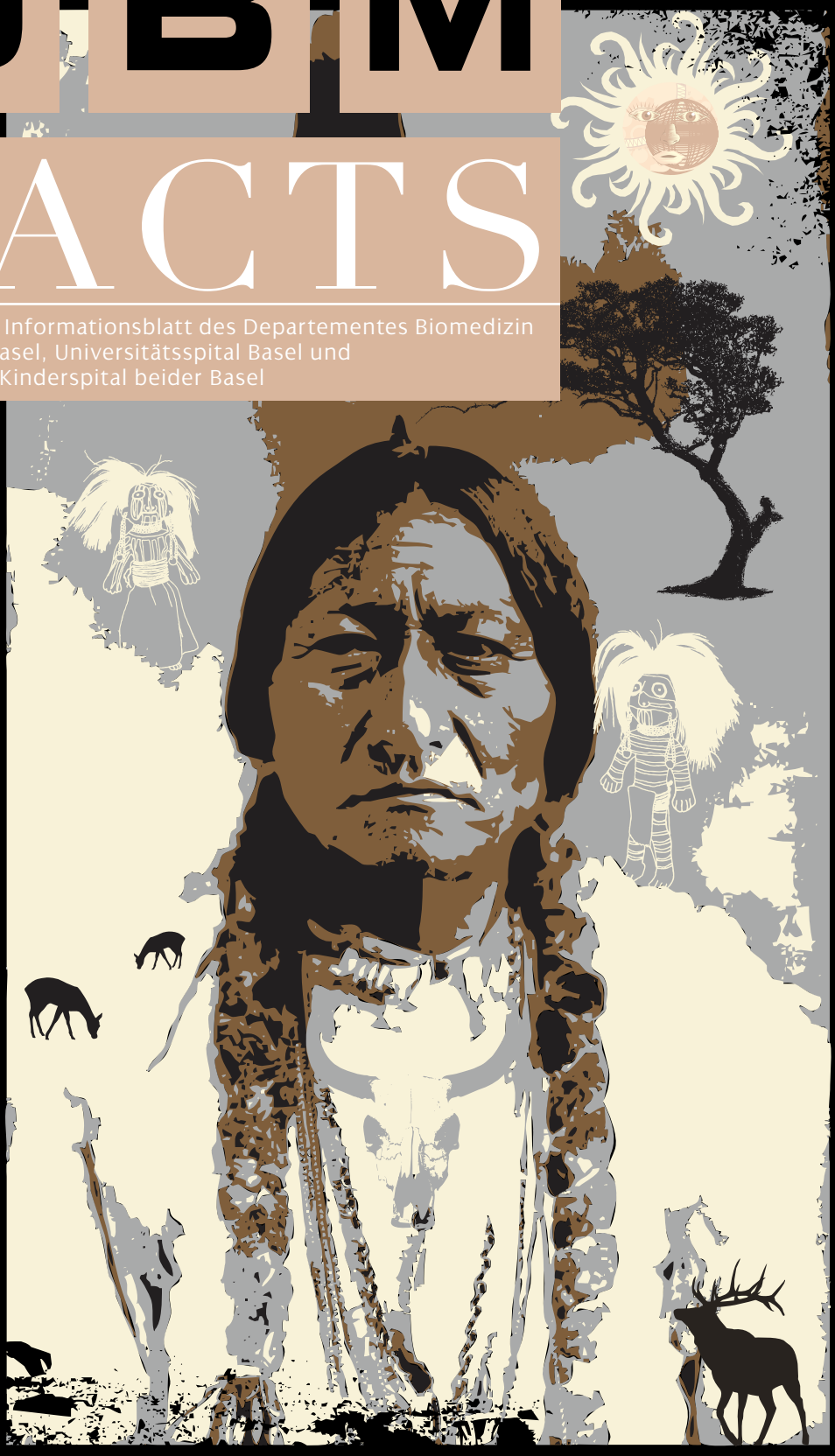
DBM FACTS

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



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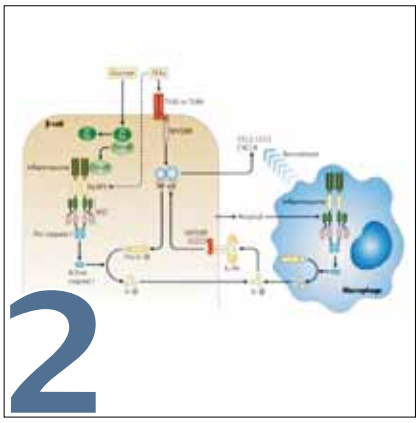

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IMPRESSUM

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Ein ruhiger Sommer liegt hinter uns. Der Unirat hat in seiner Sitzung vom 25. August 2011 Christoph Rochlitz zum Ordinarius für Medizinische Onkologie ernannt. Gleichzeitig wurde Verdon Taylor zum Extraordinarius für Embryologie und Stammzellbiologie bestimmt. Wir gratulieren beiden herzlich und wünschen ihnen viel Erfolg! Weitere gute Nachrichten: Die Medizinische Bibliothek wird in neue Räumlichkeiten an der Spiegelgasse umziehen, so dass mit der Planung für den Umbau des 2. Geschosses am ZLF begonnen werden kann.

Schwerpunkt der nun vorliegenden Herbstausgabe der DBM Facts bildet neben den neuesten Publikationen aus dem DBM das Forschungsprojekt von Marc Donath. Er führt uns in die Welt des "Immunometabolismus" ein (ab Seite 2). Lucia Mori stellt uns anschliessend das "Singapore Immunology Network" vor (ab Seite 8).

Ein Ausland ganz anderer Art erleben wir mit Benjamin Pippenger, der uns mit in seine Heimat Montana (USA) nimmt (ab Seite 26). Über die schönsten kulinarischen Seiten des Herbstes lesen Sie mehr ab Seite 32 und wie man die Folgen wieder abtrainiert ab Seite 34.

Schöne Herbsttage und viel Spass bei der Lektüre!

Dear Readers

The quiet summer is now behind us. At the University board meeting of the 25th August 2011 Christoph Rochlitz was named as Full Professor of Medical Oncology. At the same time Verdon Taylor was also chosen as Associate Professor of Embryology and Stem Cell Biology. We send them both our hearty congratulations and wish them every success! More good news: the medical library will be moving to its new premises on Spiegelgasse, so we will be able to begin planning the renovation of the second floor of the ZLF.

In addition to the latest publications form the DBM, one of the highlights of this autumnal issue of DBM Facts is the research work of Marc Donath. He introduces us to the world of the "Immunometabolism" (page 2). This is followed by Lucia Mori's introduction to the "Singapore Immunology Network" (page 8).

We take a completely different journey abroad with Benjamin Pippenger, who brings us on a visit to his homeland, Montana in the USA (page 26). We can learn more about the best culinary aspects of the autumn from page 32 onward, and how one can work off the results on page 34.

Wishing you all wonderful autumnal days and happy reading!

Immunometabolism, from physiology to diabetes

The group "Diabetes Research". From left to right and back to front: Marcela Borsigova, Helga Ellingsgaard, Erez Dror, Richard Prazak, Katharina Timper, Nadine Sauter, Marianne Böni, Kathrin Dembinski, Patrizia Zala, Eleonora Seelig, Marc Donath.

1. Background

Diabetes affects 285 million people worldwide and according to the International Diabetes Federation the number is expected to reach 438 million by the year 2030. Diabetes prevalence is rising, particularly in countries undergoing a rapid economic development, due to the increasing sedentary lifestyle and increase in obesity. The most common forms of diabetes (type 1 and type 2 diabetes) are polygenic and due to a combination of genetic and environmental factors. Of these, type1 diabetes is caused by autoimmune destruction of the insulin producing β cells in islets of the Langerhans, while type 2diabetes is strongly associated with obesity, insulin resistance and the progressive failure of β cells to produce sufficient insulin. β cell dysfunction and death determines the onset and progression of type 2 diabetes. Over the past 10 years we have discovered that metabolic stress induces an auto-inflammatory process that is detrimental to islet-cells and which is governed by the master regulatory cytokine Interleukin-1β (IL-1β). Our preclinical and clinical research mainly focuses on the physiology and pathophysiology of pro-inflammatory factors in pancreatic islets and on the therapy of decreased insulin production in type 2 diabetes. In addition to these common forms of diabetes there is a very small percentage of diabetes cases which are monogenic and caused by a single gene defect. The majority of these mutations affect the insulin secretory pathway in the absence of signs of autoimmunity. We have recently identified a novel monogenic form of diabetes in a family with the typical features of autoimmune type 1 diabetes and we are currently characterizing the underlying genetic defect.

2. Mutation of SIRT1 in familial type 1 diabetes: a novel monogenic form of diabetes

A family was analyzed in which 4 affected members display the classical features of type 1 diabetes in association with insulin resistance. At the time of diagnosis, a 26-year-old lean man presented signs of type 1 diabetes, including auto-antibodies to β cell antigens and a rapid dependence on insulin. The pattern of inheritance amongst the affected family members was indicative of an autosomal dominant mutation. Three approaches were used in order to identify the gene targeted by the inherited mutation. Microsatellite analysis, genomic screening of relevant candidate genes, and whole exome sequencing were performed. All three techniques converged on the single target gene located on the long arm of chromosome 10, Sirtuin1 (SIRT1). Direct sequencing of the SIRT1 gene revealed the presence of a T to C exchange in exon 1 leading to a Leucine107Proline mutation in the SIRT1 protein. SIRT1 is a highly conserved protein deacetylase implicated in ageing, the beneficial effects of caloric restriction and inflammation. Phenotypic characterisation of SIRT1 L107P showed that the mutation does not impair the protein stability or its catalytic function. However, there is a diminished protection from the induction of cyto- and chemokines and the stress enzyme iNOS in insulin producing cells expressing SIRT L107P relative to wild type SIRT1. A role for SIRT1 in β cell survival is further indicated by the observation of increased islet destruction in SIRT1 knockout mice challenged with a β cell toxin. Currently, the production of a knock-in mouse to mimic the human mutation is ongoing. SIRT1 L107P is the first described human SIRT1 mutation and it implicates a role for SIRT in human autoimmunity.

3. IL-1β is a key mediator of islet inflammation and dysfunction in type 2 diabetes

In type 2 diabetes increasing evidence suggests that an inflammatory process promotes islet dysfunction and death. This insulitis is due to a pathological activation of the innate immune system and governed by IL-1 signaling. Indeed, islets of patients with type 2 diabetes are characterized by the presence of increased levels of cytokines, NF-κB activation, immune cells, β cell apoptosis, amyloid deposits, and fibrosis. Supporting the critical role of IL-1β, specific blockade of IL-1 activity reduces the release of numerous inflammatory cytokines and chemokines thereby decreasing islet inflammation, improving insulin secretion and glycaemia. Studies on the regulation of IL-1β expression revealed that IL-1β is potently induced by an auto-stimulatory mechanism. Treatment of islets with metabolic stressors (FFA or glucose) results in the activation of a vicious auto-stimulatory pathway which can be blocked by either inhibit-

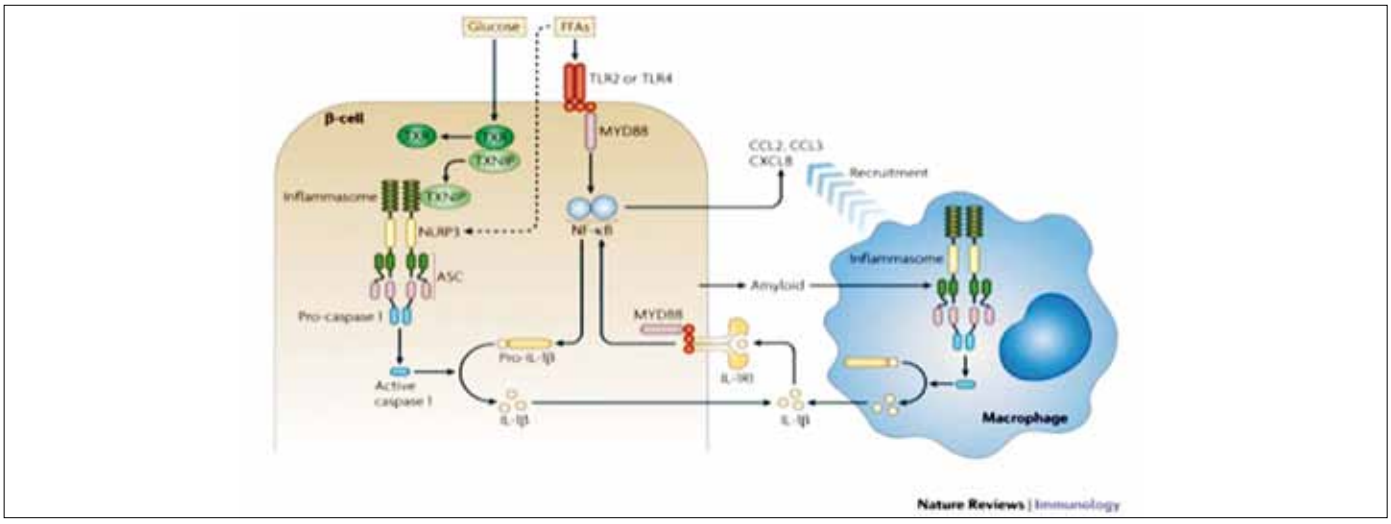

Figure 1: High concentrations of glucose promote β-cell production of interleukin-1β (IL-1β) through the dissociation of thioredoxin-interacting protein (TXNIP) from its inhibitor thioredoxin (TXR), resulting in activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, activation of caspase 1 and processing of pro-IL-1β into its mature form. IL-1β induces the production of a wide range of cytokines and chemokines such as CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 8 (CXCL8) through nuclear factor-κB (NF-κB) activation. This is enhanced by free fatty acid (FFA)-induced activation of Toll-like receptor 2 (TLR2) or TLR4 and leads to the recruitment of macrophages. FFAs may also directly activate the NLRP3 inflammasome. Islet-derived amyloid can activate the recruited macrophages through the NLRP3 inflammasome, increasing IL-1β production and the vicious cycle of IL-1β autostimulation through IL-1 receptor type 1 (IL-1R1). ASC, apoptosis-associated speck-like protein containing a CARD; MYD88, myeloid differentiation primary-response protein 88.

ing the IL-1Receptor with the IL-1R antagonist (IL-1Ra) or by neutralising IL-1β (figure 1). Unlike other secreted cytokines and chemokines, proIL-1β is processed by inflammasomes, a multiprotein platform which cleaves and releases mature IL-1β. While inflammasomes of immune cells are well characterised their role in regulating insulin producing β cells in models of type 2 diabetes is less clear and is currently under investigation by our research group using a knock out mouse model lacking the inflammasome component Nalp3. Interestingly, we observed that islet β cells express the highest level of IL-1 receptors when compared to 20 other tissue, it is even higher than in immune cells. This renders them exquisitely sensitive to IL-1β and implicates that IL-1β may have a role in healthy islets and we are currently in the process of elucidating both, the physiology and pathophysiology of IL-1β on insulin secretion.

4. Activation the local Renin-Angiotensin System (RAS): another mediator of islet inflammation?

Activators of the IL-1 system in islets, described by our research group and others, include glucose, FFA, amylin deposits and reative oxygen species. Several clinical observations led us to hypothesize that the RAS may also promote islet inflammation contributing to β cell dysfunction and precipitation of type 2 diabetes. Hypertensive patients have more than double the risk of developing diabetes and almost 70% of diabetic patients have hypertension. Furthermore, recent clinical trials suggest that lowering the blood pressure by blocking the renin-angiotensin system (RAS) reduces the incidence of new-onset diabetes in patients. The RAS is classically known as a systemic hormonal system regulating blood pressure, mostly through the action of angiotensin II (AngII). In addition to systemic RAS, the presence of local tissue RAS has been increasingly recognized and all the components of a functional RAS can be found in the pancreatic endocrine tissue. Most importantly, insulin-producing β cells express the receptor for AngII, Angiotensin II type 1 receptor (AT1R), suggesting other physiological roles of AngII besides vasoconstriction.

Our work with isolated human pancreatic islets and an insulin producing cell line has shown that hyperglycemia activates the RAS system, linking elevated glucose to elevated AngII, the main effector molecule inducing vasoconstriction. In turn, chronic AngII treatment has deleterious effects on β cell function and survival via

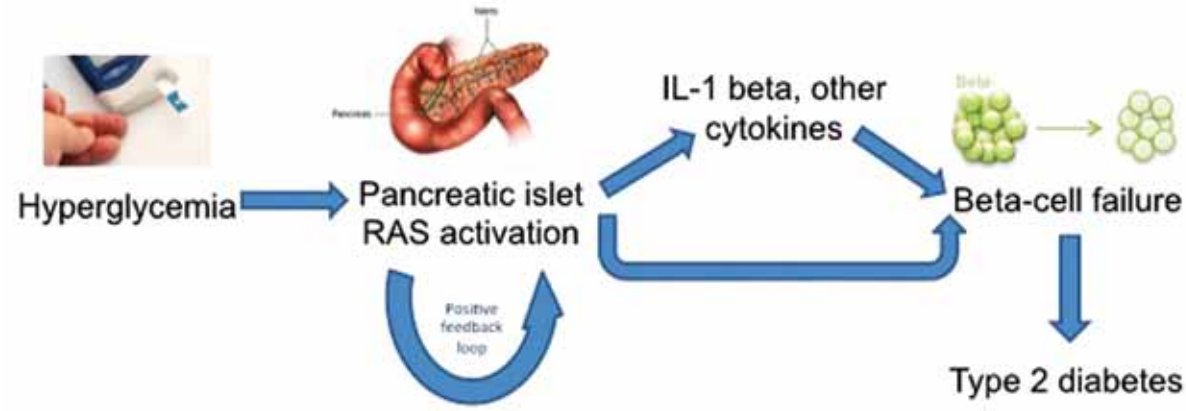

Figure 2

activation of an inflammatory process involving IL-1β. In addition, AngII also increases the expression of other components of the RAS that are involved in the production of AngII, initiating a vicious cycle contributing to further destruction of β cells and progression of the disease. These findings show that AngII has direct effects on β cells besides reducing blood flow in the islets which has important consequences for the therapy of hypertension in patients with type 2 diabetes or with the risk of developing the disease (figure 2).

5. The role of IL-6 in physiology and pathophysiology of type 2 diabetes

Obesity and type 2 diabetes are associated with inflammatory processes in many tissues. Circulating interleukin 6 (IL-6) levels are increased in obese individuals and patients with type 2 diabetes. Over the last years we have studied the role of IL-6 in the regulation of pancreatic islet function and survival. Pancreatic islet pathology in type 2 diabetes is not only characterised by reduced β cell mass, but also by an increased proportion of glucagon producing α cells relative to β cells. Our work has shown that IL-6 is a major regulator of alpha cell function and survival. IL-6 has a pro-survival effect on alpha cells inducing proliferation and preventing the apoptotic effects of metabolic stress. *In vivo,* high fat diet feeding is associated with an IL-6-dependent increased alpha cell mass as shown in IL-6 knockout mice. In the absence of alpha cell mass expansion, glucose metabolism is impaired due to impaired beta cell function (glucose-stimulated insulin secretion), revealing that alpha cells help maintain beta cell function under conditions with increased metabolic demand where the requirement for insulin is enhanced. The mechanism behind this paracrine effect from α to β cells occurs through a change in the processing of proglucagon in alpha cells favoring GLP-1 over glucagon. The beneficial effects of GLP-1 on β cells are well described. GLP-1 promotes both β cell function and survival. The change in proglucagon processing is driven by IL-6 and induced by an increased expression of the enzyme prohormone convertase (PC) 1/3 required for GLP-1 biosynthesis. The major source of GLP-1 is however the intestinal L cells, and in these cells IL-6 is also involved in the increased GLP-1 biosynthesis in response to high fat diet feeding.

Hence, IL-6 mediates a cross talk between insulin sensitive tissues, L cells and pancreatic islets to adapt to changes in insulin demand by increasing L cell GLP-1 secretion and reprogramming α cells to process proglucagon to GLP-1. This novel endocrine loop (figure 3) implicates IL-6 in the regulation of β cell insulin secretion in both health and disease, and suggests how drugs modulating this loop may be useful in obesity and type 2 diabetes.

While trying to understand the pathophysiological role of IL-6 in diabetes and obesity we also learned that exercise is accompanied by dramatic increases in circulating IL-6 levels. Due to our observation that IL-6 increases GLP-1 production we hypothesized that the known im-

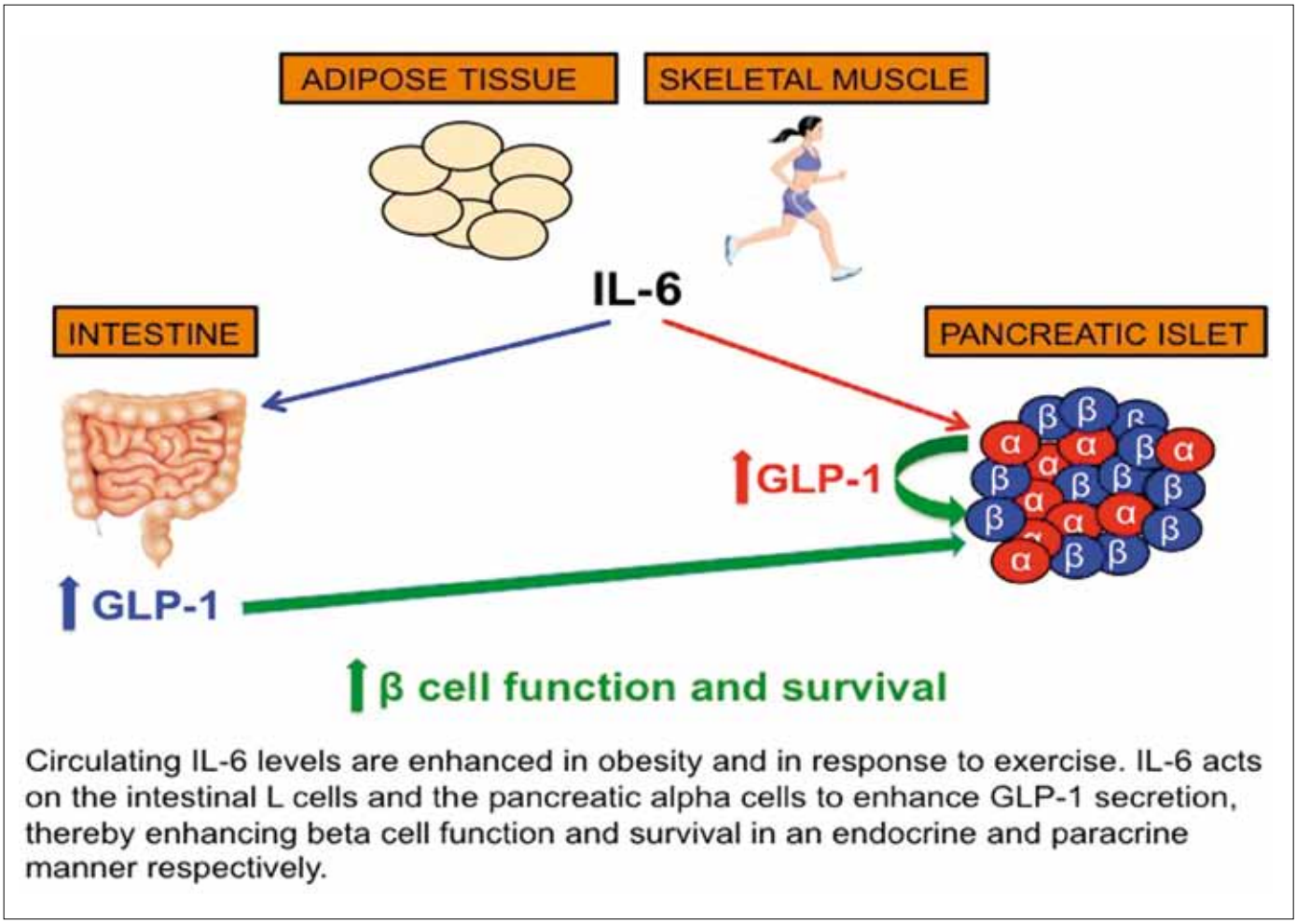

Figure 3

provements in β cell function in response to exercise are dependent on IL-6 and mediated by GLP-1. We are currently conducting an exercise study to test our hypothesis. Our expectations for this study are high and we hope that it will teach us valuable information about the physiological roles of IL-6 and GLP-1 in the metabolic adaptation to physical activity in pre-diabetic and diabetic patients.

6. Translational medicine

Our research is characterized by a translational approach. The basic question that we are following, i. e. mechanisms of insulin secretion failure in diabetes, is a clinical question. Based on preclinical studies, several clinical trials were and are being carried through. Or, taken in reverse, based on clinical observation, we aim to investigate the underlying pathway in the lab. Below are a few examples:

As mentioned above, we showed that human β cells produce IL-1β in response to metabolic stress in type 2 diabetes. More recently we published several additional studies supporting the concept that an inflammatory process underlies β cell failure and apoptosis in the pathogenesis of type 2 diabetes. On the basis of this we initiated clinical trials of IL-1 antagonism in patients with type 2 diabetes that vindicates this hypothesis and opens the way for a causative treatment and possible prevention of diabetes. This program is now progressing in collaboration with companies and is entering phase 3.

Another example is our observations on the role of IL-6 as a mediator of increased insulin demand. As described above, we uncovered a new endocrine loop explaining how the increased need for insulin during insulin resistance and exercise is mediated from the insulin sensitive tissues to the insulin producing β cells. Based on these findings we have initiated a clinical study aiming

at testing the validity of the findings in humans. Furthermore, we are trying to use this novel pathophysiological observation in order to improve current treatment. Indeed, we combine exercise with an existing drug that prevents the degradation of GLP-1. Therefore, we expect to enhance the benefit of exercise-induced GLP-1.
The discovery of the first human mutation in SIRT1 is an example of translation from the clinic to the lab. As also described above, we have uncovered a family carrying a mutation in SIRT1 leading to type 1 diabetes. This unexpected phenotype invites us to perform animal and *in vitro* studies to understand the underlying mechanism. We then hope to develop a therapeutic strategy for patients with type 1 diabetes.

Marianne Böni,
Nadine Sauter,
Helga Ellingsgaard
and Marc Y. Donath

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Singapore,

a Swiss Island in Southeast Asia

Over the past two years I have been travelling back and forth between Switzerland and Singapore and I would like to share with you my impressions and my experiences about the Island-City-State of Singapore. Singapore is a wonderful multi-ethnic metropolis, sparkling and glittering, which always shows the very best of itself to the traveller in transit. Every time I arrive at Changi International Airport, the business card of the city, I am enchanted by how this city receives the guests arriving from all over the world. Singapore always shows a fresh and a beautiful face: gardens with tropical trees inside the terminal halls, orchid bushes along the transit areas capturing the attention of women or botanists because of the magnificence of their unusual colours and crosses, and a green wall 300 meter long with climbing plants near the exit.

The city of contrasts

I find Singapore attractive and intriguing mainly for the numerous contrasts: the mixture of people of many different ethnic groups and religions, the modern and the old buildings, the wild jungle and city parks and the magnificent botanic gardens.

After a few initial visits, I was however less distracted by the numerous signs of modernity and became more investigative, and each time upon my arrival my intention is to unmask this city and finally be able to find its hidden face.

Everywhere one can breathe the air of efficiency and optimization necessary for running a city of almost 5 million inhabitants. One of the most impressive aspects is that in Singapore we can drink the tap water. With a land area of just 700 sq km, Singapore does not have watersheds from which to draw water and must therefore buy a large part of its water from neighbouring Malaysia. One goal of the government is to become self-sufficient, thus there is currently a huge investment in research into water technologies. Today drinking water is derived from several sources, including desalinated sea-water, used water treated by a sophisticated membrane ultrafiltration technology (the so-called NEWater) and rainwater channelled through a comprehensive network of drains, canals, rivers and storm-water collection ponds to several reservoirs for storage. These large open-air reservoirs are true lakes located in several areas of the city and also serve as recreation areas. Singaporeans have large concerns about water supply sustainability and to give you a significant example the newly opened ArtScience museum of the architect Moshe Safdie has a lotus flower-like structure and uses the large petals that make up the roof to collect the rainwater which falls in copious amounts almost daily.

On the other hand, Singaporeans use enormous amounts of energy to light the city in a way we do only at Christmas-time, and to cool the air of the buildings to polar temperatures, a characteristic that has led to Singapore being given the nickname "Island with air-conditioning".

Singapore is a melting pot of Chinese, Malay, Indian and Caucasian people, living together peacefully, following ceremonies and rituals spelled out during the year, with Buddhist and Hindu temples near Mosques and Christian Churches in the various districts of the city. Many people wear traditional clothing and accessories, including the business people of the Financial Centre (the top one in Asia, the third one in the world) who are recognizable by their business bags and dark suits already worn at 9 in the morning. Everybody is, or looks, young, possibly due to their diet and to their shiny black hair. Everywhere smiling faces walk the streets or inside shopping malls (where shops open 7 days a week from 11 am to 10 pm) which are almost like another city, dug into the underground and as large as the city at the surface. I still do not understand if they are happy to walk around after work (the unemployment rate is only 2%) or they are just excited "shopaholics".

An almost hidden aspect in this city of the future is that a large number of Expats, this is the name given to the one-and-a-half million foreigners working and living in Singapore, have housemaids from Philippines or Indonesia, living in 2 m^2 "maid-rooms", usually the house bomb shelters.

I was told by more than one taxi driver that a target of Singaporeans is to achieve the same levels of perfection as Switzerland and in some instances they have already overtaken Switzerland. Because the import, selling, and use of chewing-gum are forbidden by law, Singapore is cleaner than the cleanest Swiss city. Furthermore, there are more banks than in Zürich and taxes are lower than in Zug! There are indeed several things in common between Switzerland and Singapore: 4 official languages, English, Mandarin, Malay, Tamil (but everybody speaks dialect), Singaporeans and Swiss like barbecues (Satays, the local "Spiessli" are very popular), and police is invisible, although everywhere.

Science in Singapore

Research is not an exception in this contrasting society. Singapore is a young Nation, only 46 years have passed since it gained its independence from Malaysia, and in the past year the government has invested 6 billion Singapore Dollars (~ 4 billion CHF) in research and development. The number of research scientists and engineers is around 30 000. With little difference between the research institutions, industries, national agencies and the universities, researchers are confronted by the double reality of having to make great advances in discoveries to improve human health, while at the same time making revenue by selling highly technological products as well as intellectual property.

A*STAR, the Agency for Science, Technology and Research of the Government of Singapore, under the Ministry of Trade and Industry was created a few years ago at one degree North of the Equator, a research campus with two main areas, Biopolis and Fusionopolis (have a look at the impressive website http://www.a-star.edu.sg). This area is in continuous expansion and the work on additional buildings for laboratories, research facilities, enterprises and offices has already started and will be completed by 2013. Construction costs for Biopolis alone are over 700 million SGD, ~ 500 million CHF.

A*STAR currently oversees 14 research institutes as well as 7 consortia and centers and supports extramural research in collaboration with Universities, Hospital Research Centers and other local and international partners. The various A*STAR Institutes are involved in research in a wide range of scientific fields, coordinated and for a large extent funded by Singapore's Biomedical Research Council (BMRC) and Science and Engineering Research Council (SERC).

The Research Institutes located in the Biopolis Campus are the Institutes of Medical Biology, Molecular and Cell Biology, Bioengineering and Nanotechnologies, Bioinformatics, Bioprocessing Technology, the Genome Institute and the Experimental Therapeutics Centre. In the same campus industries like GlaxoSmithKline and Novartis have opened their buildings and others are currently investing with the aim of fostering collaborations between the private and public scientific communities. The names of the institute buildings: Nanos, Proteos, Centros, Helios, Chromos, Neuros and Immunos, reminds me of Snow White's dwarfs. We are in Immunos, of course!

Singapore Immunology Network

The Singapore Immunology Network, SIgN, is a new Institute centered on the study of human immunology.
SIgN was founded in 2008 by Philippe Kourilsky, its farsighted Chairman, and its Scientific Director is "La Pasionaria" Paola Castagnoli. SIgN is now a Research Institute composed of 20 research groups, lead by senior or young principal investigators approaching immunology from different points of view and includes both basic research and research applied to human diseases.
SIgN's scientific mission is to investigate the complexity of the human immune system. In particular, the aim is to study immune regulation in physiological conditions and during infections and inflammation, includ-

Hindu temple in Singapore.

ing cancer. Strength points are the in-house functional platforms and core facilities, directed by scientist technologists of excellence, which operate and give critical support to the research groups. They include: functional imaging with multi-photon and confocal microscopy, flow cytometry, the human monoclonal antibody platform, functional genomics with microarray and deep sequencing, and bioinformatics. The immunomonitoring platform and preclinical development teams provide support to those directly working with human samples from the clinic to implement applied and translational projects.
SIgN actively partners companies to co-develop preclinical drug candidates, vaccines and novel technologies which could potentially translate into useful clinical applications.

SIgN is, like Singapore, multi-ethnic with more than 200 researchers speaking 26 different languages. An international PhD program in collaboration with the School of Biological Sciences of the Nanyang Technological University (NTU), hosts international students from all over the world and offers 4-year scholarships for research projects on human immunology.

It is very challenging to be in a new institute and to contribute to the shaping and the growth of immunology in South-East Asia. We are studying the fascinating phenomenon of antigen recognition and activation of T lymphocytes, the thinker cells of the immune system. The variety of molecules considered antigens and stimulating our immune system is enormous and derives from both exogenous and the endogenous sources. Several classes of molecules stimulate T lymphocytes: i) proteins stimulate classical cells expressing T cell receptor (TCR) with α and β chains, ii) phosphorylated metabolites stimulate TCR $\gamma\delta$ cells, and iii) lipids stimulate non classical TCR $\alpha\beta$ cells. The finding that lipid molecules can make cognate interaction and stimulate specific TCRs, is only a very recent acquisition. The difficulty encountered in understanding how lipids can be antigenic was due to their physical properties, as they are poorly soluble in water, and thus it was difficult to envisage their direct interaction with TCR in biological fluids. Only

Swiss Club in Singapore main building.

when the first T cells recognizing target cells expressing CD1 molecules were described in 1989, when the first lipid antigen, mycolic acid from *Mycobacterium tuberculosis,* was identified, and when the crystal structure of the first CD1 antigen-presenting molecule was solved, was it clear how lipid molecules could be antigenic for T cells. Since then, the field has flourished, but many seeds have still to germinate.

As well as peptide-specific cells, lipid-specific T cells recognize self-antigens under physiological and pathological conditions and many open issues remain in the understanding of lipid-specific immunity. A fundamental one is about the mechanisms of thymic selection of lipid-specific human T cells (restricted to group 1 CD1 molecules, namely CD1a, CD1b and CD1c). It is likely that the thymus plays the most important role, as shown with other immature T cell populations and we are investigating whether both positive and negative selections operate on these T cells. The bases are: i) identification of the antigens involved in the selection mechanisms, ii) knowledge of the antigen structural requirements to allow binding onto CD1 molecules and to generate antigenic complexes, and iii) affinity of interaction of these complexes with the TCRs. Only by knowing the fine nature of these molecules and the cell types involved in selection of specific T cells will it be possible to unveil the rules of this branch of the immune response.

Swiss Club in Singapore summer house.

The aim of the research conducted at SIgN is to elucidate the molecular mechanisms that maintain the balance between T cell tolerance and immunity to self-lipids. These studies have particular relevance in autoimmune and inflammatory diseases including multiple sclerosis, atherosclerosis and diabetes, in which lipid-specific immune responses are involved. Unlike T cell responses to peptide antigens, lipid-specific responses are characterized by the absence of functional polymorphism in CD1 molecules and the lack of lipid structural changes during immune selection. Due to the characteristics of this system, lipids and lipid specific T cells are excellent targets for novel immunotherapeutic approaches.

The important perspective of my studies is to identify lipid molecules which can be target of autoimmune attacks and also to open the search for lipids as biomarkers of autoimmune diseases.

Lucia Mori

Dissertationen

Am 10. Juni 2011 stellte sich **Tatjana Zalac** von der Forschungsgruppe Pediatric Immunology (Departement Biomedizin UKBB) dem Dissertationskomitee. Der Titel ihrer Dissertation lautete: "The Role of the Transcription Factor Sox9 for Thymic Epithelial Cell Differentiation and Function".

Mit der Doktorprüfung am 28. Juni 2011 schloss **Rosaria Santoro** von der Forschungsgruppe TIssue Engineering (ICFS/Departement Biomedizin USB) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "Introducing monitoring and automation in cartilage tissue engineering, toward controlled clinical translation".

Am 30. Juni 2011 stellte sich **Roland Huber** von der Forschungsgruppe Neurooncology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "The molecular role of non-canonical Notch signaling via Deltex-1 in high grade glioma".

Seit dem 1. Juli 2011 darf sich **Beatrice Tonnarelli** von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin USB) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Towards bone draft manufacturing via endochondral ossification".

Am 30. August 2011 konnte **Silvia Reginato** von der Forschungsgruppe Cell and Gene Therapy (ICFS/Departement Biomedizin USB) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema "Promoting vessel stabilization: toward a safe mode of therapeutic angiogenesis".

Beförderungen

Christoph Rochlitz wird Ordinarius für Medizinische Onkologie

Christoph Rochlitz von der Forschungsgruppe Medical Oncology (Departement Biomedizin USB) wurde vom Universitätsrat in seiner Sitzung am 25. August 2011 zum Ordinarius für Medizinische Onkologie an der Medizinischen Fakultät der Universität Basel ernannt. Gleichzeitig wurde er zum Chefarzt Medizinische Onkologie am Universitätsspital Basel gewählt.

Herzliche Gratulation an alle!

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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.

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Blood blood **28 July 2011, Volume 118, Number 4** IF 10,5

Generation of a multipathogen-specific T-cell product for adoptive immunotherapy based on activation-dependent expression of CD154

Nina Khanna[1-2], Claudia Stuehler[2], Barbara Conrad[2], Sarah Lurati[2], Sven Krappmann[3], Hermann Einsele[2], Carsten Berges[2], and Max S. Topp[2]

Viral and fungal infections remain a lead-ing cause of mortality in patients after hematopoietic stem cell transplantation (HSCT). Adoptive transfer of multipathogen-specific T cells is promising in restoring immunity and thereby preventing and treating infections, but approaches are currently limited because of time-consuming and laborious procedures. Therefore, we investigated a new strategy to simultaneously select T cells specific for viral and fungal pathogens based on activation-dependent expression of CD154. Single-and multipathogen-specific T-cell lines with high specificity for adenovirus (AdV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), *Candida albicans,* and/or *Aspergillus fumigatus* could be readily generated within 14 days irrespective of the precursor frequency. The T-cell lines responded reproducibly to endogenously processed antigen and specifically proliferated upon antigenic stimulation. Although isolation based on CD154 favors enrichment of $CD4^+$ T cells, AdV-, EBV-and CMV-specific $CD8^+$ T cells could be expanded and demonstrated lysis of target cells. Conversely, T cell–mediated alloreactivity was almost abrogated compared with the starting fraction. This selection and/or expansion strategy may form the basis for future adoptive immunotherapy trials in patients at risk for multiple infections and may be translated to other antigens.

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PNAS PNAS 14228–14233 Aug. 23, 2011 Vol. 108 no. 34 IF 9,7

Fine tuning by human CD1e of lipid-specific immune responses

Federica Facciotti[1], Marco Cavallari[1], Catherine Angénieux[2], Luis F. Garcia-Alles[3], François Signorino-Gelo[2], Lena Angman[1], Martine Gilleron[3], Jacques Prandi[3], Germain Puzo[3], Luigi Panza[4], Chengfeng Xia[5], Peng George Wang[6], Paolo Dellabona[7], Giulia Casorati[7], Steven A. Porcelli[8], Henri de la Salle[2], Lucia Mori[1,9], and Gennaro De Libero[1]

CD1e is a member of the CD1 family that participates in lipid antigen presentation without interacting with the T-cell receptor. It binds lipids in lysosomes and facilitates processing of complex glycolipids, thus promoting editing of lipid antigens. We find that CD1e may positively or negatively affect lipid presentation by CD1b, CD1c, and CD1d. This effect is caused by the capacity of CD1e to facilitate rapid formation of CD1–lipid complexes, as shown for CD1d, and also to accelerate their turnover. Similar results were obtained with antigen-presenting cells from CD1e transgenic mice in which lipid complexes are assembled more efficiently and show faster turnover than in WT antigen-presenting cells. These effects maximize and temporally narrow CD1-restricted responses, as shown by reactivity to *Sphingomonas paucimobilis*-derived lipid antigens. CD1e is therefore an important modulator of both group 1 and group 2 CD1-restricted responses influencing the lipid antigen availability as well as the generation and persistence of CD1–lipid complexes.

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European Cells and Materials eCELLS&MATERIALS Vol. 21 2011 (445–458) IF 9,6

A 3D *in vitro* bone organ model using human progenitor cells

Adam Papadimitropoulos[1], Arnaud Scherberich[1], Sinan Güven[1], Naseem Theilgaard[3], Hendrikus J.A. Crooijmans[2], Francesco Santini[2], Klaus Scheffler[2], Alberta Zallone[4], and Ivan Martin[1]

Abstract

Three-dimensional (3D) organotypic culture models based on human cells may reduce the use of complex and costly animal models, while gaining clinical relevance. This study aimed at developing a 3D osteoblastic-osteoclasticendothelial cell co-culture system, as an *in vitro* model to mimic the process of bone turnover. Osteoprogenitor and endothelial lineage cells were isolated from the stromal vascular fraction (SVF) of human adipose tissue, whereas CD14+ osteoclast progenitors were derived from human peripheral blood. Cells were co-cultured within 3D porous ceramic scaffolds using a perfusion-based bioreactor device, in the presence of typical osteoclastogenic factors. After 3 weeks, the scaffolds contained cells with endothelial (2.0 ±0.3%), pre/osteoclastic (14.0 ±1.4%) and mesenchymal/ osteoblastic (44.0 ±8.4%) phenotypes, along with tartrate-resistant acid phosphatase-positive ($TRAP^+$) osteoclastic cells in contact with deposited bone-like matrix. Supernatant analysis demonstrated sustained matrix deposition (by C-terminus procollagen-I propeptides), resorption (by N-terminus collagen-I telopeptides and phosphate levels) and osteoclastic activity (by TRAP-5b) only when SVF and $CD14^+$ cells were co-cultured. Scanning electron microscopy and magnetic resonance imaging confirmed the pattern of matrix deposition and resorption. The effectiveness of Vitamin D in replacing osteoclastogenic factors indicated a functional osteoblast-osteoclast coupling in the system. The formation of human-origin bonelike tissue, blood vessels and osteoclasts upon ectopic implantation validated the functionality of the developed cell types. The 3D co-culture system and the associated non-invasive analytical tools can be used as an advanced model to capture some aspects of the functional coupling of bone-like matrix deposition and resorption and could be exploited toward the engineering of multi-functional bone substitute implants.

Keywords: Perfusion bioreactor, human stem cells- population regulation, tissue engineering / regenerative medicine, bone remodelling, non invasive tools, multi-cell co-culture.

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American Association for Cancer Res. **Cancer Research** 71 (17); 5717–27, 2011 IF 8,2

Angiopoietin-1 and -2 Exert Antagonistic Functions in Tumor Angiogenesis, yet Both Induce Lymphangiogenesis

Ernesta Fagiani, Pascal Lorentz, Lucie Kopfstein, and Gerhard Christofori

Abstract

Members of the Angiopoietin family regulate various aspects of physiologic and pathologic angiogenesis. Although Angiopoietin-1 (Ang-1) decreases endothelial cell permeability and increases vascular stabilization via recruitment of pericytes and smooth muscle cells to growing blood vessels, Angiopoietin-2 (Ang-2) mediates angiogenic sprouting and vascular regression. In this study, we used the Rip1Tag2 transgenic mouse model of pancreatic β-cell carcinogenesis to investigate the roles of Ang-1 and Ang-2 in tumor angiogenesis and tumor progression. On their own, transgenic expression of human Ang-1 or Ang-2 in pancreatic β cells caused formation of peri-insular lymphatic vessels in the absence of effects on blood vessel density, islet morphology, or physiology. When crossed to Rip1Tag2 mice, both Ang-1–and Ang-2–expressing β-cell tumors showed increased peritumoral lymphangiogenesis in the absence of metastasis to local lymph nodes or distant organs. There was no alteration in tumor outgrowth, blood vessel density, or vessel maturation in Ang-1–expressing tumors. In contrast, Ang-2–expressing tumors exhibited diminished pericyte recruitment to blood vessels that were dilated, nonfunctional, and highly permeable. These tumors were hemorrhagic, highly infiltrated by leukocytes, and impaired in outgrowth. Together, our findings establish that Ang-2 antagonizes Ang-1 function, leading to excessive vessel sprouting with impaired pericyte recruitment and vessel stabilization. The poor perfusion of immature blood vessels results in retarded tumor growth, defining an important pathophysiologic pathway required for efficient tumorigenesis.

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Biomaterials **Biomaterials** 32 (2011) 5801–5809 IF 7,3

Engineering of large osteogenic grafts with rapid engraftment capacity using mesenchymal and endothelial progenitors from human adipose tissue

Sinan Güven[1], Arne Mehrkens[1], Franziska Saxer[1], Dirk J. Schaefer[1], Roberta Martinetti[2], Ivan Martin[1], Arnaud Scherberich[1]

Abstract

We investigated whether the maintenance in culture of endothelial and mesenchymal progenitors from the stromal vascular fraction (SVF) of human adipose tissue supports the formation of vascular structures in vitro and thereby improves the efficiency and uniformity of bone tissue formation in vivo within critically sized scaffolds. Freshly-isolated human SVF cells were seeded and cultured into hydroxyapatite scaffolds (1 cm-diameter, 1 cm-thickness) using a perfusion-based bioreactor system, which resulted in maintenance of CD34þ/CD31þ endothelial lineage cells. Monolayer-expanded isogenic adipose stromal cells (ASC) and age-matched bone marrow stromal cells (BMSC), both lacking vasculogenic cells, were used as controls. After 5 days in vitro, SVF-derived endothelial and mesenchymal progenitors formed capillary networks, which anastomosed with the host vasculature already 1 week after ectopic nude rat implantation. As compared to BMSC and ASC, SVF-derived cells promoted faster tissue ingrowth, more abundant and uniform bone tissue formation, with ossicles reaching a 3.5 mm depth from the scaffold periphery after 8 weeks. Our findings demonstrate that maintenance of endothelial/mesenchymal SVF cell fractions is crucial to generate osteogenic constructs with enhanced engraftment capacity. The single, easily accessible cell source and streamlined, bioreactor-based process makes the approach attractive towards manufacturing of clinically relevant sized bone substitute grafts.

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Cancer Genetics 2011; 48: 526–529 IF 7,0

Detection of *APC* germ line mosaicism in patients with de novo familial adenomatous polyposis: a plea for the protein truncation test

Judith Necker[1], Michal Kovac[1], Michèle Attenhofer[1], Bruno Reichlin[2], Karl Heinimann[1]

Abstract

Background Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited colorectal cancer predisposition caused by germ line mutations in the *APC* (adenomatous polyposis coli) gene. Current recommendations for *APC* mutation analysis advise full gene sequencing to identify point mutations and small insertions/ deletions as well as the multiplex ligation dependent probe amplification (MLPA) technique to detect gene dosage alterations. Use of the protein truncation test (PTT) as a pre-screening tool has thus been largely replaced with direct end-to-end sequencing, mainly because of its limited sensitivity and failure to identify *APC* missense alterations.

Methods and results This report describes two unrelated patients with classical polyposis coli and unremarkable family history in whom neither full sequencing nor MLPA on leucocyte derived DNA could identify a pathogenic *APC* mutation. Applying the PTT, however, provided evidence of aberrant bands in both patients. Subsequent targeted mutation analysis of their tumour derived DNA allowed the identification of two novel, pathogenic *APC* alterations present in a mosaic state, at blood levels (1–15%) below the detection limits of conventional Sanger sequencing.

Conclusion The findings demonstrate the value of the PTT in identifying mosaic mutations in apparently *APC* mutation negative FAP patients with de novo classical polyposis and the need to keep the PTT within the diagnostic repertoire for *APC* mutation analysis.

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Telomeric Rather than Centromeric Activating KIR Genes Protect from Cytomegalovirus Infection after Kidney Transplantation

M. Stern[1], K. Hadaya[2], G. Hönger[3], P.-Y. Martin[2], J. Steiger[3], C. Hess[4], and J. Villarde[5]

Cytomegalovirus (CMV) infection is a common complication after organ transplantation. Previous stud-ies have demonstrated that activating killer-cell immunoglobulin-like receptors (KIR) may reduce the rate of CMV infection. KIR genes can be divided into haplotype A (containing a fixed set of inhibitory receptors) and haplotype B (carrying additional activating KIR genes). The KIR locus is divided into a centromeric and a telomeric portion, both of which may carry A or Bhaplotype motifs. We studied a cohort of 339 kidney transplant recipients to elucidate which KIR genes protect from CMV infection. CMV infection occurred in 139 patients (41%). Possession of telomeric (hazard ratio 0.64, 95% confidence interval 0.44–0.94, p = 0.02) but not centromeric (HR 0.86, 95% CI 0.60–1.23, p = 0.41) B motifs was associated with statistically significant protection from CMV infection. Due to linkage disequilibrium, we were not able to identify a single protective gene within the telomeric B complex (which may contain the KIR2DS1, KIR3DS1, KIR2DL5A and KIR2DS5 genes). The presence of known or putative ligands to activating KIR did not significantly modify the influence of telomeric B group genes. We confirm that B haplotypes protect from CMV infection after kidney transplantation and show that this arises from telomeric B haplotype genes.

Key words: Activating KIR genes, centromere KIR, CMV infection, kidney transplantation, telomere KIR

Abbreviations: CMV, cytomegalovirus; HR, hazard ratio; KIR, killer-cell immunoglobulin-like receptors; NK cell, natural killer cell; PCR, polymerase chain reaction; SOT, solid organ transplantation.

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The Journ. of Clin. Endocrinology & Metabolism JCEM Sept. 2011, 96 (9) 2844–2850 IF 6,4

Sex Differences in the Effects of MDMA (Ecstasy) on Plasma Copeptin in Healthy Subjects

Linda D. Simmler, Cédric M. Hysek, and Matthias E. Liechti

Background: 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) misuse is associated with hyponatremia particularly in women. Hyponatremia is possibly due to inappropriate secretion of plasma arginine vasopressin (AVP).

Objective: To assess whether MDMA increases plasma AVP and copeptin in healthy male and female subjects and whether effects depend on MDMA-induced release of serotonin and norepinephrine. Copeptin, the C-terminal part of the AVP precursor preprovasopressin, is cosecreted with AVP and can be determined more reliably.

Methods: We used a randomized placebo-controlled crossover design. Plasma and urine osmolalities as well as AVP and copeptin levels were measured in 16 healthy subjects (eight female, eight male) at baseline and after MDMA (125 mg) administration. In addition, we tested whether effects of MDMA on AVP and copeptin secretion can be prevented by pretreatment with the serotonin and norepinephrine transporter inhibitor duloxetine (120 mg), which blocks MDMA-induced transporter-mediated release of serotonin and norepinephrine.

Results: MDMA significantly elevated plasma copeptin levels at 60 min and at 120 min compared with placebo in women but not in men. The copeptin response to MDMA in women was prevented by duloxetine. MDMA also nonsignificantly increased plasma AVP levels in women, and the effect was prevented by duloxetine. Although subjects drank more water after MDMA compared with placebo administration, MDMA tended to increase urine sodium levels and urine osmolality compared with placebo, indicating increased renal water retention.

Conclusion: MDMA increased plasma copeptin, a marker for AVP secretion, in women but not in men. This sex difference in MDMA-induced AVP secretion may explain why hyponatremia is typically reported in female ecstasy users. The copeptin response to MDMA is likely mediated via MDMA-induced release of serotonin and/or norepinephrine because it was prevented by duloxetine, which blocks the interaction of MDMA with the serotonergic and noradrenergic system.

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Clinical Pharmacology & Therapeutics Clinical Pharmacology & Therapeutics Volume 90/Number 2/August 2011 IF 6,3

The Norepinephrine Transporter Inhibitor Reboxetine Reduces Stimulant Effects of MDMA ("Ecstasy") in Humans

CM Hysek[1], LD Simmler[1], M Ineichen[1], E Grouzmann[2], MC Hoener[3], R Brenneisen[4], J Huwyler[5], and ME Liechti[1]

This study assessed the pharmacodynamic and pharmacokinetic effects of the interaction between the selective norepinephrine (NE) transporter inhibitor reboxetine and 3,4-methylenedioxymethamphetamine (MDMA,"ecstasy") in 16 healthy subjects. The study used a double-blind, placebo-controlled crossover design. Reboxetine reduced the effects of MDMA including elevations in plasma levels of NE, increases in blood pressure and heart rate, subjective drug high, stimulation, and emotional excitation. These effects were evident despite an increase in the concentrations of MDMA and its active metabolite 3,4-methylenedioxyamphetamine (MDA) in plasma. The results demonstrate that transportermediated NE release has a critical role in the cardiovascular and stimulant-like effects of MDMA in humans.

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The Journal of Immunology | The Journal of Immunology | 2011, 186: 6543–6552 IF 5,7

Microparticles (Ectosomes) Shed by Stored Human Platelets Downregulate Macrophages and Modify the Development of Dendritic Cells

Salima Sadallah, Ceylan Eken, Perrine J. Martin, and Jürg A. Schifferli

Microparticles (MP) shed by platelets (PLT) during storage have procoagulant activities, but little is known about their properties to modify inflammation or immunity. In this study, we studied the capacity of MP present in PLTconcentrates to alter the function of macrophages and dendritic cells (DC). The size of the purified MP was between 100 and 1000 nm, and they expressed phosphatidylserine; surface proteins of PLT (CD61, CD36, CD47), including complement inhibitors (CD55, CD59), but not CD63; and proteins acquired from plasma (C1q,C3 fragments, factorH).These characteristics suggest that the MP shed by PLT are formed bybudding from the cell surface, corresponding to ectosomes. The purified PLTectosomes (PLT-Ect) reduced the release of TNF-α and IL-10 by macrophages activated with LPS or zymosan A. In addition, PLT-Ect induced the immediate release of TGF-β from macrophages, a release that was not modified by LPS or zymosan A. Macrophages had a reduced TNF-α release even 24h after their exposure to PLT-Ect, suggesting that PLT-Ect induced a modification of the differentiation of macrophages. Similarly, the conventional 6-d differentiation of monocytes to immature DC by IL-4 and GM-CSF was modified by the presence of PLT-Ect during the first 2 d. Immature DC expressed less HLA-DP DQ DR and CD80 and lost part of their phagocytic activity, and their LPS-induced maturation was downmodulated when exposed to PLT-Ect. These data indicate that PLT-Ect shed by stored PLT have intrinsic properties that modify macrophage and DC differentiation toward less reactive states.

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Free Radical Biology & Medicine | 51 (2011) 609–618 IF 5,7

β_1-Integrin is up-regulated via Rac1-dependent reactive oxygen species as part of the hypertrophic cardiomyocyte response

Stéphanie P. Häuselmann[1], Berit I. Rosc-Schlüter[1], Vera Lorenz[1], Isabelle Plaisance[2], Marijke Brink[2], Otmar Pfister[1,3], Gabriela M. Kuster[1,3]

Abstract

β_1-Integrin mediates cardiomyocyte growth and survival and its proper regulation is essential for the structural and functional integrity of the heart. β_1-Integrin expression is enhanced in hypertrophy, but the mechanism and significance of its up-regulation are unknown. Because reactive oxygen species (ROS) are important mediators of myocardial remodeling we examined their role in regulated β_1-integrin expression. Hypertrophy was induced in neonatal cardiomyocytes by endothelin-1 (ET-1), which activated the regulatory NADPH oxidase subunit Rac1, evoked ROS, and enhanced fetal gene expression and cardiomyocyte size. ET-1 also enhanced cell adhesion and FAK phosphorylation and inhibited oxidative stress-induced cardiomyocyte apoptosis. Further, ET-1 increased β_1-integrin mRNA and protein expression via Rac1-ROS-dependent MEK/ERK and EGF receptor-PI3K/Akt activation as shown by adenoviral dominant-negative Rac1 or overexpression of copper/zinc-superoxide dismutase. The relevance of regulated β_1-integrin expression was examined in cardiomyocytes, in which targeting siRNA impeded the ET-1-induced β_1-integrin up-regulation. In these cells, ET-1-induced cell adhesion, FAK phosphorylation, and hypertrophic response were significantly blunted, whereas its antiapoptotic effect was predominantly unchanged, suggesting at least partial dissociation of prohypertrophic and prosurvival signaling elicited by ET-1. In conclusion, β_1-integrin upregulation in response to ET-1 is mediated via Rac1-ROS-dependent activation of prohypertrophic pathways and is mandatory for ET-1-induced FAK activation, cell adhesion, and hypertrophic response.

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European Respiratory Journal 2011; 38: 50–58 IF 5,5

House dust mite extract downregulates C/EBPα in asthmatic bronchial smooth muscle cells

N. Miglino, M. Roth, M. Tamm and P. Borger

Abstract: Reduced translation of *CEBPA* mRNA has been associated with increased proliferation of bronchial smooth muscle (BSM) cells of asthma patients.

Here, we assessed the effect of house dust mite (HDM) extracts on the cell proliferation ([^{3}H]thymidine incorporation), inflammation (interleukin (IL)-6 release) and upstream translation regulatory proteins of CCAAT/enhancer-binding protein (C/EBP) α in human BSM cells of healthy controls and asthmatic patients.

HDM extract significantly increased IL-6 protein and proliferation of BSM cells of asthma patients only. HDM extract reduced the C/EBPα expression in BSM cells of asthma patients, which coincided with significantly increased levels of calreticulin (CRT) protein, an inhibitor of *CEBPA* mRNA translation. HDM extract elicited both protease-dependent and -independent responses, which were mediated *via* protease-activated receptor (PAR)2 and CRT, respectively.

In conclusion, HDM extract reduced *CEBPA* mRNA translation, specifically in asthmatic BSM cells, and 1) upregulated CRT, 2) activated PAR2, and increased 3) IL-6 expression and 4) the proliferation of asthmatic BSM cells. Hence, HDM exposure contributes to inflammation and remodelling by a nonimmune cell-mediated mechanism via a direct interaction with BSM cells. These findings may potentially explain several pathological features of this disease, in particular BSM cell hyperplasia.

Keywords: Asthma, bronchial smooth muscle cells, CCAAT/enhancer-binding protein α, house dust mite extract, mRNA translation

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Neurobiology of Disease | Neurobiology of Disease | 43 (2011) 388–396 IF 5,1

The RNA-binding protein RBM3 is involved in hypothermia induced neuroprotection

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Abstract

Induced hypothermia is the only therapy with proven efficacy to reduce brain damage after perinatal asphyxia. While hypothermia down-regulates global protein synthesis and cell metabolism, low temperature induces a small subset of proteins that includes the RNA-binding protein RBM3 (RNA-binding motif protein 3), which has recently been implicated in cell survival. Here, immunohistochemistry of the developing postnatal murine brain revealed a spatio-temporal neuronal RBM3 expression pattern very similar to that of doublecortin, a marker of neuronal precursor cells. Mild hypothermia (32 °C) profoundly promoted RBM3 expression and rescued neuronal cells from forced apoptosis as studied in primary neurons, PC12 cells, and cortical organotypic slice cultures. Blocking RBM3 expression in neuronal cells by specific siRNAs significantly diminished the neuroprotective effect of hypothermia while vector-driven RBM3 over-expression reduced cleavage of PARP, prevented internucleosomal DNA fragmentation, and LDH release also in the absence of hypothermia. Together, neuronal RBM3 up-regulation in response to hypothermia apparently accounts for a substantial proportion of hypothermia-induced neuroprotection.

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European Journal of Immunology | European Journal of Immunology | 2011, 41: 1–9 IF 4,9

High-frequency and adaptive-like dynamics of human CD1 self-reactive T cells

Claudia de Lalla[1], Marco Lepore[1], Francesco M. Piccolo[1], Anna Rinaldi[1], Andrea Scelfo[1], Claudio Garavaglia[1], Lucia Mori[2], Gennaro De Libero[2], Paolo Dellabona[1], and Giulia Casorati[1]

CD1 molecules present lipid antigens to T cells. An intriguing subset of human T cells recognize CD1-expressing cells without deliberately added lipids. Frequency, subset distribution, clonal composition, naïve-to-memory dynamic transition of these CD1 selfreactive T cells remain largely unknown. By screening libraries of T-cell clones, generated from $CD4^+$ or $CD4^-CD8^-$ double negative (DN) T cells sorted from the same donors, and by limiting dilution analysis, we find that the frequency of CD1 self-reactive T cells is unexpectedly high in both T-cell subsets, in the range of 1/10–1/300 circulating T cells. These T cells predominantly recognize CD1a and CD1c and express diverse TCRs. Frequency comparisons of T-cell clones from sorted naïve and memory compartments of umbilical cord and adult blood show that CD1 self-reactive T cells are naïve at birth and undergo an age-dependent increase in the memory compartment, suggesting a naïve/ memory adaptive-like population dynamics. CD1 self-reactive clones exhibit mostly Th1 and Th0 functional activities, depending on the subset and on the CD1 isotype restriction. These findings unveil the unanticipated relevance of self-lipid T-cell response in humans and clarify the basic parameters of the lipid-specific T-cell physiology.

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Antimicrobial Agents and Chemotherapy | Antimicrobial Agents and Chemotherapy | Vol. 55, No. 7, July 2011, p. 3510-3516 IF 4,6

Reversible Daptomycin Tolerance of Adherent Staphylococci in an Implant Infection Model

Anne-K. John, Mathias Schmaler, Nina Khanna, and Regine Landmann

Daptomycin (DAP) is bactericidal against methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro,* but it failed to eradicate MRSA in an experimental model of implant-associated infection. We therefore investigated various factors which could explain treatment failure by evaluating DAP activity, including the role of different cell wall components, adherence, biofilm, and calcium ions ($Ca2^+$) *in vitro* and *in vivo.* In the tissue cage infection model, DAP was active only prophylactically and against low inocula. To identify the mechanisms of treatment failure, the *in vitro* activity of DAP against planktonic and adherent growing S. *aureus* and *S. epidermidis* mutants, differing in their capacity of biofilm formation and adherence, was determined. For planktonic staphylococci, the MIC was 0.625 μg/ml. For adherent staphylococci, DAP reduced biofilms at 30 μg/ml. However, it did not kill adherent bacteria up to 500 μg/ml, independent of biofilm biosynthesis (the *ica* mutant strain), nuclease (the *nuc1/nuc2* mutant strain), LPXTG-anchored adhesin (the *srtA* mutant strain), autolysin (the *atl* mutant strain), or alanyl-LTA (the *dltA* mutant strain). Resistance of adherent staphylococci was not due to mutations of adherent bacteria, since staphylococci became DAP susceptible after detachment. Phenotypic tolerance was not explained by inactivation of DAP or inability of initial Ca^{2+}-DAP complex formation. However, the addition of up to 100 mg/liter (2.5 mmol/liter) Ca^{2+} gradually improved bactericidal activity toward adherent staphylococci *in vitro* and increased the prevention rate in the cage model from 40% to 60%. In summary, adherent staphylococci are resistant to DAP killing unless Ca^{2+} is supplemented to physiologic concentrations.

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Europäischer Laubfrosch, Riehen, 2006. Foto: Andreas Ochsenbein

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Herzlich willkommen, allerseits!

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MONTANA, OF COURSE

Loyal readers,

We've heard about Rome and the splendors it flaunts, we've heard about Nepal and its vertiginous plethora of peaks, and we've even heard about Russia and its offer of a fairy-tale Christmas, but let's be serious. These places are old news. We need somewhere new and exotic. A place that with the simple mention of its name, you are whisked away from your pipette and into an enchanted world of wild animals, soaring mountains, gushing rivers, endless skies and only a slight murmur of the outside world's economic woes. Luckily for you, I hold the key to this momentary mental escape. Allow me to unfasten the lock and open the door for you. Do you hear it? Smell it? Feel it (or "taste it" for the Italian readers)? "It seems like paradise," you say? "What is this magical land of which you speak" I hear? Montana, of course.

At this point, I can imagine you are feeling slightly let down. I built you up for paradise, and I've delivered its reclusive brother. But please, bear with me. It's really quite a lovely place, as long as you are not one of these people who travel in hope to impress your friends with stories of personal visits to world-renowned museums, UNESCO protected mountains or drunken white nights. Don't get me wrong, I love to travel to probably all the same places as any of you. But, I have been given the daunting task of introducing you to my homeland, and it seems appropriate to use this opportunity to advertise the wares, as it were, of my otherwise unknown territory. So, let's get started, shall we?

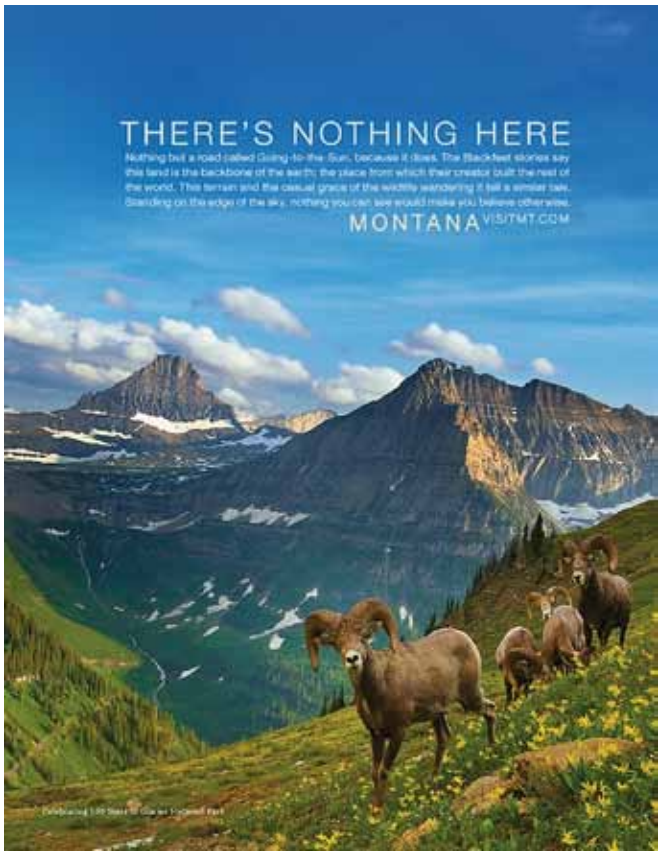
Let's begin by situating this fair land on a map. First hint: it's in the United States (for the geographically challenged, that's to the left of Basel and on the other side of the big blue spot). Second hint: it's near Saskatchewan. (Now you probably think I'm deliberately trying to mislead you. Alas, dear reader, I'm not. There really is a place called Saskatchewan.) Let's try one more hint: it's in the Northwest of the United States and on the Canadian border. So, just put your finger on that incredibly straight line (the border) that divides North American civilization from the barbaric Canadian provinces, and follow it west until you cross another perfectly straight line (Americans are so clever!) perpendicularly heading down. That's the beginning of Montana. If you continue west, you'll eventually leave the state and make your way into another wonderful state, albeit to a lesser extent: Idaho. Back to the east, on the other side of that painfully straight line, you can find the Dakotas, but for all intents and purposes, we can pretend they don't exist (everybody else does). To the south, you can find the least populated state in terms of landmass in the contiguous United States; a place where you can pass through towns on the "Autobahn", proudly signposting a local population of 7 inhabitants. This state is called Wyoming and you perhaps know it better for two reasons: being the state that encompasses the largest part of Yellowstone National Park and being the chosen land for the filming of Brokeback Mountain. By now, you've most likely guessed that Montana is at the epicenter of the most under-populated region of the USA (excluding Alaska, but they produced Sarah Palin, so their credibility and right to statehood is under review). Voila! It's time to shift away from the geography lesson and delve into the splendors of this American cave of Ali-Baba! I earlier promised to whisk you away from your workday tedium, and into a mental paradise. Well fasten your seatbelts. We are ready to depart!

If one word could be employed to sum up Montana, it would be "Nothing". At first glance, this sounds very disappointing indeed, as if our much anticipated depart amounted to a false start. But there's more to this word "Nothing" than meets the eye. At least I hope there is, because this is the official advertising slogan currently employed by the state: "Montana, there's nothing here". Shocking, but effective! One needs to understand that Montana has always been, and will always be, out-of-the-way. For the "classic foreign traveler" making their first foray into the United States as a tourist, I could predict with a fair amount of reliability that you will visit one of the four corners of the United States: New York City (fair enough), Miami (you're making a mistake), Los Angeles (can be substituted with San Francisco), or Seattle (can be substituted with Vancouver). For the "scientific professional-opportunities explorer", the number of places visited becomes halved to either Boston (if you're really serious about your career) or California (if you're really serious about your sunbathing). The last main class of tourists we shall call the "adventure-seeking enthusiasts". These people will most assuredly spend a few days in any of the above locations, and then arrive with drooling enthusiasm in Utah, Colorado, Arizona, or anywhere in California (Perhaps I should mention that there is one last group that deserves note: "the secret forth group". There is a very small minority of visitors that, probably due to bad planning or taste, end up in Texas. But we rarely hear from these people ever again so this little tangent should only serve as a warning). If you've been to the United States and had the good fortune to visit a place not listed above, you are not only skewing my statistics, but most likely not proud enough to admit it openly. My wife, for example, has had the good fortune to visit such exotic places as Missouri ("Misery" for Americans), Illinois, Arkansas and Mississippi, but reflecting on these travels generally occurs behind closed doors. Having said all of this, it should be quite clear that Montana is nowhere near any of these oft-visited destinations. In fact, even if you had a lot of time on your hands and decided to drive from one of the above des-

tinations to the next, effectively seeing most the USA, you would still have to make a major detour to enter into Montana-land.

To the great pleasure of most Montanans, it has always been like this. Montanans are proud of the wild and remote land they call home. Accordingly, the development of a major city or airport in Montana has never come to fruition, nor do I think it is particularly desired. In fact, Montana, while being 5 times larger than Switzerland, has less than a million of inhabitants. So what do you do with a land that is half mountains and half plains, and boasts an average 7-month long winter? Exactly the same thing as Switzerland: you brag about the quality and quantity of your cows and crops; then you go hiking! But, with such a large landmass, it's hard to fill all of the available space with grazing animals and fields of plenty. This land so copiously endowed with open space also harbors one of the largest concentrations of American Indians in the United States.

Historically speaking, Montana was considered as a land so isolated and hostile (slightly less true today), that it seemed like a great place to set aside vast amounts of land for Indian reservations. So, even today, you can go to Montana and visit seven different reservations, some of them larger than Basel-Stadt, Basel-Landschaft, Solothurn, Jura and Aargau combined. While these reservations serve as a protected "country within a country" for the Indians to live as they like, they also remind us that their existence is only necessary because of the



severe constraints the early American government placed on Indian population and culture. This is of course just a diplomatic way of saying that throughout the 18th and 19th centuries, the territory available to Indians was reduced bit by bit through planned population decimation and treaty defaulting until everybody woke up one morning and asked, "Where did all the Indians go?" Only then did people realize that it would be a good idea to give them a little space to themselves. Thus, Indian Reservations were born. But no conservation effort would be complete without a little bit of hypocrisy. Land was reserved, and lots of it, but it would be an overstatement on my part to call this land inviting or even livable. The United States, at that time, had established the center of the country as the richest farming and grazing area around, while the east was the center of all economic activity. What was left? Deserts, badlands, and places that remained cold for so long, that nobody could be bothered to live there (California was still just an afterthought).

And now we come to the intriguing photo that has blessed the cover of this edition of the DBM. Who is that? He happens to be one of the most famous American Indian leaders to have ever lived, and he had a huge impact on Montana: Sitting Bull. Unfortunately, we do not always become famous in the manner we would like. And for Sitting Bull, I would imagine he would have preferred a different life altogether than one he was offered as a resistance fighter. During this tumultuous period of American expansionism, Montana and surrounding lands became the theater of some of the fiercest fighting encountered during this time period. The most famous battle to have come from this is called the "Battle of the Little Bighorn" and, interestingly, was the first major battle ever won by the Indians and served as the "beginning of the end" of the Indian Wars. If you're curious to know more, I invite you to visit the Little Bighorn Battlefield National Monument and some of the Reservations in Montana and the Dakotas, where you will see a land that has evolved over the centuries with the telltale signs of American heavy-handedness, and serves as a great place to familiarize yourself with a very long and particularly dark chapter in American history.

But please, don't just stop there! There is ever so much more to see. I hope you have a reasonable image in your head of the rolling planes in the eastern part of the state that served as a perfect spot to argue over. Now let's move west, into the mountains. This is where I come from, and the

scenery, objectively speaking, is breathtaking. It's hard to explain its uniqueness though, especially for those used to the mountains of Switzerland, but I'll give it a try. Montana's mountains are tall and rocky, like the Alps. They are covered with snow in winter, offering great skiing opportunities, like the Alps. Summertime is a period of rivers gushing cloudy white with snowmelt silt and a time when the fantastically remote hiking trails reappear for the pleasure of all, like in the Alps. Springtime is a time of crisp mornings and rebirth of the color green, like in the Alps. And autumn is highlighted with a multitude of colors shining from the changing leaves while animals are moved and homes are stocked, like in the Alps. But with all of these similarities between western Montana and the stereotypical Swiss geography, these similarities are superficial at best. Physically speaking, the space between two mountain ranges is called a valley, and for people who live in and around the mountains, this is where all the action happens. This is where the town and cities grow, this is where the highways wind, and, accordingly, this is where "civilized" stuff happens. By weight of comparison, a valley in the Alps could be visually described as cramped, while a valley in the Rockies of Montana is rather spacious. This aspect alone changes everything, making the "feeling" of these two similar mountain chains very different. You see, there is a lot of flat land between one mountain range to the next in Montana, but ironically, the mountains remain an ever-present fixture of the scenery. One may stand in the valley, and see for dozens of miles (kilometers for the uncivilized) around in every direction... and in every direction there are mountains. Otherwise stated, a Montana valley is like a Swiss valley on steroids. I only say this to prepare you. You are assuredly in the preparatory phase a holiday to Montana, and I wouldn't want you to arrive and be disappointed. People say everything is bigger in the States. While this does seem to be true (body-mass index included), it creates a somewhat disconcerting perception where valleys and mountains are concerned. There is an uncomfortably large amount of empty space, and this is the origin of the renowned Montanan labels of "Big Sky Country" and "There's nothing here".

From a tourism perspective, massive untamed tracks of rugged, empty land leave room for only a few possibilities. And these possibilities revolve almost exclusively around outdoor activities. From world renowned national parks (Glacier NP and Yellowstone NP) to numerous endemic species of large, carnivorous animals, Montana has much to offer for the nature enthusiast. Of particular note,

if you are one to enjoy solitude during an outdoor excursion, the United States has a unique preservation system called Wilderness reserves (the biggest thing I miss from the USA). These "parks", normally of considerable size, are strictly regulated, flaunting absolutely no roads (dirt included) and disallowing all modes of transport within the boundaries except pedestrian or horse. Mountain biking is even forbidden due to the potential impact they might have on the trails and, slightly less believable, the oil they drop from their chains. Needless to say, this is where you should go if you are looking for virgin forests and a total lack of human intervention. Other popular summertime activities include kayaking, fly-fishing and rock climbing. Winter embodies all of the same fun as Switzerland, but perhaps with a little longer season and at slightly lower temperatures. If you are not interested in any of this nature stuff, there is the other aspect of Montana that is preciously cultivated: the Wild West. Cowboys, ranches, ghost towns, abandoned gold mines and saloons abound. In between these two tourist extremes, it's also nice to simply drive through some of the smaller towns in Montana and witness the old Americana alive and kicking, with "Mom and Pop" cafes smiling at you from every Main Street and ancient-looking old men slowly ambling towards your car to pump your gas and talk about the weather. Montana is a perfect destination for the great "American Roadtrip". If you're still not convinced, try watching a couple of movies filmed in Montana before you go: *A River Runs Through It, The Horse Whisperer and Legends of the Fall are just a few.*

Finally, I would like to leave with this. I've tried to purposefully weight this article towards more of the rustic aspects for which Montana is famous. If you need to understand one thing about Montana, it's that Montanans like what they have, and more importantly, like it as it is. Any government campaign to open investment opportunities in Montana is often met with strong, local opposition. From this perspective, it's a world not so different from Asterix and Obelix. We're happy in our relative solitude. But, this doesn't make unwelcoming either! So come one, come all! Here's something to whet your appetite: www.visitmt.com
Now get back to pipetting and stop wasting time!

Benjamin Pippenger

Recipes for the Autumn Season

Turkey Brine *(5–6 kg turkey)*

Ingredients: 2 1/2 gallons cold water (10 Liters), 2 cups salt (~ 480 ml), 1 cup sugar , 2 bay leaves, torn into pieces (Lorbeerblätter), 1 bunch fresh thyme, 1 whole head of garlic, cloves separated and peeled , 5 whole allspice berries, crushed (Nelkenpfeffer), 4 juniper berries, smashed (Wacholderbeere)

Method: Place the water in a large non-reactive pot that can easily hold the liquid and the turkey. Add all the ingredients and stir for a minute or two until the sugar and salt dissolve. Put the turkey (without neck/organs/etc.) into the brine and refrigerate for 24 hours. If the turkey floats to the top, cover it with plastic wrap and weight it down with a plate and cans to keep it completely submerged in the brine.
Note: You may halve or double the recipe. The important thing is to prepare enough brine to cover the turkey completely. To roast: Remove the bird from the brine and drain well. Pat dry.
Roast at 200° C. It is done when a meat thermometer reads 74° C at the thickest part of the thigh.

Carolyn King

Roast Goose

Ingredients: 1 goose, 4–5 kg in weight, 1/2 tsp black pepper, 1/2 tsp salt, 1 tsp root ginger, finely chopped, 1 orange, 1/2l red wine or vegetable broth

Stuffing: 500g pre-cooked chestnuts finely diced, 100g walnuts finely chopped, 3 onions finely diced, 500g apples finely diced, 200–300g day old walnut bread, finely diced and soaked in red wine for 10min, 100g dried apricots, thinly sliced, 100 g dried dates, thinly sliced, 3–4 tblsps rosehip puree (Buttenmost), 1 tblsp fresh parsley leaves, chopped, 1 tsp thyme leaves, chopped, 2 sage leaves, chopped, 1 tblsp dried marjoram or oregano, 1 chili, finely chopped, 1 tsp mugwort (Beifuss), if available, helps digesting the fat!!, salt and pepper to season

Method: Rinse goose in cold water, pat dry with paper towels. Remove as much fat as possible from the body cavity. Mix together the pepper, salt and ginger and use to season in- and outside; rub the body cavity with the freshly cut inside of an orange. Mix the stuffing ingredients together and stuff it into the body cavity. Close tightly with skewers or clamps or sew with special food-string (should be easy for the surgeons in the institute!!!) But please don't disinfect beforehand as that would give a strange and unwanted taste! Fix the haunches together with string for easier handling of the bird. Pierce the skin with a tooth pick (to drain the fat!). Place the goose breast side down onto a rack in the roasting pan; add a cup of water to the bottom of the pan. Roast in the pre-heated oven at approx. 200°C for about 20 min, then turn down to approx. 170°C for 60 min. Then turn the goose over and roast for another 60–90 min, depending on the weight of the goose. Once in a while drain the fat from the pan and baste the goose with red wine (or salty water) to make the skin tasty and crunchy. To test if the goose is cooked just pierce where the thigh attaches to the body. If the juices released are clear it should be done. Remove the bird from the pan, keep it warm in the oven (now turned off) and prepare a nice gravy from the concentrated roasted brown layer which remains at the bottom of the pan after you have removed the remaining fat. That can be made with wine, apple juice, cream or whatever you prefer, you can also add rosehip puree (Buttenmost), fried chanterelles and grapes. The meat can be just eaten with the stuffing or can be served in the traditional manner with potato-dumplings and red cabbage.

Brigitte Schneider

Steak and Kidney pie

In England this is often traditionally made with a suet pastry crust. We have always made ours with puff pastry. The stew itself can also just be served with boiled or creamed potatoes.

Ingredients to serve 6:
1kg rump beef, or any stewing beef, about 400g kidney (I use lamb or veal), 50g flour well seasoned with salt and pepper, 3 tbsp groundnut oil, 1 large onion, peeled and thickly chopped, 2 large carrots, peeled and cut into chunks, 1 parsnip (optional), peeled and cut into chunks, 600ml beef stock, 600g puff pastry

Method: Cut the beef into cubes. Trim and cut up the kidneys into similar sized chunks. Toss the meat in the seasoned flour, then remove and shake off the excess flour. Heat the oil in a pan over high heat and fry off the meat in batches till browned on all sides. Remove each batch to a dish till all the meat is cooked. Reduce the heat to medium and fry the 2–3 mins, then add the carrots and parsnips (if using) and cook for a further 5 mins. Add any remaining flour to the pan, cook for 1 min then add the meat back in along with the stock. Cover the pan, reduce the heat to low and simmer for 2–3 hours till the meat is tender, stirring from time to time. If the sauce becomes too thick add a little water to thin it down. Preheat the oven to 220°C. Lightly grease an oven proof dish. Divide the pastry into two portions, one slightly larger than the other. Roll out the larger portion so it is large enough to line the base of the pie dish. Roll out the second portion so it is large enough to form a lid for the pie dish.
Line the pie dish with the larger portion of the pastry. Spoon the meat and veg from the stew into the pie, leaving any excess sauce behind (this can be served separately). Dampen the edges of the pastry around the top of the dish, place the pastry lid on top and press firmly on the edges to seal. Using a sharp knife cut a small cross in the middle of the lid to allow excess steam to escape as the pie cooks. The pastry can be glazed with a little milk if wanted.
Bake in the preheated oven for 40–45 mins till the pastry is risen and nicely browned.
Serve with some boiled potatoes and the reheated extra sauce on the side.

Paula Cullen

For dessert :

Apple Gratin

Ingredients to serve 4: 1kg apples, butter, breadcrumbs, 5–6 dsp sugar, 100g ground almonds, 100g raisins, 150ml milk, 100ml cream, 3 eggs, 125g flour, 1 tsp baking powder, cinnamon sugar

Method: Peel the apples and cut into thin slices. Grease a baking dish and sprinkle with the breadcrumbs. Mix the sugar, almonds and raisins together. Layer half of the apples in the baking dish and sprinkle with half the sugar mix. Repeat with the remaining apples and sugar mix. Whisk together the milk, cream, eggs, flour and baking powder to form a batter. Pour the batter over the apples and bake at 200oC for approximately 1 hour. Serve warm, sprinkled with cinnamon sugar. This would be lovely served with some vanilla sauce or a scoop of vanilla ice-cream.

Heidi Hoyermann

Tarte Tatin

A French dessert for the autumn season

Supplies: A 24 cm diameter round cake tin. **Ingredients:** 175 g powdered sugar, 6 large apples (or more depending on size, enough to cover the mold), Pie crust (pate brisee), 25g butter

Method: Preparing the apples: Peel all the apples. Cut them into halves and scoop out the cores with a spoon. Keep and reserve. Preparing the caramel: In a saucepan, add 175 g of sugar to 100ml cold water. Cook until the sugar turns a dark caramel colour. Turn off the heat.
Pour the caramel into the round cake tin such that it is spread everywhere. Building the tart:
On the caramel, place the pieces of apples upright tightly together to ensure a tight fit. Evenly place some butter slices on top, and sprinkle some sugar over the whole surface. Place the pastry on top of the apples and scribe it around the tin with a knife and tuck the edges in. Cooking the tart: Bake the tart in the preheated oven for 30 minutes at least. Remove the tart from the oven and allow to cool down for an hour. For serving, turn the tart onto a flat serving dish, pastry side down. Serve it with lots of fresh double cream or vanilla ice cream.

Sylvie Miot

Illustration "Village in Autumn Mist": Emmanuel Traunecker

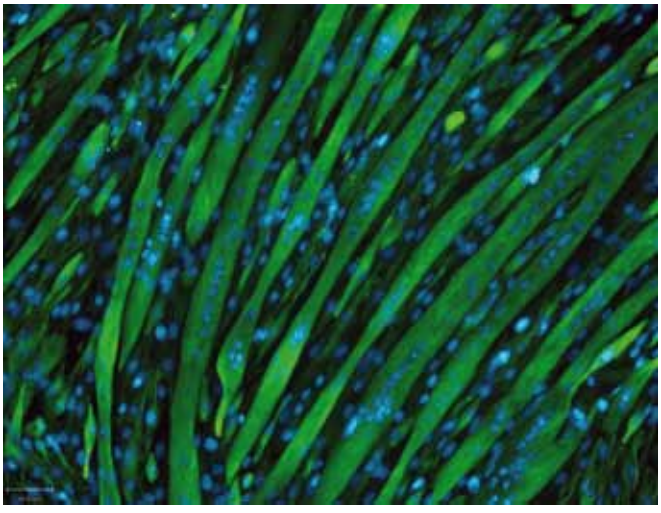
Bodybuilding: From bench to bench

"There is no secret routine; there is no magical number of repetitions and sets. What there is is confidence, belief, hard work on a consistent basis and a desire to succeed." – Steve Justa

Muscle building originated in antiquity, beginning with the ancient Greeks and ancient Egyptians. They developed their muscles through everyday practice in order to survive. By the end of the twentieth century, muscle building became a worldwide phenomenon, as mere weightlifting developed into a separate discipline of gaining strength through bodybuilding. Bodybuilding, per se, is an art. It is the art of defining muscular symmetry and proportionality. Most bodybuilders strive to produce muscle hypertrophy, which is to say, to increase muscle size. To achieve this goal, bodybuilders expend endless energy and effort exercising at a gym. Contrary to popular belief, this is not the only regimen for inducing muscle hypertrophy. Anyone can increase their muscle strength and induce hypertrophy (within natural limits), regardless of body type, gender and amount of time spent at the gym.

Understanding how muscle hypertrophy occurs begins in the laboratory, through the science of muscle development and maintenance. Differences in body type and muscle development are believed to depend on the differences between two major muscle groups: slow-twitch muscle fibers and fast-twitch muscle fibers, which are also known as type I and type II fibers, respectively. Fast-twitch fibers are rapidly contracting muscle fibers that generate a lot of force but fatigue very quickly. On the other hand, slow-twitch fibers contract more slowly and generate less force but ensure longer endurance than fast-twitch fibers. Few repetitions with a heavy weight will activate fast-twitch fibers in response to the heavy force. Fast-twitch fibers are favoured by body builders, who use heavy weights to build their muscles. On the other hand, a lighter weight with more repetitions will activate slow-twitch fibers, since endurance is required. As such, slow-twitch fibers are favoured by marathon runners, who depend on long-lasting muscle stamina.

In recent years, scientists have made considerable progress towards understanding the molecular mechanisms of how exercise induces muscle growth (hypertrophy) or muscle wasting (atrophy). These studies have allowed the identification of complex regulatory processes that involve satellite cell activation, gene transcription, protein synthesis and/or protein degradation (proteolysis). Weightlifting plays a critical role in controlling muscle growth by regulating the Akt/TSC2/mTOR pathway in skeletal muscles. This pathway can integrate many regulatory influences from hormonal, mechanical, and bioenergetic origins. Activation of this pathway can lead to increased muscle size by inducing protein synthesis and inhibiting proteolysis. Many industries target factors in this pathway to develop pharmacological molecules that can chemically induce muscle hypertrophy.



Myoblasts and myotubes: the origin of muscles

Before moving to the gym's workout bench, it is crucial that you schedule at least one session with a personal trainer. Only he or she can help you understand the characteristics of your own body in order to design a bodybuilding workout that will produce the desired results. The personal trainer should know about your workout purpose (to build muscle mass versus muscle tone, to increase cardio and stamina, etc), your health status, your projected workout schedule (once, twice, four times a week) in order to design the optimal conditions and exercises for your training. After all, there are many different workout programs that will achieve the same end-result, just as many different chefs can use different recipes or different personal touches to create the same delicious dish. Trying to self-design a workout program poses the risk of causing personal harm, both temporary and potentially permanent. Common mistakes observed at the gym include mimicking other people's workouts or overexerting your muscles by using weights that are much too heavy or by performing too many sets for a single exercise. One can cause serious and irreversible damage to the muscle, which would lead to muscle atrophy instead of hypertrophy.

The principal characteristics for body building are the intensity, number of sets and repetitions, rest interval between sets, order of exercises, movement velocity and training frequency.

The intensity is defined by the capacity of the trainee to lift a weight for more than three repetitions. Increasing the weights between sets can enable you to achieve a higher intensity during each training session. As for the number of sets and repetitions, it is recommended to have three different sets with 10–12 repetitions per set for each muscle movement. The duration of the rest interval between sets depends on the trainee's purpose. When aiming for muscular power, the rest interval should be four minutes to allow for recovery. When training for muscular hypertrophy, maintaining testosterone levels is one of the best ways to help build muscle. The rest intervals should not exceed one minute because exercise-induced testosterone levels rapidly decrease after two minutes of rest. When training for muscular endurance, rest intervals between sets should be very short.

Bilal is helping Alessio to lift weights. Working with someone is motivational and help is always welcome.

The training frequency is very important for complete muscle regeneration. You should allow your muscles to rest and regenerate for at least 24 hours. Exercising (and thus injuring) the same muscle group every day will reduce the capacity of the muscle to regenerate and may lead to muscle atrophy. Moreover, dividing the body into muscle groups, and alternating muscle groups each workout session, allows the body to recover faster even during training days.

To obtain muscle hypertrophy, proper nutrition is just as important to bodybuilders as their training program at the gym. Muscle hypertrophy requires a balance between muscle protein synthesis (proteosynthesis) and muscle protein breakdown (proteolysis). Assuming that myofibrillar proteins represent about 85% of the muscle fiber volume, any disruption in this balance may thus contribute to muscle hypertrophy or atrophy.

Studies have shown that carbohydrate uptake after performing sports, specifically bodybuilding, is not enough to completely regenerate the muscles. Instead, protein uptake is required within the first few minutes following exercise, especially if your goal is

to induce muscle hypertrophy. Exercise performed in the absence of protein or amino acid availability can lead to an improvement in the net muscle fiber balance, but importantly it causes a net loss in muscle protein levels, thus delaying the healing process that is essential for muscle regeneration and hypertrophy. On the other hand, when exercise is accompanied by an increased availability of amino acids, the result is a synergistic stimulation of protein synthesis, which is greater than that achieved in the absence of amino acid supplementation. Furthermore, early protein uptake before training can be considered necessary for promoting muscle hypertrophy. So the bottom line for bodybuilding is that protein uptake is necessary before and after working out, to ensure amino acid availability for subsequent muscle protein synthesis and hypertrophy.

Protein sources can be natural (such as those provided by red meat, chicken, fish and some beans) or artificial (such as protein powders or concentrated liquids). Because of the difficulty of having a protein-rich nutrient source readily available before and immediately after exercising, companies have developed a vast variety of protein forms to respond to the market need. These range from protein powders to protein bars to ready-to-drink protein liquids. Furthermore, artificial proteins can be subdivided into several types depending on the speed of absorption, the speed of digestion, the availability, the source and the purification process. Whey protein is a fast-absorbing source of protein that supports lean muscle development; it can be taken anytime of the day especially post-workout. Hydro whey protein is digested and absorbed faster than standard whey protein; it is perfect for pre- and post-workout uptake. Whey isolate is a low fat, low carbohydrate, fast-absorbing source of protein that is great for helping to build muscle and lose fat. Casein is a slow digesting protein source; it is ideal to take before bed to block muscle breakdown during the night. For lactose-intolerant people, egg protein can be the alternative to whey protein; it is a high-quality lactose-free protein source that supports lean muscle development. For vegetarians, soy protein is a low-fat protein source that can reduce the sensitivity that some people may exhibit towards protein shakes.

Gym is also for cardio and fitness. Sabrina is having fun. Her destination: a healthier body.

The main question is how much protein should a bodybuilder consume per day? The answer remains unknown, as it depends on the training level and the purpose of the bodybuilder. For muscle hypertrophy, the range can be between 2g to 4g of protein per kilogram of body weight per day. Protein uptake should not exceed 25g at one time, as studies showed that this is the optimum absorption capacity. Larger amounts of protein will be discarded by the body's urine system and can be harmful to the kidneys over time.

Moderate bodybuilding without any exogenous sources of hormones (such as steroids and growth hormones) or manipulation of the threshold of muscle growth can contribute to improvements in any sport performance and give rise to a complete satisfaction with the way you feel about your body. It can also be beneficial in the treatment of some illnesses, such as diabetes.

So whatever your purpose may be, fitness or building muscles; whatever your schedule may be; whatever your health status may be; devote a little time towards your body and let's go move some muscles!

Bilal Azakir

Special thanks to Sabrina Di Fulvio, Alessio Cremonesi and the Forum Sports Club Basel

DBM-IT News

"Nothing stays as it is...."

We would like to present here the current and future projects of the DBM-iT.

Synchronisation of ADS and IDN! From now on only one password will be needed to access all services of the university. In the past, if somebody changed their password for their email account (http://viaweb.unibas.ch), this change was only valid for the email. Now it will be valid for all other services as well. It will, for example, also be valid for access to the fileserver on dbm-anat.unibas.ch, dbm-matt.unibas.ch, dbm-pot.unibas.ch und dbm-imm.unibas.ch. The passwords for VPN-solutions and access to homepage http://urz-ps.urz.unibas.ch/ or http://vpn.mobile.unibas.ch will also change at the same time. Therefore one need only remember one password from now on.

In the current year there will also be changes to the mail server of the university. Windows Exchange Server will be installed. From then on "Groupware" functions can be used, so it will be possible to manage and coordinate multiple calendars for queries over the booking of rooms or the making of reservations for instruments. In order to make full use of this function, Microsoft Outlook must be used. This will apply to all groups who wish to use the above function. Those who use Macs must upgrade to Outlook Office 2011. Unfortunately synchronisation between Outlook and iCal, address book and mail is not yet fully developed. Therefore conflicts can arise when one tries to use AppleMail, iCal and the address book in parallel with Outlook. If you wish to install Microsoft Outlook then please check with us f it is actually worth your while. We can then review the course of progress and the details of the organisation. We then need to migrate the data from iCal, AppleMail and the address book.

While the new version of OSX Lion (10.7) is there, both the university and we advise against upgrading at the moment. The reasons for this are that there are not yet upgraded versions of all of the necessary third-party software, we have not tested all of it yet, the new multitouch gestures require a trackpad and most of all the migration should not be made without careful planning and testing.

We would also advise that due to the current US$ echange rate it is currently advantageous to purchase Prism or Flow Jow.

Niklaus Vogt

Operation Christmas Child

In Eastern Europe many girls and boys are still living in great poverty. We can each bring great joy to these children with ˝Christmas shoeboxes˝. Very simple, without great effort and with complete financial flexibility. Each gives what they wish.

What to do: Get a few colleagues together. Cover the outside and lid of a standard commercial shoe box with gift wrap and fill the package with small gifts. You can either prepare a gift for a girl or a boy in the age classes 2–4 years, 5–9 years or 10–11 years (which should be noted on the outside of the box). The best gifts are a mixture of toys, toiletries, school material, clothing and sweets (see box below) as well as a personal Christmas greeting. This can be in the form of a photograph or a card that has been signed by everyone.

The probable countries to receive packages from our region this year are: Bulgaria, Moldova, Romania, Serbia and Slovakia.

It would be great if each lab was to put together a package. Everyone can put something towards it. I would imagine that shopping for and assembling the packages would bring great joy. I took part in this operation last year and on Christmas Eve found myself thinking of the young boy in Georgia who would be unpacking our parcel at that time. The packages can be left at the collection points listed below from now until November 1st 2011. If anyone doesn't have time to put packages together they can also donate a few francs at the some points towards the transport of the packages. The packages will then be collected from the individual drop off points and brought to the University Hospital, who also took part in this action last year. From there the packages will be transported to the official collection point of the «Geschenke der Hoffnung» organisation before they begin their journey eastward. For those who wish to learn more about this organisation, and watch a video that shows close-up how pleased the children are, further details are available at **www.weihnachten-im-schuhkarton.org**

Collection points in the DBM:
Anatomy: Hanna Pacek, Institute Secretary
Biochemistry and Genetics: Erika Visscher, Secretary of Prof. Christofori
Department of Biomedicine (USB): Manuela Bernasconi, Department Secretary
Microbiology: Institute Secretary
Physiology: Ramona Felix, Institute Secretary

If anyone has further questions then please feel free to ask either Manuela Bernasconi or myself.

Heidi Hoyermann

Gift ideas for the shoe boxes:

Clothes: hat, scarf and gloves set, t-shirt, socks, jumper
Soft toys

Toys: small dolls, car, ball, yo-yo, jigsaw, marbles, colouring books etc.

Toiletries: toothbrush with toothpaste, hair brush, lotion, hand towel

School items: copybook, colouring pencils and pencils with sharpener and eraser, solar calculator

Sweets in their original packaging: hard candy, lozenges and milk chocolate. Note: the best before date must be at least June 2012.

Personal greetings: a photo or Christmas card with a personal greeting

The following items are not allowed due to customs regulations:
Used, old and broken items
Food items such as nuts, trail mix, sugar, noodles, coffee, tea, juice, dairy products, biscuits, Lebkuchen, cakes, etc
Chocolate with nuts, biscuit, crispy bits or other fillings
Jelly sweets such as gummi bears, wine gums, and chewy sweets
Sweets that have a best before date before June 2012
Breakable or liquid items and perfumed soaps
Toy weapons, scissors, knives, tools or other dangerous items
Electronic items
Medicines
Vitamin tables
Any items relating to witchcraft or magic

Cristobal Tostado, Brain Tumor Biology

Ich wurde in Veracruz, Mexico, geboren und wuchs dort in meinen ersten acht Lebensjahren auf, inmitten der tropischen Vegetation, der gemässigten Armut und kaum 100 Meter vom Meer entfernt.

Wir lebten nicht schlecht für dortige Verhältnisse. Mit einem eigenen Häuschen und am Rande der Stadt, unsere Nachbarn waren entweder Lehrer, (Tier-)Ärzte oder Anwälte. Wir hatten eine (namenlose) Katze, die in unserem Garten Junge bekam; ich erinnere mich, wie meine Schwester, die Nachbarsjungen und ich die frisch geborenen, noch nassen Kätzchen bestaunten. Wie wir mit den riesengrossen Blattschneiderameisen spielten – und auch, wie wir von ihnen gebissen wurden.

Oft gingen wir Verwandte besuchen, die viel näher am Meer wohnten – ca. 50 Meter entfernt. Als kleine Kinder assen wir fleissig Sand, bauten Sandburgen, jagten den kleinen Krebschen nach, schnorchelten eifrig und sammelten Muscheln.

Ich erinnere mich auch, dass meine Patentante immer süsse Brötchen mitbrachte, wenn sie uns besuchte ...

Dass wir heute in der Schweiz leben, hatte damals verschiedene Gründe.

Da meine Mutter aus der Schweiz kommt, wusste sie, dass die Qualität der hiesigen Primarschulen besser war als die derjenigen in Mexico.
Dann gab es mal einen Putsch, der Präsident flüchtete mit der halben Staatskasse ins Exil, und der mexikanische Peso verlor 60% seines Wertes. Und wir entdeckten, dass die Milch, die wir tranken, mit irgend einer weissen Farbe gestreckt war...

Die Schweiz

Also kamen wir in die Schweiz, als ich acht Jahre alt war. Die Schweiz war ein kaltes, nasses Land. Die Menschen waren diskret, subtil

und höflich. Ich hatte zum ersten Mal in meinem Leben etwas Langärmliges an und wusste nicht recht, wie ich meine Arme damit zu bewegen hatte.

Aber die Banken verdienten so viel, dass die Bevölkerung relativ wenig Steuern zu zahlen brauchte. Und die Busse rumpelten nicht, hatten keine Rostlöcher und stiessen keinen dicken, schwarzen Rauch aus; überhaupt war alles sehr sauber und nett gehalten ... Es gab keine Bettler und fast keine Kriminalität, man konnte in Wälder gehen, ohne Angst zu haben, überfallen zu werden; Leitungswasser zu trinken war eine Selbstverständlichkeit, und man beklagt(e) sich über Kleinigkeiten, immer ohne irgend welche Existenzängste und aus einem wohligen Komfort heraus.
Es war also wie ein Schlaraffenland.

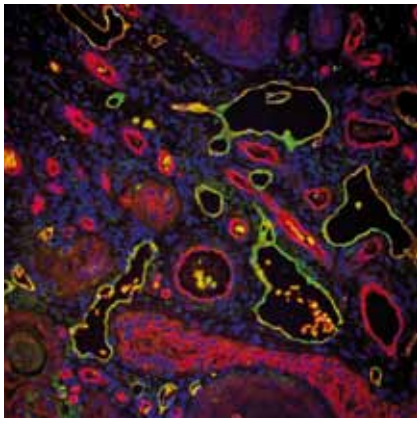
Zum Glück hatte meine Mutter schon in Mexico Deutsch mit mir geredet, die Sprache war nicht so das Problem, auch wenn ich Nachhilfe für die Grammatik nehmen musste. Da ich Bücher aber kiloweise las, war das sehr schnell kein Problem mehr.

Und nun bin ich hier und höre, wie die Arbeitslosigkeit überall in der Welt sprunghaft zugenommen hat, wie der afrikanische Kontinent ausgebeutet wird und verarmt, wie der Dollar und der Euro fast nichts mehr wert sind, höre vom ewigen Drogenkrieg in Mexico, und finde, dass wir Schweizer es doch recht gut haben.

Cheers
Cristobal

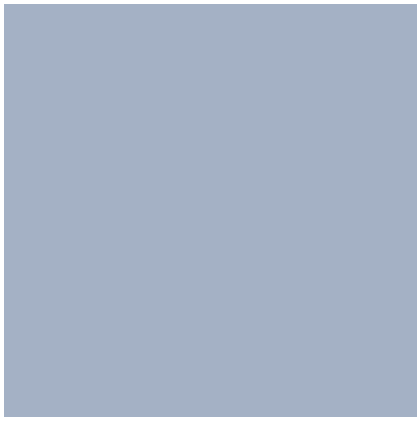
VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



... nimmt uns Thérèse Resink mit in die Welt der Signal Transduction

...erfahren wir von Regine Landmann, wie man in Vietnam ein Labor aufbaut



... bereiten wir uns mit Martin Gassmann auf die Curling-Weltmeisterschaft in Basel vor

... zeigen wir, dass Weihnachten nicht immer besinnlich sein muss

... schauen wir, wie viele Schuhkartons das DBM gepackt hat und schicken sie auf den Weg

Herbstlied

Der Frühling hat es angefangen,
Der Sommer hat‘s vollbracht.
Seht, wie mit seinen roten Wangen
So mancher Apfel lacht!

Es kommt der Herbst mit reicher Gabe,
Er teilt sie fröhlich aus,
Und geht dann, wie am Bettelstabe
Ein armer Mann, nach Haus.

Voll sind die Speicher nun und Gaden,
Dass nichts uns mehr gebricht.
Wir wollen ihn zu Gaste laden,
Er aber will es nicht.

Er will uns ohne Dank erfreuen,
Kommt immer wieder her:
Lasst uns das Gute drum erneuen,
Dann sind wir gut wie er.

(August Heinrich Hoffmann von Fallersleben, 1798-1874)