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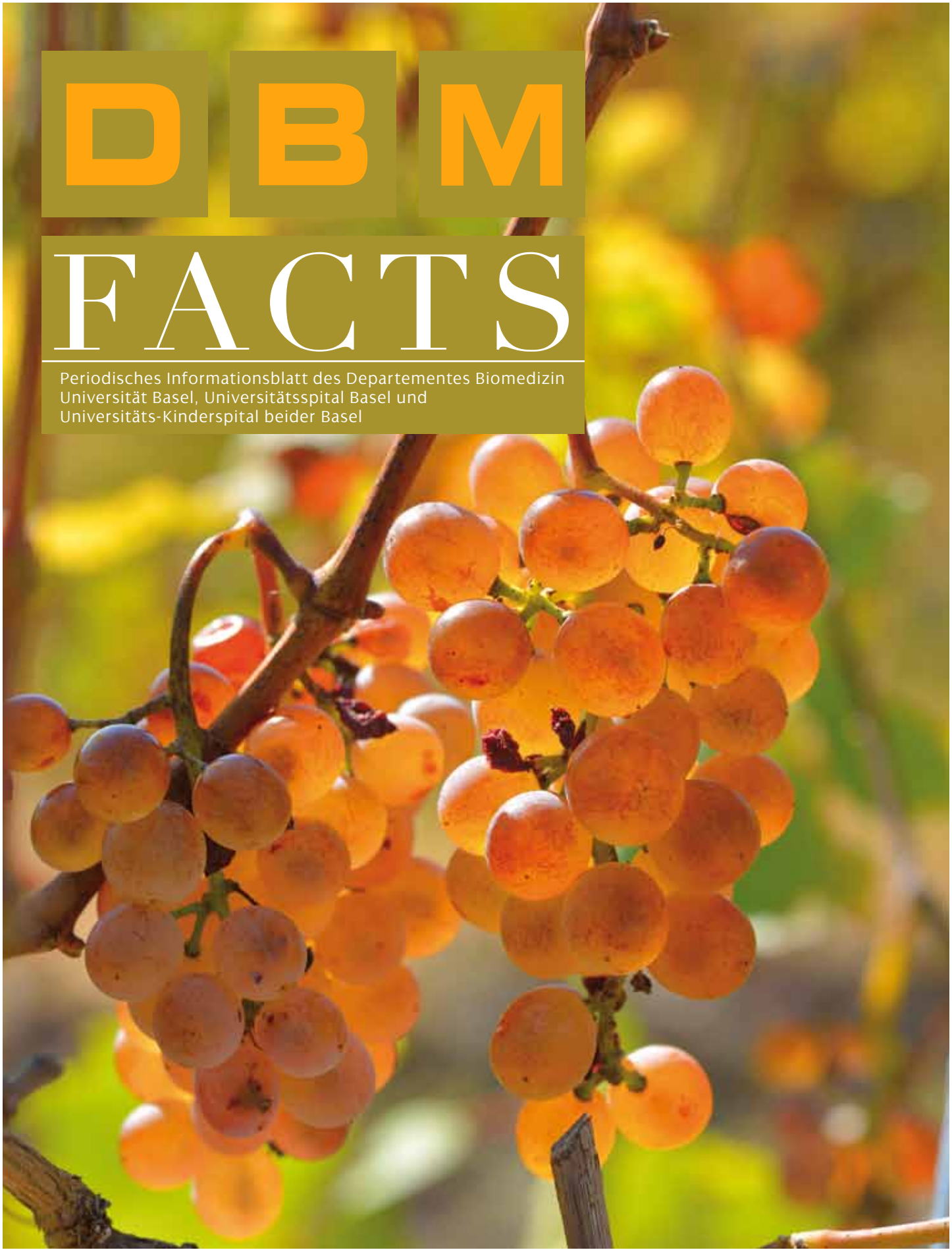

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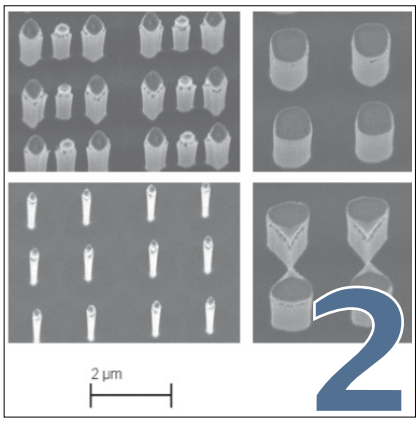

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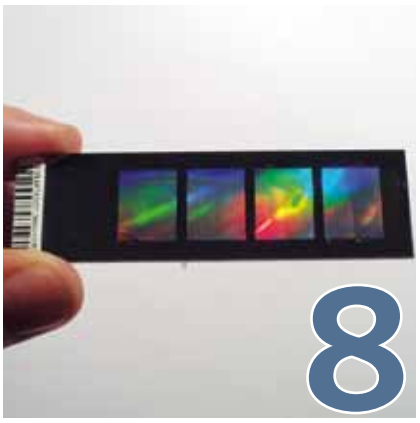

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Ein erfolgreicher Sommer liegt hinter uns. Das 15jährige Jubiläum des DBM wird uns mit seinem international und interdisziplinär hervorragend besetztem Symposium in Erinnerung bleiben, ebenso wie die anschliessende stimmungsvolle Feier am wunderschönen Sommerabend des 21. August 2015 am Rheinufer (siehe Seite 28).
Jan Niess hat seine Tätigkeit als neuer Professor für Gastroenterologie am USB am 1. Oktober 2015 aufgenommen und wird jetzt seine Forschungsgruppe am DBM aufbauen. Wir wünschen ihm und seiner Gruppe einen guten Start und viel Erfolg! Wir verabschieden Christoph Beglinger, der als Forschungsgruppenleiter am DBM und zuletzt als Dekan der Medizinischen Fakultät das Geschick des DBM entscheidend mitbestimmt hat. Wir danken Christoph Beglinger herzlich für sein grosses Engagement für die Forschung und wünschen ihm für die Zukunft alles Gute!
In dieser Ausgabe nehmen uns Lukas Jeker und sein Team mit in die Welt der "Molecular Immune Regulation" (Seite 2) und Stefan Herms stellt uns die Herausforderungen in der Analyse des Humangenoms vor (Seite 8). Ab Seite 14 folgen die neuesten Publikationen aus dem DBM. Maki Nakamura zeigt uns ihre Heimat Japan (Seite 30) und Friederike Schulze lädt uns in ihren Buchclub ein (Seite 32). Richtig zur Sache geht es beim Fisherman's Friend Strongman Run (Seite 34). Ihr besonderes Augenmerk sollten Sie dieses Mal auch auf die Seite der DBM IT richten (Seite 38), da ein reibungsloser IT Support nur mit Ihrer Mithilfe gewährleistet werden kann.

Viel Freude bei der Lektüre!

Dear Readers

A successful summer is behind us. The well attended international and interdisciplinary symposium that was held as part of the celebrations for the 15 year anniversary of the DBM will remain in our memories, as will the atmospheric closing celebrations held on the banks of the Rhine on the beautiful summer evening of August 21st 2015 (see page 28).
On October 1st 2015 Jan Niess took up his position as the new Professor for Gastroenterology at the USB and will now build up his research group at the DBM. We wish him and his group a very good start and every success! We say good-bye to Christoph Beglinger who, as a research group leader here at the DBM and more recently as the dean of the Medical Faculty, was crucial in contributing to the fate of the DBM. We sincerely thank Christoph Beglinger for his considerable contributions and his research and we wish him all the very best for the future!
In this edition Lukas Jeker and his team bring us on a journey into the world of Molecular Immune Regulation (page 2) and Stefan Herms shares the challenges involved in analyzing the human genome (page 8). The latest publications from the DBM follow on page 14. Maki Nakamura introduces us to her homeland, Japan, on page 30 and Friederike Schulze invites us into her book club on page 32. We get down to business with the Fisherman's Friend Strongman Run on page 34. We would ask you to be especially attentive to the pages of DBM IT (page 38) who ask for your help in maintaining a smooth running IT support service.

Happy reading!

RNA-mediated Immune regulation

The mammalian immune system is a complex and very powerful system composed of many diverse cell types and molecules which collectively continuously monitor the host body for abnormalities. When an infection is detected the immune system mounts a vigorous response to eliminate the intruding microorganism. An overshooting response is undesirable however, since it can lead to collateral damage through destruction of the host's own tissues. In contrast, immune defects lead to increased risks of infection and prove the importance of this defense system. Hence, in order to control and combat the potential threat by the myriads of microorganisms that surround us on a daily basis we need a strong immune system. However, because of the power of this system we need effective regulation. Multiple layers of regulatory checkpoints ensure that immune responses are only mounted when needed and don't overshoot. An unrestrained or misdirected immune system is just as dangerous as a weakness, i.e. immunodeficiencies. When an immune response gets mounted against an antigen of the host body, rather than a foreign pathogen, things can get out of control. These types of immune diseases are called autoimmune diseases. Much like immune defects which cover the whole spectrum from very mild defects to a risk for lethal infections, autoimmune reactions can be anything from

From left to right: Marianne Dölz; Lukas Jeker; Mara Kornete; Oliver Gorka; Romina Matter Marone; Madeleine Vollmer (PhD advisor: Werner Krenger). Picture by Frank Neumann.

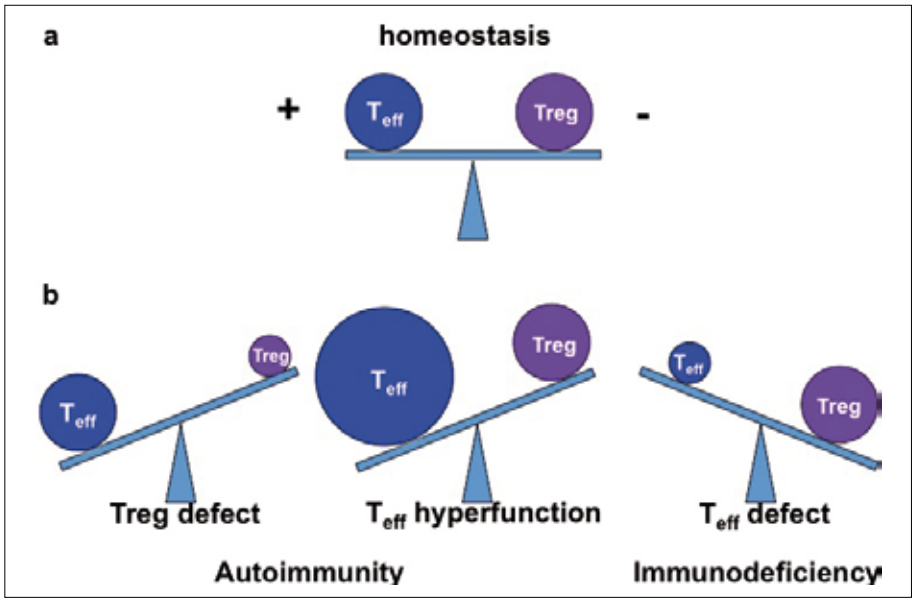

Figure 1
Balance is critical to maintain immune homeostasis
Schematic representation of proinflammatory (Teff) and anti-inflammatory (Treg) T cells. a) Homeostasis requires a balance between Teff and Treg. b) A dysbalance between effector and regulatory T cells leads to different diseases. A numeric or functional Treg defect leads to autoimmunity (left panel). Similarly, a numeric or functional excess of effector T cells can promote autoimmunity (middle panel). In contrast, a defect in Teff leads to immunodeficiency (right panel).

harmless (e.g. Vitiligo) to lethal (e.g. type 1 diabetes). Thus, immune regulation is critical to balance effective host defense and controlling the unwanted side effects (Figure 1).

Moreover, immune regulation is not only key during infections and to prevent autoimmune disease but also highly relevant for oncology. Tumors are exploiting many of the mechanisms that are in place to control the immune system. The recent clinical success of cancer immunotherapies, which aim to boost anti-tumor immune responses, underscores what has been described in model organisms for many years: The immune system plays a critical role in recognizing and combating tumors. The tumors themselves, however, learn to dampen immune responses in order to prevent their own removal.

Thus, a thorough understanding of immune regulation underlies the rational design of immunotherapies that aim to boost or dampen the immune system according to the needs of each disease. Our lab is interested in how lymphocytes are controlled on a molecular level. Among the many mechanisms that control immune cells we are particularly interested in RNA-mediated gene regulation. Specifically, as a postdoc in Jeff Bluestone's lab in San Francisco I started to investigate the role of microRNAs (miRNAs) in T cells. Since the early "gold rush" on miRNA research we have learned a great deal about these fascinating molecules. miRNAs are endogenous genes that are transcribed as long precursor RNA molecules much like protein-coding genes. The primary transcripts then get cut into small pieces in a series of enzymatic reactions. In the cytoplasm the mature miRNA binds to target RNAs with the help of a multi-protein complex called RNA-induced silencing complex (RISC). (Figure 2). As this name suggests miRNAs are gene repressors. The human genome encodes a few hundred miRNAs and about half of all protein-coding genes are directly regulated by miRNAs. From their discovery in 1993 in the worm *c. elegans*[1] it took 10 years to realize that small non-protein-coding RNAs with regulatory activity were not an oddity of *c.elegans* but that miRNAs are abundant in most species. On the contrary, in mammals it is now clear that only very few cells do not depend on miRNAs for their proper function. Thus, miRNAs have been recognized as important regulators of many biologic processes. However, in recent years other exciting developments in biology have been drawing attention and it was realized that miRNAs are mostly regulating their target genes mildly, at best. In fact, miRNAs are often highly redundant and classic genetic approaches such as deleting a miRNA to study its function often does not result in an observable phenotype. Furthermore, many miRNA target genes are controlled by more than one miRNA and vice versa, an individual miRNA can bind and regulate dozens of target genes. These combined properties (multiplex mild and context-dependent gene regulation) have slowed down miRNA research and created a sense of frustration among many investigators studying miRNAs.

So why are we still interested in miRNA research?

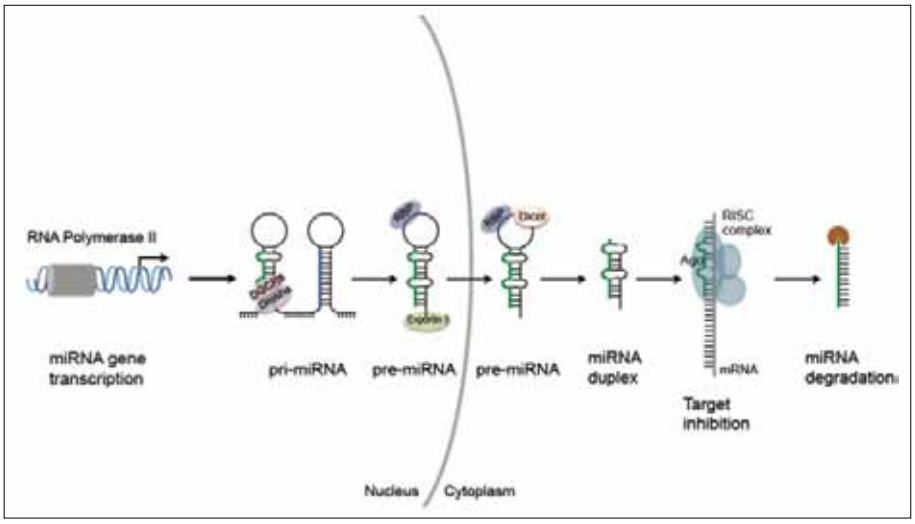

Figure 2
microRNA biogenesis
After transcription by polymerase II a series of enzymatic cropping steps lead to the generation of mature single stranded miRNAs. These interact with their target mRNAs in a multiprotein complex called RNA-induced silencing complex (RISC) which leads to repression of the targeted gene. Figure adapted from Ref [6].

First, their strong evolutionary conservation suggests important functions. Second, we and others have found one particular miRNA cluster called miR-17-92 to be very important for T cell function and immune regulation[2]. And third (to just name a few reasons) there is still so much to be uncovered and learned that we are ready to face the challenges.

Current projects aim at elucidating in much greater detail than we have previously done what genetic networks are regulated by the miR-17-92 cluster in two types of T cells called regulatory T cells (Treg) and T follicular helper cells (T_{FH}). These two T cell subsets are functionally antagonistic. Regulatory T cells are critical to dampen the immune system while TFH cells are the prototypic "helper" T cells that "help" B cells generate better antibodies. Too many T_{FH} or unrestrained T_{FH} cells cause autoimmunity (Figure 1).

One model to study miRNA function in T_{FH} cells is a cellular adoptive transfer system in mice. First we use donor mice to isolate naïve T cells that have not encountered antigen before. We do so from mice that harbor T cells which lack or overexpress specific miRNAs. We then transfer those cells into host mice which we either immunize with protein (vaccination) or infect with Lymphocytic choriomeningitis virus (LCMV). This work is being done in collaboration with Prof. Daniel Pinschewer who recently described his research group in DBM Facts. The immunization or infection causes an activation of the transferred T cells and instructs them to differentiate among others into T_{FH} cells. Using this system we have previously demonstrated that miR-17-92 is cell intrinsically important for T_{FH} generation (Figure 3). Interestingly, and somewhat unexpectedly, we found that the miR-17-92 cluster was important for T_{FH} differentiation, not only proliferation and/or survival which was expected but turned out not to be the main function of miR-17-92 in T_{FH} cells. In an attempt to understand which genes are regulated by miR-17-92 we generated a genome-wide transcriptome analysis using Affymetrix arrays. This analysis revealed a hybrid signature of two $CD4^+$ T cell subsets: T_{FH} and Th17/22-like cells. Based on a literature search we hypothesized that *rora* could be a novel direct target of the miR-17-92 cluster which needs to be repressed to allow efficient TFH differentiation. By limiting *rora* expression to one allele we were indeed able to functionally validate our hypothesis in vivo since correcting the *rora* level back to lower levels "rescued" some of the anomalies observed in the absence of miR-17-92 [REF3]. The molecular analysis of the genetic network regulated in T_{FH} cells has only started however. We have a list of dozens of dysregulated genes but it is unclear which ones are directly targeted by miR-17-92 and, more importantly, which ones are functionally relevant to cause the T_{FH} differentiation defect. Unfortunately, the chosen approach is powerful but very slow and labour intense. We needed quadruple transgenic mice to test our hypothesis which can take one year of breeding many mice to address one single question. Conceivably, this approach is not applicable to analyze dozens of miR-17-92 target genes and even less so to analyze cooperative regulation of multiple target genes. Therefore, we have started to develop new customized genetic tools that will allow the genetic resolution we are looking for.

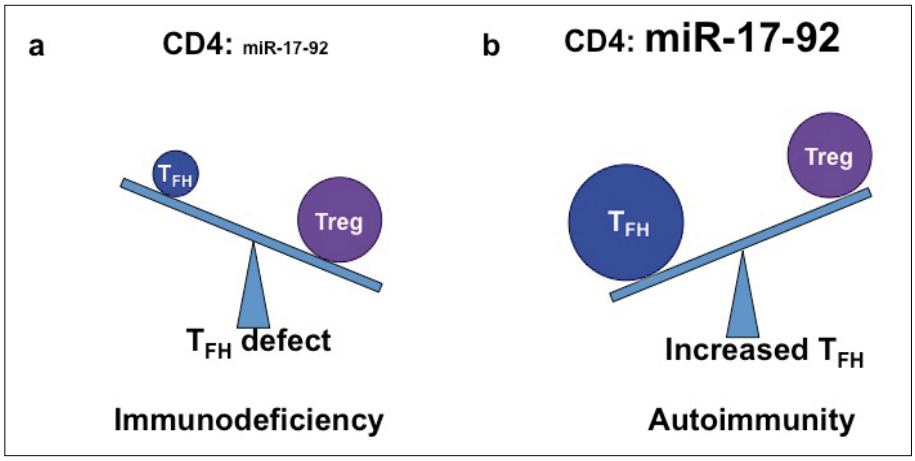

Figure 3
microRNA-17-92 dose in T cell subsets is important for immune regulation
a) T_{FH} differentiation is impaired when the differentiating T cells have reduced miR-17-92 expression or lack miR-17-92 expression entirely. This leads to defective B cell help and a reduced antibody response[3]. b) Over-expressing miR-17-92 in lymphocytes leads to a lupus-like syndrome with lymphoproliferation, multiorgan tissue infiltration and autoantibody formation7. In part, this is due to increased differentiation of T_{FH} cells[3].

Analysis of the genetic network regulated by miR-17-92 in T_{FH} cells using the CRISPR/Cas9 genome engineering system

The recent development of novel genome editing tools involving the RNA guided endonuclease Cas9 from the microbial type II CRISPR (clustered regularly interspaced short palindromic repeat) system allows relatively straightforward gene manipulations[4]. Thus, we hypothesized that use of the CRISPR/Cas9 technology will provide us with a quick and efficient way to functionally validate several important candidate miRNA target genes in mouse T_{FH} cells. The system utilizes a short single guide RNA (sgRNA) to direct the endonuclease Cas9 to virtually anywhere in the genome. Upon targeting, Cas9 generates DNA double strand breaks which can be exploited to delete genes. In addition, if a DNA template is provided the approach allows insertion of precise mutations. Importantly, multiple sgRNAs can be combined to allow multiplexed genome editing. As such, much more complex analyses, including the analysis of many more genes in a shorter time frame and multiplexed analysis of genetic networks, could be achieved. At least this is the theory.

Mara's project is to establish the CRISPR/Cas9 system in primary T cells as a novel tool to analyze miRNA function with a particular focus on T_{FH} cells. We have successfully used the CRISPR system in the human Jurkat cell line and in primary T cells to delete CD4 and other genes (Figure 4). Building on these results current efforts intend to establish a protocol to be able to introduce precise mutations in primary T cells with a high efficiency. We will then use this new approach to functionally test the candidate genes obtained in the transcriptional profiling. Our results suggest that this new technology is indeed a true disruptive game changer. We are therefore working on improving and adapting this platform to our purposes.

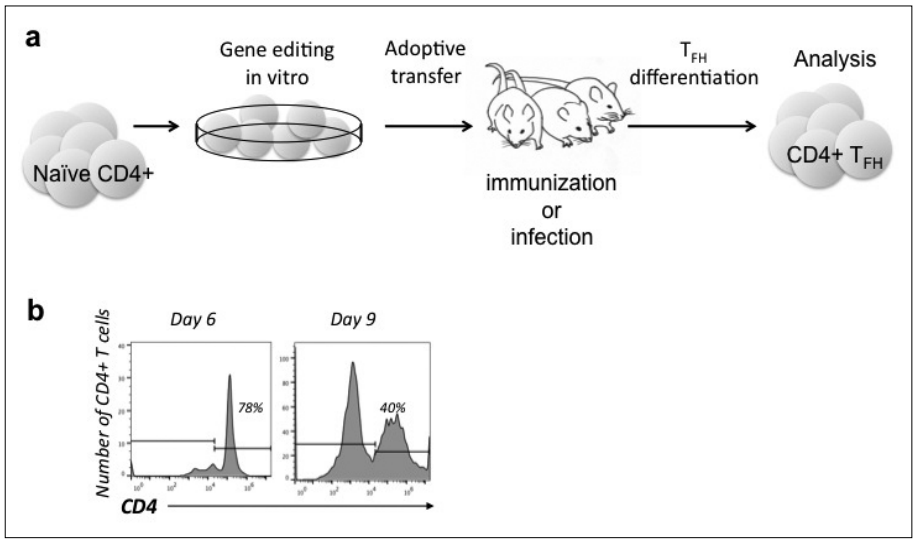

Figure 4
Molecular T cell analysis using genome engineering
a) We isolate naïve $CD4^+$ T cells, perform genome editing in vitro and then transfer the edited cells into host mice. These mice are then immunized to induce T_{FH} differentiation. b) An example where we used an sgRNA designed to disrupt CD4. After 6 days in culture we see some cells which are losing CD4 expression and by day 9 60% of cells have lost CD4 expression.

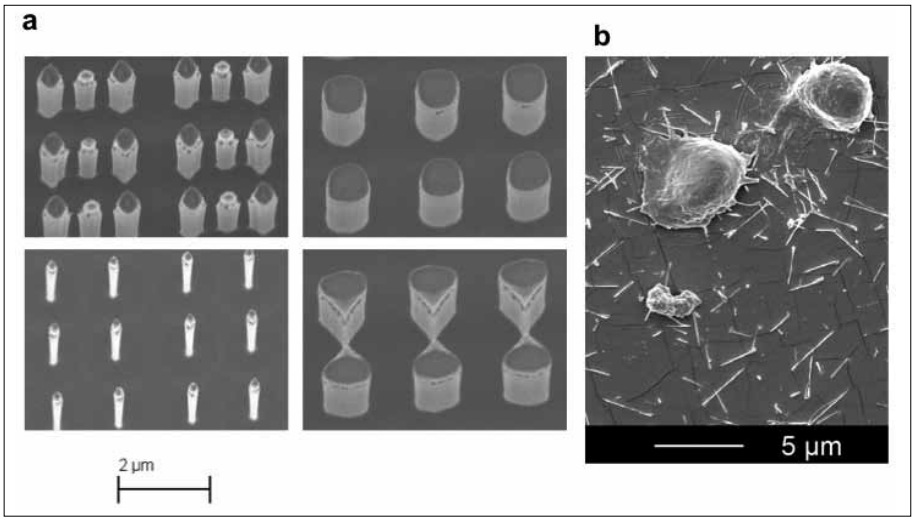

Figure 5
Nanowires to transfect T cells
a) Four different examples of nanowires with varying diameter and shape.
b) An electronmicroscopy image of Jurkat cells incubated on nanowires.

Molecular analysis of microRNA function in regulatory T cells

As mentioned above, Treg represent a powerful suppressive and regulatory subset of CD4 T cells. Treg are critical to maintain peripheral tolerance and suppression of autoimmune disease. We have previously reported the importance of miR-17-92 for T_{reg} function in experimental autoimmune encephalomyelitis (EAE) in mice but the target genes have not been analyzed yet. Marianne's project is to analyze these target genes and to compare if miR-17-92 regulates an overlapping or a distinct set of genes in T_{FH} and Treg isolated from different inflammatory sites.

Furthermore, since Treg are rare, a very efficient method is required to transfect these cells with specific molecules (e.g siRNA, CRISPR/Cas9 components) to interfere with their genetic network. However, primary $CD4^+$ T cells are difficult to transfect and established methods require an activation step which precludes the analysis of the very early steps of T cell activation. Marianne is therefore testing a new methodology based on nanowires (NW) (Figure 5). The idea is basically to impale the cells on needles with a diameter of only a few nanometers. The NW are coated with the transfection material which will be released once inside the cell.

Finally, for the activation of a T cell, costimulatory signals are essential. We have previously shown that the costimulatory molecule CD28 is important for the upregulation of miR-17-92 [REF5]. Since CD28 costimulation is also an important regulator of T cell metabolism we have started a collaboration with Prof. Christoph Hess who is a local expert on immune metabolism. Indeed preliminary results suggest that miR-17-92 might regulate T cell metabolism.

Studying the role of the 3'untranslated region in gene regulation in T cells

As outlined above, proper control of T cell differentiation is of foremost importance for the prevention of autoimmunity. Most miRNAs interact with their target genes in the 3' untranslated region (3'UTR). Of note, proliferating lymphocytes exhibit a phenomenon of global shortening of mRNA transcript 3'UTRs by alternative polyadenylation (APA). This process results in shorter mRNA species that potentially lack complementary miRNA binding sites and thus escape regulation through specific miRNAs (Figure 6). However, if, to what degree and how exactly 3'UTR shortening contributes to an evasion from miRNA-control during T cell differentiation is unknown. A central hypothesis of Oliver's project is that fine-tuning of T cell differentiation happens through mutual microRNA-3'UTR interaction networks. miRNA binding and 3'UTR shortening might have coevolved to generate an intricate balance of regulation versus counter regulation during cell fate decisions. To study these effects, we will investigate 3'UTR shortening in different T cell subsets by an RNA-sequencing approach to identify potential T cell subset-specific APA events. In the long run, we will also generate a mouse model of forced 3'UTR shortening which will contribute to a deeper understanding of miRNA-regulation and APA-mediated evasion in the immune system. This research will eventually shed light on this novel level of complexity in miRNA biology and will provide new in-

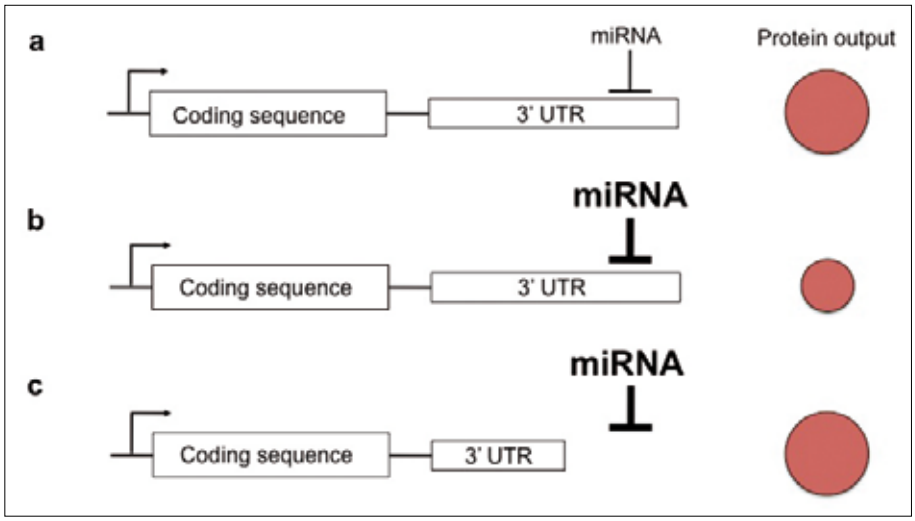

Figure 6
Alternative polyadenylation regulates miRNA-mediated gene repression
Schematic model how shortening of the 3' untranslated region (UTR) theoretically could interfere with miRNA regulation. a) Equilibrium between a miRNA and an mRNA. b) Increased miRNA expression leads to repression of the target gene. c) Proliferating cells globally shorten 3'UTRs through alternative polyadenylation (APA). When this process leads to a transcript without the initial miRNA binding site in the target site then theoretically the miRNA loses its repressive activity.
Figure adapted from Ref[2].

sights into the yet vaguely investigated role of APA in the immune system.

Therapeutic manipulation of miRNA function for immunomodulation

Finally, we aim to translate our basic findings into novel therapeutic concepts. The goal of Romina's project is to find chemical substances which specifically inhibit miRNA function. We have developed a cell-based screening system which stably expresses a miRNA reporter gene. In collaboration with a university center in San Francisco we have demonstrated the robustness of our reporter assay for high throughput screening. Currently, we are developing so-called orthogonal/secondary screens in order to validate initial hits. The discovery of small molecule chemical inhibitors of specific miRNAs is important for the treatment of diseases such as lymphoma, solid tumors and autoimmune or other inflammatory diseases because the existing nucleic acid-based miRNA inhibitors practically do not penetrate lymphocytes. In contrast, the small chemical molecules that we use penetrate readily into cells. The price, however, is that unlike nucleic acid-based substances, it is almost impossible to predict which miRNAs are inhibited, which is why large screening campaigns need to be performed to find specific inhibitors [REF6].

Other lab activities

Since we started our group in spring 2014 we have established several collaborations with researchers and clinicians at the DBM, the university hospital, and the biocentre. In addition, we are organizing a monthly DBM-wide "Genome editing club" which allows us to cope better with the fast-paced advances in this field. Apart from the lab our group is collectively interested in Jazz, sports, cooking, fine dining, paleontology, marine biology (particularly cetaceans) and travelling. If you'd like to know who's interested in what, please come find us at Hebelstrasse in lab 313.

Lukas and lab members

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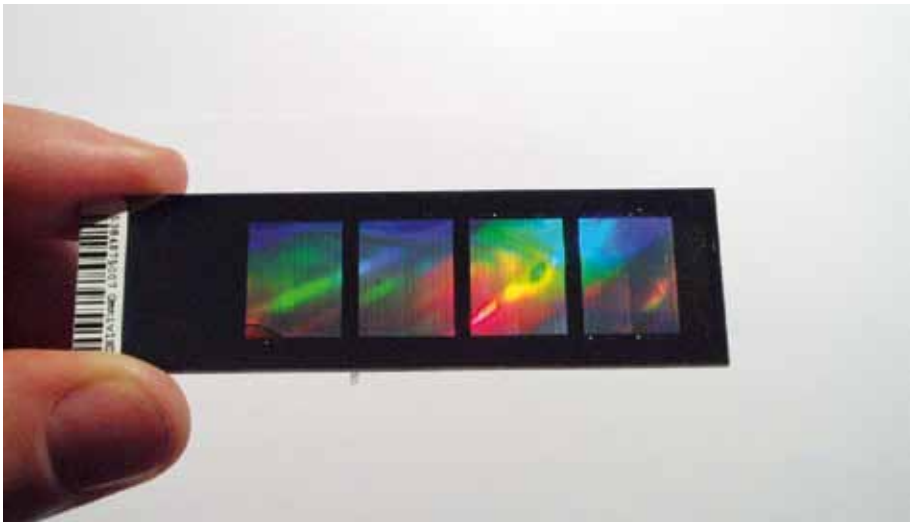
DNA Microarray analysis of the human genome

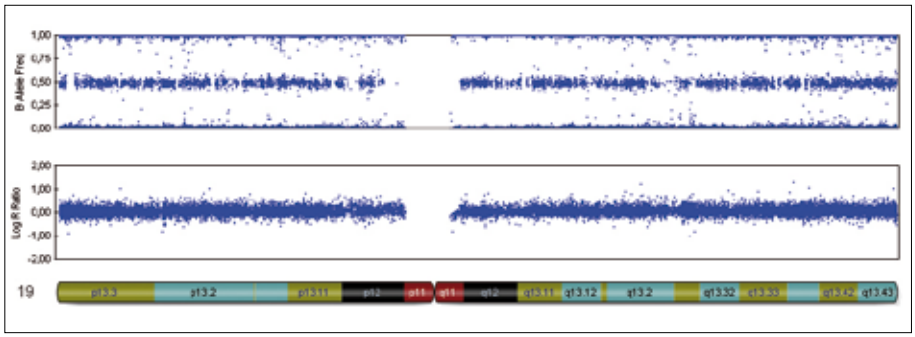
Some insight into the challenges that might arise when performing research within the human genome using microarrays

Roughly 2,5m of desoxyribonucleidic acid molecules in 46 packages of variable length are stuffed into every cell's core. Anybody trying to unwind the cable of head phones stuffed in their pockets knows how difficult it is not to mess it up. But nature has somehow found ways to handle the task of managing our genome in every single cell of our bodies. Besides these sterical challenges there remain many questions including: What is in the 2 times 3.3 billion nucleotides that form our genome? Why is the total amount of coding sequence less than 3% of it? And which mutations are causal for diseases? These are just some of the questions scientists working in the genome context are trying to address. This article does not want to discuss all of these issues in depth, but wants to give a bit of an insight into some of the everyday hurdles that are arising when conducting research on the human genome … with microarrays!

Since the first draft of the human genome in the year 2000 a lot of insight into our genetic architecture has been achieved. But besides the successful acquisition of the raw sequence, the notion that the genome is by far more complex than anticipated loomed in the research community. Therefore several projects were launched to evaluate and curate these variations in a much broader way. The International HapMap Project started in 2002 to map all single nucleotide variations – the so-called single nucleotide polymorphisms (SNPs) – in the genome. Within the time period of the project technologies were developed to evaluate these polymorphisms at high numbers and in efficient ways. At the end a first map of the haplotype structure of the human genome had been generated. Companies like Affymetrix, Illumina, and PerleGen profited from the funding and kick-started the production of arrays that were, and are, applied by scientists worldwide to unravel the genetics of a broad range of diseases and inherited traits. With the appearance of next-generation sequencing technologies the 1000Genomes project was launched to give a more detailed insight into the haplotype structure and the variation in the human genome. But this is a different story to tell…



Picture 1:
Photo of a dna micro array. Modern arrays have a multitude in probes around for normalization and reduction of probe failures. Roughly 200 million single signals will be evaluated during the scan of an array.



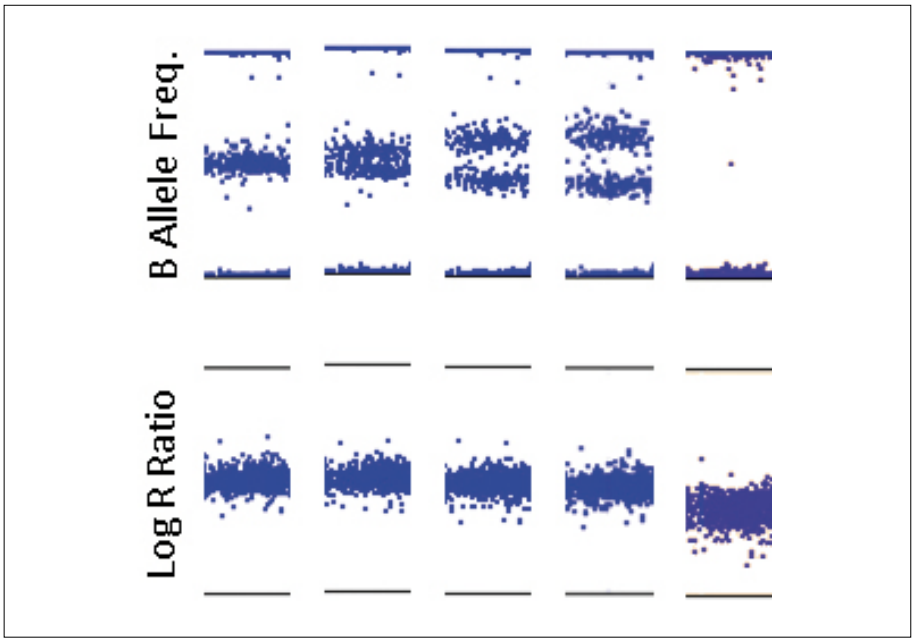
Picture 2
Normal state: Upper diagram shows the frequency of the b allele, which is in a two state system 0, 0.5 or 1. The lower diagram depicts the ratio of the summed intensity of one marker as a ratio to all other intensities in a given analysis (Log R ratio), which is in the range of -0.3 to 0.3 with a decrease in the state of deletion or increase in a duplication.

SNP Microarray Technologies

One of the first, and up to now very successful, applications resulting from the human genome sequence was the development of DNA microarrays. Companies who developed these microarrays were, and are, Agilent, Affymetrix, Illumina and some smaller enterprises. As we are mostly analyzing microarrays from Illumina, we are referring to the Bead Arrays for the rest of the article unless stated otherwise (Picture 1). Microarrays evaluate the binding of DNA fragments in a given sample to query the state of a SNP. As millions of SNPs are evaluated in parallel, the processing of sample DNA comprises a genome-wide amplification as the first step. Afterwards shearing and hybridization to the probes affixed to the array surface take place. Finally, the alleles of the SNPs are marked fluorescently and the read-out is done by measuring the fluorescence signal. These raw or scan data are normalized and converted into genotype data by software algorithms in the so-called clustering step. The conversion from intensities to genotypes is not very reliable for small sample sizes (<200) as the algorithm needs all three possible states (AA, AB, BB). Since the normalization process is using the fluorescent signal intensities, measured variances arising from batch issues or private mutations are also changing the outcome of the cluster evaluation. It is therefore very important to cluster all samples of a study together or at least to use properly generated cluster data, so that a homogenous clustering of all markers can be achieved. To get even more confidence in the clustering results and to avoid false positives it is highly recommended that the cluster plots of the top markers arising from the analysis are manually checked.

Since arrays from different manufacturers as well as from different generations have an individual composition of markers, the combined analysis is tricky. Using just the overlapping markers often results in very small SNP sets leading to a severe power loss of the whole project. To be able to combine different cohorts a procedure called "imputing" can be used. Several algorithms have been developed to predict (impute) non-typed SNPs. Why can you predict SNPs? This is due to two reasons. The first reason is that recombination in the genome is not taking place randomly but mostly at recombination hotspots. This means there are large stretches in the genome that are always inherited together. The second reason is that a large proportion of the single nucleotide variations are quiet frequent in the genome. Taking both reasons together imply that there is a high probability that neighboring variations are inherited together and therefore can predict each other. This term is also called linkage disequilibrium. Using this approach you can predict around 4.5million SNPs from only 700.000 physically genotyped SNPs. Unfortunately preparing a data set for imputation can be very annoying, since the annotation of a marker to a position and the alleles of markers are often not the ones found in the reference data. This requires intensive reediting of the sample data. At the end there is normally a conversion of the dosage into genotypes.

Statistical analysis itself normally does not cause bigger issues. Thanks to well established tools like plink and R based workflows, genome wide association analysis (GWAS) can easily be done. Problems arise afterwards when variations found in the genome are to be mapped to genes. Very often the genome build of the genotypes is not stated. This information is critical since the position on a given chromosome can change with new versions of the reference genome. The most frequently



Picture 3
Mosaicism: Depiction of a chromosome 20 region of about 2.5Mbp. Showing the overgrowth of original cell culture by a subclone that is carrying a deletion. Percentage of subclone population: 0%, 20%, 50% 66%, 100%

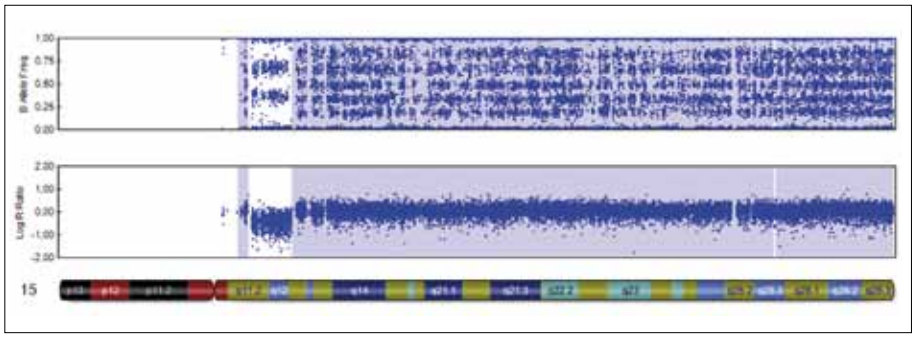
used genome builds are the University of California Santa Cruz (UCSC) and the human reference genome curated by the Genome Reference Consortium. The actual versions are the hg19 and the GRCh37.2 but the versions hg38 and GRCh38 have been released, waiting for wider acceptance by the scientific community. So if a SNP is not annotated in the vicinity of an expected gene, it is worthwhile to check in dbSNP for the chromosomal position of the marker.

Copy number analysis

But it is not just the genotype data that are of interest in the microarray field. Having the intensities of the probes, the copy number state can be derived. Since each probe senses the availability of a given amount of a dna sequence in a given dna sample it can be expected, that the normalized intensity is in the same range in all samples analyzed (Picture 2). Having deviations from this two-chromosomal state can be observed as a decrease or increase in the intensity. A single marker might show greater variations due to processing specific changes or due to private mutations. But having several adjacent markers being altered in the same direction is supporting evidence for changes of larger stretches of dna. These mutations are referred to as structural or copy number variations (cnvs). These variations are characterized by the deletion or duplication of larger stretches of dna. These events are less frequently found in the genome, but are not exceptionally special. They are tricky to analyze since the start and end points are not easy to determine to the base and different events might be in the same region.

In research these events are of interest, because a deletion or duplication of genomic material is often related to a change in expression and thus to a phenotype. Having a region being hit by several cnvs might be a good starting point for the hunt for less frequent but more damaging mutations.

Another interesting application is the check for genomic integrity of cell cultures. During passaging the cell culture adapts to the growth conditions and reacts with certain mutations. These mutations can lead to chromosomal instabilities that can easily be detected by microarrays. This molecular karyotyping can be used to monitor these changes and track subpopulations of cell down to 20%. The genotypes can be used as a fingerprint to identify the cell line (Picture 3, 4). If you are interested in validating the identity of your cell line only, then you should use fingerprinting by STR fragment length analysis. This approach checks about 20 STR marker in the genome which are also widely used in forensics. By comparing the length of the microsatellites against published patterns of the cell lines used you can identify your cell line and also contaminants.



Picture 4
Mix up of three dna samples at the same concentration, chromosome 15: It is worthwhile to realize that the Log R Ratio band is around zero level, indicating that the dna concentration has been adjusted after mixture. Two of the samples show a larger cnv event on 15q11.2/q12. This might be through the share of a larger proportion of dna of a deletion event.

Since the assay is run on a Sanger sequencer it has the potential to identify cross contaminating cell lines down to 5% of the total cell population.

What can you expect from Microarrays

If you are interested in common phenotypes or common disorders you can use microarrays to perform GWAS analysis at low costs in thousands of samples. Most probably you can even increase your cohort by adding samples from other groups that already have been genotyped. You might need to use imputation but hey, nothing is for free. If you are interested in the genomic integrity of your cell culture, mircorarrays will give you a more detailed insight than classical g-banding and are much less work. If you are interested in CNV than microarrays are much more reliable then NGS.

If you want to detect something new or are working on rare diseases with very small samples sizes, than you probably should use NGS instead…But wait, even if you are performing Whole Exome or Whole genome sequencing microarrays are a very valuable for validation of the NGS results and to make sure nothing happened at the pooling step.

Outlook

What have we learnt in the end? We do not have a more clever way to store our headphones nor have we solved the issue of how nature has managed this task. However, our understanding is further increasing empirically into this field every day… What we hope to show to you is that the micro arrays technology had, and still has, a big influence on the analysis of the genetics of diseases. It is a cheap and powerful way to analyze thousands of samples,but the focus now shifts to new technologies like Next Generation sequencing. The focus is not as much into exome sequencing, which tries to just analyze the coding regions only, but is more toward whole genome sequencing which ultimately unravels all of the genetic information of an individual. Besides SNP microarrays there are of course microarrays which analyze the Epigenome or the Transcriptome. The latter have already been introduced in an earlier edition of DBM facts. Having data from all three types of microarrays opens another world of analyzes and information: The quantitative trait loci (QTLs). But this is quite another topic, or a story to tell if you pass by in our lab in room 319.

Stefan Herms

Farewell lecture of Christoph Beglinger

With his farewell lecture «Problems and perspectives in academic medicine» on July 2, 2015 Christoph Beglinger formally retired from the University Hospital of Basel. His retirement marks the end of 35 years of faithful service in several capacities that include chief physician in the Department of Gastroenterology, Dean of the faculty of Medicine, Board member of the former DF and research group leader. We will miss his support, excellent scientific contributions and humaneness, and gratefully acknowledge his many contributions to our Department.

Dissertationen

Am 16. April 2015 konnte **Bernd Schwendele** von der Forschungsgruppe Brain Ischemia and Regeneration (Departement Biomedizin Hebelstrasse) seine Dissertation an der Universität Tübingen mit Erfolg beenden. Er widmete sich in seiner Doktorarbeit dem Thema "Functional Characterization of Microglia in Mouse Models of Alzheimer's Disease".

Seit dem 19. Juni 2015 darf sich **Robert Kölm** von der Forschungsgruppe Clinical Immunology (Departement Biomedizin Hebelstrasse) Herr Dr. nennen. Er befasste sich in seiner Doktorarbeit mit dem Thema: "Von Willebrand factor binds surface-bound C1q and induces platelet rolling".

Auszeichnungen

Alumni Preis an Adrian Egli

Adrian Egli von der Forschungsgruppe Applied Microbiology Research (DBM Hebelstrasse) hat für seine Forschungstätigkeit den diesjährigen Alumni Preis der Medizinischen Fakultät der Universität Basel erhalten.

Das DBM gratuliert ganz herzlich!

Immunity **Immunity** 916–928, May 2015 IF 21.561

Klf4 Expression in Conventional Dendritic Cells Is Required for T Helper 2 Cell Responses

Roxane Tussiwand[1,3], Bart Everts[1,4], Gary E. Grajales-Reyes[1], Nicole M. Kretzer[1], Arifumi Iwata[1], Juhi Bagaitkar[5], Xiaodi Wu[1], Rachel Wong[1], David A. Anderson[1], Theresa L. Murphy[1], Edward J. Pearce[1], and Kenneth M. Murphy[1,2,*]

Summary

The two major lineages of classical dendritic cells (cDCs) express and require either IRF8 or IRF4 transcription factors for their development and function. IRF8-dependent cDCs promote anti-viral and T-helper 1 (Th1) cell responses, whereas IRF4-expressing cDCs have been implicated in controlling both Th2 and Th17 cell responses. Here, we have provided evidence that Kruppel-like factor 4 (Klf4) is required in IRF4-expressing cDCs to promote Th2, but not Th17, cell responses in vivo. Conditional Klf4 deletion within cDCs impaired Th2 cell responses during Schistosoma mansoni infection, Schistosoma egg antigen (SEA) immunization, and house dust mite (HDM) challenge without affecting cytotoxic T lymphocyte (CTL), Th1 cell, or Th17 cell responses to herpes simplex virus, Toxoplasma gondii, and Citrobacter rodentium infections. Further, Klf4 deletion reduced IRF4 expression in pre-cDCs and resulted in selective loss of IRF4-expressing cDCs subsets in several tissues. These results indicate that Klf4 guides a transcriptional program promoting IRF4-expressing cDCs heterogeneity.

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Immunity **Immunity** 1033–1047, June 2015 IF 21.561

Complement Regulates Nutrient Influx and Metabolic Reprogramming during Th1 Cell Responses

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Summary

Expansion and acquisition of Th1 cell effector function requires metabolic reprogramming; however, the signals instructing these adaptations remain poorly defined. Here we found that in activated human T cells, autocrine stimulation of the complement receptor CD46, and specifically its intracellular domain CYT-1, was required for induction of the amino acid (AA) transporter LAT1 and enhanced expression of the glucose transporter GLUT1. Furthermore, CD46 activation simultaneously drove expression of LAMTOR5, which mediated assembly of the AA-sensing Ragulator-Rag-mTORC1 complex and increased glycolysis and oxidative phosphorylation (OXPHOS), required for cytokine production. T cells from CD46-deficient patients, characterized by defective Th1 cell induction, failed to upregulate the molecular components of this metabolic program as well as glycolysis and OXPHOS, but IFN-γ production could be reinstated by retrovirus-mediated CD46-CYT-1 expression. These data establish a critical link between the complement system and immunometabolic adaptations driving human CD4+ T cell effector function.

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[9] Co-senior author

Blood blood April 2015, Volume 125, Number 17 IF 10.452

Impaired thymic expression of tissue-restricted antigens licenses the de novo generation of autoreactive CD4$^+$ T cells in acute GVHD

Simone Dertschnig[1], Mathias M. Hauri-Hohl[2], Madeleine Vollmer[3], Georg A. Holländer[1,4], and Werner Krenger[3]

During acute graft-versus-host disease (aGVHD) in mice, autoreactive T cells can be generated de novo in the host thymus implying an impairment in self-tolerance induction. As a possible mechanism, we have previously reported that mature medullary thymic epithelial cells (mTEC^{high}) expressing the autoimmune regulator are targets of donor T-cell alloimmunity during aGVHD. A decline in mTEC^{high} cell pool size, which purges individual tissue-restricted peripheral self-antigens (TRA) from the total thymic ectopic TRA repertoire, weakens the platform for central tolerance induction. Here we provide evidence in a transgenic mouse system using ovalbumin (OVA) as a model surrogate TRA that the de novo production of OVA-specific CD4$^+$ T cells during acute GVHD is a direct consequence of impaired thymic ectopic OVA expression in mTEC^{high} cells. Our data, therefore, indicate that a functional compromise of the medullary mTEChigh compartment may link alloimmunity to the development of autoimmunity during chronic GVHD.

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Biomaterials Biomaterials 62 (2015) 138–146 IF 8.557

Bioreactor-engineered cancer tissue-like structures mimic phenotypes, gene expression profiles and drug resistance patterns observed "in vivo"

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Abstract

Anticancer compound screening on 2D cell cultures poorly predicts "in vivo" performance, while conventional 3D culture systems are usually characterized by limited cell proliferation, failing to produce tissue-like-structures (TLS) suitable for drug testing. We addressed engineering of TLS by culturing cancer cells in porous scaffolds under perfusion flow. Colorectal cancer (CRC) HT-29 cells were cultured in 2D, on collagen sponges in static conditions or in perfused bioreactors, or injected subcutaneously in immunodeficient mice. Perfused 3D (p3D) cultures resulted in significantly higher ($p < 0.0001$) cell proliferation than static 3D (s3D) cultures and yielded more homogeneous TLS, with morphology and phenotypes similar to xenografts. Transcriptome analysis revealed a high correlation between xenografts and p3D cultures, particularly for gene clusters regulating apoptotic processes and response to hypoxia. Treatment with 5-Fluorouracil (5-FU), a frequently used but often clinically ineffective chemotherapy drug, induced apoptosis, down-regulation of anti-apoptotic genes *(BCL-2, TRAF1,* and *c-FLIP)* and decreased cell numbers in 2D, but only "nucleolar stress" in p3D and xenografts. Conversely, BCL-2 inhibitor ABT-199 induced cytotoxic effects in p3D but not in 2D cultures. Our findings advocate the importance of perfusion flow in 3D cultures of tumor cells to efficiently mimic functional features observed "in vivo" and to test anticancer compounds.

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Epigenetic changes as a common trigger of muscle weakness in congenital myopathies

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Abstract

Congenital myopathies are genetically and clinically heterogeneous conditions causing severe muscle weakness, and mutations in the ryanodine receptor gene (RYR1) represent the most frequent cause of these conditions. A common feature of diseases caused by recessive RYR1 mutations is a decrease of ryanodine receptor 1 protein content in muscle. The aim of the present investigation was to gain mechanistic insight into the causes of this reduced ryanodine receptor 1. We found that muscle biopsies of patients with recessive RYR1 mutations exhibit decreased expression of muscle-specific microRNAs, increased DNA methylation and increased expression of class II histone deacetylases. Transgenic mouse muscle fibres overexpressing HDAC-4/HDAC-5 exhibited decreased expression of RYR1 and of muscle-specific miRNAs, whereas acute knockdown of RYR1 in mouse muscle fibres by siRNA caused up-regulation of HDAC-4/HDAC-5. Intriguingly, increased class II HDAC expression and decreased ryanodine receptor protein and miRNAs expression were also observed in muscles of patients with nemaline myopathy, another congenital neuromuscular disorder.

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Antibody response to BK polyomavirus as a prognostic biomarker and potential therapeutic target in prostate cancer

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Abstract

Infectious agents, including the BK polyomavirus (BKPyV), have been proposed as important inflammatory pathogens in prostate cancer. Here, we evaluated whether the preoperative antibody response to BKPyV large T antigen (LTag) and viral capsid protein 1 (VP1) was associated with the risk of biochemical recurrence in 226 patients undergoing radical prostatectomy for primary prostate cancer. Essentially, the multivariate Cox regression analysis revealed that preoperative seropositivity to BKPyV LTag significantly reduced the risk of biochemical recurrence, independently of established predictors of biochemical recurrence such as tumor stage, Gleason score and surgical margin status. The predictive accuracy of the regression model was denotatively increased by the inclusion of the BKPyV LTag serostatus. In contrast, the VP1 serostatus was of no prognostic value. Finally, the BKPyV LTag serostatus was associated with a peculiar cytokine gene expression profile upon assessment of the cellular immune response elicited by LTag. Taken together, our findings suggest that the BKPyV LTag serology may serve as a prognostic factor in prostate cancer. If validated in additional studies, this biomarker may allow for better treatment decisions after radical prostatectomy. Finally, the favorable outcome of LTag seropositive patients may provide a potential opportunity for novel therapeutic approaches targeting a viral antigen.

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Effect of Immunosuppression on T-Helper 2 and B-Cell Responses to Influenza Vaccination

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Background. Influenza vaccine immunogenicity is suboptimal in immunocompromised patients. However, there are limited data on the interplay of T-and B-cell responses to vaccination with simultaneous immunosuppression.

Methods. We collected peripheral blood mononuclear cells from transplant recipients before and 1 month after seasonal influenza vaccination. Before and after vaccination, H1N1-specific T-and B-cell activation were quantified with flow cytometry. We also developed a mathematical model using T-and B-cell markers and mycophenolate mofetil (MMF) dosage.

Results. In the 47 patients analyzed, seroconversion to H1N1 antigen was demonstrated in 34%. H1N1-specific interleukin 4 (IL-4)–producing $CD4^+$ T-cell frequencies increased significantly after vaccination in 53% of patients. Prevaccine expression of H1N1-induced HLA-DR and CD86 on B cells was high in patients who seroconverted. Seroconversion against H1N1 was strongly associated with HLA-DR expression on B cells, which was dependent on the increase between prevaccine and postvaccine H1N1-specific IL-4^+CD4^+ T cells ($R^2 = 0.35$). High doses of MMF (≥2 g/d) led to lower seroconversion rates, smaller increase in H1N1-specific IL-4^+CD4^+ T cells, and reduced HLA-DR expression on B cells. The mathematical model incorporating a MMF-inhibited positive feedback loop between H1N1-specific IL-4^+CD4^+ T cells and HLA-DR expression on B cells captured seroconversion with high specificity.

Conclusions. Seroconversion is associated with influenza-specific T-helper 2 and B-cell activation and seems to be modulated by MMF.

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Brain, Behavior, and Immunity | Brain, Behavior, and Immunity | 48 (2015) 313–325 | IF 5,889

Metabolic gene expression changes in astrocytes in Multiple Sclerosis cerebral cortex are indicative of immune-mediated signaling

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Abstract

Emerging as an important correlate of neurological dysfunction in Multiple Sclerosis (MS), extended focal and diffuse gray matter abnormalities have been found and linked to clinical manifestations such as seizures, fatigue and cognitive dysfunction. To investigate possible underlying mechanisms we analyzed the molecular alterations in histopathological normal appearing cortical gray matter (NAGM) in MS. By performing a differential gene expression analysis of NAGM of control and MS cases we identified reduced transcription of astrocyte specific genes involved in the astrocyte–neuron lactate shuttle (ANLS) and the glutamate–glutamine cycle (GGC). Additional quantitative immunohistochemical analysis demonstrating a CX43 loss in MS NAGM confirmed a crucial involvement of astrocytes and emphasizes their importance in MS pathogenesis. Concurrently, a Toll-like/IL-1β signaling expression signature was detected in MS NAGM, indicating that immune-related signaling might be responsible for the downregulation of ANLS and GGC gene expression in MS NAGM. Indeed, challenging astrocytes with immune stimuli such as IL-1β and LPS reduced their ANLS and GGC gene expression *in vitro*. The detected upregulation of *IL1B* in MS NAGM suggests inflammasome priming. For this reason, astrocyte cultures were treated with ATP and ATP/LPS as for inflammasome activation. This treatment led to a reduction of ANLS and GGC gene expression in a comparable manner. To investigate potential sources for ANLS and GGC downregulation in MS NAGM, we first performed an adjuvant-driven stimulation of the peripheral immune system in C57Bl/6 mice *in vivo*. This led to similar gene expression changes in spinal cord demonstrating that peripheral immune signals might be one source for astrocytic gene expression changes in the brain. *IL1B* upregulation in MS NAGM itself points to a possible endogenous signaling process leading to ANLS and GGC downregulation. This is supported by our findings that, among others, MS NAGM astrocytes express inflammasome components and that astrocytes are capable to release Il-1β *in-vitro*. Altogether, our data suggests that immune signaling of immune-and/or central nervous system origin drives alterations in astrocytic ANLS and GGC gene regulation in the MS NAGM. Such a mechanism might underlie cortical brain dysfunctions frequently encountered in MS patients.

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Scientific Reports | SCIENTIFIC REPORTS | 5:10288 | DOi: 10.1038/srep10288 IF 5.578

High-Throughput Microfluidic Platform for 3D Cultures of Mesenchymal Stem Cells, Towards Engineering Developmental Processes

Paola Occhetta[1,2,*], Matteo Centola[2,*], Beatrice Tonnarelli[2], Alberto Redaelli[1], Ivan Martin[2] & Marco Rasponi[1]

The development of *in vitro* models to screen the effect of different concentrations, combinations and temporal sequences of morpho-regulatory factors on stem/progenitor cells is crucial to investigate and possibly recapitulate developmental processes with adult cells. Here, we designed and validated a microfluidic platform to (i) allow cellular condensation, (ii) culture 3D micromasses of human bone marrow-derived mesenchymal stromal cells (hBM-MSCs) under continuous flow perfusion, and (ii) deliver defined concentrations of morphogens to specific culture units. Condensation of hBM-MSCs was obtained within 3 hours, generating micromasses in uniform sizes (56.2 ± 3.9 μm). As compared to traditional macromass pellet cultures, exposure to morphogens involved in the first phases of embryonic limb development (i.e. Wnt and FGF pathways) yielded more uniform cell response throughout the 3D structures of perfused micromasses (PMMs), and a 34-fold higher percentage of proliferating cells at day 7. The use of a logarithmic serial dilution generator allowed to identify an unexpected concentration of TGFβ3 (0.1 ng/ml) permissive to hBM-MSCs proliferation and inductive to chondrogenesis. This proof-of-principle study supports the described microfluidic system as a tool to investigate processes involved in mesenchymal progenitor cells differentiation, towards a 'developmental engineering' approach for skeletal tissue regeneration.

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An immature B cell population from peripheral blood serves as surrogate marker for monitoring tumor angiogenesis and anti-angiogenic therapy in mouse models

Ernesta Fagiani[1], Ruben Bill[1], Laura Pisarsky[1], Robert Ivanek[1], Curzio Rüegg[2], Gerhard Christofori[1]

Abstract

Tumor growth depends on the formation of new blood vessels (tumor angiogenesis) either from preexisting vessels or by the recruitment of bone marrow-derived cells. Despite encouraging results obtained with preclinical cancer models, the therapeutic targeting of tumor angiogenesis has thus far failed to deliver an enduring clinical response in cancer patients. One major obstacle for improving antiangiogenic therapy is the lack of validated biomarkers, which allow patient stratification for suitable treatment and a rapid assessment of therapy response. Toward these goals, we have employed several mouse models of tumor angiogenesis to identify cell populations circulating in their blood that correlated with the extent of tumor angiogenesis and therapy response. Flow cytometry analyses of different combinations of cell surface markers that define subsets of bone marrow-derived cells were performed on peripheral blood mononuclear cells from tumor-bearing and healthy mice. We identified one cell population, $CD45^{dim}VEGFR1^{-}CD31^{low}$, that was increased in levels during active tumor angiogenesis in a variety of transgenic and syngeneic transplantation mouse models of cancer. Treatment with various anti-angiogenic drugs did not affect $CD45^{dim}VEGFR1^{-}CD31^{low}$ cells in healthy mice, whereas in tumor-bearing mice, a consistent reduction in their levels was observed. Gene expression profiling of $CD45^{dim}VEGFR1^{-}CD31^{low}$ cells characterized these cells as an immature B cell population. These immature B cells were then directly validated as surrogate marker for tumor angiogenesis and of pharmacologic responses to anti-angiogenic therapies in various mouse models of cancer.

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British Journal of Pharmacology BJP BRITISH JOURNAL OF PHARMACOLOGY (2015) 172 3412–3425 IF 4.842

Pharmacological profile of novel psychoactive benzofurans

Anna Rickli[1], Simone Kopf[1], Marius C Hoener[2] and Matthias E Liechti[1]

Background and purpose
Benzofurans are newly used psychoactive substances, but their pharmacology is unknown. The aim of the present study was to pharmacologically characterize benzofurans *in vitro.*

Experimental approach
We assessed the effects of the benzofurans 5-APB, 5-APDB, 6-APB, 6-APDB, 4-APB, 7-APB, 5-EAPB and 5-MAPDB and benzodifuran 2C-B-FLY on the human noradrenaline (NA), dopamine and 5-HT uptake transporters using HEK 293 cells that express the respective transporters. We also investigated the release of NA, dopamine and 5-HT from monoamine-preloaded cells, monoamine receptor-binding affinity and 5-HT_{2A} and 5-HT_{2B} receptor activation.

Key results
All of the benzofurans inhibited NA and 5-HT uptake more than dopamine uptake, similar to methylenedioxymethamphetamine (MDMA) and unlike methamphetamine. All of the benzofurans also released monoamines and interacted with trace amine-associated receptor 1 (TA_1 receptor), similar to classic amphetamines. Most benzofurans were partial 5-HT_{2A} receptor agonists similar to MDMA, but also 5-HT_{2B} receptor agonists, unlike MDMA and methamphetamine. The benzodifuran 2C-B-FLY very potently interacted with 5-HT_2 receptors and also bound to TA_1 receptors.

Conclusions and implications
Despite very similar structures, differences were found in the pharmacological profiles of different benzofurans and compared with their amphetamine analogues. Benzofurans acted as indirect monoamine agonists that interact with transporters similarly to MDMA. The benzofurans also interacted with 5-HT receptors. This pharmacological profile probably results in MDMA-like entactogenic psychoactive properties. However, benzofurans induce 5-HT_{2B} receptor activation associated with heart valve fibrosis. The pharmacology of 2C-B-FLY indicates predominant hallucinogenic properties and a risk for vasoconstriction.

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Molecular and Cellular Biology AMERICAN SOCIETY FOR MICROBIOLOGY | Molecular and Cellular Biology June 2015, Vol. 35, No. 11 IF 4.777

Growth Cone Localization of the mRNA Encoding the Chromatin Regulator HMGN5 Modulates Neurite Outgrowth

Francesca Moretti[a], Chiara Rolando[b], Moritz Winker[a], Robert Ivanek[c,d], Javier Rodriguez[e], Alex Von Kriegsheim[e], Verdon Taylor[b], Michael Bustin[f], Olivier Pertz[a]

Neurons exploit local mRNA translation and retrograde transport of transcription factors to regulate gene expression in response to signaling events at distal neuronal ends. Whether epigenetic factors could also be involved in such regulation is not known. We report that the mRNA encoding the high-mobility group N5 (HMGN5) chromatin binding protein localizes to growth cones of both neuronlike cells and of hippocampal neurons, where it has the potential to be translated, and that HMGN5 can be retrogradely transported into the nucleus along neurites. Loss of HMGN5 function induces transcriptional changes and impairs neurite outgrowth, while HMGN5 overexpression induces neurite outgrowth and chromatin decompaction; these effects are dependent on growth cone localization of *Hmgn5* mRNA. We suggest that the localization and local translation of transcripts coding for epigenetic factors couple the dynamic neuronal outgrowth process with chromatin regulation in the nucleus.

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European Journal of Immunology | European Journal of Immunology | 2015. 45: 1414–1425 | IF 4.518

Blocking of LFA-1 enhances expansion of Th17 cells induced by human CD14^{+}CD16^{++} nonclassical monocytes

Emmanuel Traunecker[1], Rui Gardner[2,3], João Eurico Fonseca[4], Joaquim Polido-Pereira[4], Michael Seitz[5], Peter M.Villiger[5], Giandomenica Iezzi[6] and Elisabetta Padovan[6]

Among human peripheral blood (PB) monocyte (Mo) subsets, the classical CD14^{++}CD16^{-} (cMo) and intermediate CD14^{++}CD16^{+} (iMo) Mos are known to activate pathogenic Th17 responses, whereas the impact of nonclassical CD14^{+}CD16^{++} Mo (nMo) on T-cell activation has been largely neglected. The aim of this study was to obtain new mechanistic insights on the capacity of Mo subsets from healthy donors (HDs) to activate IL-17^{+} T-cell responses in vitro, and assess whether this function was maintained or lost in states of chronic inflammation. When cocultured with autologous CD4^{+} Tcells inthe absence of TLR-2/NOD2 agonists, PB nMos from HDs were more efficient stimulators of IL-17-producing T cells, as compared to cMo. These results could not be explained by differences in Mo lifespan and cytokine profiles. Notably, however, the blocking of LFA-1/ICAM-1 interaction resulted in a significant increase in the percentage of IL-17^{+} T cells expanded in nMo/T-cell cocultures. As compared to HD, PB Mo subsets of patients with rheumatoid arthritis were hampered in their T-cell stimulatory capacity. Our new insights highlight the role of Mo subsets in modulating inflammatory T-cell responses and suggest that nMo could become a critical therapeutic target against IL-17-mediated inflammatory diseases.

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Journal of Virology | JVI | March 2015, Vol. 89, No. 6 | IF 4.439

Sp1 Sites in the Noncoding Control Region of BK Polyomavirus Are Key Regulators of Bidirectional Viral Early and Late Gene Expression

Tobias Bethge[a], Helen A. Hachemi[a], Julia Manzetti[a], Rainer Gosert[a,b], Walter Schaffner[c], Hans H. Hirsch[a,b,d]

Abstract

In kidney transplant patients with BK polyomavirus (BKPyV) nephropathy, viral variants arise bearing rearranged noncoding control regions (*rr*-NCCRs) that increase viral early gene expression, replicative fitness, and cytopathology. *rr*-NCCRs result from various deletions and duplications of archetype NCCR (*ww*-NCCR) sequences, which alter transcription factor binding sites (TFBS). However, the role of specific TFBS is unclear. We inactivated 28 TFBS in the archetype NCCR by selective point mutations and examined viral gene expression in bidirectional reporter constructs. Compared to the archetype, group 1 mutations increased viral early gene expression similar to rr-NCCR and resulted from inactivating one *Sp1* or one *Ets1* TFBS near the late transcription start site (TSS). Group 2 mutations conferred intermediate early gene activation and affected NF1, YY1, and p53 sites between early and late TSS. Group 3 mutations decreased early and late gene expression and included two other *Sp1* sites near the early TSS. Recombinant viruses bearing group 1 NCCRs showed increased replication in human renal epithelial cells similar to clinical *rr*-NCCR variants. Group 2 and 3 viruses showed intermediate or no replication, respectively. A literature search revealed unnoticed group 1 mutations in BKPyV nephropathy, hemorrhagic cystitis, and disseminated disease.

Importance

The NCCRs of polyomaviruses mediate silent persistence of the viral genome as well as the appropriately timed (re)activation of the viral life cycle. This study indicates that the basal BKPyV NCCR is critically controlled by a hierarchy of single TFBS in the archetype NCCR that direct, modulate, and execute the bidirectional early and late viral gene expression. The results provide new insights into how BKPyV NCCR functions as a viral sensor of host cell signals and shed new light on how transcription factors like Sp1 control bidirectional viral gene expression and contribute to replication and pathology.

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European Neuropsychopharmacology (2015) 25, 365–376 IF 4.369

Monoamine transporter and receptor interaction profiles of novel psychoactive substances: Para-halogenated amphetamines and pyrovalerone cathinones

Anna Rickli[a], Marius C. Hoener[b], Matthias E. Liechti[a]

Abstract

The pharmacology of novel psychoactive substances is mostly unknown. We evaluated the transporter and receptor interaction profiles of a series of para-(4)-substituted amphetamines and pyrovalerone cathinones. We tested the potency of these compounds to inhibit the norepinephrine (NE), dopamine (DA), and serotonin (5-HT) transporters (NET, DAT, and SERT, respectively) using human embryonic kidney 293 cells that express the respective human transporters. We also tested the substance-induced efflux of NE, DA, and 5-HT from monoamine-loaded cells, binding affinities to monoamine receptors, and 5-HT_{2B} receptor activation. Para-(4)-substituted amphetamines, including 4-methylmethcathinone (mephedrone), 4-ethylmethcathinone, 4-fluoroamphetamine, 4-fluoromethamphetamine, 4-fluoromethcatinone (flephedrone), and 4-bromomethcathinone, were relatively more serotonergic (lower DAT:SERT ratio) compared with their analogs amphetamine, methamphetamine, and methcathinone. The 4-methyl, 4-ethyl, and 4-bromo groups resulted in enhanced serotonergic properties compared with the 4-fluoro group. The para-substituted amphetamines released NE and DA. 4-Fluoramphetamine, 4-flouromethamphetamine, 4-methylmethcathinone, and 4-ethylmethcathinone also released 5-HT similarly to 3,4-methylenedioxymethamphetamine. The pyrovalerone cathinones 3,4-methylenedioxypyrovalerone, pyrovalerone, α-pyrrolidinovalerophenone, 3,4-methylenedioxy-α-pyrrolidinopropiophenone, and 3,4-methylenedioxy-α-pyrrolidinobutiophenone potently inhibited the NET and DAT but not the SERT. Naphyrone was the only pyrovalerone that also inhibited the SERT. The pyrovalerone cathinones did not release monoamines. Most of the para-substituted amphetamines exhibited affinity for the 5-HT2A receptor but no relevant activation of the 5-HT_{2B} receptor. All the cathinones exhibited reduced trace amine-associated receptor 1 binding compared with the non-β-keto-amphetamines.

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European Neuropsychopharmacology (2015) 25, 17–25 IF 4.369

Effects of methylphenidate and MDMA on appraisal of erotic stimuli and intimate relationships

Yasmin Schmid[a], Cédric M. Hysek[a], Katrin H. Preller[b], Oliver G. Bosch[b], Amy C. Bilderbeck[c], Robert D. Rogers[d], Boris B. Quednow[b], Matthias E. Liechti[a]

Abstract

Methylphenidate mainly enhances dopamine neurotransmission whereas 3,4-methylenediox-ymethamphetamine (MDMA, "ecstasy") mainly enhances serotonin neurotransmission. However, both drugs also induce a weaker increase of cerebral noradrenaline exerting sympathomimetic properties. Dopaminergic psychostimulants are reported to increase sexual drive, while serotonergic drugs typically impair sexual arousal and functions. Additionally, serotonin has also been shown to modulate cognitive perception of romantic relationships. Whether methylphenidate or MDMA alter sexual arousal or cognitive appraisal of intimate relationships is not known. Thus, we evaluated effects of methylphenidate (40 mg) and MDMA (75 mg) on subjective sexual arousal by viewing erotic pictures and on perception of romantic relationships of unknown couples in a double-blind, randomized, placebo-controlled, crossover study in 30 healthy adults. Methylphenidate, but not MDMA, increased ratings of sexual arousal for explicit sexual stimuli. The participants also sought to increase the presentation time of implicit sexual stimuli by button press after methylphenidate treatment compared with placebo. Plasma levels of testosterone, estrogen, and progesterone were not associated with sexual arousal ratings. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others.

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European Journal of Immunology | European Journal of Immunology | 2015. 45: 932–942 IF 4.034

A stromal cell free culture system generates mouse pro-T cells that can reconstitute T-cell compartments in vivo

Nadine Gehre[1,*], Anja Nusser[1,*], Lilly von Muenchow[1,*], Roxane Tussiwand[2], Corinne Engdahl[1], Giuseppina Capoferri[1], Nabil Bosco[1], Rhodri Ceredig[3] and Antonius G. Rolink[1]

T-cell lymphopenia following BM transplantation or diseases such as AIDS result in immunodeficiency. Novel approaches to ameliorate this situation are urgently required. Herein, we describe a novel stromal cell free culture system in which Lineage$^-$Sca1$^+$c-kit$^+$ BM hematopoietic progenitors very efficiently differentiate into pro-T cells. This culture system consists of plate-bound Delta-like 4 Notch ligand and the cytokines SCF and IL-7. The pro-T cells developing in these cultures express CD25, CD117, and partially CD44; express cytoplasmic CD3ε;and have theirTCRβ locus partially D–J rearranged. They could be expanded for over 3 months and used to reconstitute the T-cell compartments of sublethally irradiated T-cell-deficient CD3ε$^{-/-}$ mice or lethally irradiated WT mice. Pro-T cells generated in this system could partially correct the T-cell lymphopenia of pre-Tα$^{-/-}$ mice. However, reconstituted CD3ε$^{-/-}$ mice suffered from a wasting disease that was prevented by co-injection of purified CD4$^+$ CD25^{high} WT Treg cells. In a T-cell-sufficient or T-lymphopenic setting, the development of disease was not observed. Thus, this in vitro culture system represents a powerful tool to generate large numbers of pro-T cells for transplantation and possibly with clinical applications.

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[*] These authors contributed equally to this work

J. of Cellular and Molecular Medicine | Journal of Cellular and Molecular Medicine | Vol 19, No 6, 2015 pp. 1390–1399 IF 4.014

Bone-forming capacity of adult human nasal chondrocytes

Benjamin E Pippenger[a], Manuela Ventura[b], Karoliina Pelttari[a], Sandra Feliciano[a], Claude Jaquiery[a], Arnaud Scherberich[a], X Frank Walboomers[b], Andrea Barbero[a], Ivan Martin[a]

Abstract

Nasal chondrocytes (NC) derive from the same multipotent embryological segment that gives rise to the majority of the maxillofacial bone and have been reported to differentiate into osteoblast-like cells *in vitro*. In this study, we assessed the capacity of adult human NC, appropriately primed towards hypertrophic or osteoblastic differentiation, to form bone tissue *in vivo*. Hypertrophic induction of NC-based micromass pellets formed mineralized cartilaginous tissues rich in type X collagen, but upon implantation into subcutaneous pockets of nude mice remained avascular and reverted to stable hyaline-cartilage. In the same ectopic environment, NC embedded into ceramic scaffolds and primed with osteogenic medium only sporadically formed intramembranous bone tissue. A clonal study could not demonstrate that the low bone formation efficiency was related to a possibly small proportion of cells competent to become fully functional osteoblasts. We next tested whether the cues present in an orthotopic environment could induce a more efficient direct osteoblastic transformation of NC. Using a nude rat calvarial defect model, we demonstrated that *(i)* NC directly participated in frank bone formation and *(ii)* the efficiency of survival and bone formation by NC was significantly higher than that of reference osteogenic cells, namely bone marrow-derived mesenchymal stromal cells. This study provides a proof-of-principle that NC have the plasticity to convert into bone cells and thereby represent an easily available cell source to be further investigated for craniofacial bone regeneration.

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The J. of Pharmacology and Exp. Ther. | The Journal of PHARMACOLOGY And Experimental Therapeutics | 353:102–111, April 2015 IF 3.972

Interactions between Bupropion and 3,4-Methylenedioxymethamphetamine in Healthy Subjects

Yasmin Schmid*, Anna Rickli*, Antonia Schaffner, Urs Duthaler, Eric Grouzmann, Cédric M. Hysek, and Matthias E. Liechti

Abstract

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy")is a popular recreational drug. The aim of the present study was to explore the role of dopamine in the psychotropic effects of MDMA using bupropion to inhibit the dopamine and norepinephrine transporters through which MDMA releases dopamine and norepinephrine. The pharmacodynamic and pharmacokinetic interactions between bupropion and MDMA in 16 healthy subjects were investigated using a double-blind, placebo-controlled, crossover design. Bupropion reduced the MDMA-induced elevations in plasma norepinephrine concentrations and the heart rate response to MDMA. In contrast, bupropion increased plasma MDMA concentrations and prolonged its subjective effects. Conversely, MDMA increased plasma bupropion concentrations. These results indicate a role for the transporter-mediated release of norepinephrine in the cardiostimulant effects of MDMA but do not support a modulatory role for dopamine in the mood effects of MDMA. These results also indicate that the use of MDMA during therapy with bupropion may result in higher plasma concentrations of both MDMA and bupropion and enhanced mood effects but also result in lower cardiac stimulation.

Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland (Y.S., A.R., A.S., U.D., C.M.H., M.E.L.); and Biomedicine Service, University Hospital Lausanne, Lausanne, Switzerland (E.G.)
*These authors contributed equally to this work.

Selected publications by DBM members

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

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

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

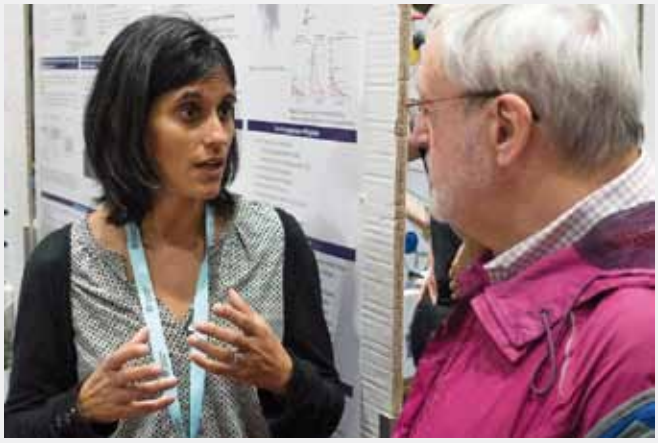
If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is November 30, 2015

Impressions from the Uninacht

An impressive number of approx. 15'000 visitors attended the Uni-Nacht on September 18, 2015. A prominent piece to the "University puzzle" were the contributions by 12 DBM research groups: experiments, games, exhibitions, demonstrations, presentations, talks, interviews, etc. The impressions on this page not only demonstrate the variety of research in our department represented at the Uni-Nacht but also show the extraordinary commitment of our researchers who enthusiastically shared their passion from 6pm to midnight.

The next opportunity to present the DBM to the general public and to everyone interested in our department will be the "Tag der Biomedizin" at DBM-Hebelstrasse and DBM-Mattenstrasse on Saturday April 9, 2016. Please save the date.



Photos: Frank Neumann

With sadness and sorrow we say goodbye to Renate Looser, who passed away after loosing the fight with cancer. She left us too early, but left behind memories and a legacy that will last. Renate worked as a technician in my research group. Her skills and expertise made her an asset, but it was her personality and her communication skills that gained her respect and a leading role within our group and beyond. She created a unique spirit of collaboration and teamwork. We remember her for her many contributions and for her friendship and we miss her very much.

Radek Skoda

DEPARTEMENT BIOMEDIZIN HEBELSTRASSE

Sara Meyer
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Veronica Baldoneschi
Oncology Surgery
Maurizio Cortada
Inner Ear Research
Philippe Dehio
Immunobiology
Paul Erne
Signal Transduction
Barbara Erni
Clinical Neuroimmunology
Yasmin Grether
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Experimental Virology
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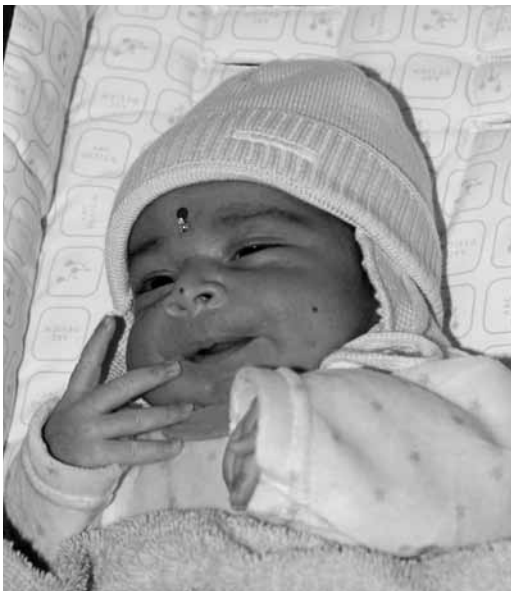
Transplantation Virology
Tünde Fekete
Experimental Rheumatology

Congratulations

Das DBM gratuliert ganz herzlich!

Candice Meira Bokalot
Geboren am 12.06.2015



Maanvitha Simha Uda
Geboren am 05.09.2015

Herzlich willkommen, allerseits!

Gefüllte Rote Bete auf russische Art

(Farschirowannaja swjokla)

Zutaten:
4 mittelgrosse Rote Bete
200 g Hackfleisch vom Rind
100 g Champignons
2 mittelgrosse Zwiebeln
100 g Butter
3 EL Öl
1 EL Essig
Salz
Pfeffer, aus der Mühle

Zubereitung:

Arbeitszeit: ca. 45 Min. / Schwierigkeitsgrad: normal / Kalorien p. P.: ca. 450 kcal

Die Rote Bete schälen. In einen Topf mit kaltem Wasser geben, den Essig zufügen und etwa 45 Minuten garen. Herausnehmen und abtropfen lassen.

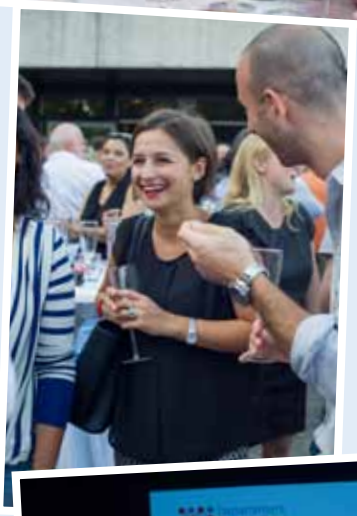
Champignons putzen und klein schneiden. Zwiebeln abziehen und fein würfeln. Die Hälfte der Butter in einem Topf erhitzen, die Champignons und die Zwiebeln darin etwa 10 Minuten braten. Das Hackfleisch mit der Pilz-Zwiebel-Mischung vermengen und mit Salz und Pfeffer würzen.

Von den roten Beten jeweils einen Deckel abschneiden und die Knollen mit einem Löffel aushöhlen.

Die Hackmischung in die Rote Bete füllen, den Deckel aufsetzen und die Rote Bete mit 100 ml Wasser und dem Öl in einen Bräter geben. Die restliche Butter in Flöckchen darauf verteilen.

Die Rote Bete zugedeckt im vorgeheizten Backofen bei 220° auf der mittleren Schiene etwa 55 Minuten garen.

15 years Department of Biomedicine




15th Anniversary of the
Departement of Biomedicine
2000 - 2015
UKBB


Basel.
Forschungszentrum im Medizin-Bereich

Japan

Japan is my home country. Located in East Asia, the land is 378,000 km^2 and an island nation consisting of five mainland and 6847 small islands. Kyushu, one of the mainland islands (indicated in red on Fig.1, area 42000 km^2) is around the same size as Switzerland.

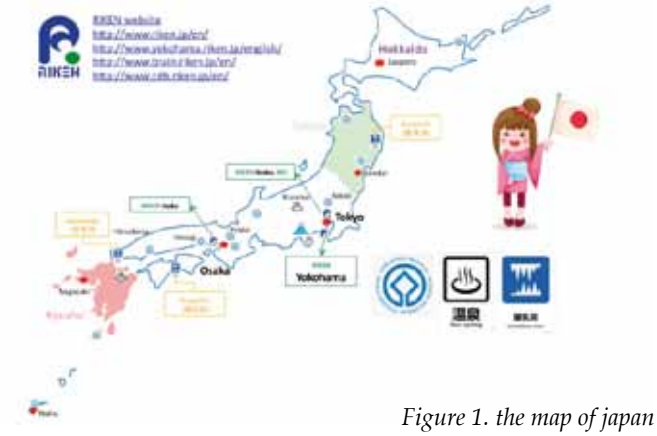


Figure 1. the map of japan

-Mountain-

Switzerland has many mountains and everyone can climb up by train and enjoy the excellent panorama view from 3454m height (Jungfraujoch station). In Japan, we have the Mount-Fuji (the top is 3776m high) that has a very beautiful shape (Fig.2). But unfortunately we can only reach to 2380m by bus, and then we need to climb the rest. Many people just enjoy seeing the shape of Mount-Fuji from a distance.

Figure 2. Mount-Fuji

-Hot Spring-

I visited Leukerbad hot spring in June, 2015 (amount of discharge of natural hot water is 2,708 litter/minute). The small caverned bath tub in Therme was really good. If you also love hot springs, we have a thousand hot springs all over Japan. Our hot springs are bigger and have a wide variety of health benefits due to the different content of minerals. We also have unique bathing styles (for example, Sunayu or Sunamushi where you sleep on the beach covered with the warm sand by the hot spring). Kusatsu-onsen (Fig.3) is one of my favourite hot springs (amount of discharge is 23,313 litter /minute).

Figure 3. hot springs

-Yokohama-

I was born and grew up in Yokohama, a city south of the capital Tokyo. Yokohama is the 2nd biggest city of Japan and one of the major ports opened to foreign trade since 1859. Yokohama's population is now 3,689,000 people, it is about 21 times bigger than Basel-Stadt (174,000 people). Yokohama has the biggest Chinatown in East Asia.

Figure 4. the night view of Yokohama and Chinatown

-RIKEN-

I cannot overlook introducing the Yokohama Campus of RIKEN. I worked there for 8 years before Harvard. RIKEN is the only and largest comprehensive institute in Japan that carries out all fields of natural sciences from basic research to applied research. RIKEN has three major campuses in Kobe, Yokohama and Wako. The Kobe campus focuses on Developmental Biology and Life Science. The Wako campus has the Brain Science Center (BSI) and all kinds of research. The Yokohama campus is active in the area of Life Science, new medical science for the future human health.

Figure 5. RIKEN Yokohama campus

These campuses always recruit post-docs and professors globally. If you are interested in doing research at RIKEN, please check their websites above (Fig.1). For grad-students and post-docs who are interested in neuroscience, BSI offers a summer program every year (http://www.brain.riken.jp/en/summer/). It is very good opportunity to gain science experience and discover Japan.

Alternatively you may be interested in an academic conference. MBSJ (the molecular biology society of Japan) has the annual meeting for 2016 in Yokohama from November 30 to December 2nd (http://www.mbsj.jp/en/index.html). The Japan Neuroscience Society also has the annual meeting for 2016 in Yokohama between July 19 and 22 (http://www.jnss.org/en/meeting/).

-Sightseeing-

If you visit Japan for the BSI summer program, for a conference or for the Tokyo 2020 Olympic Games, we have 19 UNESCO-designated World Heritage sites. One place to visit near Tokyo would be the Nikko temples in Tochigi. You can easily go there for one day trip by train.

Figure 6. Nikko temples

I myself always enjoy trips with a theme. I picked up my three top choices below.

Festival: http://www.tohokumatsuri.jp/english/index.html

Figure 7. Festival in Tohoku region

Limestone caves: http://www.iwate-ryusendo.jp/top.html
http://www.ryugadou.or.jp/about.html
http://english.karusuto.com/

Figure 8. limestone cave

Castle: http://www.japanese-castle-explorer.com/

Figure 9. Himeji castle, Unesco world heritage site

I hope you will enjoy this article and get a sense of familiarity with Japan!

Mari's briefly bio-sketch

I majored in the histopathology of Fish from the graduate school of Nagasaki University. After being involved in Molecular biology research at RIKEN, I jumped into the neuroscience field and worked as lab manager for 8 years at Harvard University. I joined the Brain and Sound Lab at the DBM in March 2015. ***Mari Nakamura***

Talking about books

Some years ago, my friend Daryl asked me to join his newly founded book and movie club. He had already found some other members, all medical students like us. But after only two books and one or two movie nights the club rapidly faded away due to the dramatic dropout rate. *"So it goes." (1)*

With this in mind, I was skeptical when Daryl wanted to found a new book club this year. But I still love books *("Überall Bücher! Die Wände waren mit überfüllten, doch ordentlichen Regalen bestückt. Den Wandanstrich konnte man fast nirgends sehen (…) Der Anblick gehörte zu den schönsten, die Liesel Meminger je gesehen hatte. Erfüllt von diesem Wunder, lächelte sie." (2))*, and like to talk about them, so it was worth the second trial. We recruited our first members at the end of January (perhaps you remember my advertisement hanging on the second floor by the elevators) and met for the first time in early February after reading the first half of "Die Bücherdiebin" by Markus Zusak.

Now there are four people in the club. That's not a lot, but enough to have interesting discussions even if not everybody can attend every meeting or has time to read the current book. Daryl and I are, of course, still medics, but we also have now a psychologist and an architectural draftswoman, perhaps that's why it works this time.

It has never been the idea of our book club to agonize ourselves over high literature and to discuss it *("Was sollte das bedeuten? Gut, es war eine Anspielung auf das Buch von James Joyce. Aber…" (3), "Zu Wills Erleichterung fand nicht nur das ganze intellektuelle Gerede endlich ein Ende…" (4))*, we've had enough of that during school. The idea is to read popular books we'd read anyway and then have the opportunity to talk about them over a coffee (we always meet at Starbucks) with people who just read the same. You will never find us reading "A la recherche du temps perdu" or "Faust II". We'd rather read crime novels, fantasy, satire, autobiographies and thrillers. The only criterion we have is that no-one of the group has read the book before.

At the beginning we tried to choose what to read in the plenum, but we soon realized, that even with only four people it is much easier to take turns in choosing the next book. This has the nice side effect that we nearly always choose books that the others would not have considered for themselves, or didn't even hear about before. Thus we learn about new authors and broaden our horizon *("Ich wusste, dass es irgendwo weit weg Städte gab, hatte sie aber nicht gesehen. Ob die Erde rund oder flach ist, wusste ich nicht, ich hatte überhaupt keine Vorstellung von der Welt!" (5))*

When people who like reading meet, one always gets good recommendations: *Hard-Boiled Wonderland and the End of the World* by Haruki Murakami, the Discworld novels by Tarry Prattchet or Die Therapie by Sebastian Fitzek for example.

We also discuss the advantages and disadvantages of e-book readers and big bookshelves (I recently moved. All of our packing cases were at least half full of books. That's when I thought about buying an

e-book reader for the first time in my life…), movie adaptations (the good, the bad and the ugly) or buying on amazon vs. in bookstores. Sometimes we talk a little about politics, after reading "Noah", or about history, after reading "Slaughterhouse Five". It never gets boring.

We have learned that our tastes and opinions differ most of the time. But on some things we agree upon, for example that *Wittgenstein's Mistress* is an awful book. Most of the time it is unreadable. *"Die Sprache ist in dieser Hinsicht häufig ungenau, habe ich festgestellt." (6)* We didn't read it to the end and one of us even burned it! That's one of the true advantages of a hardcopy.

Would you like to join our club? ("Sie wollen mich anwerben?, *fragte er die anonyme Unbekannte, die offenbar über die Macht verfügte, auf hoher See zu einem Häftling der US-Marine durchgestellt zu werden." (7))* Nevermind if you do not speak or read German, we all read and speak English. Just write me an e-mail (f.schulze@unibas.ch) or ask me when you see me on the corridor. See you soon!

Friederike Schulze

(1) Vonnegut, K. (1969). *Slaughterhouse Five*. New York, Dell Publishing.
(2) Zusak, M. (2008). Die Bücherdiebin. München, Blanvalet Verlag.
(3) Steinfest. H. (2008). Mariaschwarz. München, Piper Verlag.
(4) Barlow, T. (2014). Baba Jaga. Hamburg, Hoffman und Campe Verlag
(5) Souad (2005). Bei lebendigem Leib, München, Blanvalet Verlag
(6) Markson, D. (2013). Wittgensteins Mätresse, Berlin, Berlin-Verlag
(7) Fitzek, S. (2013). Noah, Köln, Bastei-Lübbe

The book club. From the left: Dominique, Natascha, Fritzi and Daryl.

The strongest run in Switzerland - FISHERMAN'S FRIEND StrongmanRun

It was a hot summer day, the 6th June 2015. It felt like the sun would burn our skin. A good sunscreen was necessary. The tension was already rising, when we stepped out of the car. A runway of a small airport was now a big parking lot. We put on the sun cream and took with us only what was necessary for the run. On the way to the bus, we started eating our high-calorie foods. After a 5-minute walk next to a line of parked cars we reached the shuttle bus which would bring us to Engelberg. Our co-worker Nicola had told us about the run. In the crammed shuttle bus we started thinking about what would await us. We knew some things from Nicola, but we didn't know what had changed this year and how hard it was really going to be. After a while we reached the mountains. On top of the mountains there was still snow, but when we stepped out of the bus, we could only feel the heat. The sun was burning, even more at 1'000 meters above sea level. We ate our last breads, fully stuffed with butter and Nutella. The butter and chocolate layers were as thick as the bread. We also ate some nut bars of course, to gain yet more energy. Then it was time to get our run number. In the icehockey hall we received the run number and a chip. The chip tracked our whole run and the time so you couldn't take a shortcut to cheat.

Strangely dressed people in costumes were around us everywhere. We were early. We didn't want to get in a hurry. We decided to check out the starting point and the marketing stand. Then it was time to get to the starting point. The crowd was already gathering to get into the starting queue. We felt like a herd of goats with more than 7'000 participants. We still had 45 minutes to start squeezed into this mass of people. Then the DJ started kicking in and the warm-up started, but it felt more like a big party for athletes. While Marc was saving his energy for the run, I couldn't resist dancing along with the crowd. La Olas were getting up and down through-out the

crowd. To prevent heatstroke the staff was hosing us down with ice-cold water. Not everybody liked it, but it's called the Strongman Run for a reason and it was little foretaste of what we could expect.

Finally the whistle blew for the start. In front of us there were still about 5'000 athletes to go. The staff filled up our bottles with water. We needed it. Another 45 minutes passed before we could actually start and we were waiting in the sun without a hint of shade. Close to the beginning we decided not to go together as our skills were too different. Then it started. It was time to ignore the music and focus on the run. We had to climb up a fishnet at the beginning. On top, there was a boardwalk made out of tree trunks. But it was not that easy of course. They put in some trees that you had to dodge. It looked like a small forest up there. After these obstacles, you had to go down a set of stairs made out of hay. That was easy. But the pile of tires directly afterwards was already a bit harder to pass. Finally we could run a bit (about 200 meters) and then the next obstacle was already waiting. We had to get under a net. The ground was sludge. No hesitating was allowed for a real strongman. So we jumped in. I noticed a familiar taste at the beginning. My grandparents were farmers and they mixed the sludge with dung. I realized that once you closed your mouth then nothing could come in. After a few meters crawling I realized that my knees started to hurt while on all fours. I knew then that they had also mixed the dung with rough sand. My knees started bleeding. Suddenly I hit something. Stones were also hidden in the sludge. We had to be careful of injuries in this obstacle. Finally we got out of it. I tried to shake of some sludge, but there wasn't a chance. It stuck to us like glue. Every part of our bodies felt very heavy now because we were covered with sludge. There was no time to complain. We had to continue. Smelling terrible the next obstacle was already waiting for us. There was a puddle in front of a haystack. You could not jump with full speed over it because of the puddle before it. We had to use power to get over it. Immediately afterwards there was a famous obstacle - the ski-jump. But instead of flying down, we had to run or climb up it. With the sludge on us it was even harder. At this point I thought for a short moment: "You can turn around and go home anytime. Other people are relaxing in the open-air pool. But stop, we had already overcome 5 obstacles and we hadn't even passed the 1 km mark. They made about 36

obstacles on 18,5 kilometer course". I knew then, it would be easier afterwards. All the hard preparation couldn't have been for nothing. After the ski-jump there was no break in the obstacles. There was a pile of tree trunks to overcome. Finally the obstacles stopped. But the running didn't feel easier, because we had to run up the hill. On the way up, there was a restaurant. I noticed a board and on it they had posted that the restaurant had ice cream that day. How could they do this to us! After finally mastering the hill a funny obstacle was waiting for us. It was called "Und tschüss" (good bye). It was a water slide. After all the strain, it didn't feel that funny anymore. At the end of the slide there was puddle, perfect to clean the sludge away. Completely wet, we started running a longer track.

Motivation came back! I started to overtake other runners. That gave me the necessary motivation to continue, with even more enthusiasm because I knew that was my strength. On the next hill there was a small wooden stair as the next obstacle. That was easy to pass. We didn't lose time there at all. Then you had to run a kilometer to the next obstacle. The third kilometer started. You had to jump over and crawl under metal bars. At the end there we had to crawl under a net again, this time without sludge. Not long after that there was a pile of tires again. That was exhausting. I didn't expect it would be that hard to get over such a pile. Starting kilometer four, there was a mud bath. We haven't been clean for long. Some people had troubles getting out of it because it was sticky but we managed it with success. However, there was another problem. The mud was mixed with sand as well. The mud was more fluid than the previous sludge. Now the sand was everywhere, including in our shoes and socks. Marc chose the hard way. He continued with the sand in

his shoes filing his feet. After a while a stand offering something to drink and nut bars appeared. I always took two or three cups to drink because we lost so much fluid during the run. I knew that the sand in my shoes could cause blisters. After a kilometre I saw a small stream so I took off my shoes and washed them quickly. Without sand in my shoes, I could continue running faster. Then an additional obstacle appeared: The other runners. Because I was faster than a lot of other runners, I always had to dodge them. Some girls were just walking and chatting, blocking the whole track. There was no time to get annoyed with such things. If these obstacles annoyed you then you were participating in the wrong run. The next obstacle was a fishnet. Again, it was an easy one. It was a roughly 30 meters long net where you just had to duck und run. The next obstacle was called the "Kinderbecken" (children's pool). We had to climb through a skip (container) filled with water. "That was easy", I thought. But then, the next thing we saw was a board and on it was written "max 7 degrees" and "minimum 1.4 meters". It was the river and it was as cold as ice. It probably was melt water from the glacier or snow in the mountains. Now that was the children's pool. For those with health issues there was an alternative route called "pussy lane". Nobody realized it. We were so focused on the obstacles, that we didn't notice it. The first step into the river was hard. We kneeled into the river to wash of the mud and to cool down a bit. With every step in the cold river, we realized we were feeling better. So we walked through the river with as much of our body in it as we could. What had sounded like a hard obstacle in the beginning was actually something really supportive.

We didn't feel pain any more. It was like we were starting again from the beginning. We could speed up our run again. More and more people were overtaken, than were overtaking us. And we were clean again. The next obstacle was made to cross the street. We had to get over a set of wooden stairs, but the steps were tiny so you had to pay attention how you were standing on them. After a short run of 500 meters the next obstacle was waiting. It was called "Ölwechsel" (oil change). You had to crawl under some trailers (of a truck). It was getting harder and harder to duck every time, and as well to climb over obstacles. After another short run, we had to climb over some wooden stairs again, but this time it was a bit different. The last time you could run on it, this time you really had to climb. After a while, the "Hurrikan" came. A snow machine was blowing snow against you. I crossed it close to the machine to get cooled down more but it was a mistake. The snow or water was very strong there and it felt like a rain of needles on the skin. Completely wet a really mean obstacle was waiting for us. There were some power cords hanging down that you had to dodge. You can imagine how the electricity liked our wet bodies. I had luck. Not one power cord unloaded its electricity on me while Marc was not that lucky. A cable was fully charged and hit him and feet started slip away from the ground. Focused on the power cords, again nobody noticed the pussy lane. Then there was another short run, but this time through the village of Engelberg. Some inhabitants were really nice, but some not. Some kids were screaming things like "you only live once" at us. Other inhabitants were offering us water in cups or hosing us with water. At one point, some inhabitants were having a party in their garden. They screamed funny things at us and offered beer, which they provided with a self-made lifting block over the river. We had to run again for a while. Then we had to cross a street with

another wooden stair as before. After that they had put a gas tank on a haystack. Because it was round, you couldn't get a grip anywhere. Some people had real troubles getting over it. Some of them tried it two or three times until they got over it. We luckily had enough energy to jump on it with speed and we got over it easily, at least in the first round. A slightly bigger haystack came next. There were four stairs made out of this haystack, but one stair was about 1.2 meters high. In the first round, we could manage this easy. But in the second round it was more like climbing. Finally after a short run the last obstacle was waiting. It was the Halloween party. You got into a room with filled with artificial fog. You couldn't see your hand in front of your face anymore and there was also a strobe light flashing. You felt dizzy very quickly in this room, but you didn't know what was coming. Suddenly realized that the girl in front of me had started climbing so I knew there was something. It was yet another haystack. In the next moment, something from the left was splashing water at me. My senses were really irritated. You really had to focus on climbing over the haystacks to avoid falling over them.

And then the second round started, this time beginning at the ski-jump. Everybody told us it would be annoying knowing you have to do all the obstacles again, but somehow it was the other way round. We knew with every obstacle we overcame, we had gotten one step closer to the goal. At kilometer 16 I felt a slight pain in my right knee. I was getting cramps but there was no stopping so close to the goal. I didn't run that fast anymore. A German runner noticed that I was having cramps. He shouted at me not to stop running because if I did the cramps would get worse. What a nice hint. I started running faster again. It was really getting better, even though the cramps didn't fully go away. The pile of tires was really brutal. Every time I got stuck in the tires I got a really bad cramp but I turned off my brain and continued. At the end there was a jam. A lot of people were getting really slow over the haystack, the forest and the fishnet that led to the goal. It made the pain worse at the end. But knowing that the finish line was waiting after this obstacle gave us the motivation to overcome this last obstacle. Finally we passed the finish line. We received our wanted "Finisher-medal" and "Finisher-T-Shirt". It was an incredible feeling, that we could manage this exhausting run. I made it to 1'358th while Marc managed place 3'428th. This was a satisfying result.

Proud that we made it, we felt damaged heading to the showers. After the shower we felt much better again. The first thing we had to do then was write a message to our family that we were fine and had no injuries. Of course we had to take a selfie in the finisher shirts with the medals, before heading back home in the shuttle bus. Even though it was such an exhausting and painful run, we had laugh about quite a lot of things. For instance Marc mentioned once, that every time he overcame an obstacle he saw that one big mountain. And I was like "Which mountain?". I was so focused on the obstacles that I didn't even realize the beautiful view you had during the run. What came next?

Due to our good preparation, we didn't stop the training. After two or three days we went running again without any troubles. For training, we went to the nearest mountain, the Weissenstein in Kanton Solothurn. We'd run up the mountain and back down even though it was nearly raining ice. It was good preparation to become harder for the run. And no, we didn't take the cable car up. By the way, it is a nice mountain to go hiking on as well and it's not that far away. From the top, you can see the whole mountain when the sun is shining. And yes, we are definitely up for the next Strongman Run 2016 (but maybe with a costume then). If you like suffering and having fun, then don't hesitate to preregister for the FISHERMAN'S FRIEND Strongman Run 2016!

Ilija Lujic and Marc Bichsel

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

Very Important DBM-IT News...

1. Request for extension of account – mail from URZ “Ihr Account läuft aus”

Recently many of the staff at the DBM have started to receive emails from the university computer services department informing them that their email account is expiring. This email has nothing to do with the message that you must change your password annually.

All those who were never employed by the university, who are no longer employed by the university or who have graduated are affected.

The extension request must be initiated by the staff member. After that it will be discussed with the relevant research group leader before being confirmed. Following that process the account will be extended.

Please initiate the request once you receive the first email. If you ignore all of the emails that are sent then your account will automatically be deactivated. It requires considerable effort from the DBM-IT to reactivate accounts that have been deactivated and it can take up to two working days for the account to be reactivated and usuable.

Exact directions on this process can be found on http://gadget.dbm.unibas.ch an (under the topic “Viaweb”). After that you can go to https://viaweb.unibas.ch and initiate the extension request.

2. Changing your email password

The password for all Unibas email accounts must be changed at least once per year. This can also be done at http://viaweb.unibas.ch

You will receive multiple emails that will prompt you to do this. It is also important that you do this once notified; otherwise the account will be blocked.

A reactivation is a great deal of work for DBM-IT. In the worst case you will have to make a personal request to the URZ to request a reactivation. In such cases you will have to personally show your identification to the secretary of the URZ.

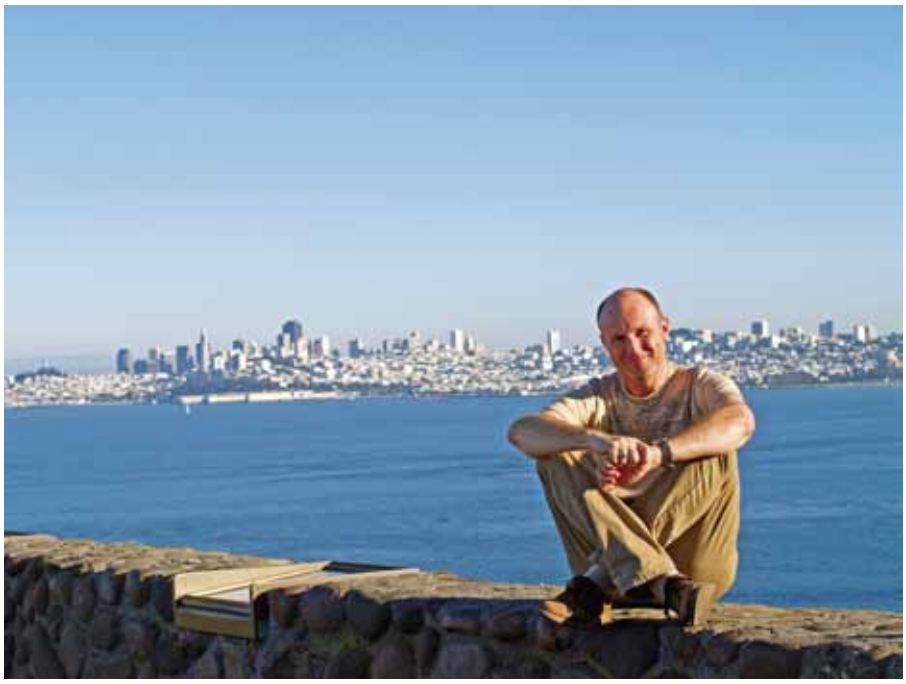
Please note that once you have successfully changed your password you must also update the logins on your Mac or PC. If you have selected the option “automatically remember password” then the printer services and the connection to the file servers will also be affected by the change.
If you have problems with printing after you have changed your password then you can try the following:

- On the Mac open /HD/Applications/Utilities/Keychain
- Search for the printer (e.g. DBM204-211) and delete all of the printers found
- Open a Program (e.g. Word) and print any document as a test
- You will then be prompted to enter your username and password
- Once you click on “save password” it will be saved in the keychain and you won’t have to enter it every time in the future

Heute: Raimond Dollnik, Anatomie

Hätte mir irgendjemand prophezeit, dass ich einmal bei der Universität arbeiten würde, ich hätte wahrscheinlich sehr an ihrem oder seinem Verstand gezweifelt.

Und doch: Seit zwölf Jahren habe ich nun bei der Universität Basel meinen Arbeitsplatz. Elf Jahre davon im Studiendekanat der Medizinischen Fakultät und seit einem Jahr in der Administration des DBM Pestalozzistrasse (landläufig noch als Anatomisches Institut bekannt). Und es geht mir sehr gut dabei! Ich arbeite in einem multikulturellen Umfeld, treffe tagtäglich viele interessante Menschen und darf dabei mitwirken, dass auch in der Zukunft unser Land mit guten Ärzten versorgt wird. Gerade dieser Umgang mit der jungen, engagierten Generation macht die Aufgabe hier so interessant und gibt ihr einen besonderen Stellenwert. Meine Kolleginnen und Kollegen hier im Haus und in allen Abteilungen, mit denen ich tagtäglich zu tun habe, sind etwas Besonderes und ich möchte sie nicht missen.



Meine beruflichen Wurzeln liegen jedoch im Tourismus. In jener Zeit konnte es für mich nichts Schöneres geben, als Menschen dabei zu unterstützen, dass ihre kostbarsten Wochen des Jahres auch etwas ganz Besonders werden. So war ich viele Jahre im Reisebüro und bei Fluggesellschaften tätig, die alle in dieser Form nicht mehr existieren (Stichwort Imholz Reisen, Crossair oder Swissair). Kaum eine Branche hat in den letzten Jahren einen solchen Wandel erlebt wie die Reisebranche. Heute ist Reisen kein Privileg mehr. Man steigt in ein Flugzeug wie in den Stadtbus. Ich bedauere diese Entwicklung ein wenig. Viele Destinationen verlieren ihre kulturelle Identität und, seien wir ehrlich, die wenigsten von uns bereiten sich noch gut auf eine Reise vor. Die «dos» und die «don'ts», die zu einem grossen Teil eine Gesellschaft ausmachen, werden kaum noch beachtet.

Ich durfte in den Jahren, die ich im Tourismus tätig war, sehr viel erleben und konnte bereits in der Zeit vor Easyjet & Co, viel von der Welt sehen. Meine Lieblingsdestination wurde San Francisco an der amerikanischen Westküste und ich hatte jedes Mal, wenn ich dorthin kam, das Gefühl, «nach Hause» zu kommen.

In der Zwischenzeit stehen Langstreckenflüge viel seltener auf dem Programm und ich habe als Ferienziel die französische Atlantikküste kennen- und liebengelernt. Das

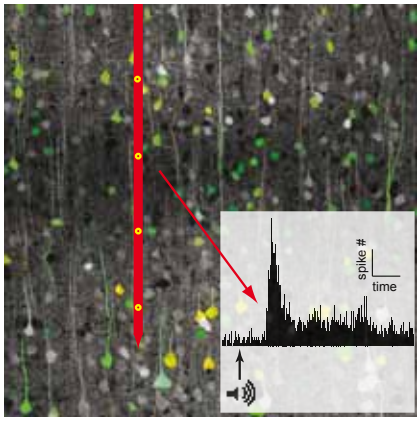
Vendée hat es mir dabei besonders angetan, eine Gegend, die hier eher unbekannt, bei den Franzosen als Feriendestination jedoch sehr beliebt ist. Bei Ebbe über die Passage du Gois auf die Insel Noirmoutier zu fahren, ist ein unvergessliches Erlebnis (http://www.passagedugois.com/). Bei Flut ist von dieser Strasse nichts zu sehen und die «Rettungstürme», die entlang der Strasse errichtet wurden, zeugen davon, dass so mancher, von der «herangaloppierenden» Flut überrascht, sich in die Höhe retten musste, während sein Fahrzeug vom Wasser fortgetragen wurde.

Im Vendée zieht ein Freizeitpark, der ganz anders ist als alle anderen, jedes Jahr viele Besucher an und in seinen Bann: der Puy du Fou (http://www.puydufou.com/de/). Achterbahnen sucht man dort vergebens. Dafür werden spektakuläre Shows geboten. Ich habe noch keinen erlebt, der z.B. beim «Bal des Oiseaux Fantômes» nicht verzaubert wurde. Aber auch bei den Wikingern, im römischen Kolosseum u.a. mit einem Wagenrennen à la Ben Hur oder bei dem Reiteraufführungen vor einer traumhaften Fassade wird der Zuschauer in faszinierende Welten entführt. In den Sommermonaten präsentieren zudem etwa 1'200 Darsteller jeweils in den Nächten von Freitag auf Samstag und Samstag auf Sonntag auf einer 23 Hektar grossen «Bühne» ein unvergleichliche Musik-Tanz-Feuerwerk-Spektakel, «La Cinéscénie», in der die Geschichte des Vendée erzählt wird.

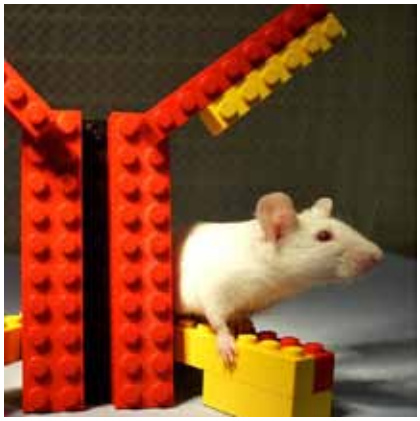
So schön das Reisen ist, gerne komme ich immer wieder hierher zurück. Nach einem Bummel durch Basel oder einem ausgiebigen Spaziergang in den Franches-Montagnes sind die Lebensgeister wieder aktiviert und die Batterien wieder aufgeladen. Kaum eine Region ist so abwechslungsreich, vielseitig, modern und traditionell wie die unsrige. Ja, hier bin ich daheim und hier geht's mir gut!

VORSCHAU PREVIEW

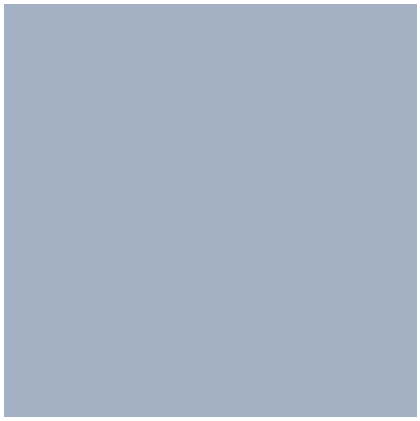
In der nächsten Ausgabe . . .



. . . schwingt uns Tania Rinaldi ein auf „Brain and Sound“



. . . lernen wir mit Caroline Johner die Tierbetriebe besser kennen



. . . feiern wir mit Martine Singer Französische Weihnachten

. . . wird es very british mit Hilary Ireland

. . . lassen wir das Jahr 2015 Revue passieren

Im Herbst
Im Herbst steht in den Gärten die Stille,
für die wir keine Zeit haben.

Aubertin Victor, 1870–1928