during CHC does not efficiently interfere with IFN induction, IFN signaling, or transcription of ISG mRNA.

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Complex subclone structure that responds differentially to therapy in a patient with essential thrombocythemia and chronic myeloid leukemia

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BCR-ABL translocation and JAK2-V617F mutation can sometimes be found concomitantly in the same patient (reviewed in Hummel et al). To date, 4 studies have examined the chronology and architecture of BCR-ABL and JAK2-V617F clones at the molecular level. In 3 studies, the 2 mutations were sequentially acquired by the same stem cell, with JAK2-V617F preceding the acquisition of BCR-ABL. Another report concluded that BCR-ABL and JAK2-V617F represented 2 distinct clones.

Here, we studied a 56-year-old female patient diagnosed in May 2005 with JAK2-V617F-positive essential thrombocythemia (ET), normal cytogenetics, and absence of BCR-ABL (Figure 1A). With anagrelide (2 mg/day), platelet levels normalized. However, in October 2010, thrombocyto-

sis, leukocytosis (white blood cell count = 30 × 10⁹/L) and the presence of myelocytes and metamyelocytes in the peripheral blood was noted. Bone marrow showed typical features of chronic myeloid leukemia (CML) and cytogenetic analysis revealed the Philadelphia chromosome translocation t(9;22)(q34;q11). Molecular analysis confirmed expression of a BCR-ABL fusion (b3a2). Treatment with dasatinib induced remission of CML, but thrombocytosis persisted. Therefore, low-dose hydroxyurea (500 mg every second day) was added. A complete molecular remission with a 10⁻⁴ to 10⁻⁵ reduction of BCR-ABL transcripts (CMR) was reached within 12 months.

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Loss of *Stat1* decreases megakaryopoiesis and favors erythropoiesis in a *JAK2-V617F*-driven mouse model of MPNs

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The interferon- γ (IFN γ)/signal transducer and activator of transcription 1 (Stat1) pathway shows higher activity in patients with essential thrombocythemia (ET) than in polycythemia vera (PV) and was proposed to be promoting the ET phenotype. We explored the phenotypic consequences of Stat1 deficiency on the effects of Janus kinase 2 (*JAK2*)-V617F *in vivo* by crossing mice expressing *JAK2-V617F* with *Stat1* knockout mice. *JAK2-V617F*;*Stat1*^{-/-} double transgenic mice showed higher red cell parameters and lower platelet counts compared with *JAK2-V617F*;*Stat1*^{+/+} mice. Bone marrow transplantation reproduced these phenotypic changes in wild-type recipients, demonstrating that the effect of Stat1 is cell-intrinsic and does not require a *Stat1*-deficient microenvironment. Deletion of *Stat1* in-

creased burst-forming unit-erythroid and reduced colony-forming unit-megakaryocyte colony formation driven by *JAK2-V617F*, but was not sufficient to completely normalize the platelet count. *Gata1*, a key regulator of megakaryopoiesis and erythropoiesis, was decreased in *Stat1*-deficient platelets. *V617F* transgenic mice with thrombocytosis had higher serum levels of IFN γ than normal controls and patients with ET showed higher IFN γ serum levels than patients with PV. Together, these results support the concept that activating Stat1 in the presence of *JAK2-V617F*, for example, through IFN γ , constrains erythroid differentiation and promotes megakaryocytic development, resulting in ET phenotype.

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Tissue-engineered dermo-epidermal skin grafts prevascularized with adipose-derived cells

Agnieszka S. Klar¹, Sinan Güven², Thomas Biedermann¹, Joachim Luginbühl¹, Sophie Böttcher-Haberzeth¹, Claudia Meuli-Simmen⁴, Martin Meuli³, Ivan Martin², Arnaud Scherberich², Ernst Reichmann¹

Abstract

The major problem in skin grafting is that tissue-engineered skin grafts after their transplantation are initially entirely dependent on diffusion. Since this process is slow and inefficient, nutrients, growth factors, and oxygen will insufficiently be supplied and the regenerating graft will undergo a physiological crisis, resulting in scar-like dermal structures and shrinkage. The tissue-engineering of a vascular network in human dermo-epidermal skin substitutes (DESS) is a promising approach to overcome this limitation. Here we report, for the first time, on the use of the adipose stromal vascular fraction (SVF)-derived endothelial cell popula-

tion to tissue-engineer DESS containing a highly efficient capillary plexus. To develop vascular networks *in vitro*, we employed optimized 3D fibrin or collagen type I hydrogel systems. Upon transplantation onto immune-deficient rats, these pre-formed vascular networks anastomosed to the recipient's vasculature within only four days. As a consequence, the neo-epidermis efficiently established tissue homeostasis, the dermis underwent almost no contraction, and showed sustained epidermal coverage *in vivo*. Overall, the here described rapid and efficient perfusion of SVF-based skin grafts opens new perspectives for the treatment of hitherto unmet clinical needs in burn/ plastic surgery and dermatology.

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Immunomodulatory Function of Interleukin 28B During Primary Infection With Cytomegalovirus

Adrian Egli^{1,2}, Aviad Levin¹, Deanna M. Santer¹, Michael Joyce¹, Daire O'Shea¹, Brad S. Thomas¹, Luiz F. Lisboa¹, Khaled Barakat^{1,3}, Rakesh Bhat¹, Karl P. Fischer¹, Michael Houghton¹, D. Lorne Tyrrell¹, Deepali Kumar⁴, and Atul Humar⁴

Background.

Feedback mechanisms between interferons α and λ (IFNs) may be affected by single nucleotide polymorphisms (SNP) in interleukin 28B (IL-28B; IFN- λ 3) promoter region and may influence cytomegalovirus (CMV) replication.

Methods.

We associated IL-28B SNPs with the risk of CMV replication after transplantation. Next, we examined the effect of IL-28B genotypes on IL-28B, and IFN-stimulated gene (ISG) expression, and CMV replication in human foreskin fibroblast (HFF) and peripheral blood mononuclear cells (PBMCs).

Results.

Transplant recipients with an IL-28B SNP (rs8099917) had significantly less CMV replication ($P = .036$). Both HFF-cells and PBMCs with a SNP showed

lower IL-28B expression during infection with CMV, but higher "antiviral" ISG expression (eg, OAS1). Fibroblasts with a SNP had a 3-log reduction of CMV replication at day 4 ($P = .004$). IL-28B pretreatment induced ISG expression in noninfected fibroblasts, but a relative decrease of ISG expression could be observed in CMV-infected fibroblasts. The inhibitory effects of IL-28B could be abolished by siRNA or antagonistic peptides against the IL-28 receptor. In fibroblasts, inhibition of IL-28 signaling resulted in an increase of ISG expression and 3-log reduction of CMV-replication ($P = .01$).

Conclusions.

We postulate that IL-28B may act as a key regulator of ISG expression during primary CMV infection. IL-28B SNPs may be associated with higher antiviral ISG expression, which results in better replication control.

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Quality control of oxidatively damaged mitochondrial proteins is mediated by p97 and the proteasome

Charles Hemion¹, Josef Flammer², Albert Neutzner^{1,2}

Abstract

Protein quality control is essential for maintaining mitochondrial fidelity. Proteins damaged by reactive oxygen species necessitate quality control to prevent mitochondrial dysfunction connected to aging and neurodegeneration. Here we report a role for the AAA ATPase p97/VCP and the proteasome in the quality control of oxidized mitochondrial proteins under low oxidative stress as well as normal conditions. Proteasomal inhibi-

tion and blocking p97-dependent protein retrotranslocation interfered with degradation of oxidized mitochondrial proteins. Thus, ubiquitin-dependent, p97-, and proteasome-mediated degradation of oxidatively damaged proteins plays a key role in maintaining mitochondrial fidelity and is likely an important defense mechanism against aging and neurodegeneration.

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Increased protein kinase C gamma activity induces Purkinje cell pathology in a mouse model of spinocerebellar ataxia 14

Jingmin Ji, Melanie L. Hassler, Etsuko Shimobayashi, Nagendher Paka, Raphael Streit, Josef P. Kapfhammer

Abstract

Spinocerebellar ataxias (SCAs) are hereditary diseases leading to Purkinje cell degeneration and cerebellar dysfunction. Most forms of SCA are caused by expansion of CAG repeats similar to other polyglutamine disorders such as Huntington's disease. In contrast, in the autosomal dominant SCA-14 the disease is caused by mutations in the protein kinase C gamma (PKC γ) gene which is a well characterized signaling molecule in cerebellar Purkinje cells. The study of SCA-14, therefore, offers the unique opportunity to reveal the molecular and pathological mechanism eventually leading to Purkinje cell dysfunction and degeneration. We have created a mouse model of SCA-14 in which PKC γ protein with a mutation found in SCA-14 is specifically expressed in cerebellar Purkinje cells. We find that in mice expressing the mutated PKC γ protein the mor-

phology of Purkinje cells in cerebellar slice cultures is drastically altered and mimics closely the morphology seen after pharmacological PKC activation. Similar morphological abnormalities were seen in localized areas of the cerebellum of juvenile transgenic mice in vivo. In adult transgenic mice there is evidence for some localized loss of Purkinje cells but there is no overall cerebellar atrophy. Transgenic mice show a mild cerebellar ataxia revealed by testing on the rotarod and on the walking beam. Our findings provide evidence for both an increased PKC γ activity in Purkinje cells in vivo and for pathological changes typical for cerebellar disease thus linking the increased and dysregulated activity of PKC γ tightly to the development of cerebellar disease in SCA-14 and possibly also in other forms of SCA.

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MiR-126: a novel route for natalizumab action?

Maria Meira, Claudia Sievers, Francine Hoffmann, Tobias Derfuss, Jens Kuhle, Ludwig Kappos and Raija LP Lindberg

Abstract

Background: MicroRNAs (miRNAs) have emerged as a family of post-transcriptional regulators of gene expression that mediate diverse aspects of immunity. MiRNA dysregulation has been found in multiple sclerosis (MS), reflecting the growing need to identify disease-specific miRNA expression signatures. Our previous low-density array studies reveal differential miR-126 expression in the CD4⁺T cells of untreated relapsing–remitting MS (RRMS) patients. Here, we investigated miR-126 expression in natalizumab-treated patients.

Methods: We isolated CD4⁺ T cells from untreated ($n = 12$) and natalizumab-treated MS patients ($n = 24$), and from healthy volunteers ($n = 12$). We analyzed the expression of miRNAs and potential targets by real time reverse transcription polymerase chain reaction (RT-PCR). We assessed specific inhibition of miR-126, in vitro.

Results: MiR-126 was down-regulated in cells of patients under natalizumab treatment and up-regulated during relapse, supporting a regulatory role in MS immunopathogenesis. MiR-126 expression correlated with the expression of POU2AF1, a regulator of Spi-B that binds to the promoter/enhancer sequences of JC virus (JCV), the pathogen of progressive multifocal leukoencephalopathy (PML), a rare complication of natalizumab treatment. The same trend was found for Spi-B. Strong up-regulation of both genes appeared to be treatment duration-dependent. Specific inhibition experiments supported the link between the expression of miR-126 and POU2AF1/Spi-B.

Conclusions: Our findings provided deeper insight into the mode of action of natalizumab, with possible implications for understanding both the effects of natalizumab on MS activity and its specific adverse event profile.

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Regulation of contractile signaling and matrix remodeling by T-cadherin in vascular smooth muscle cells: Constitutive and insulin-dependent effects

Agne Frismantiene^{1,*}, Dennis Pfaff^{1,*}, Audrey Frachet¹, Matteo Coen², Manjunath B. Joshi¹, Kseniya Maslova^{1,3}, Marie-Luce Bochaton-Piallat², Paul Erne³, Therese J. Resink¹, Maria Philippova¹

Abstract

Expression of GPI-anchored T-cadherin (T-cad) on vascular smooth muscle cells (VSMC) is elevated in vascular disorders such as atherosclerosis and restenosis which are associated with insulin resistance. Functions for T-cad and signal transduction pathway utilization by T-cad in VSMC are unknown. The present study examines the consequences of altered T-cad expression on VSMC for constitutive and insulin-induced Akt/mTOR axis signaling and contractile competence. Using viral vectors rat (WKY and SHR) and human aortic VSMCs were variously transduced with respect to T-cad-overexpression (Tcad+VSMC) or T-cad-deficiency (shT-VSMC) and compared with their respective control transductants (E-VSMC or shC-VSMC). Tcad+VSMC exhibited elevated constitutive levels of phosphorylated Akt^{ser473}, GSK3 β ^{ser9}, S6R^{ser235/236} and IRS-1^{ser636/639}. Total IRS-1 levels were reduced. Contractile machinery was constitutively altered in a man-

ner indicative of reduced intrinsic contractile competence, namely decreased phosphorylation of MYPT1^{thr696 or thr853} and MLC₂₀^{thr18/ser19}, reduced RhoA activity and increased iNOS expression. Tcad+VSMC-populated collagen lattices exhibited greater compaction which was due to increased collagen fibril packing/reorganization. T-cad+VSMC exhibited a state of insulin insensitivity as evidenced by attenuation of the ability of insulin to stimulate Akt/mTOR axis signaling, phosphorylation of MLC₂₀ and MYPT1, compaction of free-floating lattices and collagen fibril reorganization in unreleased lattices. The effects of T-cad-deficiency on constitutive characteristics and insulin responsiveness of VSMC were opposite to those of T-cad-overexpression. The study reveals novel cadherin-based modalities to modulate VSMC sensitivity to insulin through Akt/mTOR axis signaling as well as vascular function and tissue architecture through the effects on contractile competence and organization of extracellular matrix.

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* These authors contributed equally to this study.

Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: analysis of underlying signal transduction pathways and potential diagnostic utility

Chanchal Sur Chowdhury^{1,*}, Stavros Giaglis^{1,2,*}, Ulrich A Walker³, Andreas Buser⁴, Sinuhe Hahn¹ and Paul Hasler²

Abstract

Introduction: Neutrophil extracellular traps (NETs) have recently been implicated in a number of autoimmune conditions, including rheumatoid arthritis (RA). We examined the underlying signaling pathways triggering enhanced NETosis in RA and ascertained whether the products of NETosis had diagnostic implications or usefulness.

Methods: Neutrophils were isolated from RA patients with active disease and from controls. Spontaneous NET formation from RA and control neutrophils was assessed *in vitro* with microscopy and enzyme-linked immunosorbent assay (ELISA) for NETosis-derived products. The analysis of the signal-transduction cascade included reactive oxygen species (ROS) production, myeloperoxidase (MPO), neutrophil elastase (NE), peptidyl arginine deiminase 4 (PAD4), and citrullinated histone 3 (citH3). NET formation was studied in response to serum and synovial fluid and immunoglobulin G (IgG) depleted and reconstituted serum. Serum was analyzed for NETosis-derived products, for which receiver operator characteristic (ROC) curves were calculated.

Results: Neutrophils from RA cases exhibited increased spontaneous NET formation *in vitro*, associated with elevated ROS production, enhanced

NE and MPO expression, nuclear translocation of PAD4, PAD4-mediated citrullination of H3, and altered nuclear morphology. NET formation in both anti-citrullinated peptide antibody (ACPA)-positive and -negative RA was abolished by IgG depletion, but restored only with ACPA-positive IgG. NETosis-derived products in RA serum demonstrated diagnostic potential, the ROC area under the curve for cell-free nucleosomes being >97%, with a sensitivity of 91% and a specificity of 92%. No significant difference was observed between ACPA-positive and -negative cases.

Conclusions: Signaling elements associated with the extrusion of NETs are significantly enhanced to promote NETosis in RA compared with healthy controls. NETosis depended on the presence of ACPA in ACPA-positive RA serum. The quantitation of NETosis-derived products, such as cell-free nucleosomes in serum, may be a useful complementary tool to discriminate between healthy controls and RA cases.

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The microtubule-depolymerizing agent ansamitocin P3 programs dendritic cells toward enhanced anti-tumor immunity

Kea Martin^{1,*}, Philipp Müller^{1,*}, Jens Schreiner¹, Spasenija Savic Prince², Didier Lardinois³, Viola A. Heinzlmann-Schwarz⁴, Daniela S. Thommen^{1,5}, Alfred Zippelius^{1,5}

Abstract

In addition to direct tumor cell cytotoxicity, chemotherapy can mediate tumor reduction through immune modulation of the tumor microenvironment to promote anti-tumor immunity. Mature dendritic cells (DCs) play key roles in priming robust immune responses in tumor-bearing hosts. Here, we screened a panel of 21 anticancer agents with defined molecular targets for their ability to induce direct maturation of DCs. We identified ansamitocin P3, a microtubule-depolymerizing agent, as a potent inducer of phenotypic and functional maturation of DCs. Exposure of both murine spleen-derived and human monocyte-derived DCs to ansamitocin P3 triggered up-regulation of maturation markers and production of pro-inflammatory cytokines, resulting in an enhanced T cell stimulatory capacity. Local administration of ansamitocin P3 induced maturation of skin Langerhans cells *in vivo* and promoted antigen uptake and extensive homing of tumor-resident DCs to tumor-draining lymph nodes. When used as an adjuvant in a specific vaccination approach, ansamitocin P3 dramatically increased activation of antigen-specific T cells. Finally, we demonstrate that ansamitocin P3, due to its immunomodulatory properties, acts in synergy with antibody-mediated blockade of the

T cell inhibitory receptors PD-1 and CTLA-4. The combination treatment was most effective and induced durable growth inhibition of established tumors. Mechanistically, we observed a reduced regulatory T cell frequency and improved T cell effector function at the tumor site. Taken together, our study unravels an immune-based anti-tumor mechanism exploited by microtubule-depolymerizing agents, including ansamitocin P3, and paves the way for future clinical trials combining this class of agents with immunotherapy.

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KIR-associated protection from CMV replication requires pre-existing immunity: a prospective study in solid organ transplant recipients

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Previous studies have associated activating Killer cell Immunoglobulin-like Receptor (KIR) genes with protection from cytomegalovirus (CMV) replication after organ transplantation. Whether KIR-associated protection is operating in the context of primary infection, re-activation, or both, remains unknown. Here we correlated KIR genotype and CMV serostatus at the time of transplantation with rates of CMV viremia in 517 heart ($n = 57$), kidney ($n = 223$), liver ($n = 165$) or lung ($n = 72$) allograft recipients reported to the Swiss Transplant Cohort Study. Across the entire cohort we found B haplotypes—which in contrast to A haplotypes may contain multiple activating KIR genes—to be protective in the most immunosuppressed patients (receiving anti-thymocyte globulin induction and intensive maintenance immunosuppression) (hazard ratio after adjustment for covariates 0.46, 95% confidence interval 0.29–0.75, $P = 0.002$). Notably, a significant protection was detected only in recipients who were CMV-seropositive at the time of transplantation (HR 0.45, 95% CI 0.26–0.77, $P = 0.004$), but not in CMV seronegative recipients

(HR 0.59, 95% CI 0.22–1.53, $P = 0.28$). These data indicate a prominent role for KIR—and presumably natural killer (NK) cells—in the control of CMV replication in CMV seropositive organ transplant recipients treated with intense immunosuppression.

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Hepatic toxicity of dronedarone in mice: Role of mitochondrial β oxidation

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Abstract

Dronedarone is an amiodarone like antiarrhythmic drug associated with severe liver injury. Since dronedarone inhibits mitochondrial respiration and β oxidation *in vitro*, mitochondrial toxicity may also explain dronedarone associated hepatotoxicity *in vivo*. We therefore studied hepatotoxicity of dronedarone (200 mg/kg/day for 2 weeks or 400 mg/kg/day for 1 week by intragastric gavage) in heterozygous juvenile visceral steatosis (*jvs*^{+/-}) and wild type mice. *jvs*^{+/-} mice have reduced carnitine stores and are sensitive for mitochondrial β oxidation inhibitors.

Treatment with dronedarone 200 mg/kg/day had no effect on body weight, serum transaminases and bilirubin, and hepatic mitochondrial function in both wild type and *jvs*^{+/-} mice. In contrast, dronedarone 400 mg/kg/day was associated with a 10–15% drop in body weight, and a 3–5 fold increase in transaminases and bilirubin in wild type mice and, more

accentuated, in *jvs*^{+/-} mice. *In vivo* metabolism of intraperitoneal ¹⁴C palmitate was impaired in wild type, and, more accentuated, in *jvs*^{+/-} mice treated with 400 mg/kg/day dronedarone compared to vehicle treated mice. Impaired β oxidation was also found in isolated mitochondria *ex vivo*. A likely explanation for these findings was a reduced activity of carnitine palmitoyltransferase 1a in liver mitochondria from dronedarone treated mice. In contrast, dronedarone did not affect the activity of the respiratory chain *ex vivo*.

We conclude that dronedarone inhibits mitochondrial β oxidation *in vivo*, but not the respiratory chain. *jvs*^{+/-} mice are slightly more sensitive for the effect of dronedarone on mitochondrial β oxidation than wild type mice. The results suggest that inhibition of mitochondrial β oxidation is an important mechanism of hepatotoxicity associated with dronedarone.

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Hepatocellular toxicity of benzbromarone: Effects on mitochondrial function and structure

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Abstract

Benzbromarone is an uricosuric structurally related to amiodarone and a known mitochondrial toxicant. The aim of the current study was to improve our understanding in the molecular mechanisms of benzbromarone-associated hepatic mitochondrial toxicity. In HepG2 cells and primary human hepatocytes, ATP levels started to decrease in the presence of 25–50 μ M benzbromarone for 24–48 h, whereas cytotoxicity was observed only at 100 μ M. In HepG2 cells, benzbromarone decreased the mitochondrial membrane potential starting at 50 μ M following incubation for 24 h. Additionally, in HepG2 cells, 50 μ M benzbromarone for 24 h induced mitochondrial uncoupling, and decreased mitochondrial ATP turnover and maximal respiration. This was accompanied by an increased lactate concentration in the cell culture supernatant, reflecting increased glycolysis as a compensatory mechanism to maintain cellular ATP. Investi-

gation of the electron transport chain revealed a decreased activity of all relevant enzyme complexes. Furthermore, treatment with benzbromarone was associated with increased cellular ROS production, which could be located specifically to mitochondria. In HepG2 cells and in isolated mouse liver mitochondria, benzbromarone also reduced palmitic acid metabolism due to an inhibition of the long-chain acyl CoA synthetase. In HepG2 cells, benzbromarone disrupted the mitochondrial network, leading to mitochondrial fragmentation and a decreased mitochondrial volume per cell. Cell death occurred by both apoptosis and necrosis. The study demonstrates that benzbromarone not only affects the function of mitochondria in HepG2 cells and human hepatocytes, but is also associated with profound changes in mitochondrial structure which may be associated with apoptosis.

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Efficient Neutrophil Extracellular Trap Induction Requires Mobilization of Both Intracellular and Extracellular Calcium Pools and Is Modulated by Cyclosporine A

Anurag Kumar Gupta¹, Stavros Giaglis^{1,2}, Paul Hasler², Sinuhe Hahn¹

Abstract

Excessive or aberrant generation of neutrophil extracellular traps (NETs) has recently become implicated in the underlying aetiology of a number of human pathologies including preeclampsia, systemic lupus erythematosus, rheumatoid arthritis, auto-antibody induced small vessel vasculitis, coagulopathies such as deep vein thrombosis or pulmonary complications. These results imply that effective pharmacological therapeutic strategies will need to be developed to counter overt NETosis in these and other inflammatory disorders. As calcium flux is implicated in the generation of reactive oxygen species and histone citrullination, two key events in NETosis, we analysed the roles of both extra- and intracellular calcium pools and their modulation by pharmacological agents in the NETotic process in detail. Interleukin-8 (IL-8) was used as a physiological stimulus of NETosis. Our data demonstrate that efficient induction of NETosis requires mobilisation of both extracellular and intracellular cal-

cium pools. Since modulation of the calcineurin pathway by cyclosporine A has been described in neutrophils, we investigated its influence on NETosis. Our data indicate that IL-8 induced NETosis is reduced by ascromycin and cyclosporine A, antagonists of the calcineurin pathway, but not following treatment with rapamycin, which utilizes the mTOR pathway. The action of the G protein coupled receptor phospholipase C pathway appears to be essential for the induction of NETs by IL-8, as NETosis was diminished by treatment with either pertussis toxin, a G-protein inhibitor, the phospholipase C inhibitor, U73122, or staurosporine, an inhibitor of protein kinase C. The data regarding the calcineurin antagonists, ascromycin and cyclosporine A, open the possibility to therapeutically suppress or modulate NETosis. They also provide new insight into the mechanism whereby such immune suppressive drugs render transplant patients susceptible to opportunistic fungal infections.

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Versatile Recombinant SUMOylation System for the Production of SUMO-Modified Protein

Alain R. Weber, David Schuermann, Primo Schär

Abstract

Posttranslational modification by small ubiquitin-like modifiers (SUMO) is being associated with a growing number of regulatory functions in diverse cellular processes. The biochemical investigation into the underlying molecular mechanisms, however, has been lagging behind due to the difficulty to generate sufficient amounts of recombinant SUMOylated proteins. Here, we present two newly designed two-component vector systems for the expression and purification of SUMO-modified target proteins in *Escherichia coli*. One system consists of a vector for SUMO conjugation, expressing human SUMO-activating (SAE1/SAE2) and conjugating (Ubc9) enzymes together with His₆-tagged SUMO1, 2 or 3, that can be

combined with commonly used expression constructs for any gene of interest. To facilitate SUMOylation of targets normally requiring a SUMO-E3 ligase for efficient modification, a second system is designed to express the target protein as a fusion with the human SUMO-conjugating enzyme Ubc9, thus compensating the absence of a potential SUMO ligase. We demonstrate the proficiency of these systems by SUMOylation of two DNA repair proteins, the thymine DNA glycosylase (TDG) and XRCC1, and describe purification schemes for SUMOylated proteins in native and active form. This SUMO toolbox facilitates "in-cell" and "in-extract" production and purification of recombinant SUMO-modified target proteins for functional and structural analysis.

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A Study of the Relationship between Serum Bile Acids and Propranolol Pharmacokinetics and Pharmacodynamics in Patients with Liver Cirrhosis and in Healthy Controls

Anne B. Taegtmeyer^{1,*}, Manuel Haschke^{1,2,*}, Lydia Tchambaz^{1,*}, Mirabel Buylaert¹, Martin Tschöpl¹, Ulrich Beuers³, Jürgen Drewe^{1,2}, Stephan Krähenbühl^{1,2}

Abstract

The main objectives of the study were to determine the exposure and bioavailability of oral propranolol and to investigate their associations with serum bile acid concentration in patients with liver cirrhosis and in healthy controls. A further objective was to study the pharmacodynamics of propranolol. An open-label crossover study was performed to determine the pharmacokinetics and pharmacodynamics of propranolol after oral (40 mg) and intravenous (1 mg) administration as well as the concentration of total and individual fasting serum bile acids in 15 patients with liver cirrhosis and 5 healthy controls. After intravenous propranolol, patients showed a 1.8-fold increase in the area under the plasma concentration-time curve ($AUC_{0-\infty}$), a 1.8-fold increase in volume of distribution and a 3-fold increase in the elimination half-life (mean \pm SEM: 64 ± 100 vs.

205 ± 43 minutes) compared to controls. After oral application, $AUC_{0-\infty}$ and elimination half-life of propranolol were increased 6- and 4-fold, respectively, and bioavailability 3-fold (83 ± 8 vs. $27 \pm 9.2\%$). Maximal effects on blood pressure and heart rate occurred during the first 4 and first 2 hours, respectively, after intravenous and oral application in both patients and controls. Total serum bile acid concentrations were higher in patients than controls (42 ± 11 vs. 2.7 ± 0.3 $\mu\text{mol/L}$) and were linearly correlated with the serum chenodeoxycholic acid concentration. There was a linear correlation between the SBA concentration and propranolol oral $AUC_{0-\infty}$ in subjects not receiving interacting drugs ($r^2 = 0.73$, $n = 18$). The bioavailability of and exposure to oral propranolol are increased in patients with cirrhosis. Fasting serum bile acid concentration may be helpful in predicting the exposure to oral propranolol in these patients.

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Proteasome-mediated quality control of S-nitrosylated mitochondrial proteins

Anne-Sophie Benischke¹, Charles Hemion¹, Josef Flammer², Albert Neutzner^{1,2}

Abstract

Accumulating low level mitochondrial insults are thought to be key to aging processes and neurodegeneration. Among other stressors, protein damage due to nitrosative stress negatively impacts mitochondrial function and is linked to neurodegeneration. Using biotin switch technique, we show that mitochondrial proteins are S-nitrosylated not only in the presence but also in the absence of exogenous nitrosative stress. In ad-

dition, we revealed a role for the ubiquitin–proteasome system and the outer mitochondrial membrane associated degradation (OMMAD)-component p97 in the quality control of S-nitrosylated mitochondrial. Taken together, constant proteasome-mediated clearance of nitrosatively-damaged proteins from mitochondria is likely important for maintaining organelle function.

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REVIEWS

Nature Reviews

nature
REVIEWS

Vol. 13, June 2014, 465

IF 37,231

Targeting inflammation in the treatment of type 2 diabetes: time to start

Marc Y. Donath

Abstract

The role of inflammation in the pathogenesis of type 2 diabetes and associated complications is now well established. Several conditions that are driven by inflammatory processes are also associated with diabetes, including rheumatoid arthritis, gout, psoriasis and Crohn's disease, and various anti-inflammatory drugs have been approved or are in late stages

of development for the treatment of these conditions. This Review discusses the rationale for the use of some of these anti-inflammatory treatments in patients with diabetes and what we could expect from their use. Future immunomodulatory treatments may not target a specific disease, but could instead act on a dysfunctional pathway that causes several conditions associated with the metabolic syndrome.

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Science

Science

August 2014, Vol. 345 Issue 6196

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In Turing's hands—the making of digits A Turing network controls the periodic pattern of fingers and toes during development

by Aimée Zuniga and Rolf Zeller

Alan Turing is best known as the father of theoretical computer sciences and for his role in cracking the Enigma encryption codes during World War II. He was also interested in mathematical biology and published (1) a theoretical rationale for the self-regulation and patterning of tissues in embryos. The so-called reaction-diffusion model allows mathematical simulation of diverse types of embryonic patterns with astonishing accuracy (1–3). During the past two decades, the existence of Turing-type mechanisms has been experimentally explored and is now well established in developmental systems such as skin pigmentation patterning in

fishes, and hair and feather follicle patterning in mouse and chicken embryos (3). However, the extent to which Turing-type mechanisms control patterning of vertebrate organs is less clear. Often, the relevant signaling interactions are not fully understood and/or Turing-like features have not been thoroughly verified by experimentation and/or genetic analysis (3). Raspopovic et al., on page 566 in this issue, now make a good case for Turing-like features in the periodic pattern of digits by identifying the molecular architecture of what appears to be a Turing network functioning in positioning the digit primordia within mouse limb buds (4).

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Selected publications by DBM members

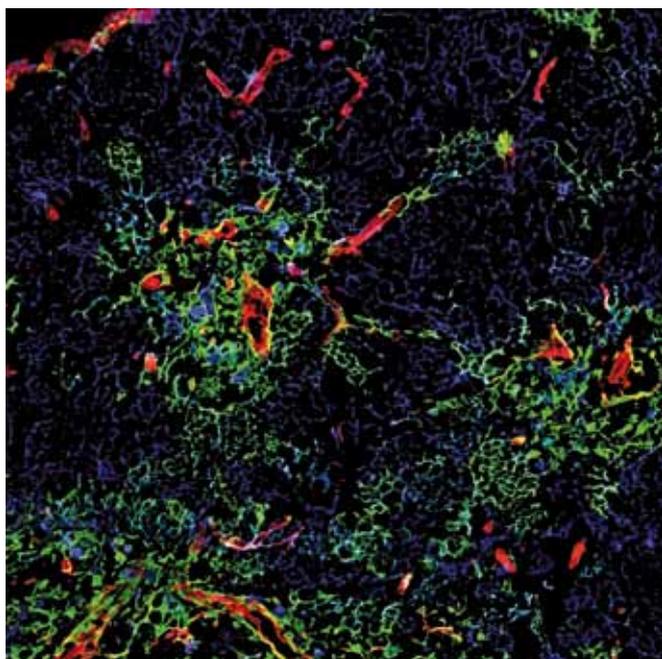
Below you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. 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 October 31, 2014



DBM Research Day

Please reserve the date for the 2015 Department of Biomedicine Research Day. It will be held on Thursday, January 29, 2015 at the DBM-Hebelstrasse (ZLF, Small Lecture Hall).

The speakers will be:

Sven Cichon	Claudia Lengerke
Daniela Finke	Olivier Pertz
Georg A. Holländer	Michael Roth
Gabriela Kuster Pfister	Michael Tamm
Markus Heim	Marten Trendelenburg

A more detailed announcement will follow.



**DEPARTEMENT
BIOMEDIZIN
HEBELSTRASSE**



Antonio Pires
DBM IT



Pascal Odermatt
DBM IT



Nicola Niklaus
DBM IT



Simon Egli
Translational Immunology



Isabel Fofana
Hepatology



Celeste Manfredonia
Cancer Immunotherapy



Anna Lenard
Stem Cells and
Hematopoiesis



Elisa Alghisi
Stem Cells and
Hematopoiesis



Joëlle Müller
Stem Cells and
Hematopoiesis

**DEPARTEMENT
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PESTALOZZI-
STRASSE**



Raimond Dollnik
Administration
Pestalozzistrasse

Rezept zu Seite 24: Verzasca-Kastanienbrot

Kastanien über Nacht in lauwarmem Wasser einweichen, dann mit frischem Wasser bedeckt weichkochen (ca. 40 Min., länger gelagerte Kastanien brauchen mehr Zeit). Kochwasser abgiessen, Kastanien von Zwischenhäutchen befreien und in haselnussgrosse Stücke zerbrechen. Hefe in Wasser auflösen, Mehl in eine Schüssel sieben. In der Mitte in eine Vertiefung die aufgelöste Hefe geben, mit etwas Mehl zu einem dünnen Brei verrühren. 15 Minuten stehenlassen. Kastanien und Salz zugeben, mit einem Kochlöffel bei portionsweiser Zugabe von Wasser zu einem Teig verarbeiten. Auf der Arbeitsfläche zu einem geschmeidigen Teig kneten.

In der Schüssel unter feuchtem Tuch am warmen Ort 1 ½ Stunde gehenlassen. Von Neuem durchkneten. Teig zur Kugel formen, diese pro Brot in drei gleich grosse Stücke teilen. Jedes Stück kurz durchkneten, zu einem ca. 35 cm langen Strang rollen, den zu einem Zopf schlingen und auf ein gefettetes oder mit Backpapier belegtes Blech legen. Im auf 200 Grad vorgeheizten Backofen 1 ½ Stunden backen.
Zutaten:
600 dl Wasser, 40 g Hefewürfel, 1 kg Weizenmehl
125 g getrocknete Kastanien, 25 g Salz

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN HEBELSTRASSE

Charles Hemion

Ocular Pharmacology and
Physiology

Romina Matter-Marone

Molecular Immune Regulation

Menelaos Petrovas

Prenatal Medicine

Melanie Neutzner

Stem Cells and Hematopoiesis

Sophia Wiedemann

Immunobiology

Banu Sürücü

Transplantation Immunology
& Nephrology

Stella Marbot

Immunonephrology

Tanja Dittmar

Brain Ischemia and
Regeneration

Sulamith Egloff

Inner Ear Research

Leonie Wieland

Inner Ear Research

Isabelle Vock

Clinical Neuroimmunology

Stefan Wieland

Hepatology

Norina Koch

Diabetes Research

Julian Reinisch

Psychopharmacology
Research

Marc Stawiski

Ocular Pharmacology and
Physiology

Tarek Ismail

Tissue Engineering

Jordan Löliger

Immunobiology

Srinivas Madduri

Brain Ischemia and
Regeneration

DEPARTEMENT BIOMEDIZIN MATTENSTRASSE

Ryan Goosen

Tumor Biology

DEPARTEMENT BIOMEDIZIN PESTALOZZISTRASSE

Sandra Blache

Musculoskeletal Research

DEPARTEMENT BIOMEDIZIN PETERSPLATZ

Anke Gehringer

Rheumatology

Esther Sutter

Infrastruktur Petersplatz

Die Pfütze

Eigentlich müsste ich Glungge oder Gunte schreiben, denn sie ist eine Schweizer Pfütze. Sie liegt auf helvetischem Boden genau zwischen meinen Bürofenster und dem Spielplatz, auf dem sich nur selten ein Kind verirrt. Zumindest ist er verwaist, wenn ich hinschaue, was ich aber nur selten tue. Im Gegensatz zur Pfütze. Sie ist immer da und mir in diesem Sommer ans Herz gewachsen. Ich muss mich nur ein bisschen nach links drehen, mit dem Stuhl zurückgehen und meinen Hals recken. Da ist sie dann. Sie ist nicht gross. Nicht auffällig. Eher klein. Ein bisschen dunkler hebt sie sich vom Umfeld ab. Aber ich kann mich auf sie verlassen. Sie sagt mir, wann ich einen Regenschirm brauche, wann es Zeit ist, so richtig melancholisch zu werden oder nach Hause zu gehen. Sie bleibt, wenn ich gehe, begrüsst mich am nächsten Morgen aufs Neue. Zwischen uns herrscht ein stilles Einvernehmen.

Für viele Menschen gelten Pfützen als Beeinträchtigungen, besonders für Fussgänger. Dann werden Wege gepflastert oder asphaltiert. Auch in Grünflächen versucht man, Senken zu planieren. Meiner Pfütze bleibt bisher dieses Schicksal noch erspart. Sie darf für viele Kleinlebewesen Kühle, Feuchtigkeit und Wasser bieten. Auch Kinder könnten in ihr spielen.

Experten sagen, dass Pfützen dazu neigen, immer grösser und dauerhafter zu werden, die sogenannte Selbstverstärkung. Wer eine grosse Pfütze werden möchte, muss sich strategisch richtig ansiedeln, den Boden aufweichen, schlammiges Wasser verspritzen und gröber mit dem Umfeld umgehen. Feine Tonteilchen fliesen dann mit dem Wasser zurück in die Pfütze, so dass das Wasser kaum noch versickern kann. Nicht so meine Pfütze. Sie ist einfach da.



Heidi Hoyer mann

Congratulations

Das DBM gratuliert ganz herzlich!



Jovie Lynn Kreuzaler

Geboren am 29.06.2014



**Leo Navin Gremmelmaier
Khanna**

Geboren am 07.09.2014

***Herzlich
willkommen,
allerseits!***



Amit Elijah Nordmann

Geboren am 30.08.2014

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

News aus der DBM-iT

Seit einigen Wochen ist das DBM-iT Team durch folgende neue Mitarbeiter verstärkt worden:



Antonio Pires (Bild links) ist seit Anfang August bei uns als Praktikant dabei. Er wird dann nächstes Jahr bei uns die Informatiker-Lehre absolvieren. Wir heissen Antonio herzlich willkommen und freuen uns, dass er dabei ist.

Nicola Niklaus (Bild rechts) hat das Team ebenfalls per 1. August verstärkt. Er ist temporär bis Ende Februar bei uns und wird vor allem das ganze Team mit seinen Windows-Kenntnissen schulen. Auch soll er uns helfen, die Langzeitpendenzen in diesem



Bereich abzuarbeiten. Auch ihn begrüßen wir herzlich in unserem Team.



Pascal Odermatt (Bild links) hat auf den 1. September bei uns angefangen und ist von der Ingenodata zu uns als Verstärkung ins Apple Macintosh Team gekommen. Sein Standort ist die Hebelstrasse, aber auch die Mattenstrasse und der Petersplatz, wo er mithilft, die dortige Infrastruktur zu betreuen. Es freut uns, dass er den Weg zu uns gefunden hat, und begrüßen auch ihn ganz herzlich.

Wir wünschen allen drei neuen Mitarbeitern einen guten Start am DBM!

Endjahresbeschaffung 2014

Falls Sie partizipieren wollen, so melden Sie sich bitte umgehend bei niklaus.vogt@unibas.ch, damit wir Ihre Bestellung platzieren können. Preislich gibt es ca. 16% auf die Listenpreise im Apple Store auf allen iMacs, Macbooks Pro, MacPros und Macbooks Air. Jedoch nicht auf iPads, iPhones und iPods etc.

Discovering the end of the world

When I knew that I would have to write an article about my lovely Santiago, it was hard to organize my ideas. There are so many things I would like to write and I did not know where to start. I realized my problem was the context. Why the context one might ask? Because the context is Chile, and Chile is a country full of contrasts.

Chile is a very long country with a longitude of 4,270 km, more or less the same distance from Athens to the north of Sweden! It is also very thin, with a maximum width of 450 km and a minimum of just 90 km. It lies between the imposing Andes on the east and the Pacific Ocean on the west. The small width of Chile allows you to begin the day in the mountains and finish it having dinner on the seashore.

Chile is a country which, geologically speaking, has everything; in the northern region of the country we have the Atacama Desert, the most arid desert in the world. This area is also home of many colorful lagoons, which over time have obtained their unique hues due to the accumulation of different metals. Additionally, the flamingos, that call



Flamingos in San Pedro de Atacama

these lagoons home, and the Tatio's geysers make this place unique... it is called "the Moon valley". Finally, despite being the Atacama Desert, the driest of all deserts, not too far away you will find beautiful beaches in "Bahía Inglesa", with warm and crystalline waters.

Moving south, we can find the gorgeous "Valle de Elqui" a place known for its production of the special grapes from which Pisco is produced. A bit further south, we find the central valley, or the "Aconcagua valley", known for the excellent quality of the grapes grown there, which are also harvested and used to produce the world famous Chilean wine. Looking towards the ocean, we find a small town called "Pichilemu", famous for being one of the surf capitals of South America.

As we travel even further south, we arrive at the "Rivers and Lakes" region, with exceptional breath taking views. In this region you will find the millenary Araucaria forest where native trees can be found, wonderful volcanoes, such as "Villarica" and "Llanquihue" each with their respective lakes. Of special note is San Rafael Lake, where you can



Chilean flag, Laguna San Rafael



Torres del Paine, Patagonia

enjoy a cruise with a glass of whiskey on the rocks with ice from the glacier, making for an unforgettable postcard! Finally, further south is the Chilean Patagonia, with the stunning “Torres del Paine”.

Also we cannot forget that more than 3,000 km off the Chilean coast we have “Rapa nui” or Easter Island, where we can see the mysterious “moais”.

Chile does have everything!! The most beautiful aspect of this country is that even though the climate and the local environment can differ, the kindness of the people is a common factor. From Arica in the north to Punta Arenas in the south, people always smile and try their best to please and to make feel a visitor welcome.

The “fruits” of the land also do not leave you wanting more. You have the opportunity to eat a fruit just picked from the tree; to prepare a salad with very fresh lettuce or tomatoes... it is just priceless! Furthermore, you can enjoy a great Chilean BBQ, called “asado”, which consists of a variety of grilled meats and sausages served with several fresh vegetables and of course, a bottle of Chilean wine! And for dessert, you might enjoy a delicious “mote con huesillos” or the most delicious fruits in season. In addition to meat, seafood abounds. The

variety of seafood and fish that you can find in Chile, a country with more than 4,000 km of coast, is impressive. You will be able to find mussels native to the region like “Concholepas” or “Pyrúa Chilensis”, several varieties of fish including “Genypterus chilensis”, which is cooked in a teaming cauldron, and whose special flavor served as an inspiration for the Literature Nobel Prize winner, the poet Pablo Neruda.

But let us return to the original story; let’s talk about Santiago. This beautiful city is located in a valley

at the foot of the Andes mountain range. The Mapocho river cuts through the middle of the city, and in the capital itself you will find several “hills” (which for many may themselves be considered mountains), that offer incredible panoramic views of the city. Despite having a land mass larger than the state of Texas, more than half of the Chilean population lives in Santiago, which can generate a lot of traffic and congestion difficulties. And like Chile, Santiago is full of contrasts, where history and modernity share the same space. Walking through the city you will find a famous church built in 1586. As you leave this church you can take the most modern subway in South America. In the same area are some of the oldest buildings still standing in the city, the presidential “Moneda” akin to the American “White House”, as well as the banking and finance sector. Santiago is a vast city full of different architectural styles. Some of these impressive buildings were designed by famous architects, such as the Italian Gioacchino Toesca, who was in charge of the construction of the Governmental Palace (“La Moneda”). The central train station, known as “Estación Central”, was indeed designed by Gustave Eiffel in 1897 and the French architect Francisco Brunet de Baines along with engineer Augusto Charme and Charles Garnier (who was behind projects such as the Paris Opera and

the Montecarlo Casino) built the Municipal Theatre of Santiago.

Upon walking through the old neighborhoods of the city, one will encounter long streets lined with colonial houses that have survived time and many earthquakes. Living in such a seismic country teaches you from an early age to learn how to react calmly even when confronted with tragedy. From very early on, children partake in earthquake drills called "Operation Daisy," which we enjoyed because it allowed an unexpected break during classes. But more than that, it taught us important lessons for those growing up in Chile, like how to evacuate a building during an earthquake, despite the fact that when there was an actual earthquake, most simply tried to escape by any possible means! Nonetheless, I should admit that normally people were calm and very few died as a result.

On the other hand, it has been funny to see the evolution of my city over time. For example, the public transit system from the 80s was very peculiar. Buses called "las micros" were available to pick you up on any corner, regardless of whether or not there was a legitimate "bus stop" and they let you off where ever it was that you needed to go, be it the end of the block, right smack in the middle, or even at your front door! This has all changed since the new system was implemented, where buses now are only allowed to stop at designated places, which, unfortunately for many Santiago residents, are inconvenient.



Huaso Chileno, Fiestas patrias



Moais in Easter Island

On a happier note, the month of September is when the whole country stops to celebrate Independence Day (which normally lasts for a few days!). This September 18th, Chile celebrates 214 years of independence. During this holiday, one can observe exactly what "being Chilean" means. You will find many "fondas," large family BBQs where much wine is drunk, along with the traditional "Chicha," a special beverage that originates from the 7th region of Chile and made of fermented apples. During "fiestas patrias," as they are called, children will often fly kites in the spring breeze, a more typical South American pastime.

As September passes by, the following holiday eagerly awaits, the 12th of October, where we celebrate the discovery of America and the arrival of Christopher Columbus to this part of the world. Chileans, like many people around the world, especially enjoy the Christmas season as well as New Year. However, what is special about these holidays in Chile is that they mark the beginning of summer! Christmas in Chile is typically celebrated by having dinner on the night of the 24th waiting until midnight for the arrival of Santa Claus...and not to forget to open gifts! Children will usually stay up quite late enjoying and playing with their new toys. Inflatable pools begin to fill backyards and patios, children chase each other around with water guns, new bikes and dolls can be seen everywhere. Similarly, the New Year is celebrated with a

feast the night of December 31st, followed by fireworks at the stroke of midnight. The various municipalities will each have their own celebration in the local plaza or park. Celebrations always involve being outside, and enjoying the warm summer air. In the nearby historically protected city Valparaiso, the most beautiful firework can be seen. That night, the beautiful bay that encompasses the city shines with light.

Now I would like to share with you some interesting facts about my beautiful country. Did you know that in the south of Chile there is a significant German and Austro-Hungarian population? Indeed, more than 30,000 immigrants made that region home, inhabiting cities such as Valdivia, Osorno, and Llanquihue during the 19th century. In fact, one of the most important beer breweries in Chile is in Valdivia: the "Kunstmann Brewery." Interestingly, Germany and Chile have many things in common, one of them being that they are the two countries with the highest consumption of bread! In Chile, the Atacama Desert is home to the some of oldest mummies ever discovered, some as



Margarita at Santa Lucia hill, Santiago, 1982

old as 7,000 years. Chile had the first democratically elected socialist president and also the strongest earthquake ever registered in history, which reached a magnitude of 9.5 and took place in Valdivia in 1960. Puerto Williams is the most austral city in the world, with 1,600 inhabitants. Unfortunately, Chile is also one of the countries with the highest level of socioeconomic inequality where the richest can achieve up to 27 times more than the poorest. Nonetheless, Chile is the second most pacific country in Latin America. In terms of education, in Chile you will find the highest ranked university in South America, The Pontifical Catholic University of Chile. However, the cost of higher education is more expensive in Chile than in any other Latin American country and it is the only country in Latin America where there are no free universities.

12,126 km separate Chile and Switzerland and these countries probably do not have very much in common. One is a developing nation; the other is the country with the second highest level of income per capita in the world. Chile exports avocados and copper while Switzerland produces clocks and knives. However, we share the fact that a large mountain range crosses both our countries; the Alps and the Andes. Furthermore, if you go to the south of Chile and walk around places like Pucón and Villarica, you may forget that you are not in Switzerland, but indeed in Chile!

We may come from two different worlds, but at the end of the day I believe that all people are simply looking for happiness, serenity and peace. For those of us who live far from our country of origin, this feeling of happiness is never complete. We miss the unique smells, the flavors, the noises, or the simple act of waking up seeing the imposing and majestic Andes. However, if you close your eyes, you are able to remember and feel these sensations... so, have no problem moving forward in life as long as you do not forget where you came from.

Margarita Dinamarca Ceballos

«Abseits ist, wenn der Schiedsrichter pfeift»

Ein Rückblick auf die Fussball-WM aus weiblicher Sicht

Die meisten Männer sind von Haus aus fussballbegeistert. Bei uns Frauen beschränkt sich die Begeisterung oft auf Grossereignisse und häufig geht diese Begeisterung dann auch ins Ästhetische über. Der weibliche holländische Fan lackiert die Fingernägel in den Landesfarben und auch der Bildschirmhintergrund bleibt von knalligem Orange nicht verschont, worauf hin die deutsche Frau nicht nachstehen kann und ihren Hintergrund mit dem deutschen Trikot schmückt. Allerdings schauen wir nicht Fussball, weil uns die Frisur von Mats Hummels gefällt oder weil Cristiano Ronaldos Körper so schön anzuschauen ist. Auch wir verstehen, was Fussball ist, können uns über die Strategie «unserer» Mannschaft aufregen und mögen es nicht, wenn «Mann» immer noch glaubt, dass wir die Abseitsregel nicht verstehen. Man kann es natürlich halten wie Franz Beckenbauer: «Abseits ist, wenn der Schiedsrichter pfeift». Oder aber für alle, die es immer noch nicht verstanden haben:

Du befindest Dich in einem Schuhladen an der Kasse. Vor Dir steht nur noch eine einzige Dame. Da entdeckst Du auf dem Regal hinter der Kassiererin ein Paar Schuhe, das Du unbedingt haben musst! Plötzlich bemerkst Du, wie die Dame vor Dir mit



demselben Paar liebäugelt! Per Blickkontakt signalisiert sie der Kassiererin, dass das Paar nicht in Deine Hände gelangen soll. Ihr beide habt jedoch nicht genügend Geld dabei. Die Verkäuferin schaut Euch geduldig zu. Schliesslich erkennt Deine Freundin Deine missliche Lage und reagiert, wie es eine solidarisch-loyale Freundin tut. Sie will Dir ihren Geldbeutel geben, damit Du die Konkurrenz vor Dir umrunden und die Schuhe kaufen kannst. Sie wird Dir das Geld über die Dame hinweg nach vorne zuwerfen, und während es sich in der Luft befindet, umrundest Du den Gegner, fängst das Geld und kaufst die Schuhe – so wie ein Fussballspieler den Ball ins





Tor donnert. Aber! So lange Deine Freundin den Akt des Zuwerfens nicht abgeschlossen hat, d.h. das Geld sich noch in ihrer Hand und nicht in der Luft befindet, darfst Du Dich beim Überholen zwar auf gleicher Höhe, jedoch nicht schon vor der anderen Kundin befinden ... andernfalls bist Du im Abseits! (siehe auch blog-8.de)

Die 20. Fussball-WM ist Geschichte. Neben all der Freude, die in Brasilien über die Vergabe der WM herrschte, darf man sicher nicht die Proteste rund um

die WM vergessen. Trotzdem war es ein gelungenes Fussballfest, dass direkt mit einer Überraschung begann: Der amtierende Weltmeister Spanien flog bereits in der Gruppenphase aus dem Turnier. Aber auch das frühe Aus der Engländer und der Italiener war so nicht erwartet. Es gab spannende Spiele, traurige Spieler und viele Tränen, schöne Tore, tolle Paraden und jede Menge weiterer grossartiger Momente. Das erste Tor der WM war gleich ein Eigentor. Es gab Schiedsrichterschele, Beissattacken, Kung-Fu-Einlagen und Kopfnüsse, aber auch schöne Bilder mit tröstenden Gegnern, tanzenden Fans und Anerkennung für überragende Leistungen. Der Stern von James Rodriguez ging auf – er schoss die meisten Tore bei dieser WM, und der deutsche Torhüter mauserte sich zum waschechten Libero, während ein anderer Torhüter zum Elfmeterschiessen eingewechselt wurde und Hollands Weiterkommen sicherte. Brasilien kassierte die höchste Klatsche seiner WM-Geschichte und Miro Klose wurde alleiniger WM-Torschützenkönig. Wir gewöhnten uns in den vier Wochen an das Freistosspray und auch die Torlinientechnik kam zum Einsatz. Zum ersten Mal gewann eine europäische Mannschaft den Weltmeistertitel in Südamerika und es war ein bisschen so wie Gary Lineker es einmal so schön formuliert hat: «Fussball ist ein Spiel, bei dem 22 Spieler hinter einem Ball herjagen und am Ende gewinnt immer Deutschland».

Martina Konantz

Dear all,

Next year the DBM (formerly DKBW) will be celebrating its 15th birthday. In honor of the jubilee there will be two events:

1. A **Scientific Symposium** held at DBM Hebelstrasse, followed by a celebration for collaborators and invited guests on **Friday August 21, 2015**.
2. An **Open-house** event at **DBM Mattenstrasse and DBM Hebelstrasse** for the public and families on **Saturday August, 29, 2015**.

Please save both dates in your agenda.

Alsace Wines, on the road again

“A small glass of Alsatian wine is like a light dress, a spring flower, the ray of sunshine that brightens life” (Christian Dior)



Vineyard in the “Pays de Colmar”

No idea how best to start autumn? Then come and discover my region by traveling the Alsace Wine Route by car, by bike or even on foot. Launched in 1953 as a popular automobile rally, it is one of the oldest wine routes in France. It crosses the region from North to South, from the North door of Marlenheim to the South door of Thann. A dozen cross-community routes allow one to journey through the wine region on foot or by bicycle and around fifty marked wine paths lead you to the discovery of prestigious vineyards.

At the foothills of the Vosges, this 170km long historical track passes the Alsatian vineyards passing through a succession of beautiful villages, each looking like picture-postcard images. Most of those typical villages share several characteristics. They are often fortified villages with remaining ram-

parts, towers, old churches or even castles straight out of the Middle Ages. Their little cobbled streets are flanked by traditional colourful half-timbering houses still prettified by geraniums hanging on the balconies or blossoming at the windows. And, of course, their main cultural and economic activities concern grapes and wine.

Just want to have a glimpse? Then, not far from Basel (around 40 minutes by car), in the “Pays de Colmar” area, Kaysersberg, Eguisheim (elected favourite village by the French population in 2013), Ribeauvillé or Riquewihr are among the most typical Alsace villages nestling in the middle of vineyard hills. If you are travelling with children, and like Alsatian symbols, you may favour Eguisheim and its stork run. If you are married and work in a lab, you may well enjoy visiting Riquewihr and



A typical narrow street in Eguisheim

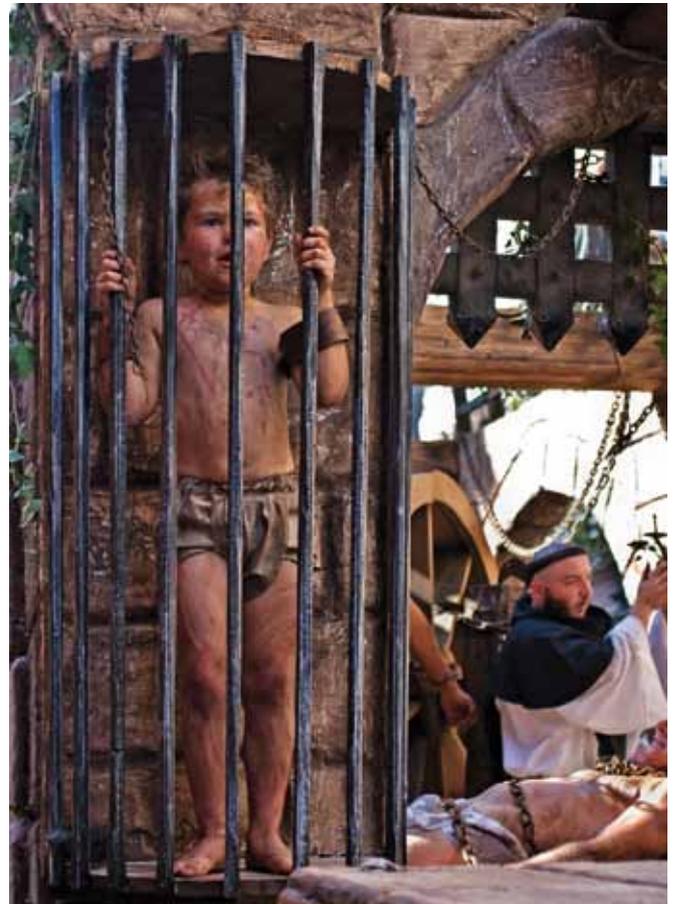
with its “Thieves Tower” which was used both as a prison and a place to practice torture.

But wherever you go you should meet the winegrowers, visit their cellars, awake your visual, olfactory and gustative senses and discover the geometry of the wine. In other words, try a horizontal or vertical tasting. I cannot advise you one or the other, both are really very appreciable, but I highly recommend the wiser way to really fully enjoy it: spend the night on site! During a horizontal tasting, you will admire, breathe, drink and compare different wines of the same designation and same year of production like a one-year overview and a define terroir. The vertical one is more like time travel, a tasting of the same wine from different vintage years. Like experiencing watching pictures of Clint Eastwood from “A Fistful Of Dollars” up to now, you will appreciate the flavours of the wine, its aging potential, its evolution.

If you want to know and understand everything about the technical aspects of winegrowing or learn about the former methods used to fight against cryptogamic diseases like phylloxera, then go to Kientzheim (don't mix up with Kintzheim

situated in Bas-Rhin). Located 1km far from Kayserberg, at the foot of the Furstentum vineyard, it harbours the Museum *Vignoble et Vins d'Alsace*. It exhibits different tools used for harvesting the grapes, working in the vineyards and in the cellar: wine presses, barrels, vats, wine jars, taps, wine pumps, bottling and corking devices. This museum is located in the Castle of Lazarus of Schwendi that belongs now to the “Con-

frérie Saint-Etienne”, one of the oldest brotherhoods in France who preciously keep 60 000 bottles of all



Pfifferdaj in Ribeaupville

the different Alsatian grape varieties from 1947 to date! They are keepers of the tradition and they promote Alsace Wines in France and abroad. They regularly organize meetings, offer a program of events throughout the year and award a quality label for wines (the "Sigille").

That place is highly symbolic for Alsatian wine makers (or lovers) as a previous owner, the Baron Lazare of Schwendi, introduced the wine-making knowledge to the Alsace around 1565. As he served the Austrian house during its conflict against the Turks, he overcame the fortress of Tokaj in Hungary and grasped 4000 wine barrels as well as Tokay plants to be planted in Kientzheim, dreaming of producing Hungarian Tokay, a much-appreciated fortified wine produced from the grape variety Furmint. Despite the fact that the Hungarian Tokay grape variety did not provide the expected results



Wine cellar in Eguisheim

and was substituted during the XVIIIth century by the Pinot Gris from Burgundy, the wine referred to as Grauer Tokayer before 1970. It was then successively named Tokay Gris, then Tokay d'Alsace, followed by Tokay Pinot Gris and definitively (?) renamed "Pinot Gris" d'Alsace in 2007. Ending, at last, a long lasting juridical conflict between Hungary and Alsace. Well, whatever the name, the taste remains!



Picture 5 Wine tasting room

Nowadays, going to meet Alsatian wine is to discover its variety: from *rosé* or red wine, Pinot Noir, to white wines like Sylvaner or Pinot Blanc, blended wines like Edelzwicker or sparkling wine Crémant. But the real sun's rays that brighten up the life of the Alsatians are mostly Riesling, Muscat (dry wines), Pinot Gris and Gewurztraminer (highly fruity



Pfifferdaj in Ribeauvillé

wines). They are still more appreciated as a “*Vendange Tardive* or *Grains Nobles*”. “*Vendange Tardive*” designs wines produced from grapes collected by hand several weeks after the official begin of the harvest. The grapes start to become overripe. It requires specific conditions, warm daytime and humid chilled night-time, to allow the dehydration of the grapes and the development of the Noble Rot, *Botrytis Cinerea*. As a consequence, the sugars are much more concentrated and the flavours more intense. “*Grains Nobles*” is an even sweeter wine obtained from harvested grapes affected by Noble Rot and selected by successive sorting.

The Alsace Wine Route is also a popular gathering place. Each year starting in September, many different celebrations highlight the Alsatian wines. Folklore entertainment, processions and wine-tastings take place all day, or night, long in a lively and friendly atmosphere! One of the most colourful takes place in Ribeauvillé. For over five hun-

dred years, the famous *Pfifferdaj*, the fiddlers’ festival, celebrates wine and the links between the Lords Ribeaupierre of Ribeauvillé and the minstrels they used to protect. There are lots of activities: medieval market and festival dances, lantern procession and music concerts. You could join the hundreds of participants dressed in medieval costumes, troubadours and jugglers, knights and fire-throwers. And once the cortege comes to the end, you may slake your thirst at the fountain of the city hall square, where the wine flows like water at the end of the day and accentuate the festal atmosphere! Indeed this elixir is driving you “tonic and merry”!

Voilà, I hope I make you want to stimulate all your senses. Attend the Wine festivals in September-October, stroll in the vineyard paths, visit the cellars, enjoy the wines, and discover the lovely Bacchus temples, the winstubs, where you are going to enjoy the Alsatian specialities.

Bonne découverte et régalez-vous!

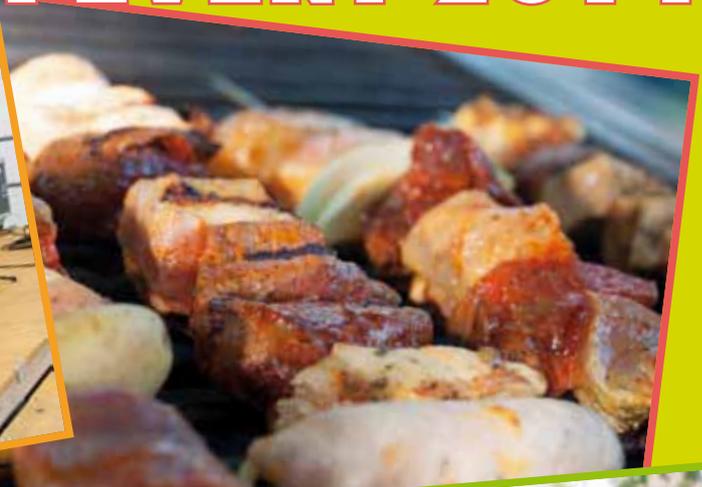
Text: Anne-Catherine Feutz

Photos: Gilbert Urier



Pfifferdaj in Ribeauvillé

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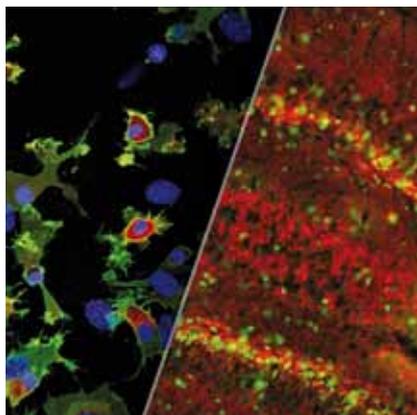




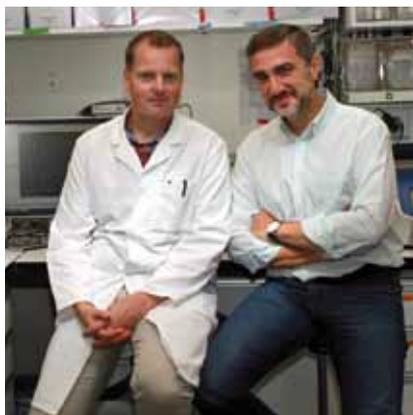
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VORSCHAU PREVIEW

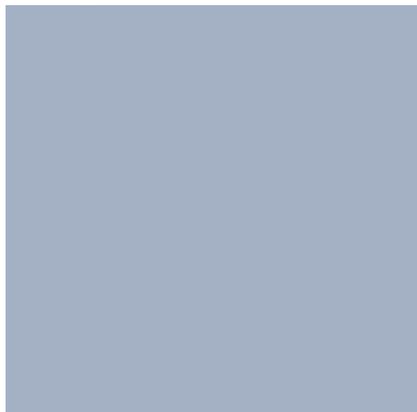
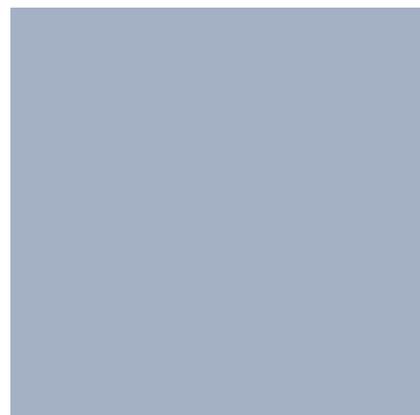
In der nächsten Ausgabe ...



... geben uns Raphael Guzman und sein Team einen Einblick in das Forschungsgebiet Brain Ischemia and Regeneration



... stellen uns Philippe Demougin und Andreas Papassotiropoulos die Life Science Training Facility (LSTF) vor



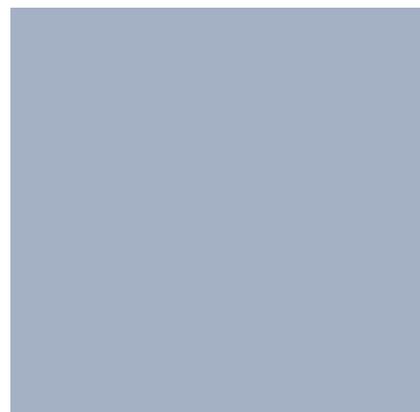
... erleben wir Handfestes auf dem Eis mit Pascal Rem



... feiern wir mit Paula Cullen Irische Weihnachten



... lassen wir uns entführen in die geheimnisvollste Zeit des Jahres



EINE HERBSTNACHT HAT SIEBEN SONNEN.
(AUS ESTLAND)

