DBM FACTS

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Universität Basel, Universitätsspital Basel und
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Translational Research in Neuromuscular Diseases | A new GMP lab at the DBM | From Asia to Europe less than in one hour!

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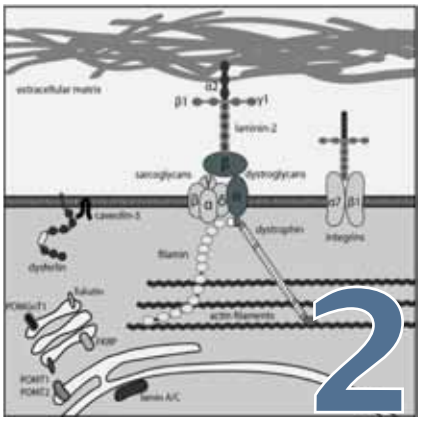

Translational Research in Neuromuscular Diseases
from Michael Sinnreich

A new GMP lab at the DBM
from Werner Krenger

From Asia to Europe less than in one hour!
from Artem Kalinichenko

Reykjavik – Nordic City by the Sea
from Elfa and Elín Ellertsdætur

So schmeckt der Bodensee

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

In der nun vorliegenden Ausgabe stellt uns Michael Sinnreich ab Seite 3 die neuesten Forschungsinhalte aus seinem Labor "Neuromuscular Research" vor. Werner Krenger gibt uns einen Einblick in die Tätigkeit der neu aufgebauten GMP Facility am DBM (ab Seite 8). Ab Seite 15 folgen dann die neuesten Publikationen aus dem DBM, die diesmal sehr gut ausgefallen sind.

Wichtige Positionen konnten besetzt werden: Caroline Johner hat am 1. April 2014 ihre Tätigkeit als Leiterin der Mouse Core Facility der Universität aufgenommen, zu der auch alle Versuchsstationen des DBM gehören. Roy Allenspach wird zum 1. Juli 2014 am DBM Hebelstrasse seine neue Funktion als Betriebsassistent (Nachfolge Yves Hartmann) übernehmen. Claudio Cannavo übernimmt ebenfalls ab dem 1. Juli 2014 den IT Support am DBM Mattenstrasse. An dieser Stelle allen ein herzliches Willkommen!

Dass Artem Kalinichenko nicht nur Ausdauer in der Forschung beweist, zeigt er ab Seite 34. Ab Seite 36 stellt uns Elin Ellertsdottir ihre Heimat Island vor und ein paar feine Rezepte vom Bodensee stimmen uns auf die schönsten Wochen des Jahres ein (ab Seite 40). Das Titelbild zeigt es schon – mit vollen Segeln geht es in den Sommer. Geniessen Sie Ihre Ferien!

Dear Readers

On page 3 of this edition Michael Sinnreich shares with us the latest research from his Lab "Neuromuscular Research". Werner Krenger gives us an insight into the function of the newly built GMP facility at the DBM (page 8). The latest publications from the DBM, which have turned out very well, follow on page 15.

Several important positions have been filled. Caroline Johner took up her position as head of the Mouse Core Facility at the university on April 1st 2014. On the 1st July 2014 Roy Allenspach will start as the new technical assistant (successor to Yves Hartmann). Claudio Cannavo will take over IT Support at DBM Mattenstrasse from the 1st of July 2014. We welcome them all to their new positions.

Artem Kalinichenko shows us that he doesn't just have endurance for research on page 34. From page 36 on Elin Ellertsdottir introduces us to her home, Iceland, and a couple of recipes from the Bodensee get us in the mood for the nicest weeks of the year (page 40). As we can see from the cover photo it is full sail ahead into the summer. Enjoy your holidays!

Translational Research in Neuromuscular Diseases

Introduction

In our interdisciplinary Neuromuscular Center within the Department of Neurology we care for patients with muscle, nerve and motor neuron diseases. Our research laboratory at the Pharmacenter develops therapeutic strategies for genetically determined diseases of skeletal muscle. Patients with these rare diseases face particular challenges, on the one hand there are those that are associated with the difficulties of obtaining a precise diagnosis and on the other hand, the difficulties that arise with progressive muscle weakness. As patients get weak they may become dependent on family members and loved ones for displacement, personal hygiene and feeding.

Muscular dystrophies is a general term for genetically determined diseases of muscle that show signs of necrosis and regeneration, fiber size variability as well as increased connective tissue when examined histologically (1). Historically, muscular dystrophies were subdivided according to their clinical phenotype (figure 1). This group of diseases is caused by mutations in a large variety of genes encoding proteins of the contractile apparatus of the muscle cell, structural proteins, enzymes, or nuclear proteins (2) (figure 2). The disease causing mutations lead, in most cases, to loss of function, but may also cause toxic gain of function. Although most mutations in muscular dystrophies encode altered proteins, in some instances the genetic alterations exert their pathogenic effect at the DNA or the RNA level (3). The obvious primary molecular targets for the treatment of muscular dystrophies are the affected genes and/or their respective products. Theoretically, the most effective strategy would be to correct the mutated DNA by genetic engineering. Although recent developments in genetic engineering are promising, this approach is still technically challenging, therefore current efforts focus on the development of pathophysiologically based treatment strategies (2).

The most commonly encountered forms of muscular dystrophy in adults are myotonic dystrophy (MD), facioscapulo-humeral muscular dystrophy (FSHD) and the

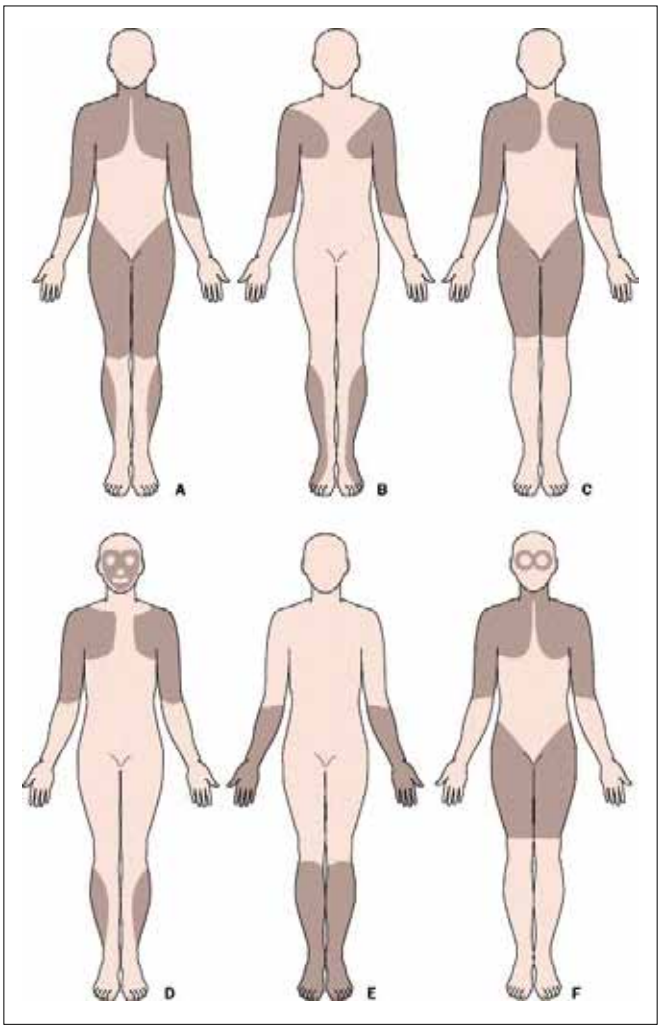

Figure 1: Classification of Muscular Dystrophies according to clinical phenotype. Shaded areas depict primarily affected muscle groups. A, Duchenne and Becker muscular dystrophy; B, Emery-Dreifuss muscular dystrophy; C, limb-girdle muscular dystrophy; D, facio-scapulo-humeral muscular dystrophy; E, distal myopathy; F, oculopharyngeal muscular dystrophy. From (14).

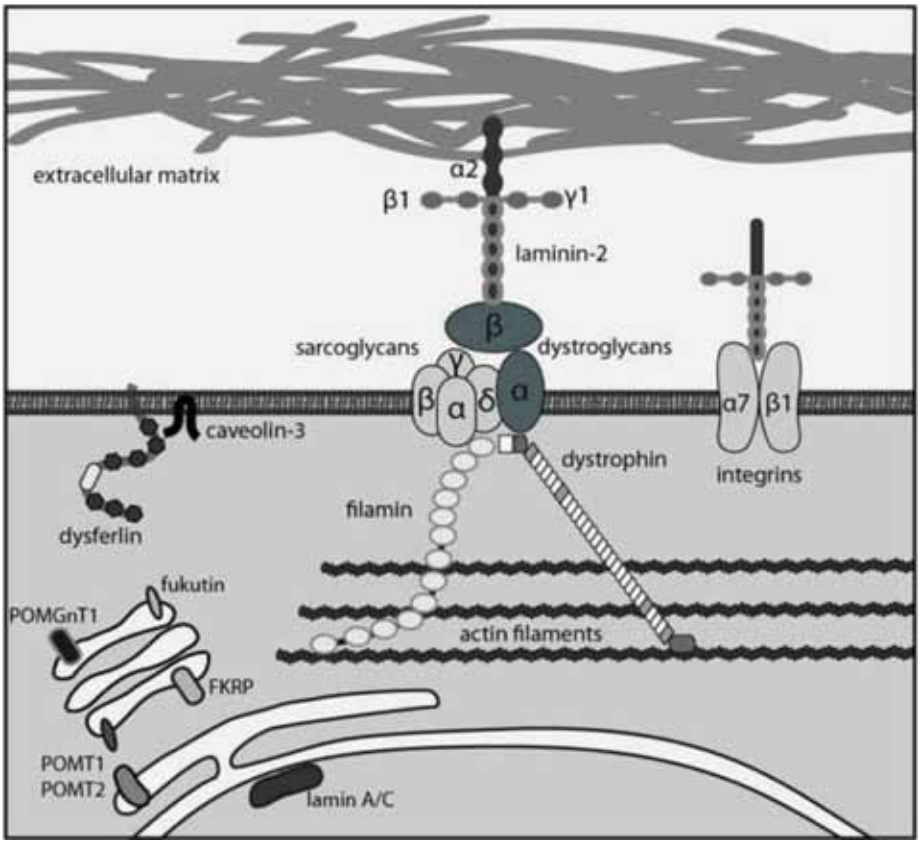

Figure 2: Molecular mechanism of muscle surface membrane repair. Upper panel: dysferlin recruits subsarcolemmal vesicles to the injury site. Fusion of vesicles leads to an exocitotic patch which reseals the membrane gap. Middle panel: missense mutated dysferlin is degraded by the proteasome and is no longer available to reseal membrane injuries, leading to degeneration of the muscle cell. Lower panel: Proteasome inhibitors salvage missense-mutated dysferlin from degradation. The salvaged protein can reseal membrane injuries in muscle cells. From (2).

large group of limb girdle muscular dystrophies (LGMD). The most common childhood form of muscular dystrophy is Duchenne muscular dystrophy (DMD) (figure 1). Here we discuss novel therapeutic strategies for dysferlinopathies, representing one of the most common subgroup of limb girdle muscular dystrophies, and for myotonic dystrophy, the most common muscular dystrophy in adults. In addition, translational research projects in our laboratory include gene therapeutic approaches for dysferlinopathies using viral vectors (4–6), the development of nucleic acid based therapies for facio-scapulo-humeral muscular dystrophy (FSHD), and, in collaboration with the laboratory of Prof. Markus Rüegg, the investigation of molecular mechanisms leading to muscle atrophy in diseases of skeletal muscle (7).

Limb Girdle Muscular Dystophies

The LGMDs are a heterogeneous group of muscle disorders characterized clinically by weakness and wasting in the muscles of the pelvic and shoulder girdle (1, 2). This group of disorders can be divided into two types according to the basis of their pattern of inheritance: type 1 – autosomal dominant, and type 2 – autosomal recessive. The dominantly inherited LGMDs are rare, representing less than 10% of all LGMDs. The more common autosomal recessive forms have a prevalence of about 1:15,000 to 1:100,000. LGMDs are further subdivided according to their different genetic loci (table 1 and figure 2).

Table 1: Limb Girdle Muscular Dystrophies

type	inheritance AD = autosomal dominant AR = autosomal rezessiv	gene	chromosome
LGMD 1A	AD	Myotilin	5q31
LGMD 1B	AD	Lamin A/C	1q22
LGMD 1C	AD	Caveolin	3p25
LGMD 1D	AD	DNAJ6	7q36
LGMD 1E	AD	DES	2q35
LGMD 2A	AR	Calpain-3	15q15.1-q21-
LGMD 2B	AR	Dysferlin	2p12-14
LGMD 2C	AR	g-sarcoglycan	13q12
LGMD 2D	AR	a-sarcoglycan	17q21
LGMD 2E	AR	b-sarcoglycan	4q12
LGMD 2F	AR	d-sarcoglycan	5q33-q34
LGMD 2G	AR	Telethonin	17q12
LGMD 2H	AR	TRIM32	9q33.2
LGMD 2I	AR	FKRP	19q13.32
LGMD 2J	AR	Titin	2q31
LGMD 2K	AR	POMT1	9q34.1
LGMD 2L	AR	ANO5	11p14-12
LGMD 2M	AR	Fukutin	9q31-33
LGMD 2N	AR	POMT2	14q24.3
LGMD 2O	AR	POMGNT1	1p34.1
LGMD 2Q	AR	PLEC1	8q24

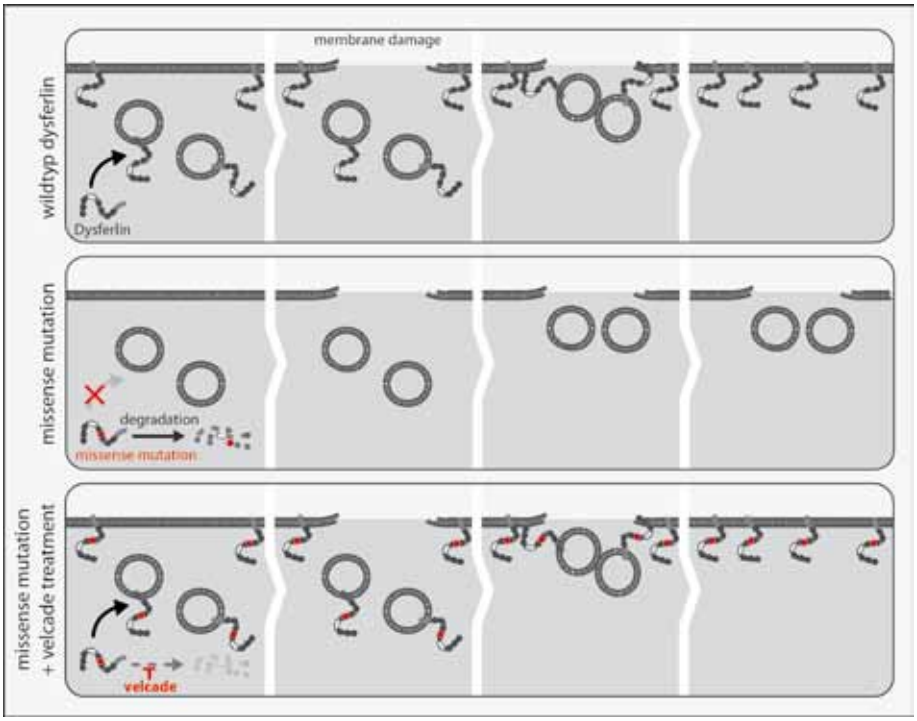

Figure 3: Missense mutated dysferlin can rescue defective membrane resealing. A plasma membrane repair assay was performed on patient derived myoblasts, which harbor the dysferlin missense allele R555W. Quantitative data of relative fluorescence intensity over time after laser-induced injury of patient-derived myoblasts treated with increasing concentrations of lactacystin (A) or bortezomib (Velcade) (C) are presented. B and D, show the fluorescence accumulation of the fluorescent FM1-43 dye over time at the plasma membrane injury site. The lack of fluorescence intensity increase at the wound site indicates that the injured plasma membrane has been resealed. Scale bars, 1 um. From (10).

Clinically, age at onset and rate of disease progression are variable in LGMDs, both within the same disease group and even within members of the same family, which points to the existence of modifying factors. Such phenotypic variability makes prediction of disease course difficult and should be considered when counseling patients. Currently, immunohistochemistry of histological sections and western blot analysis on muscle homogenates are performed as first diagnostic steps to determine the putative protein defect in LGMDs, which is then confirmed by DNA sequencing (1). We are developing a parallel sequencing platform as a diagnostic tool for patients with muscular dystrophies in order to shorten the diagnostic process and to reduce costs.

Dysferlinopathies

Dysferlin mutations account for about 20% of patients with the recessively inherited LGMDs. Dysferlin is a membrane protein of about 230kD, which contains several C2 motifs (8). These motifs are present in many membrane-associated proteins that bind calcium and phospholipids. Dysferlin is necessary for the repair of membrane tears in muscle cells, which arise during exercise (9). In dysferlin deficient muscle the plasma membrane cannot be restored following injury, leading to muscle fiber necrosis (figures 3 and 4).

Patients with dysferlinopathies present with two distinct phenotypes that are characterized by either proximal or distal weakness and wasting. Facial and pharyngeal muscles remain unaffected and cardiac, respiratory, or cognitive impairment is not part of the disease. Serum creatine kinase (CK) levels can be very high (up to 150 times normal) and, occasionally, inflammatory infiltrates are seen on skeletal muscle biopsy, which may be mistaken for an acquired inflammatory myopathy. Age of onset can be variable, but is mostly in the teenage years. Patients can be engaged in athletic activities prior to disease onset.

All pathogenic dysferlin mutations in patients reduce protein levels in skeletal muscle. Significantly reduced dysferlin levels in patients harboring missense mutations imply that dysferlin encoded by missense alleles is degraded by the cell's quality-control system (8). This system recognizes misfolded proteins and initiates their degradation. Our hypothesis is that dysferlin which harbors certain missense mutations might be functional, if salvaged from degradation. To this end we studied the degradation pathway of missense mutated dysferlin in patient derived myoblasts and measured dysferlin protein levels and resealing kinetics of laser-induced plasmalemmal wounds in response to treatment with vari-

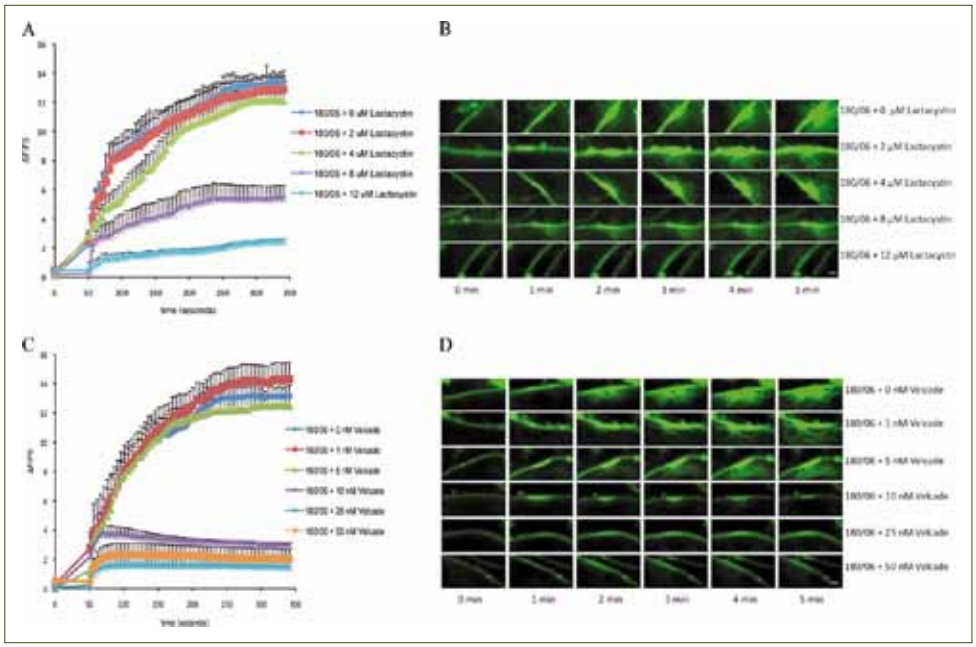

Figure 4: Molecular Pathomechanisms in Myotonic Dystrophy Type 1 (DM1). The molecular basis of DM1 is an expansion of an unstable repeat sequence in the 3' untranslated part of the DMPK gene. As the mutation is located in a noncoding region it does not alter the protein sequence, but leads to toxic RNA hairpins. Sequestration of the alternative splicing factor MBNL1 by expanded CUG-RNA leads to altered splicing of target mRNAs like the muscle-specific CLCN1 chloride channel. The missplicing of the chloride channel RNA leads to a loss of the chloride channel and to myotonia. We are screening for molecules that liberate MBNL1 from the toxic RNA hairpins and have thus the potential to reverse the molecular defect in DM1 patients. From (2).

ous inhibitors of the protein degradation machinery of the cell (10).

We showed that endogenous missense mutated dysferlin is degraded by the proteasome, and that inhibition of the proteasome by the proteasome inhibitors lactacystin or bortezomib markedly increases the levels of missense mutated dysferlin. The salvaged missense mutated dysferlin protein is functional as it restores plasma membrane resealing in cultured patient derived human myoblasts, and reverses their deficit in myotube formation (10). Our results suggest that proteasome inhibitors could be tested in clinical trials for patients harboring certain dysferlin missense mutations. These findings are clinically relevant, as a large proportion of dysferlinopathy patients harbor at least one dysferlin missense allele. A clinical proof-of-concept trial with the medically approved proteasome inhibitor bortezomib (Velcade™) is currently ongoing in our Neuromuscular Center at the Department of Neurology.

Myotonic dystrophy

Myotonic dystrophy is an autosomal dominant multisystem disease affecting skeletal muscle, heart, brain, lens and endocrine organs. It is the most common muscular dystrophy in adults affecting about 1 in 10'000 persons. Based on genetic loci and clinical characteristics two myotonic dystrophies can be distinguished, type 1 (DM1, Curschmann-Steinert) and type 2 (DM2, proximal myotonic myopathy, PROMM). DM1 is caused by a CTG triplet repeat expansion in the 3' untranslated region of the DMPK (myotonic dystrophy protein kinase) gene (11) and DM2 by a CCTG expansion in intron 1 of the ZNF9 (zinc finger protein 9) gene (12).

The clinical phenotypes in DM1 have been subdivided according to severity: mild, classic and congenital. These phenotypes roughly correlate with CTG triplet expansion size.

Patients affected by the classical form of DM1 have a CTG triplet repeat size of up to 1000 and develop muscle weakness and wasting, myotonia (inability to relax skeletal muscle), cataract, diabetes and heart conduction abnormalities. A myopathic facial expression can develop following weakness of facial muscles. Muscle weakness affects predominantly distal muscles in lower and upper extremities. Smooth muscle involvement can result in swallowing and speech difficulties and difficulties with bowel movements. Life span is mildly reduced and the most common cause of death is respiratory insufficiency due to diaphragmatic, intercostal muscle and oropharynx involvement.

Cardiac sudden death caused by heart block and ventricular arrhythmia is the second most common cause of death in DM1 patients.

Transgenic mice with expanded CTG repeats introduced into the 3' untranslated region of a human skeletal actin gene develop myotonia and muscle pathology similar to patients with DM1 (13).

Transgenic mRNA accumulates in the nucleus and forms aggregates, similar to DMPK mRNAs in DM1 patients. These elongated CUG repeats form hairpin structures and can sequester RNA binding proteins implicated in splicing, such as the protein muscleblind-like-1 (MBNL1).

Sequestration of splice factors by the RNA CUG repeats prevents splicing of downstream target genes and leads to disease. Multiple RNAs are incorrectly spliced in DM1 such as the RNA encoding the insulin receptor, leading to insulin resistance, or the RNA encoding the chloride channel leading to myotonia, etc., which explains the multisystem involvement in DM1 (2), (figure 5).

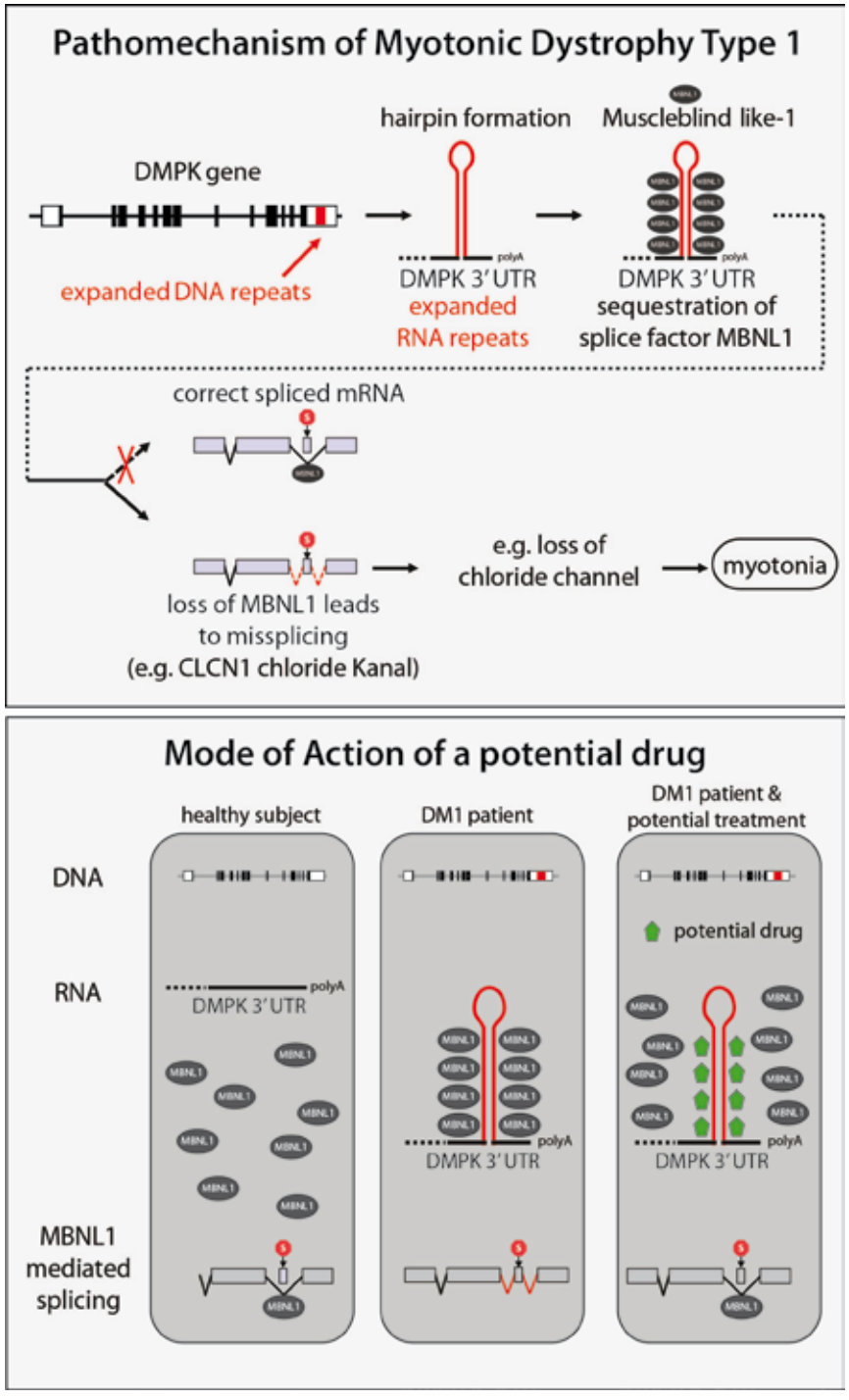

Figure 5

The concept of a "splice-opathy" as the underlying pathomechanism of DM1 raises very interesting potential therapeutic possibilities. Muscle damage is not well advanced early in disease in DM and is only slowly progressive, suggesting that restoration of the splicing abnormality may allow recovery of muscle tissue. The hairpin loops formed by expanded triplet repeats that bind and sequester MBLN proteins could be targeted by small molecular weight compounds with the idea of disrupting the hairpin structure, and thus interfering with MBLN binding (figure 5). We are following this strategy and have developed biochemical, cellular and *in-vivo* assays in mouse models to identify small molecular weight compounds able to release sequestered MBLN1 and thereby to restore correct splicing. This work is performed in collaboration with the medical parasitology group of Prof. Brun at the Swiss TPH and with the pharmaceutical biology group of Prof. Hamburger at the Pharmacenter. Our aim is to identify molecules that could serve as lead compounds for the development of pharmaceutical compounds for these disorders.

Figure 6:
Picture of present and past laboratory members. From left to right (front row) : Sabrina Di Fulvio, Marielle Brockhoff, Bilal Azakir, Frances Kern, Ruben Herrendorff, Tatiana Wiktorowicz , Beat Erne, Adeline Stiefvater, Jon Ashley, Perrine Castets, (back row) Jochen Kinter, Michael Sinnreich

The treatment strategies presented here are developed for specific diseases of skeletal muscle but may well also be generalized to other genetically determined diseases caused by similar pathomechanisms.

Acknowledgements

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Michael Sinnreich

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A new GMP lab at the DBM

What is GMP?

Imagine the following quiz question at your next scientific or clinical meeting: "GMP" stands for: A. Get More Production; B. Good Manufacturing Practice; C. Get More Pizza; D. Great Mounds of Paper. Since more pizza is more appealing than less pizza, many of us may select "C" as answer. Alas, this is the wrong choice since "B" is the correct one. For a precise definition of GMP one may - for example - consult the WHO (Word Health Organization) homepage which states that "....GMP is a system for ensuring that medicinal products are consistently produced and controlled according to quality standards appropriate to their intended use and as required by the product specification. The adherence to GMP standards at all levels of the production process is enforced by national regulatory authorities and operational inspectorates....".

Exhale and let us instead look briefly at the history of medicine in order to explore the meaning of GMP beyond wordy phrases: Medicines are perhaps as old as mankind and the concepts governing how their quality has to be ensured have evolved gradually over time. The modern medicinal product regulation started after breakthrough progress in the 19th century life sciences, especially in chemistry, physiology and pharmacology, which laid a solid foundation for the modern drug research and development.

Disastrous events have catalyzed, however, the development of medicinal product regulation more profoundly than the evolution of a knowledge base. As central event I would name the thalidomide tragedy in the 1960s. Thalidomide was marketed in Europe as a sleeping pill and to treat morning sickness. The product was not allowed on the market in the United States. After European regulatory agencies had given permission to sell the drug for its indication, it turned out that thalidomide had teratogenic activity and thus caused serious deformities in developing fetuses. An estimated 10,000 severe clinical cases were linked to thalidomide use in Europe. Thalidomide galvanized public opinion. The drug reviewer responsible for turning down the thalido-

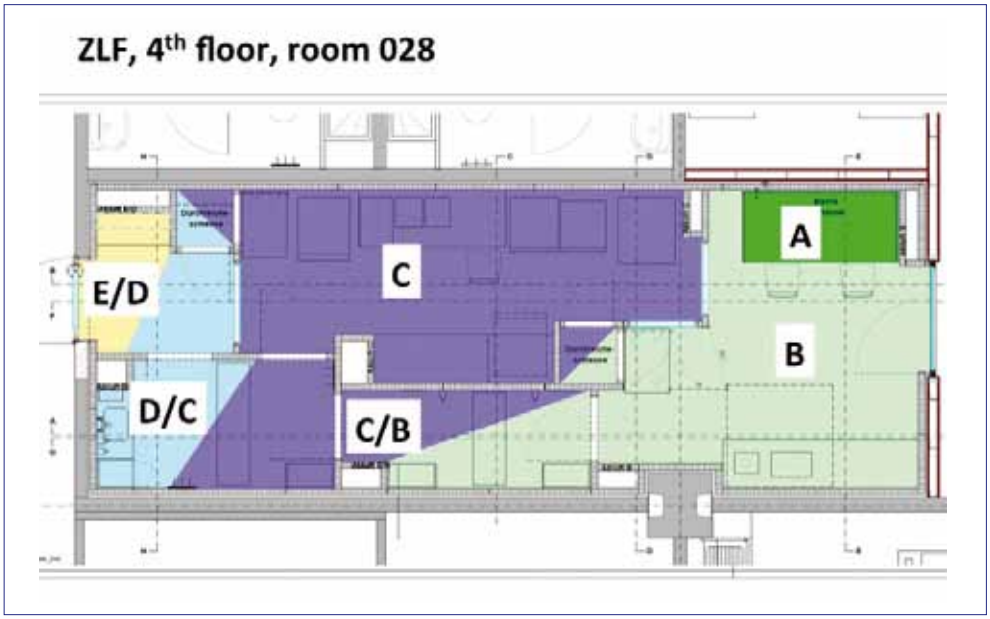


Figure 1:
Architecture and zone plan for the new GMP Lab DBM 4th floor ZLF

mide application in the United States was awarded the highest honour a government employee could earn as a civilian. In the aftermath of the European disaster, US congress laid down solid legislation that required companies to ensure that their products were safe and at the same time efficacious for their intended uses. Concurrently, specific product regulation measures were introduced in the US that required a "good manufacturing practice" for production of any drug for human use.

Similar measures set forth by international and national authorities now exist across the world. Resisting recurring arguments by certain Swiss political parties that Switzerland "should not serve foreign lords" the Swiss law ("Heilmittelgesetz" and "Arzneimittelbewilligungsverordnung") requires that manufacture of medicinal products must adhere to international guidelines set forth by the European Union (EU). The EU has established a high quality standard system of authorizations that ensures that all products from and for the European market (and that includes the Swiss) are, firstly, produced only by authorized manufacturers and, secondly, assessed by a competent local authority to safeguard compliance with contemporary GMP requirements. The standards for the manufacturing of medicinal products for human use are laid down in legislation "EudraLex Volume 4" (http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm). These official EU guidelines form the bible of any European and Swiss manufacturer of medicinal products which seemingly portrays GMP to be a simple enterprise built on three pillars:
1) Pharmaceutical substances and products intended for human use are to be manufactured in sites that are adequately equipped,
2) the producer has to demonstrate appropriate professional and technical knowledge that is provided by qualified staff, and
3) a pharmaceutical Quality Assurance system needs to be established by the manufacturer. However, as so often, the first glance is deceiving because the complexity rises logarithmically when one starts to deal with the specific details (and that's why some people would choose answer "D" in our little quiz above).

A GMP lab

Annex 1 of the EU GMP guidelines is rather lengthy and it contains statements such as these: (1) The manufacture of medicinal products should be carried out in clean rooms. (2) Entry to clean rooms should be restricted and airlocks for personnel, equipment and materials need to be installed. (3) Each manufacturing operation requires a specific environmental cleanliness level. (4) Clean rooms for the manufacture of sterile products are separated into five zones, A to E (see colour coded zones in Figure 1), with decreasing numbers of particles per air volume, where A is the local zone for high risk operations, e.g. handling of open vials, and zone E is

Figure 2:
GMP in action in Pharmacy USB

Figure 3:
Lab reconstruction on the 4th floor ZLF

the normal environment of the surrounding hallways. (5) Special protective clothing is required (an example is given in Figure 2). (6) Zone integrity should be monitored by airborne particle monitoring systems and sampled for infectious organisms at pre-defined frequencies. (7) Premises should be cleaned and disinfected according to detailed written procedures. (8) Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment....". Stopping recital at this point, it should have become clear to the reader of this article that the manufacture of medicinal products cannot be done in those laboratories we are accustomed to in the ZLF and elsewhere. Rather, they must be done using validated procedures in specially constructed and qualified facilities where working conditions are strictly regulated (just ask someone who has worked for 3 hours in a row wearing the suit shown in Figure 2).

The DBM gets a GMP lab...

I can hear a faint voice from far in the back: "Why is this of relevance to us; the DBM is not going to produce small, round, solid oral dosage forms of medication (a.k.a. 'pills'), is it?". This is probably correct. However, the definition of the term 'Medicinal product' has seen expansion as it is now understood to include "any substance used for treating or preventing disease in human beings or animals". Hence, the term will, for instance, also describe blood products and engineered tissues intended for transplantation. Since the latter types of medicinal products represent core interests of some of our research groups, the DBM had evaluated the need for such a clean room in 2012–2013 and had concluded to make its construction part of the general transformation activities with regard to the 2nd and 4th floors of the ZLF. To this end, I was appointed head of this future clean room – which is now officially called the "GMP Labor DBM" – on Jan. 1, 2014. To get planning underway, countless meetings were held between January and May with architecture, engineering and infrastructure offices internally at the USB, external architects (W+W Architekten), external technical planners and qualification commissioners (Exergie; Scherrerpartner) and entrepreneurs for clean room and monitoring technology and electric installations, you name it. At the same time a Document Management System (DMS) for all GMP activities at the DBM had to be put in effect. Such a DMS is a critical part of the Quality Assurance system for the manufacturing of any medicinal product. Now everything is in place and if today you were to walk down one

of the hallways on the 4th floor you will see that some work has already been initiated. However, as of writing these lines, the clean room still looks pretty bare (Figure 3) and is far from being ready for use. Our present timeline foresees that actual construction of the clean room technology will occur between June and August 2014, but do not hold me accountable on this statement which I have made in a bout of optimism. Construction will be paralleled and followed by qualification and validation processes which should establish and provide documentary evidence that (1) the premises, the supporting utilities and the equipment have been designed in accordance with the requirements of GMP. This step constitutes Design Qualification or DQ; (2) The clean room and the equipment have been built and installed in compliance with their design specifications (Installation Qualification or IQ); (3) Everything operates in accordance with its design specification (Operational Qualification or OQ); (4) A specific process will consistently produce a product meeting its predetermined specifications and quality attributes. This constitutes Performance Qualification or PQ. The term Process Validation, or PV, may also be used. As of writing these lines, we are in DQ phase and we are hopeful to complete all qualification and validation activities in early 2015 so as to make the room ready for inspection and certification by Swissmedic.

...for a good reason

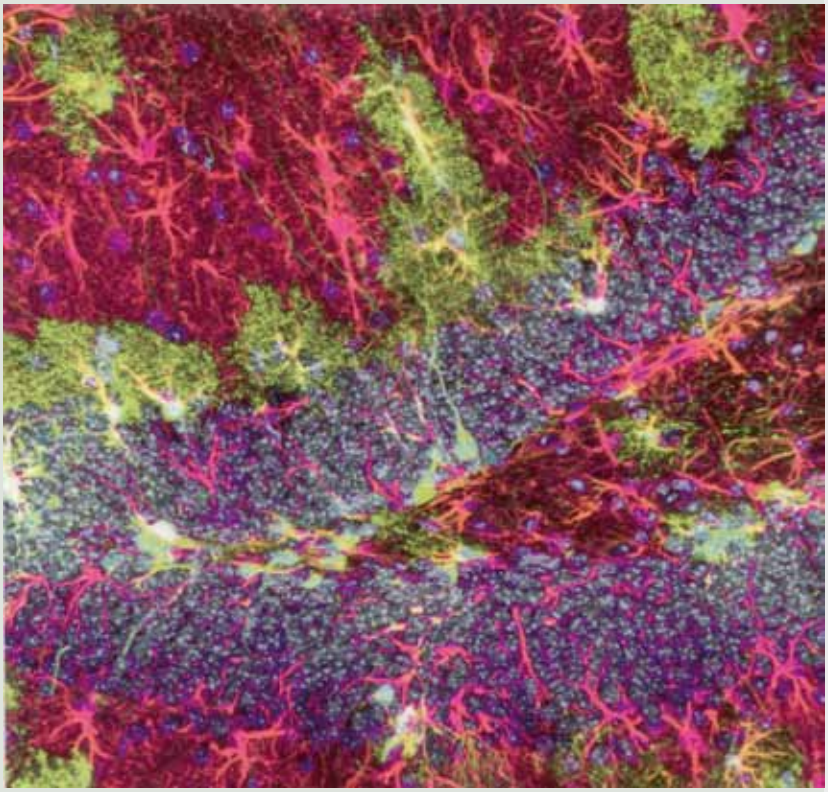
So, who is going to use our nice and tidy clean room from 2015 on? The answer can be taken from a prime example of how scientific progress should work in an organization such as the Department of Biomedicine which harbours investigators who can successfully exploit their long-standing, effective integration between their experimental group and clinical disciplines at the University Hospital. For a more specific answer to the above question, it suffices to consult the announcement by the University Hospital of April 11, 2014 with the title:" Scientists grow cartilage to reconstruct nose" (The Lancet, early online publication, doi:10.1016/ S0140-6736 (14):60544–4). Together with colleagues from the University Hospital, the DBM research group "Tissue Engineering" (principal investigator is Ivan Martin) has developed an alternative approach to treat non-melanoma skin cancer of the nose. Current procedures are invasive, painful and can lead to complications at the site of the excision. However, the group of Ivan Martin showed that it is possible to achieve nasal reconstruction using engineered cartilage from patients' own cells. To generate cartilage tissue 40-times the size of the original biopsy, and to make it ready for transplantation in the framework of a clinical phase I study, cell manipulation in a clean room was necessary. For this

Figure 4:
Tissue Engineering group in GMP facility Diagnostic Hematology

past study, the DBM group was allowed to be "guest" at the USB Pharmacy (Figure 2). There are now new studies underway that expand the scope of their clinical intervention. Until completion of the new GMP Lab DBM, cell production is currently being done in the existing GMP facility of Diagnostic Hematology (Figure 4). So we can look forward to fascinating times when production can finally be done in our very own DBM infrastructure which is expected to further enhance the standing of our institution. The DBM also hopes that the availability of the new room will stimulate transition of preclinical research done by other experimental groups into the study of exciting new investigational medicinal products.

Werner Krenger

The report DBM 2011-2013 is published.
For further copies please contact Manuela Bernasconi,
email : manuela.bernasconi@unibas.ch



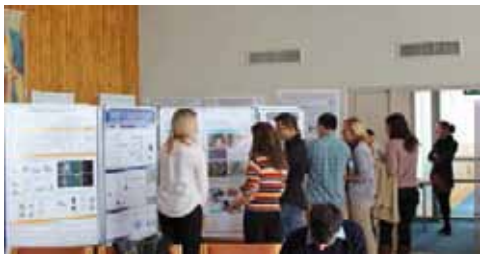
Departement Biomedizin Basel

Departement Biomedizin Basel PhD Club

Addendum: 2nd DBM PhD SCIENTIFIC WINTER RETREAT 2014

Following the successful inaugural DBM PhD Winter Retreat in 2013 in Hasliberg, the second retreat was held this year at the same location. And all thanks to the excellent planning over several months by the PhD Club committee, the event was again very successful. With the view of Eiger and Brienzersee and situated in the Bernese Alps, Hotel Viktoria in Hasliberg was once again the perfect venue. Beside its ability to accommodate 50 participants for 3 days, the hospitability made it an obvious choice for our PhD club committee. Also, for students who have not had the chance to experience the Swiss mountains, Hasliberg was a real treat to the natural beauty that Switzerland holds.

The retreat comprised scientific presentations and poster sessions, both delivered and chaired by the students. Over the first 2 days, 19 talks and 30 posters covered all four focal areas of the department. This year Prof. Thomas Klimkait and Prof. Verdon Taylor were invited as keynote speakers to share their current scientific research work. After the presentations, the students voted for Chanchal sur Chowdhury for the best presenter, while Erkan Ünal was honored with the best poster award.



During the retreat, the organizers have planned a range of activities other than presentations to promote causal discussions amongst students. This includes the candlelight fondue dinner, tea breaks in between presentation sessions and also an apéro to close off the retreat. Through these one-to-one interactions, the students are able to discuss their project and exchange their ideas and opinions. On the final day of the retreat, the ski lifts were unfortunately not operating due to strong Föhn winds. However, thanks to the organizers quick thinking, a short hike in the vicinity of the hotel was conducted to keep the participants occupied.

One of the greatest benefits of PhD retreat in the mountains is being able to take time off bench work and appreciate the research works of the other groups that are scattered over different areas of Basel. Events like this create a casual environment of the meeting of minds and in depth discussions. It encourages the fostering of scientific collaborations and innovative approaches to answer various aspects of scientific works. Leading from last year's retreat, the benefits have continued to cumulate to this year and hopefully yet more successful retreats in the following years to come.

Hong Ying Teh, Pediatric Immunology

Dissertationen

Am 31. März 2014 konnte **Karol Czaja** von der Forschungsgruppe Immunotherapy (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema "Killer cell immunoglobulin-like receptors and their ligands: Assessment of potential diagnostic and immunotherapeutic value."

Seit dem 26. Mai 2014 darf sich **Christian Hirt** von der Forschungsgruppe Oncology Surgery (ICFS/Departement Biomedizin Hebelstrasse) Herr Dr. nennen. Er befasste sich in seiner Doktorarbeit mit dem Thema: "Engineering the tumor microenvironment of colorectal cancer".

Auszeichnungen

DBM-Rat wählt Radek Skoda

Das neue Organisationsreglement des Departements Biomedizin ist per Dezember 2013 in Kraft getreten. Am 3. Juni 2014 hat nun die erste Sitzung des DBM-Rates stattgefunden. Als eine der ersten Amtshandlungen wurde **Radek Skoda** von der Forschungsgruppe Exp. Hematology (Departement Biomedizin Hebelstrasse) als Leiter Departement Biomedizin für die nächsten vier Jahre gewählt.

Susan Treves wird Titularprofessorin

In seiner Sitzung am 3. April 2014 hat der Universitätsrat der Universität Basel die von der Regenz beschlossene Ernennung von **Susan Treves** von der Forschungsgruppe Perioperative Patient Safety (Departement Biomedizin Hebelstrasse) zur Titularprofessorin für Biochemie gutgeheissen.

Viollier-Preis 2014 an Jens Kuhle

Jens Kuhle von der Forschungsgruppe Clinical Neuroimmunology (Departement Biomedizin Hebelstrasse) hat den diesjährigen Viollier-Preis für innovative Laborforschung erhalten. Die mit 10'000 CHF dotierte Auszeichnung wurde ihm an der Jahresversammlung der Schweizer Gesellschaft für Innere Medizin in Genf überreicht.

Herzliche Gratulation an alle!

6th DBM Summer Barbecue Thursday, August 21, 2014 at the Kraftwerkinsel in Birsfelden walking-tour, barbecue, several attractions

Nature Immunology | nature immunology | doi:10.1038/ni.2869 | IF 26,199

A regulatory role for TGF-β signaling in the establishment and function of the thymic medulla

Mathias Hauri-Hohl[1], Saulius Zuklys[2,3], Georg A Holländer[2–5] & Steven F Ziegler[1,5]

Medullary thymic epithelial cells (mTECs) are critical in establishing and maintaining the appropriate microenvironment for negative selection and maturation of immunocompetent T cells with a self-tolerant T cell antigen receptor repertoire. Cues that direct proliferation and maturation of mTECs are provided by members of the tumor necrosis factor (TNF) superfamily expressed on developing thymocytes. Here we demonstrate a negative role of the morphogen TGF-β in tempering these signals under physiological conditions, limiting both growth and function of the thymic medulla. Eliminating TGF-β signaling specifically in TECs or by pharmacological means increased the size of the mTEC compartment, enhanced negative selection and functional maturation of medullary thymocytes as well as the production of regulatory T cells, thus reducing the autoreactive potential of peripheral T cells.

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Neuron | Cell PRESS | Neuron 82, 1–13, June 4, 2014 | IF 15,766

Auxiliary $GABA_B$ Receptor Subunits Uncouple G Protein βγ Subunits from Effector Channels to Induce Desensitization

Rostislav Turecek[1,2], Jochen Schwenk[3,4], Thorsten Fritzius[1], Klara Ivankova[1], Gerd Zolles[3], Lisa Adelfinger[1], Valerie Jacquier[1], Valerie Besseyrias[1], Martin Gassmann[1], Uwe Schulte[3,4], Bernd Fakler[3,4], and Bernhard Bettler[1]

SUMMARY

Activation of K^+ channels by the G protein βγ subunits is an important signaling mechanism of G-protein-coupled receptors. Typically, receptor-activated K^+ currents desensitize in the sustained presence of agonists to avoid excessive effects on cellular activity. The auxiliary $GABA_B$ receptor subunit KCTD12 induces fast and pronounced desensitization of the K^+ current response. Using proteomic and electrophysiological approaches, we now show that KCTD12-induced desensitization results from a dual interaction with the G protein: constitutive binding stabilizes the heterotrimeric G protein at the receptor, whereas dynamic binding to the receptor-activated Gβγ subunits induces desensitization by uncoupling Gβγ from the effector K^+ channel. While receptor-free KCTD12 desensitizes K^+ currents activated by other GPCRs in vitro, native KCTD12 is exclusively associated with $GABA_B$ receptors. Accordingly, genetic ablation of KCTD12 specifically alters $GABA_B$ responses in the brain. Our results show that $GABA_B$ receptors are endowed with fast and reversible desensitization by harnessing KCTD12 that intercepts Gβγ signaling.

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Journal of the American College of Cardiology JACC Vol. 63, No. 10, 2014 IF 14,086

FLT3 Activation Improves Post-Myocardial Infarction Remodeling Involving a Cytoprotective Effect on Cardiomyocytes

Otmar Pfister, MD[1,2], Vera Lorenz, MSC[1], Angelos Oikonomopoulos, PHD[3], Lifen Xu, PHD[1], Stéphanie P. Häuselmann, MSC[1], Christopher Mbah, MD, MA[3], Beat A. Kaufmann, MD[1,2], Ronglih Liao, PHD[3], Aleksandra Wodnar-Filipowicz, PHD[1], Gabriela M. Kuster, MD[1,2]

Objectives
The goal of this study was to define the role of FMS-like tyrosine kinase 3 (FLT3) in the heart.

Background
FLT3 is a prominent target of receptor tyrosine kinase inhibitors (TKIs) used for anticancer therapy. TKIs can cause cardiomyopathy but understanding of the mechanisms is incomplete, partly because the roles of specific TKI target receptors in the heart are still obscure.

Methods
Myocardial infarction was induced in mice by permanent ligation of the left anterior descending coronary artery followed by intramyocardial injection of FLT3 ligand (FL) or vehicle into the infarct border zone. Cardiac morphology and function were assessed by echocardiography and histological analysis 1 week after infarction. In addition, FLT3 expression and regulation, as well as molecular mechanisms of FLT3 action, were examined in cardiomyocytes in vitro.

Results
The intramyocardial injection of FL into the infarct border zone decreased infarct size and ameliorated post-myocardial infarction remodeling and function in mice. This beneficial effect was associated with reduced apoptosis, including myocytes in the infarct border zone. Cardiomyocytes expressed functional FLT3, and FLT3 messenger ribonucleic acid and protein were up-regulated under oxidative stress, identifying cardiomyocytes as FL target cells. FLT3 activation with FL protected cardiomyocytes from oxidative stress–induced apoptosis via an Akt-dependent mechanism involving Bcl-2 family protein regulation and inhibition of the mitochondrial death pathway.

Conclusions
FLT3 is a cytoprotective system in the heart and a potential therapeutic target in ischemic cardiac injury. The protective mechanisms uncovered here may be further explored in view of potential cardiotoxic effects of FLT3-targeting anticancer therapy, particularly in patients with ischemic heart disease.

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Protein-Protein Interactions Angewandte Chemie 2014, 53, 4717 –4720 IF 13,734

Cell-Permeant and Photocleavable Chemical Inducer of Dimerization

Mirjam Zimmermann[1,*], Ruben Cal[1,*], Elia Janett[2], Viktor Hoffmann[1], Christian G. Bochet[2], Edwin Constable[3], Florent Beaufils[1] and Matthias P. Wymann[1]

Abstract:
Chemical inducers of dimerization (CIDs) have been developed to orchestrate protein dimerization and translocation. Here we present a novel photocleavable Halo-Tag-and SNAP-tag-reactive CID (MeNV-HaXS) with excellent selectivity and intracellular reactivity. Excitation at 360 nm cleaves the methyl-6-nitroveratryl core of MeNV-HaXS. MeNV-HaXS covalently links HaloTag-and SNAP-tag fusion proteins, and enables targeting of selected membranes and intracellular organelles. MeNV-HaXS-mediated translocation has been validated for plasma membrane, late endosomes, lysosomes, Golgi, mitochondria, and the actin cytoskeleton. Photocleavage of MeNV-HaXS liberates target proteins and provides access to optical manipulation of protein relocation with high spatiotemporal and subcellular precision. MeNV-HaXS supports kinetic studies of protein dynamics and the manipulation of subcellular enzyme activities, which is exemplified for Golgi-targeted cargo and the assessment of nuclear import kinetics.

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The Journal of Experimental Medicine JEM 2014 Vol. 211 No. 5 857–868 IF 13,214

IFN-λ receptor 1 expression is induced in chronic hepatitis C and correlates with the *IFN-λ3* genotype and with nonresponsiveness to IFN-α therapies

Francois H.T. Duong[1], Gaia Trincucci[1], Tujana Boldanova[1,2], Diego Calabrese[1], Benedetta Campana[1,2], Ilona Krol[1], Sarah C. Durand[3,4], Laura Heydmann[3,4], Mirjam B. Zeisel[3,4], Thomas F. Baumert[3,4,5], and Markus H. Heim[1,2]

The molecular mechanisms that link *IFN-λ3* genotypes to differential induction of interferon (IFN)-stimulated genes (ISGs) in the liver of patients with chronic hepatitis C (CHC) are not known. We measured the expression of IFN-λ and of the specific IFN-λ receptor chain (IFN-λR1) in 122 liver biopsies of patients with CHC and 53 control samples. The *IFN-λ3* genotype was not associated with differential expression of IFN-λ, but rather IFN-λR1. In a series of 30 primary human hepatocyte (PHH) samples, IFN-λ R1 expression was low but could be induced with IFN-α. IFN-α–induced IFN-λR1 expression was significantly stronger in PHHs carrying the minor *IFN-λ3* allele. The analysis of liver biopsies of patients with CHC revealed a strong association of high IFN-LR1 expression with elevated ISG expression, with *IFN-λ3* minor alleles, and with nonresponse to pegylated IFN-α and ribavirin. The findings provide a missing link between the *IFN-λ3* genotype and the associated phenotype of treatment nonresponse.

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The Journal of Clinical Investigation JCI 2014;124(4):1568–1581 IF 12,812

Pegylated IFN-α regulates hepatic gene expression through transient Jak/STAT activation

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The use of pegylated interferon-α (pegIFN-α) has replaced unmodified recombinant IFN-α for the treatment of chronic viral hepatitis. While the superior antiviral efficacy of pegIFN-α is generally attributed to improved pharmacokinetic properties, the pharmacodynamic effects of pegIFN-α in the liver have not been studied. Here, we analyzed pegIFN-α–induced signaling and gene regulation in paired liver biopsies obtained prior to treatment and during the first week following pegIFN-α injection in 18 patients with chronic hepatitis C. Despite sustained high concentrations of pegIFN-α in serum, the Jak/STAT pathway was activated in hepatocytes only on the first day after pegIFN-α administration. Evaluation of liver biopsies revealed that pegIFN-α induces hundreds of genes that can be classified into four clusters based on different temporal expression profiles. In all clusters, gene transcription was mainly driven by IFN-stimulated gene factor 3 (ISGF3). Compared with conventional IFN-α therapy, pegIFN-α induced a broader spectrum of gene expression, including many genes involved in cellular immunity. IFN-induced secondary transcription factors did not result in additional waves of gene expression. Our data indicate that the superior antiviral efficacy of pegIFN-α is not the result of prolonged Jak/STAT pathway activation in hepatocytes, but rather is due to induction of additional genes that are involved in cellular immune responses.

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Nature Communications | 5:3339 | DOI: 10.1038/ncomms4339 IF 10,015

Genome-wide association study reveals two new risk loci for bipolar disorder

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Bipolar disorder (BD) is a common and highly heritable mental illness and genome-wide association studies (GWAS) have robustly identified the first common genetic variants involved in disease aetiology. The data also provide strong evidence for the presence of multiple additional risk loci, each contributing a relatively small effect to BD susceptibility. Large samples are necessary to detect these risk loci. Here we present results from the largest BD GWAS to date by investigating 2.3 million single-nucleotide polymorphisms (SNPs) in a sample of 24,025 patients and controls. We detect 56 genome-wide significant SNPs in five chromosomal regions including previously reported risk loci *ANK3, ODZ4* and *TRANK1*, as well as the risk locus *ADCY2* (5p15.31) and a region between *MIR2113* and *POU3F2* (6q16.1). *ADCY2* is a key enzyme in cAMP signalling and our finding provides new insights into the biological mechanisms involved in the development of BD.

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Parallel T-cell cloning and deep sequencing of human MAIT cells reveal stable oligoclonal TCRβ repertoire

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Abstract

Mucosal-associated invariant T (MAIT) cells are abundant in humans and recognize conserved bacterial antigens derived from riboflavin precursors, presented by the non-polymorphic MHC class I-like molecule MR1. Here we show that human MAIT cells are remarkably oligoclonal in both the blood and liver, display high inter-individual homology and exhibit a restricted length CDR3β domain of the TCRVβ chain. We extend this analysis to a second sub-population of MAIT cells expressing a semi-invariant TCR conserved between individuals. Similar to 'conventional' MAIT cells, these lymphocytes react to riboflavin-synthesizing microbes in an MR1-restricted manner and infiltrate solid tissues. Both MAIT cell types release Th0, Th1 and Th2 cytokines, and sCD40L in response to bacterial infection, show cytotoxic capacity against infected cells and promote killing of intracellular bacteria, thus suggesting important protective and immunoregulatory functions of these lymphocytes.

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PNAS PNAS 6952–6957, May 13, 2014, vol. 111,no. 19 IF 9,737

Long-lasting fibrin matrices ensure stable and functional angiogenesis by highly tunable, sustained delivery of recombinant $VEGF_{164}$

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Clinical trials of therapeutic angiogenesis by vascular endothelial growth factor (VEGF) gene delivery failed to show efficacy. Major challenges include the need to precisely control in vivo distribution of growth factor dose and duration of expression. Recombinant VEGF protein delivery could overcome these issues, but rapid in vivo clearance prevents the stabilization of induced angiogenesis. Here, we developed an optimized fibrin platform for controlled delivery of recombinant VEGF, to robustly induce normal, stable, and functional angiogenesis. Murine $VEGF_{164}$ was fused to a sequence derived from α2-plasmin inhibitor ($\alpha2\text{-}PI_{1-8}$) that is a substrate for the coagulation factor fXIIIa, to allow its covalent cross-linking into fibrin hydrogels and release only by enzymatic cleavage. An $\alpha_2\text{-}PI_{1-8}$–fused variant of the fibrinolysis inhibitor aprotinin was used to control the hydrogel degradation rate, which determines both the duration and effective dose of factor release. An optimized aprotinin-$\alpha_2\text{-}PI_{1-8}$ concentration ensured ideal degradation over 4 wk. Under these conditions, fibrin-$\alpha_2\text{-}PI_{1-8}\text{-}VEGF_{164}$ allowed exquisitely dose-dependent angiogenesis: concentrations ≥25 μg/mL caused widespread aberrant vascular structures, but a 500-fold concentration range (0.01–5.0 μg/mL) induced exclusively normal, mature, nonleaky, and perfused capillaries, which were stable after 3 mo. Optimized delivery of fibrin-$\alpha_2\text{-}PI_{1-8}$-VEGF164 was therapeutically effective both in ischemic hind limb and wound-healing models, significantly improving angiogenesis, tissue perfusion, and healing rate. In conclusion, this optimized platform ensured *(i)* controlled and highly tunable delivery of VEGF protein in ischemic tissue and *(ii)* stable and functional angiogenesis without introducing genetic material and with a limited and controllable duration of treatment. These findings suggest a strategy to improve safety and efficacy of therapeutic angiogenesis.

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Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms

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Myeloproliferative neoplasms (MPNs) are a group of clonal disorders characterized by aberrant hematopoietic proliferationandanincreased tendency towardleukemic transformation. We used targeted next-generation sequencing (NGS) of 104 genes to detect somatic mutations in a cohort of 197 MPN patients and followed clonal evolution and the impact on clinical outcome. Mutations in calreticulin *(CALR)* were detected using a sensitive allele-specific polymerase chain reaction. We observed somatic mutations in 90% of patients, and 37% carried somatic mutations other than *JAK2* V617F and *CALR*.The presence of 2 or more somatic mutations significantly reduced overall survival and increased the risk of transformation into acute myeloid leukemia. In particular, somatic mutations with loss of heterozygosity in *TP53* were strongly associated with leukemic transformation. We used NGS to follow and quantitate somatic mutations in serial samples from MPN patients. Surprisingly, the number of mutations between early and late patient samples did not significantly change, and during a total follow-up of 133 patient years, only 2 new mutations appeared, suggesting that the mutation rate in MPN is rather low. Our data show that comprehensive mutational screening at diagnosis and during follow-up has considerable potential to identify patients at high risk of disease progression.

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VEGF-Mediated Angiogenesis Links EMT-Induced Cancer Stemness to Tumor Initiation

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Abstract

An epithelial–mesenchymal transition (EMT) underlies malignant tumor progression and metastatic spread by enabling cancer cells to depart from the primary tumor, invade surrounding tissue, and disseminate to distant organs. EMT also enriches for cancer stem cells (CSC) and increases the capacity of cancer cells to initiate and propagate tumors upon transplantation into immune-deficient mice, a major hallmark of CSCs. However, the molecular mechanisms promoting the tumorigenicity of cancer cells undergoing an EMT and of CSCs have remained widely elusive. We here report that EMT confers efficient tumorigenicity to murine breast cancer cells by the upregulated expression of the proangiogenic factor VEGF-A and by increased tumor angiogenesis. On the basis of these data, we propose a novel interpretation of the features of CSCs with EMT-induced, VEGF-A– mediated angiogenesis as the connecting mechanism between cancer cell stemness and tumor initiation.

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Reversible Top1 cleavage complexes are stabilized strand-specifically at the ribosomal replication fork barrier and contribute to ribosomal DNA stability

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Abstract

Various topological constraints at the ribosomal DNA (rDNA) locus impose an extra challenge for transcription and DNA replication, generating constant torsional DNA stress. The topoisomerase Top1 is known to release such torsion by singlestrand nicking and re-ligation in a process involving transient covalent Top1 cleavage complexes (Top1cc) with the nicked DNA. Here we show that Top1ccs, despite their usually transient nature, are specifically targeted to and stabilized at the ribosomal replication fork barrier (rRFB) of budding yeast, establishing a link with previously reported Top1 controlled nicks. Using ectopically engineered rRFBs, we establish that the rRFB sequence itself is sufficient for induction of DNA strand-specific and replication-independent Top1ccs. These Top1ccs accumulate only in the presence of Fob1 and Tof2, they are reversible as they are not subject to repair by Tdp1-or Mus81-dependent processes, and their presence correlates with Top1 provided rDNA stability. Notably, the targeted formation of these Top1ccs accounts for the previously reported broken replication forks at the rRFB. These findings implicate a novel and physiologically regulated mode of Top1 action, suggesting a mechanism by which Top1 is recruited to the rRFB and stabilized in a reversible Top1cc configuration to preserve the integrity of the rDNA.

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LIM-homeobox gene 2 promotes tumor growth and metastasis by inducing autocrine and paracrine PDGF-B signaling

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Abstract
An epithelial-mesenchymal transition (EMT) is a critical process during embryonic development and the progression of epithelial tumors to metastatic cancers. Gene expression profiling has uncovered the transcription factor LIM homeobox gene 2 (Lhx2) with upregulated expression during TGFβ-induced EMT in normal and cancerous breast epithelial cells. Loss and gain of function experiments in transgenic mouse models of breast cancer and of insulinoma *in vivo* and in breast cancer cells *in vitro* indicate that Lhx2 plays a critical role in primary tumor growth and metastasis. Notably, the transgenic expression of Lhx2 during breast carcinogenesis promotes vessel maturation, primary tumor growth, tumor cell intravasation and metastasis by directly inducing the expression of platelet-derived growth factor (PDGF)-B in tumor cells and by indirectly increasing the expression of PDGF receptor-β (PDGFRβ) on tumor cells and pericytes. Pharmacological inhibition of PDGF-B/PDGFRβ signaling reduces vessel functionality and tumor growth and Lhx2-induced cell migration and cell invasion. The data indicate a dual role of Lhx2 during EMT and tumor progression: by inducing the expression of PDGF-B, Lhx2 provokes an autocrine PDGF-B/PDGFRβ loop required for cell migration, invasion and metastatic dissemination and paracrine PDGF-B/PDGFRβ signaling to support blood vessel functionality and, thus, primary tumor growth.

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Mesenchymal stromal cells induce epithelial-to-mesenchymal transition in human colorectal cancer cells through the expression of surface-bound TGF-β

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Mesenchymal stem/stromal cells (MSC) are multipotent precursors endowed with the ability to home to primary and metastatic tumor sites, where they can integrate into the tumor-associated stroma. However, molecular mechanisms and outcome of their interaction with cancer cells have not been fully clarified. In this study, we investigated the effects mediated by bone marrow-derived MSC on human colorectal cancer (CRC) cells *in vitro* and *in vivo*. We found that MSC triggered epithelial-to-mesenchymal transition (EMT) in tumor cells *in vitro*, as indicated by upregulation of EMT-related genes, downregulation of E-cadherin and acquisition of mesenchymal morphology. These effects required cell-to-cell contact and were mediated by surface-bound TGF-β newly expressed on MSC upon coculture with tumor cells. *In vivo* tumor masses formed by MSC-conditioned CRC cells were larger and characterized by higher vessel density, decreased E-cadherin expression and increased expression of mesenchymal markers. Furthermore, MSC-conditioned tumor cells displayed increased invasiveness *in vitro* and enhanced capacity to invade peripheral tissues *in vivo*. Thus, by promoting EMT-related phenomena, MSC appear to favor the acquisition of an aggressive phenotype by CRC cells.

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Tead2 expression levels control the subcellular distribution of Yap and Taz, zyxin expression and epithelial–mesenchymal transition

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Abstract

The cellular changes during an epithelial–mesenchymal transition (EMT) largely rely on global changes in gene expression orchestrated by transcription factors. Tead transcription factors and their transcriptional co-activators Yap and Taz have been previously implicated in promoting an EMT; however, their direct transcriptional target genes and their functional role during EMT have remained elusive. We have uncovered a previously unanticipated role of the transcription factor Tead2 during EMT. During EMT in mammary gland epithelial cells and breast cancer cells, levels of Tead2 increase in the nucleus of cells, thereby directing a predominant nuclear localization of its co-factors Yap and Taz via the formation of Tead2–Yap–Taz complexes. Genome-wide chromatin immunoprecipitation and next generation sequencing in combination with gene expression profiling revealed the transcriptional targets of Tead2 during EMT. Among these, zyxin contributes to the migratory and invasive phenotype evoked by Tead2. The results demonstrate that Tead transcription factors are crucial regulators of the cellular distribution of Yap and Taz, and together they control the expression of genes critical for EMT and metastasis.

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Protein phosphatase 2A promotes hepatocellular carcinogenesis in the diethylnitrosamine mouse model through inhibition of p53

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Most HCCs develop in cirrhotic livers. Alcoholic liver disease, chronic hepatitis B and chronic hepatitis C are the most common underlying liver diseases. Hepatitis C virus (HCV)-specific mechanisms that contribute to HCC are presently unknown. Transgenic expression of HCV proteins in the mouse liver induces an overexpression of the protein phosphatase 2A catalytic subunit (PP2Ac). We have previously reported that HCV-induced PP2Ac overexpression modulates histone methylation and acetylation and inhibits DNA damage repair. In this study, we analyze tumor formation and gene expression using HCV transgenic mice that overexpress PP2Ac and liver tissues from patients with HCC. We demonstrate that PP2Ac overexpression interferes with p53-induced apoptosis. Injection of the carcinogen, diethylnitrosamine, induced significantly more and larger liver tumors in HCV transgenic mice that overexpress PP2Ac compared with control mice. In human liver biopsies from patients with HCC, PP2Ac expression was significantly higher in HCC tissue compared with non-tumorous liver tissue from the same patients. Our findings demonstrate an important role of PP2Ac overexpression in liver carcinogenesis and provide insights into the molecular pathogenesis of HCV-induced HCC.

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Synergism of peptide receptor-targeted Auger electron radiation therapy with anti-angiogenic compounds in a mouse model of neuroendocrine tumors

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Abstract

Background: Neuroendocrine tumors are well vascularized and express specific cell surface markers, such as somatostatin receptors and the glucagon-like peptide-1 receptor (GLP-1R). Using the Rip1Tag2 transgenic mouse model of pancreatic neuroendocrine tumors (pNET), we have investigated the potential benefit of a combination of anti-angiogenic treatment with targeted internal radiotherapy.

Methods: [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4, a radiopeptide that selectively binds to GLP-1R expressed on insulinoma and other neuroendocrine tumor cells, was co-administered with oral vatalanib (an inhibitor of vascular endothelial growth factor receptors (VEGFR)) or imatinib (a c-kit/PDGFR inhibitor). The control groups included single-agent kinase inhibitor treatments and [Lys^{40}(Ahx-DTPA-^{nat}In)NH_2]-exendin-4 monotherapy. For biodistribution, Rip1Tag2 mice were pre-treated with oral vatalanib or imatinib for 0, 3, 5, or 7 days at a dose of 100 mg/kg. Subsequently, [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4 was administered i.v., and the biodistribution was assessed after 4 h. For therapy, the mice were injected with 1.1 MBq [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4 and treated with vatalanib or imatinib 100 mg/kg orally for another 7 days. Tumor volume, tumor cell apoptosis and proliferation, and microvessel density were quantified.

Results: Combination of [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4 and vatalanib was significantly more effective than single treatments ($p < 0.05$) and reduced the tumor volume by 97% in the absence of organ damage. The pre-treatment of mice with vatalanib led to a reduction in the tumor uptake of [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4, indicating that concomitant administration of vatalanib and the radiopeptide was the best approach. Imatinib did not show a synergistic effect with [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4.

Conclusion: The combination of 1.1 MBq of [Lys^{40}(Ahx-DTPA-^{111}In)NH_2]-exendin-4 with 100 mg/kg vatalanib had the same effect on a neuroendocrine tumor as the injection of 28 MBq of the radiopeptide alone but without any apparent side effects, such as radiation damage of the kidneys.

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Pharmacological profiles of aminoindanes, piperazines, and pipradrol derivatives

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Abstract

Aminoindanes, piperazines, and pipradrol derivatives are novel psychoactive substances found in ''Ecstasy'' tablets as replacements for 3,4-methylenedioxymethamphetamine (MDMA) or substances sold as ''ivory wave.'' The pharmacology of these MDMA-and methylphenidate-like substances is poorly known. We characterized the pharmacology of the aminoindanes 5,6-methylenedioxy-2-aminoindane (MDAI), 5-iodoaminoindane (5-IAI), and 2-aminoindane (2-AI), the piperazines meta-chlorophenylpiperazine (m-CPP), trifluoromethylphenylpiperazine (TFMPP), and 1-benzylpiperazine (BZP), and the pipradrol derivatives desoxypipradrol (2-diphenylmethylpiperidine [2-DPMP]), diphenylprolinol (diphenyl-2-pyrrolidinemethanol [D2PM]), and methylphenidate. We investigated norepinephrine (NE), dopamine (DA), and serotonin (5-hydroxytryptamine [5-HT]) uptake inhibition using human embryonic kidney 293 (HEK 293) cells that express the respective human monoamine transporters (NET, DAT, and SERT). We also evaluated the drug-induced efflux of NE, DA, and 5-HT from monoamine-preloaded cells and the binding affinity to monoamine transporters and receptors, including trace amine-associated receptor 1 ($TAAR_1$). 5-IAI and MDAI preferentially inhibited the SERT and NET and released 5-HT. 2-AI interacted with the NET. BZP blocked the NET and released DA. m-CPP and TFMPP interacted with the SERT and serotonergic receptors. The pipradrol derivatives were potent and selective catecholamine transporter blockers without substrate releasing properties. BZP, D2PM, and 2-DPMP lacked serotonergic activity and $TAAR_1$ binding, in contrast to the aminoindanes and phenylpiperazines. In summary, all of the substances were monoamine transporter inhibitors, but marked differences were found in their DAT *vs.* SERT inhibition profiles, release properties, and receptor interactions. The pharmacological profiles of D2PM and 2-DPMP likely predict a high abuse liability.

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Combination of immortalization and inducible death strategies to generate a human mesenchymal stromal cell line with controlled survival

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Abstract
The hTERT-immortalization of human bone marrow-derived Mesenchymal Stromal Cells (hMSCs) was proposed to address availability/standardization issues for experimental or clinical studies, but raised concerns due to possible uncontrolled growth or malignant cell transformation. Here we report a method to generate a hMSCs line with controlled survival, through the implementation of a pre-established suicide system (inducible caspase 9, iCasp9) in hTERT-transduced hMSCs. Primary hMSCs were successfully immortalized (>280 PD) and further transduced with the iCasp9 device. A clone was selected and shown to maintain typical properties of primary hMSCs, including phenotype, differentiation and immunomodulation capacities. The successive transductions did not induce tumorigenic transformation, as assessed by analysis of cell cycle regulators and in vivo luciferase-based cell tracking. Cells could be efficiently induced toward apoptosis (>95%) both *in vitro* and *in vivo*. By combining the opposite concepts of 'induced-life' and 'inducible-death', we generated a hMSCs line with defined properties and allowing for temporally controlled survival. The cell line represents a relevant tool for medical discovery in regenerative medicine and a potential means to address availability, standardization and safety requirements in cell & gene therapy. The concept of a hTERT-iCasp9 combination, here explored in the context of hMSCs, could be extended to other types of progenitor/stem cells.

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The Survey on Cellular and Engineered Tissue Therapies in Europe in 2011

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Following the coordinated efforts of five established scientific organizations, this report describes the ''novel cellular therapy'' activity (i.e., cellular treatments excluding hematopoietic stem cells [HSC] for the reconstitution of hematopoiesis) in Europe for the year 2011. Two hundred forty-six teams from 35 countries responded to the cellular therapy survey, 126 teams from 24 countries provided data on 1759 patients using a dedicated survey and 120 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (46%; 99% autologous), cardiovascular disorders (22%; 100% autologous), hematology/oncology, predominantly including the prevention or treatment of graft-versus-host disease (18%; 2% autologous), neurological disorders (2%; 83% autologous), gastrointestinal (1%; 68% autologous), and other indications (12%; 77% autologous). Autologous cells were used predominantly for musculoskeletal/rheumatological (58%) and cardiovascular (27%) disorders, whereas allogeneic cells were used mainly for hematology/oncology (84%). The reported cell types were mesenchymal stem/stromal cells (56%), HSC (23%), chondrocytes (12%), dermal fibroblasts (3%), keratinocytes (2%), and others (4%). In 40% of the grafts, cells were delivered following *ex vivo* expansion, whereas cells were transduced or sorted, respectively, in 3% and 10% of the reported cases. Cells were delivered intraorgan (42%), intravenously (26%), on a membrane or gel (16%), or using 3D scaffolds (16%). Compared to last year, the number of teams participating in the dedicated survey doubled and, for the first time, all European Group for Blood and Marrow Transplantation teams reporting information on cellular therapies completed the extended questionnaire. The data are compared with those collected since 2008 to identify trends in the field. This year's edition specifically focuses on cardiac cell therapy.

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Non-Adherent Mesenchymal Progenitors from Adipose Tissue Stromal Vascular Fraction

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In primary human bone marrow cultures, the initial adherent cell fraction has been shown to provide a microenvironment for self-renewal of primitive non-adherent mesenchymal progenitors (non-adherent progenitors of bone marrow stroma [BM-NAMP]), with increased differentiation potential compared to adherent colonyforming units-fibroblast (CFU-f). The present study investigates whether NAMP exist also in cultures of stromal vascular fraction (SVF) cells derived from human adipose tissue. Adipose-tissue NAMP (AT-NAMP) were shown to be stably non-adherent and their number correlated with the number of the initial adhering CFU-f. Unlike BM-NAMP, AT-NAMP did not propagate in suspension in serial replating experiments and the number of colonies steadily decreased with each replating step. However, when AT-NAMP were kept on the initially adhering SVF cells, they could significantly expand without loss of clonogenic, proliferation, and differentiation potential. Although AT-NAMP progeny differentiated into mesodermal lineages similar to that of adherent CFU-f, it was enriched in early mesenchymal progenitor populations, characterized by increased expression of SSEA-4 and CD146. Furthermore, FGF-2 supported AT-NAMP survival and could not be replaced by another mitogenic factor, such as platelet derived growth factor BB. In conclusion, these data suggest that the SVF adherent fraction provides niche signals that regulate the expansion of adipose non-adherent mesenchymal progenitors with the maintenance of their potency. The biological differences described between BM-and AT-NAMP further qualify the properties of the stroma from different tissues and will be relevant for the selection of a cell source for specific regeneration strategies.

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Glucose-Induced Glucagon-Like Peptide 1 Secretion Is Deficient in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Background & Aims: The incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gastrointestinal peptide hormones regulating postprandial insulin release from pancreatic b-cells. GLP-1 agonism is a treatment strategy in Type 2 diabetes and is evaluated in Non-alcoholic fatty liver disease (NAFLD). However, the role of incretins in its pathophysiology is insufficiently understood. Studies in mice suggest improvement of hepatic steatosis by GLP-1 agonism. We determined the secretion of incretins after oral glucose administration in non-diabetic NAFLD patients.

Methods: N = 52 patients (n = 16 NAFLD and n = 36 Non-alcoholic steatohepatitis (NASH) patients) and n = 50 matched healthy controls were included. Standardized oral glucose tolerance test was performed. Glucose, insulin, glucagon, GLP-1 and GIP plasma levels were measured sequentially for 120 minutes after glucose administration.

Results: Glucose induced GLP-1 secretion was significantly decreased in patients compared to controls ($p<0.001$). In contrast, GIP secretion was unchanged. There was no difference in GLP-1 and GIP secretion between NAFLD and NASH subgroups. All patients were insulin resistant, however HOMA2-IR was highest in the NASH subgroup. Fasting and glucose-induced insulin secretion was higher in NAFLD and NASH compared to controls, while the glucose lowering effect was diminished. Concomitantly, fasting glucagon secretion was significantly elevated in NAFLD and NASH.

Conclusions: Glucose-induced GLP-1 secretion is deficient in patients with NAFLD and NASH. GIP secretion is contrarily preserved. Insulin resistance, with hyperinsulinemia and hyperglucagonemia, is present in all patients, and is more severe in NASH compared to NAFLD. These pathophysiologic findings endorse the current evaluation of GLP-1 agonism for the treatment of NAFLD.

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Transcriptional regulation induced by cAMP elevation in mouse Schwann cells

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Abstract

In peripheral nerves, Schwann cell development is regulated by a variety of signals. Some of the aspects of Schwann cell differentiation can be reproduced *in vitro* in response to forskolin, an adenylyl cyclase activator elevating intracellular cAMP levels. Herein, the effect of forskolin treatment was investigated by a comprehensive genome-wide expression study on primary mouse Schwann cell cultures. Additional to myelin-related genes, many so far unconsidered genes were ascertained to be modulated by forskolin. One of the strongest differentially regulated gene transcripts was the transcription factor Olig1 (oligodendrocyte transcription factor 1), whose mRNA expression levels were reduced in treated Schwann cells. Olig1 protein was localized in myelinating and nonmyelinating Schwann cells within the sciatic nerve as well as in primary Schwann cells, proposing it as a novel transcription factor of the Schwann cell lineage. Data analysis further revealed that a number of differentially expressed genes in forskolin-treated Schwann cells were associated with the ECM (extracellular matrix), underlining its importance during Schwann cell differentiation *in vitro*.Comparison of samples derivedfrom postnatalsciatic nerves and from both treated and untreated Schwann cell cultures showed considerable differences in gene expression between *in vivo* and *in vitro*,allowing us to separate Schwann cell autonomous from tissue-related changes. The whole data set of the cell culture microarray study is provided to offer an interactive search tool for genes of interest.

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Susceptibility of podocytes to palmitic acid is regulated by fatty acid oxidation and inversely depends on acetyl-CoA carboxylases 1 and 2

Kapil Kampe[1], Jonas Sieber[1,2], Jana Marina Orellana[1], Peter Mundel[2], and Andreas Werner Jehle[1,3]

Susceptibility of podocytes to palmitic acid is regulated by fatty acid oxidation and inversely depends on acetyl-CoA carboxylases 1 and 2. *Am J Physiol Renal Physiol* 306: F401–F409, 2014. First published December 11, 2013; doi:10.1152/ajprenal.00454.2013.— Type 2 diabetes is characterized by dyslipidemia with elevated free fatty acids (FFAs). Loss of podocytes is a hallmark of diabetic nephropathy, and podocytes are susceptible to saturated FFAs, which induce endoplasmic reticulum (ER) stress and podocyte death. Genome-wide association studies indicate that expression of acetyl-CoA carboxylase (ACC) 2, a key enzyme of fatty acid oxidation (FAO), is associated with proteinuria in type 2 diabetes. Here, we show that stimulation of FAO by aminoimidazole-4-carboxamide-1β-D-ribofuranoside (AICAR) or by adiponectin, activators of the low-energy sensor AMP-activated protein kinase (AMPK), protects from palmitic acid-induced podocyte death. Conversely, inhibition of carnitine palmitoyltransferase (CPT-1), the rate-limiting enzyme of FAO and downstream target of AMPK, augments palmitic acid toxicity and impedes the protective AICAR effect. Etomoxir blocked the AICAR-induced FAO measured with tritium-labeled palmitic acid. The beneficial effect of AICAR was associated with a reduction of ER stress, and it was markedly reduced in ACC-1/-2 double-silenced podocytes. In conclusion, the stimulation of FAO by modulating the AMPK-ACC-CPT-1 pathway may be part of a protective mechanism against saturated FFAs that drive podocyte death. Further studies are needed to investigate the potentially novel therapeutic implications of these findings.

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Journal of Viral Hepatitis 2014, 21, 9–18 IF 3,082

Hepatitis C virus dysregulates glucose homeostasis by a dual mechanism involving induction of P*GC1α* and dephosphorylation of FoxO1

C. Bernsmeier[1,2], D. Calabrese[1], M. H. Heim[1,2], and H. T. F. Duong[1]

Summary
The maintenance of glucose homeostasis is a complex process in which the insulin signalling pathway plays a major role. Disruption of insulin-regulated glucose homeostasis is frequently observed in chronic hepatitis C (CHC) infection and might potentially contribute to type 2 diabetes mellitus (T2DM) development. Presently, the mechanism that links HCV infection to insulin resistance remains unclear. Previously, we have reported that HCV protein expression in HCV transgenic mice (B6HCV) leads to an overexpression of protein phosphatase 2A (PP2A) through an ER stress response. In the present work, we describe an association of FoxO1 hypophosphorylation and upregulation of both *PGC-1α* and *G6Pase* to phenotypic hyperglycaemia and insulin resistance in B6HCV mice. In vitro, we observed that PGC1α is concomitantly induced with PP2A. Moreover, we show that the enhanced PP2A expression is sufficient to inhibit insulin-induced FoxO1 phosphorylation via blockade of insulin-mediated Akt activation or/and through direct association and dephosphorylation of pS-FoxO1. Consequently, we found that the gluconeogenic gene glucose-6-phosphatase is upregulated. These observations were confirmed in liver biopsies obtained from CHC patients. In summary, our results show that HCV-mediated upregulation of PP2A catalytic subunit alters signalling pathways that control hepatic glucose homeostasis by inhibiting Akt and dephosphorylation of FoxO1.

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Journal of Viral Hepatitis 2013, 20, 612–621 IF 3,082

Protein phosphatase 2A impairs IFNα-induced antiviral activity against the hepatitis C virus through the inhibition of STAT1 tyrosine phosphorylation

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SUMMARY. Mammalian cells have developed several mechanisms to sense viruses and initiate adequate responses such as production of interferons. Interferons activate the antiviral response through the Jak-STAT signalling pathway. To establish a chronic infection, viruses need to counteract this barrier of defence. The hepatitis C and hepatitis B viruses are known to up-regulate the expression of protein phosphatase 2A (PP2A). In this study, we show that PP2Ac associates with Jak1/Tyk2/STAT1 and reduces Jak1/Tyk2/STAT1 phosphorylation resulting in an impairment of the IFNa-induced HCV antiviral response. Using the fully infectious HCV cell culture system (HCVcc), we demonstrate that the PP2A catalytic activity is not required to block the antiviral effect of IFNa, although it is needed to support HCVcc replication. Our data suggest an important contribution of virus-induced PP2Ac up-regulation in the establishment of a chronic infection.

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Animals animals 2014, 4, 1–15

Effectiveness of Gel Repellents on Feral Pigeons

Birte Stock and Daniel Haag-Wackernagel

Simple Summary: Feral pigeons live in close association in urban areas. They constitute serious health risks to humans and also lead to high economic loss due to costly damage to buildings, historic monuments, statues and even vegetation. While numerous avian repellent systems are regularly introduced onto the market, scientific proof of efficacy and their use from the point of view of animal welfare is lacking. Therefore, two avian gel repellents were studied on free-living feral pigeons in this study. The focus was set on repellent efficacy and animal welfare concerns. This study's aim is to contribute to a better understanding of feral pigeon management in our cities.

Abstract: Millions of feral pigeons *(Columba livia)* live in close association with the human population in our cities. They pose serious health risks to humans and lead to high economic loss due to damage caused to buildings. Consequently, house owners and city authorities are not willing to allow pigeons on their buildings. While various avian repellents are regularly introduced onto the market, scientific proof of efficacy is lacking. This study aimed at testing the effectiveness of two avian gel repellents and additionally examined their application from animal welfare standpoint. The gels used an alleged tactile or visual aversion of the birds, reinforced by additional sensory cues. We mounted experimental shelves with the installed repellents in a pigeon loft and observed the behavior of free-living feral pigeons towards the systems. Both gels showed a restricted, transient repellent effect, but failed to prove the claimed complete effectiveness. Additionally, the gels' adhesive effect remains doubtful in view of animal welfare because gluing of plumage presents a risk to feral pigeons and also to other non-target birds.

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Selected publications by DBM members

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

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

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

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

Deadline for the next issue is July 31, 2014.


The Editorial Team
of DBM Facts wishes
all its readers nice
summer holidays!

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Don't forget:

6th DBM Summer Barbecue Thursday, August 21, 2014 at the Kraftwerkinsel in Birsfelden walking-tour, barbecue, several attractions

Caroline Johner wird Leiterin Mouse Core-Facility

Mit dem Konzept der Mouse Core Facility wurden die bestehenden Versuchstierstationen an der Universität Basel und dem Universitätsspital Basel zu einer Einheit zusammengefasst. Die Leitung hat per 1. April 2014 Caroline Johner übernommen. Sie hat an der Freien Universität Berlin Tiermedizin studiert und am Helmholtz Zentrum in Neuherberg, München, promoviert. Daneben hat sich Caroline Johner zur Fachtierärztin für Versuchstierkunde weitergebildet. Stationen ihrer beruflichen Laufbahn waren bisher neben dem Helmholtz Zentrum das Universitätsklinikum Freiburg und das Max-Planck-Institut für Immunobiologie und Epigenetik in Freiburg. Wenn Sie Zeit hat, geht Caroline Johner gerne wandern oder schwingt das Tanzbein im Stil der 20er- und 30er Jahre bei Lindy Hop und Balboa. Wir heissen Caroline Johner herzlich willkommen und wünschen ihr viel Freude und Erfolg bei ihrer Tätigkeit!

Claudio Cannavo übernimmt IT Support am DBM Mattenstrasse

Aufgrund seiner temporären Aushilfstätigkeit am DBM ist Claudio Cannavo schon vielen Mitarbeitenden nicht nur an der Mattenstrasse wohl bekannt. Ab dem 1. Juli 2014 gehört Claudio nun fest zum DBM IT Team. Er ist eidg. dipl. Informatiker Fachrichtung Systemtechnik und hat im internationalen Umfeld schon einige Erfahrung sammeln können (wie Novartis, UBS etc.). Claudio macht Musik, ist viel in der Natur, kocht mit Freude, geht gerne auf Reisen und liebt sein Auto und – wen wundert's – seinen Computer. Herzlich willkommen am DBM, Claudio!

Roy Allenspach wird neuer Betriebsassistent am DBM Hebelstrasse

Auch Roy Allenspach ist am DBM kein Unbekannter: Schon zweimal führte ihn sein Weg ans DBM, zunächst in die Forschungsgruppe Signaling, nach Zwischenstopps bei Roche und Novartis 2011 zurück in das Labor Ocular Pharmacology und Physiology. Roy hat bei Novartis seine Ausbildung zum diplomierten Biologielaboranten absolviert, war anschliessend lange bei Novartis tätig und kann auch das renommierte Basler Institut für Immunologie in seinem Werdegang aufführen. Roy ist verheiratet und Vater von zwei Kindern. In seiner Freizeit macht er gern etwas mit seinen Kindern oder er trainiert die Baseball-Junioren, bei denen sein Sohn natürlich auch mitspielt. Einen guten Start und viel Freude und Erfolg in der neuen Funktion, Roy!

Heidi Hoyermann

Congratulations

Das DBM gratuliert ganz herzlich!

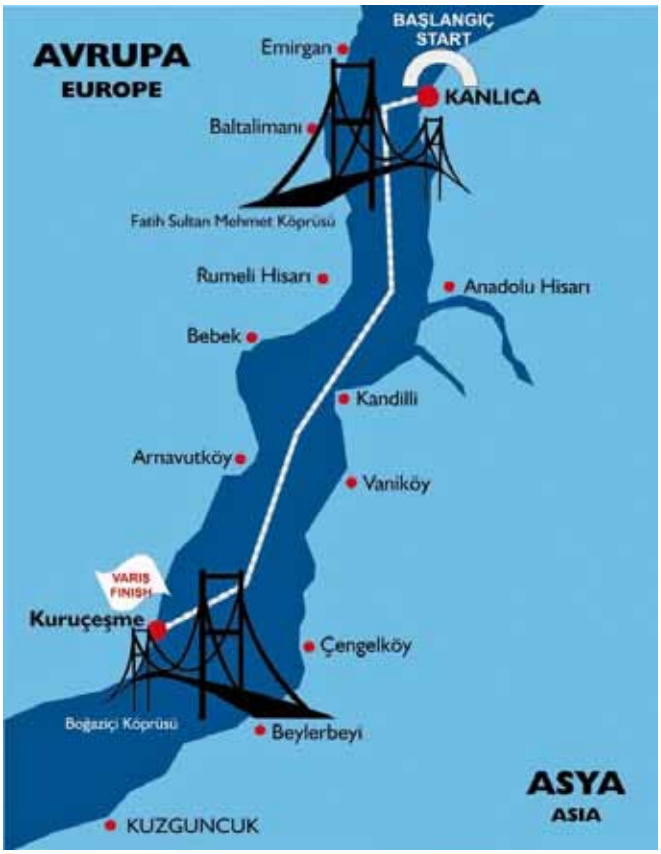
Taran Lars Fritzius
Geboren am 18.01.2014

Herzlich willkommen, allerseits!

Daniel Khan Seidel
Geboren am 18.04.2014

From Asia to Europe less than in one hour!

I think that every person has a hobby. I like swimming and train with Basel swimming club. Once, my friend and club-mate asked if I want to swim a cross-continental race. “Hmm”, I said, “I am a good swimmer, but cross-continental is perhaps too much!” He answered, “Don’t worry! It may sounds like you swim across Atlantic or Pacific Ocean, but you just cross Bosphorus in Istanbul and it’s a lot of fun!” I always wanted to try an open water race – it is an amazing experience, especially in such a beautiful oriental city as Istanbul, where I had never been yet at that time. So, I agreed and I don’t regret it at all.



Of course, I anticipated something special from my trip to Istanbul, but it overcame all my expectations. It was not just a sport event, but also an amazing trip, the adventure. The Bosphorus Cross-continental Races have been organized annually, by the National Olympic Committee of Turkey, since 1989. It has already become a world brand as a single swimming race from one continent to another, from Asia to Europe. More than a thousand athletes from more than 50 countries come to Istanbul every year to swim this race. When I realized that I would swim together with about 1500 others participants I got a bit scared. How can one organize such a crowd? In addition, there was a separate start for disabled swimmers. I was impressed that some of the participants did not have a leg, one or both arms. In general, this competition brought together people from all professions, ages and languages. English, Japanese and even Tibetans were there. The Bosphorus Cross-continental Race has no upper age limit and the oldest swimmer was at the age of 83. I have to admit that the organizers did their best to provide safety and comfort during the event. The busy traffic through the Bosphorus was closed during the competition, but only for 2 hours. So, all the participants had to start and finish within this time limit. Two big military ships were at the start and finish points making sure that no boats, ships or tankers would pass through. There were only rescue boats and a couple of helicopters around all the time. Organizers took care also about energy support for the athletes. Every

participant got a sport bag full of chocolate, energy bars, and other useful presents.

Swimming in open water is tricky and requires special skills. There are strong currents, wind, and waves that you have to take into account. Orientation from water is quite difficult as well. All this I knew only in theory. We got a lot of important information and advice from the organizers. A day before the race there were special ships organized for participants. They were cruising between the start and finish points with a guide explaining and showing how and where to swim. Total distance that we had to swim was 6,5 km – from Kanlıca to Kuruçeşme (see map). One of the important milestones was Galatasray Islet. "As soon as you pass it by swim landward" – we were told. Since we were swimming with the stream, which is quite strong, the best thing was to use it. From the start you should swim towards the middle of Bosphorus where the current is strongest, follow it and leave it at the finish. Easier said than done, especially, the last part. Many athletes missed the finish because of the strong current and had to be picked up by the rescue boats. Even the most experienced, those who swim the Bosphorus every year, say that it is unpredictable, that the current changes every year making it impossible to find one fastest route. I think, that such technical difficulties make the race even more interesting and exciting. It is not just about strength and speed. You have to learn the area with all necessary milestones on the banks, plan your route and carefully navigate yourself. I had an amazing feeling, a euphoria, already at the start, and I saw that hundreds of others swimmers around me felt just the same. Some people just enjoyed swimming, without being in a hurry. I saw some swimmers making photos and videos during the race, taking out cameras from swimming suits. At the finish I had a strong impression that it took me just 15 minutes to swim the race and when I saw my time I was surprised – 48 minutes.

That was not the end of my trip. I had another two days to discover Istanbul with its historical attractions, gastronomic delights and interesting people. I had to restore calories I lost during the race, that was my excuse. Istanbul is amazing city with its own unique atmosphere. Hagia Sophia, Topkapı Palace, Sultanahmet Mosque, Basilica Cistern and Galata tower are just the most popular sights and it is a great pleasure simply to walk around, find a nice spot and drink a cup of coffee or tea while watching people. It is simply impossible to describe the smells, tastes and sounds – you have to experience it yourself. By the way, one of the most impressive discoveries for me was a tradition of drinking tea, or, rather of making it. I realized that we, Russians, have it from Turkey! We first prepare a concentrated drink, which one should then dilute with water.

You can find more information about Bosphorus Cross Continental Race at "http://bogazici.olimpiyat.org.tr/?dil=en". And if you are interested in swimming and want to know more about Basel Swimming Club – follow the link "http://www.svbasel.ch".

Artem Kalinichenko

Reykjavik – Nordic City by the Sea

Hometown Reykjavik

I am from Iceland and for most of my childhood I lived in the capital, Reykjavik. The population of Iceland is about 320.000 people and over one third of them live in the Reykjavík area.

When flying to Iceland it says that your destination is Reykjavik. However, people do not actually land in Reykjavík but in Keflavik, a fishing town about 40 km away from the city. The airport isn't actually even there, but is outside Keflavík on the former American military airport. It is best to take the fly bus to Reykjavik from the airport.

Reykjavík is not a beautiful capital city, at least not in the way you might describe Moscow or Basel. It is historically a very young and fast growing city with harsh weather conditions.

I will never forget how surprised I was to see people in Europe walking with an umbrella in the rain, because when I grew up in Reykjavík no one would ever walk with an umbrella. Not that it didn't rain, because it does, more than it probably does in most cities in the world. No, we didn't carry one because it was too windy to carry an umbrella, and you would have been fighting with the wind and the rain. But this is something to expect on a small island in the middle of the Atlantic Ocean. It can be fascinating to stand on the island and observe this giant of an ocean on a stormy, windy day and especially on the few calm days.

Hallgrímskirkjan: *This is the largest church of the country, named after Hallgrímur Péturs-son, a poet and clergyman that wrote the 50 poet text called Passion Hymns, in the mid 1600.*

I mostly spent my childhood in Breiðholt. Due to population pressure in the 1960s, development plans were published for Breiðholt in 1966 in the hills east of the city, with the idea of building single-family houses and low-priced apartment buildings mixed together. In 1999, Breiðholt was the highest populated area in Reykjavik with 22,030 inhabitants, and there were many children in that area, making life both adventurous and sometimes troublesome. Today, despite the bad reputation this area has had, many of the former inhabitants are important persons in Icelandic society and politics, with Björk probably being the most famous person.

As I got older most of my time was spent in 101 which is the center. There you can enjoy most of what the city has to offer.

Since the crisis in 2007 there has been a huge change in tourism. Because of the weak currency it is now affordable for foreigners to travel around the country. This year it is estimated that there will be over a million tourists in Iceland, almost four times the population. Travellers do not ask you if you speak English, they ask if you are local.

Domkirkjan og Katholska: *A view from the old town. Most of the older houses have corrugated metal plates to protect them from the weather. Both the white Dómkirkjan (Reykjavík Cathedral), next to the Parliament House, and the stony Catholic Church, Landakot, can be seen.*

Hofnin: *The old whale ships at the harbour close to the town centre.*

Outside activity

If visiting Reykjavik, you should walk the coast line. There is the smábótahöfn (small boat harbour) where the fishermen go out early in the morning and come back to sell their fish for the day. After that go for coffee at Kaffivagninn (coffee wagon) at Granda. There is also the big harbour, where the famous boats such as the research boats from the Alfred Wagner Institute in Bremen, dock and where you can enjoy a view of the newest coastal landmark, Harpa, the music hall.

Nauhólsvik is on the south side of the coast and there you can enjoy long walks, sunbathe or swim in the ocean. There is also Ellidardalur, a huge green area for the citizens of the city, where people hike, or a bike. You could even buy a permit to catch a salmon in the river, Elliðardalsá. The river is one of few salmon rivers in the world that runs through a city.

Húni: *The newly built concert house, Harpa, located at the marina.*

If you happen to be in Reykjavik at the time of the year when there is ever lasting daylight, the midnight sun, you should get yourself a good bottle of wine at the "Ríkið" (governmental wine store) or a warm jug of tee and sit down at the beach, close to the lighthouse, Grótta, even if the access to immediate surroundings of the lighthouse are forbidden due to nesting birds or the tide (watch out for the tide!). You can sit at the beach and both enjoy the rich bird life and watching the sun take a brief dip into the ocean just to climb straight back up to sky. Even if you are travelling with children you should try to stay awake at least once to enjoy the atmosphere of the midnight sun.

Hvunndagshetjur: *Elliðarárdalur. Catching a salmon in the city river.*

It only takes five minutes to sail to the island Viðey from Sundahöfn. The island is part of Iceland´s architectural history as it is home to the first house constructed of stone in Iceland that was built in the 17th century. Once a home to Iceland´s treasurer it now boasts a restaurant. Videy church, built in 1774, is a great spot to visit as it still has its original furnishings.

Viðey Island is home to fascinating works of art by world-renowned artists. On the West Island a well known sculpture by American sculptor Richard Serra can be found. Serra's work, Milestones, is comprised of nine pairs of pillars columnar basalt, which "frame" certain landmarks.

In October 9th, 2007, Yoko Ono's Imagine Peace Tower was raised on the island in memory to the

Vesturbæjarsundlaug: *"Chilling out" in one of several outdoor swimming pools that are open the whole year through.*

Beatle John Lennon. The Peace Tower is actually a light, from which a strong beam of light shines upwards from the ground, 20–30 m into the air. The tower is meant to shed the light of peace on the nations of the world.

If you want to take a short hiking tour, many Reykjavik citizens hike on the Esja, the mountain 10 km away from the center (a shuttle from BSI, the central station that takes you back and forth to the airport). It is a good hike. To get to the top it can be difficult, but on the top you have a view over the whole Reykjavik area and on the other side over Whale fjord, thelocation where whales where formerly "processed" before Iceland completely stopped whale catching in 1989 (and restarted for mink whale and some other small whales around 2008). Esja is a mountain that you can view from almost every place in Reykjavik and there have been lyrics and books written about that mountain. My mother used to tell me that, yes I could spend a night in a tent with my friend if there was no snow to be seen on the Esja. That could be in July, depending on the summer.

Personally I find it easy to spend days in Reykjavik. There is lot to do and see like Húsdðragarðurinn (the domestic animal garden) or all the museums or funny houses to look at. If the weather is good you can have a fantastic time in this corny little capital.

Pubs

Reykjavík has changed a lot the past 30 years. Pubs were not in the city till the ninety's in fact it was illegal to sell beer in Iceland from 1915 to the 1st of March 1989. But since then we have had huge changes and now there are nice pubs all over the center of Reykjavik including some making good icelandic beer. I suggest that you try a beer called Kaldi and that you visit Kaldibar. Microbar is a small bar in Vallarstræti by Austurvöllur and there the host can give you a tour of the Icelandic brewery story and give you a taste of different types of beer.

Coffee houses

Mokka and Prikið are two of the oldest places that serve coffee. I strongly recommend Mokka because nothing has changed there since they opened in 1958. They also exhibit art all year around. Now it is hard to find a coffee place that does not serve good coffee. Everywhere there are places you can sit down and relax. In some of them you can read a magazine while you enjoy a cup, like at IÐA or in Eymundsson or 2nd floor at Mál og Menning. These are bookstores but they also have Coffee house inside them. Stofan, Te og Kaffi and Kaffitár specialize in good coffee as well as relaxing atmosphere. Café Babalú is very sputnik and they have a nice balcony overseeing Skólavörðustígur if the weather is good. By the old harbour you can find Café Haiti and there you can watch the ships sail in and out of the old harbour.

Ráðhús: *On the left, the city hall at the pond, Tjörnin.*

Þyrluflug-byggd: *Aerial view of the city, with the main harbour, pond and the mountain, Esja.*

In Granda there are also fine places to sit outside and enjoy the view. Sjóminjasafnið is one of them and there you can also study the museum. The same goes for Sögusafnið which is next door to the Sjominjasafnid. The National Museum is, of course, a must see. These are only some of the places in the city where you can have tea, coffee and cakes.

Wining and dining

If you look at the size of the center there is a lot to choose from when it comes to wining and dining. There are places where one can have Happy Hour or a meal. Those places are good if you are thinking about cost. Nora by Austurvöllur and Bunk at Laugavegur are nice places that have both. By the old harbour and downtown there are also very nice restaurants. At the restaurant þrír frakkar by Baldursgata 14, you can have a very good meal, especially fish. Snaps on Óðinsgata is another nice place. It is probably harder to get a bad meal than a good one and the expensive places like Holtið, Humarhúsið, Fishmarket are not necessarily better than the average ones.

Swimming in Reykjavík

If the average Icelander "goes swimming" it means to spend half of the time if not all of the time in the hot tubs to meet others and chat. There is nothing like relaxing in the hot tubs of Reykjavik's swimming pools, http://reykjavik.is/sundlaugar and I would much rather recommend them then the expensive trip to the Blue Lagoon.

The countryside

Though no one should visit Iceland without staying in Reykjavik for couple of days the real beauty is when you have left the city and started your journey in the countryside.

People come to see the land itself, with the big glaciers, geothermal areas, and raw landscape; most of it, easily accessible but not necessary cheap.

I strongly recommend a trip around Iceland or spending as much time as possible outside Reykjavík. The easiest is to sleep at the farmers place, either in housing close to the farm or small cottages on the farmers land (f. ex. http://www.farmholidays.is).

But my task was to inform you about Reykjavík and I wouldn't have been able to do that without the help of my sister Elfa, who always knows where the "up to date" locations are and what's on in the city. She also kindly provided me with all the pictures.

I hope from this short article and the web sites here below you will learn something about my home town. And I might actually be doing just one of the things mentioned above with my sister Elfa, as you read this article.

http://www.visitreykjavik.is/

http://www.iceland.is/

http://fooledbyiceland.tumblr.com

Elfa and Elín Ellertsdætur (daughters of Ellert)

Sisters at the harbour: *Enjoying a good time at some harbour even it isn't in Reykjavik with my sisters.*

So schmeckt der Bodensee

Wer sie einmal gegessen hat, wird es immer wieder tun … Fische aus dem Bodensee. Doch nicht immer hat man die Zeit ans «Schwäbische Meer» zu fahren. Nachfolgend ein paar schnelle, leichte und leckere Rezepte für laue Sommerabende zu Hause. Wer den Blick auf die Wellen oder den Sonnenuntergang über dem See vermisst, möge als Einstimmung das Titelfoto oder die letzte Seite dieses Heftes anschauen. Guten Appetit!

Bodenseefelchen

(selbstverständlich kann man als Grundlage auch Felchen aus anderen Seen verwenden)

Grundsauce

Zutaten: 1 Schalotte, 20 g Butter, 10 g Mehl, 125 ml trockenen Weißwein, 250 ml Fischfond, 250 ml Sahne, Salz, Pfeffer, Zucker

Zubereitung: Schalotten fein würfeln, Butter zerlassen und darin glasig unterrühren, Mehl darüber stäuben, anschwitzen lassen, Wein, Fischfond und Sahne zugießen, glatt rühren, 5 Minuten unterrühren, köcheln lassen, mit Salz, Pfeffer und 1 Prise Zucker würzen, durch Sieb giessen.

Felchen-Filet nach Reichenauer Art

(in Kräuterrahmsauce)

Zutaten: 4 Felchen-Filet, 0,2 l Milch, 0,2 l Brühe, 1 Becher Sauerrahm oder Schmand, Salz, Pfeffer, Zitronensaft, Oel, Mehl, 1 kleine Zwiebel, frischer Dill, Schnittlauch, Petersilie.

Zubereitung: Filet waschen, salzen, pfeffern und mit Zitronensaft beträufeln und mit Mehl bestäuben. Die Filets mit Oel in einer Pfanne kurz von beiden Seiten anbraten, Zwiebeln fein gehakt dazugeben. Mit Milch und Brühe ablöschen. Saure Sahne bzw. Schmand unterrühren. 7–8 Min. ziehen lassen. Evtl. die Sosse mit etwas Mehl binden.

Felchen-Filet nach Konstanzer Art

(in Weißweinsauce)

Zutaten: 4 Felchen-Filet, 1 kleine Zwiebel, 0,4 l Weißwein, Salz, Pfeffer, Oel, Mehl, Champignon, Tomatenwürfel.

Zubereitung: Zwiebel fein gehackt in Oel andünsten, Fischfilets anbraten, Champignonsscheiben und Tomatenwürfel zugeben, mit 0,4 l Weisswein ablöschen, Fischgewürz und Salz, mit etwas Mehl binden.

Felchen-Filet nach Thurgauer Art

(mit Apfelwürfel)

Zutaten: 4 Felchen-Filet, 1 Zitrone, 1 Apfel (leicht säuerlich z.B. Gravensteiner), Brat-Butter , normale Butter, Salz, Pfeffer, Weisswein, frischer Dill

Zubereitung: Filet waschen, salzen, pfeffern und mit Zitronensaft beträufeln, mit Mehl bestäuben, Apfel mit Schale in kleine Würfel schneiden, mit Zitronensaft und Dill marinieren. Bratbutter in Pfanne erhitzen, Filets leicht salzen, knapp eine Minute zuerst auf der Hautseite garen, wenden. Die gebratenen Filets auf Küchenpapier im 70 °C warmen Ofen beiseite stellen, die marinierten Apfelwürfel in heisser Butter schwenken, die Filets anrichten und die Apfelwürfel über die Felchen-Filets verteilen.

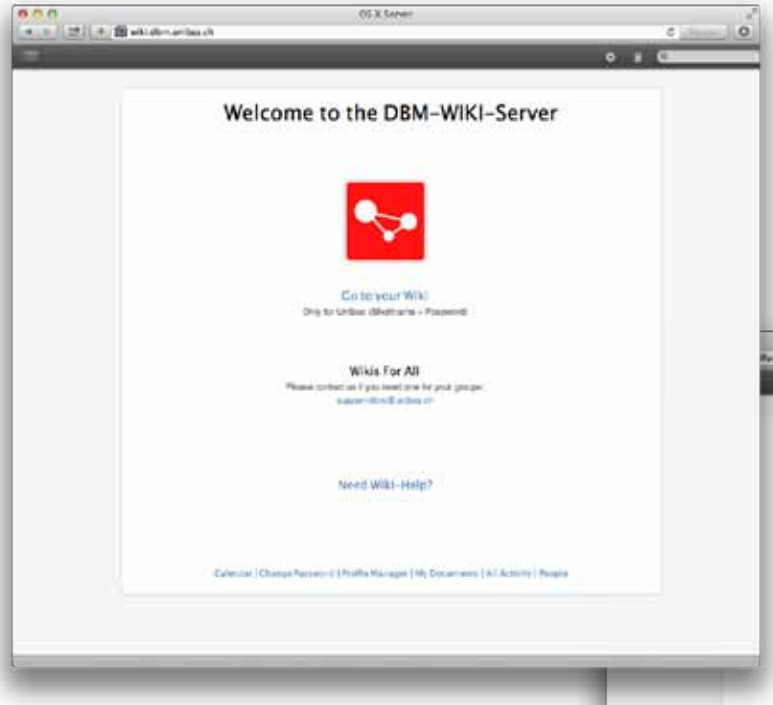
Zander

Zutaten: 600 g Zanderfilet, 4 Rosmarinzweige (ca. 10 cm lang), 70 g Bratöl, 50 g Butter, Salz und Pfeffer

Zubereitung:
Den Zander waschen und mit einem Rosmarinzweig durchstossen. Öl in einer Pfanne erhitzen. Zander mit der Hautseite in das heisse Öl legen. Wenn der Fisch zu 2/3 auf der Hautseite gegart ist, wenden und die Butter zugeben. Mit dem gewonnenen Butter-Öl-Gemisch die Filets immer wieder begießen. Wenn der Fisch fertig gegart ist, herausnehmen und den Zweig herausziehen. Erst im Anschluss daran würzen.

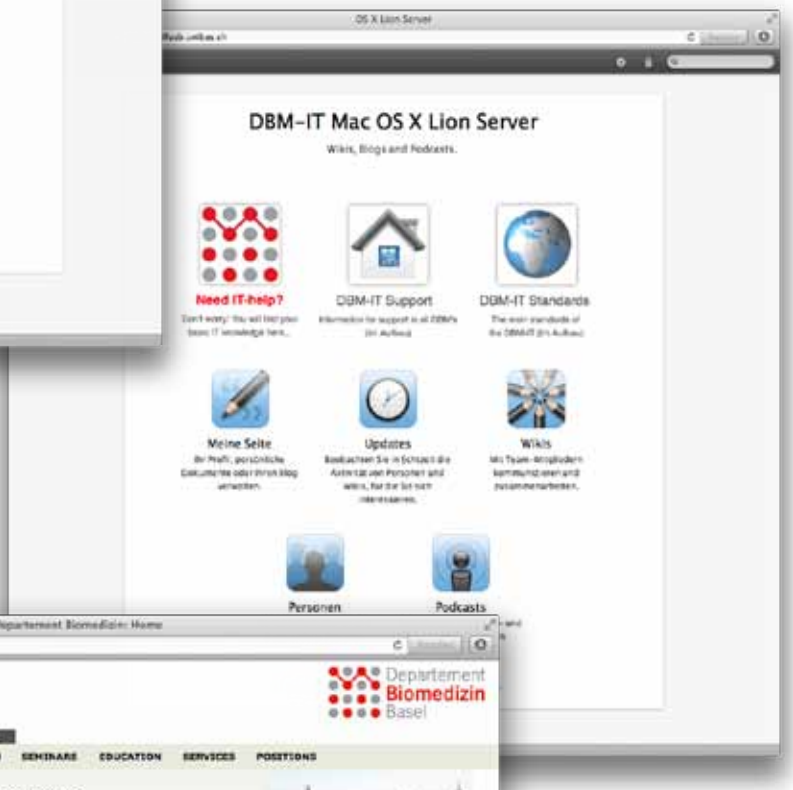
Mit Petersilienkartoffeln und einem grünen Salat servieren.

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



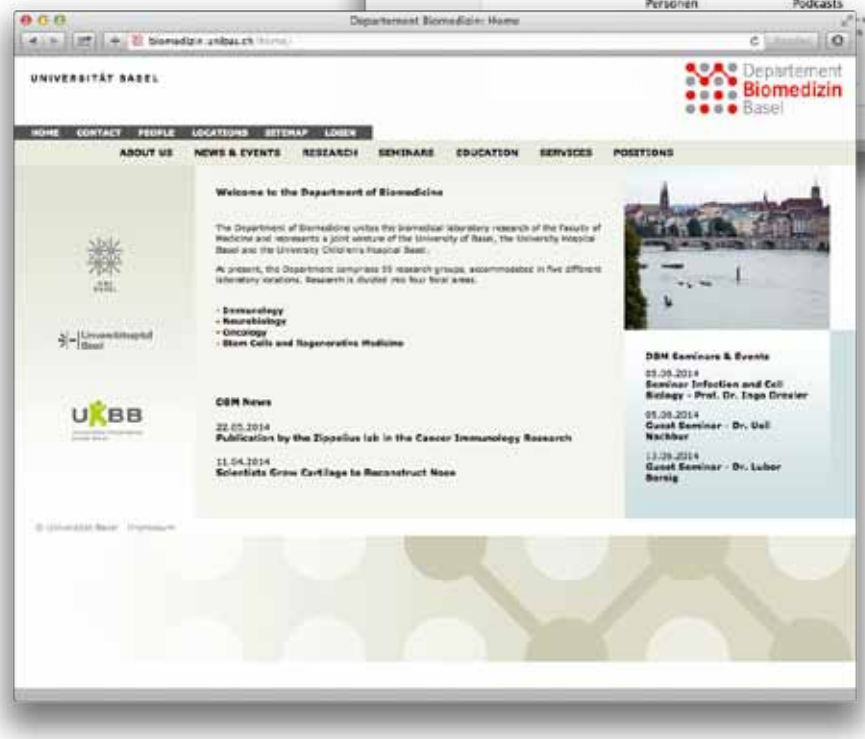
We now have a WIKI-Server for all our Lab-Groups, where each group can create their own WIKI. For more information contact: marc.bichsel@unibas.ch

http://wiki.dbm.unibas.ch



Don't forget our IT-help Wiki, there is a lot of useful information

http://gadget.dfusb.unibas.ch



And our Website http://biomedizin.unibas.ch will be updated "soon"

Heute: Friedel Wenzel, Medizinische Genetik

«Ene kölsche Jung am Basler Morgenstraich»

Eigentlich hatte ich mir meine berufliche Lebensplanung ja ganz anders vorgestellt, habe ich doch immer schon eine grosse Vorliebe für jegliche Form von Wasser gehabt. Bereits als kleiner Junge habe ich meine Eltern mit Schreikrämpfen und Ohnmachtsanfällen in die schiere Verzweiflung getrieben, wenn ich im Schwimmbad aus dem Babybecken raus sollte; als Teeny war ich im Schwimmverein, habe

es bei Wettkämpfen aber selten auf den 1. Platz geschafft. Nach dem Abitur ging ich für zwei Jahre zur Bundeswehr – natürlich kam nur die Marine in Frage – und bin dort über ein Jahr zur See gefahren. Und dann – quasi als Höhepunkt und immer noch passend zum Thema «Wasser» – habe ich mich für ein Biologiestudium mit Schwerpunkt Limnologie (Binnengewässerkunde) entschieden; dabei hat es mich in meiner jugendlichen Naivität nicht beeindruckt, dass es für diese, damals noch exotische Fachrichtung kaum Arbeitsplätze gab und so habe ich später dann ja auch keinen gefunden. Aber die Biologie ist vielfältig und so habe ich im Rahmen eines entwicklungsbiologischen Forschungsprojekt herauszufinden versucht, wieso das abgelegte Ei der südamerikanischen Trauermücke Bradysia tritici weiss, wo vorn und hinten ist, bevor mich der Ernst des Lebens als junger Familienvater eingeholt hat.

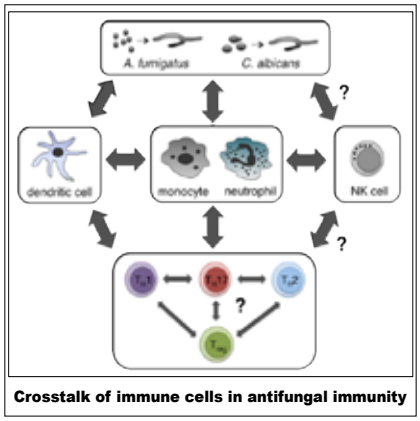
In dieser universitären Sturm- und Drangzeit wurden mir zwei Dinge relativ schnell klar: a) ich bin nicht der Forschertyp, der sein Leben

der Grundlagenforschung widmen will und b) ich mache in der Biologie alles – nur keine Genetik (das war im Studium einfach nur langweilig). Aber man soll ja nie «Nie» sagen im Leben und so bin ich als «kölsche Jung» auf diversen Umwegen vor nunmehr 25 Jahren in Basel und letztlich dann auch in der Genetik am damaligen Kinderspital gelandet. Heute engagiere ich mich als Laborleiter mit meinem Team speziell im Bereich der Labordiagnostik bei hämatologischen Neoplasien; wir werden jeden Tag aufs Neue herausgefordert, mit dem aktuell verfügbaren Methodenspektrum die individuelle klinische Situation des einzelnen Patienten aus genetischer Sicht zu beleuchten und relevante Fakten für Prognoseabschätzung und Therapieplanung abzuleiten. Trotz so mancher Schattenseiten möchte ich diesen Job auch nach all den Jahren nicht missen. Genauso wenig missen möchte ich aber auch die Basler Fasnacht, die mir – als «kölsche Jung» – nach all den Jahren genauso ans Herz gewachsen ist wie der rheinische Karneval.

Natürlich gehe ich auch nicht alleine durchs Leben; bereits während des Studiums habe ich meine Frau Christa – ebenfalls Biologin – kennengelernt. Wir haben dann mit einem Kind ein Haus geplant, mit zwei Kindern das Haus gebaut und lebten letztlich mit drei Kindern darin. Auf dem Familienbild sieht man rechts von mir unsere Tochter Janna (Studium der Molekularen Medizin) mit ihrem Freund Klemens, zwischen meiner Frau und mir unseren Sohn Lars (Studium der Veterinärmedizin) und links neben meiner Frau unsere Tochter Marisa (Ausbildung zur Logopädin) mit ihrem Freund Alexander; unsere Familie bleibt also der Medizin bzw. den Naturwissenschaften treu.

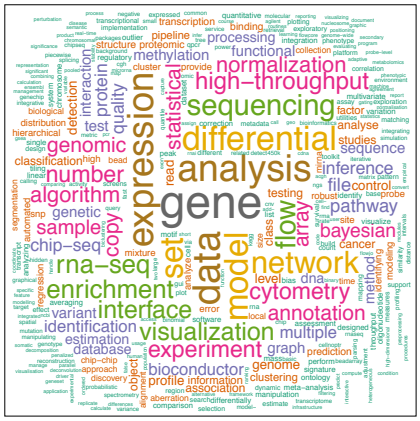
VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



Crosstalk of immune cells in antifungal immunity

… lernen wir mit Nina Khanna die Welt der Infection Biology kennen

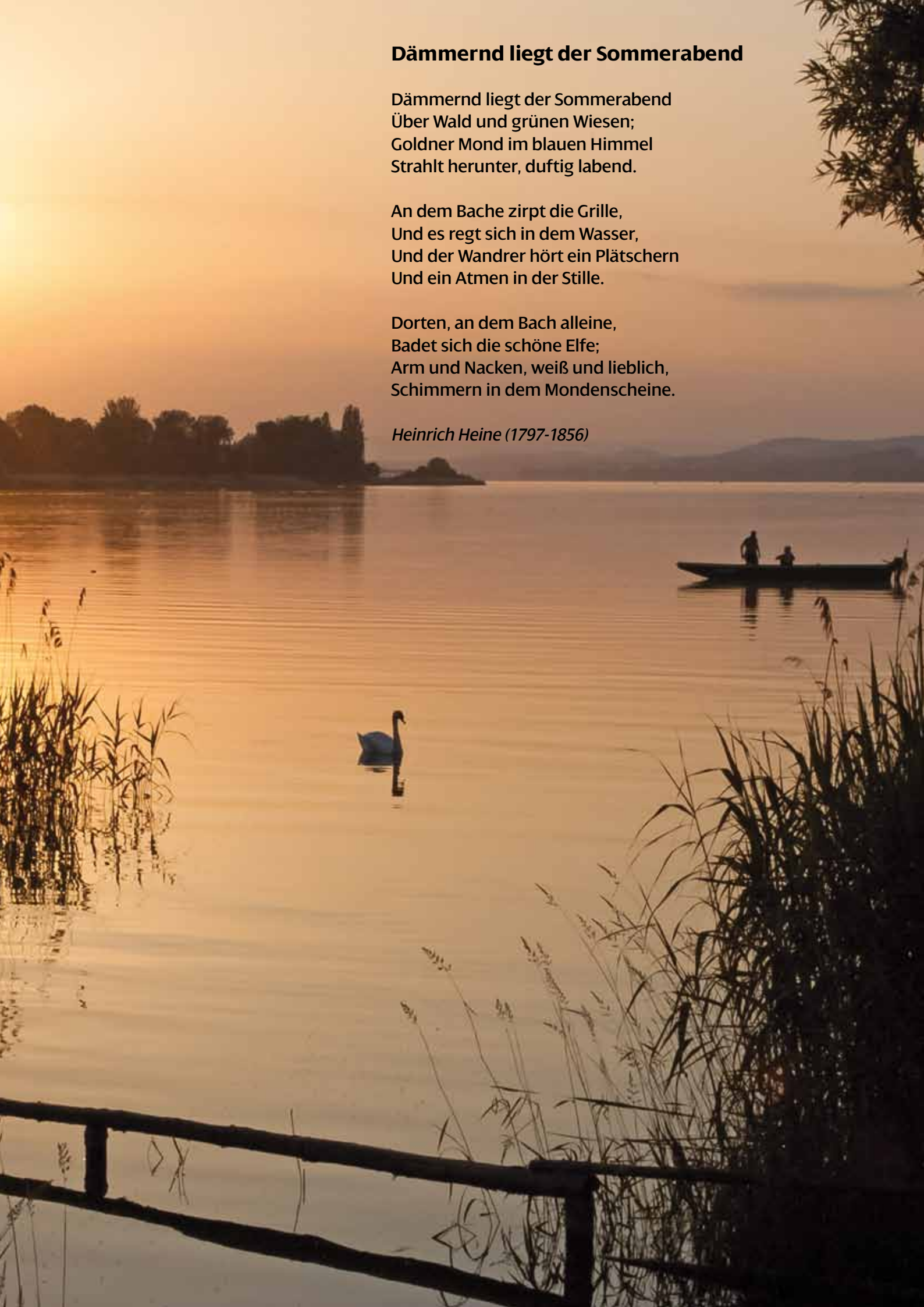


… erzählt uns Robert Ivanek, warum die Bioinformatik so spannend ist

… nimmt uns Margarita Dinamarca Ceballos mit in ihre Heimat Chile

… schauen wir mit Martina Konantz auf die WM 2014 zurück

… gehen wir mit Anne-Catherine Feutz auf Weinlese ins Elsass



Dämmernd liegt der Sommerabend

Dämmernd liegt der Sommerabend
Über Wald und grünen Wiesen;
Goldner Mond im blauen Himmel
Strahlt herunter, duftig labend.

An dem Bache zirpt die Grille,
Und es regt sich in dem Wasser,
Und der Wandrer hört ein Plätschern
Und ein Atmen in der Stille.

Dorten, an dem Bach alleine,
Badet sich die schöne Elfe;
Arm und Nacken, weiß und lieblich,
Schimmern in dem Mondenscheine.

Heinrich Heine (1797-1856)