DBM FACTS

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Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Clinical and Transplantation Virology – Working "from bedside to bench and back" | Notch Signaling in Hepatic Microcirculation and Chronic Liver Disease | Christmas in Russia

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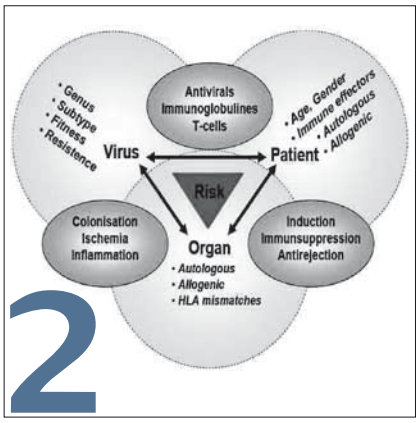
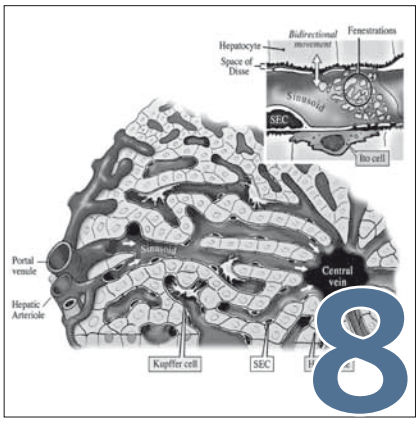
Departement Biomedizin Basel



Clinical and Transplantation Virology – Working "from bedside to bench and back"
from Hans Hirsch



Notch Signaling in Hepatic Microcirculation and Chronic Liver Disease
from David Semela

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from Maria Filippova

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from Anna Marsano

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

2010 neigt sich seinem Ende zu. Wir hoffen, dass im neuen Jahr eine Lösung für die Platzprobleme, die uns immer mehr zu schaffen machen, gefunden werden kann. Mit dem Research Day wartet am 27. Januar 2011 schon die erste grössere Departementsaufgabe auf uns.

Personell hat sich im letzten Jahresabschnitt Einiges verändert: Alex Eberle beendete Ende November nach fast dreissig Jahren seine Tätigkeit am Universitätsspital Basel, wird aber an der Universität Basel weiterhin als Vizerektor Entwicklung tätig bleiben. Wir danken ihm für den grossen Einsatz und die vielen Beiträge, die er über viele Jahre für das DBM geleistet hat und freuen uns auf eine gute Zusammenarbeit! Georg Holländer hat eine Professur an der Universität Oxford angenommen und wird zukünftig drei Viertel seiner Zeit in England tätig sein. Daniela Finke tritt seine Nachfolge als Ordinaria für Molekulare Medizin in der Pädiatrie an und übernimmt gleichzeitig auch die Leitung der Forschung am Universitäts-Kinderspital beider Basel. Beiden herzliche Gratulation und viel Erfolg in ihren neuen Tätigkeitsbereichen! Verena Jäggin verlässt die Core Facility «Flowcytometry» am DBM USB und wird zukünftig an der Mattenstrasse am Department of Biosystems Science and Engineering (D-BSSE) ihre Erfahrung als «Facs-Operatorin» einbringen. Auch ihr herzlichen Dank für alles, was sie in über 30 Jahren für das DBM geleistet hat und viel Erfolg am neuen Ort!

In der Dezemberausgabe nimmt uns Hans Hirsch mit in die Welt der „Clinical and Transplantation Virology» (ab Seite 2) und David Semela führt uns in sein Forschungsgebiet der „Liver Biology» ein (ab Seite 8). Die neuesten Publikationen finden Sie ab Seite 14. Richtung Osten geht es mit Maria Filippova, mit der wir Russische Weihnachten erleben dürfen (ab Seite 34), Anna Marsano, die uns zeigt, wie man sich mit Yoga vom wissenschaftlichen Alltag erholt (ab Seite 38) und Verena Jäggin, die neun Wochen Tibet und China bereist hat (ab Seite 40).

Frohe Weihnachten und einen guten Rutsch ins neue Jahr!

Dear Readers

2010 is drawing to a close. We hope that the New Year will bring a solution to the space issues that seem to plague us more and more. The first large Departmental function will be the Research Day on 27th January 2011.

Personnel have changed somewhat in the last part of the year: at the end of November Alex Eberle retired from his position after nearly 30 years at the University Hospital Basel, but he will continue as Vice Rector at the University of Basel. We thank him for the huge input and the many contributions he has made to the DBM over the years, and we look forward to future collaborations! Georg Holländer has accepted a professorship at the University of Oxford and will be spending three quarters of his time in England in the future. Following on her successes as chair of Molecular Medicine, Daniela Finke is moving to Paediatrics and is also taking over as Director of Research at the "Universitäts-Kinderspital beider Basel". We congratulate them both and wish them every success in their new positions. Verena Jäggin is leaving the USB DBM Core Facility Flowcytometry and will bring her experience as a Facs Operator with her to her new position at the Department of Biosystems and Engineering (D-BSSE) on Mattenstrasse. We also thank her for everything she has done at the DBM over the past 30 years and wish her all the best in her new position.

In the December issue Hans Hirsch brings us on a journey through the world of Clinical and Transplantation Virology (from page 2) and David Semela introduces us to his area of research, Liver Biology (from page 8). The latest publications can be found from page 14 onwards. We go eastward with Maria Filippova, who allows us to share a Russian Christmas with her (from page 34); Anna Marsano, who shows us how one can relax with Yoga after the everyday grind of the scientific day (from page 38); and Verena Jäggin who spent nine weeks travelling in Tibet and China (from page 40).

Wishing you all a very happy Christmas and a good slide into the New Year!

Clinical and Transplantation Virology – Working "from bedside to bench and back"

"Infectiology" is a fairly young specialization within Internal Medicine, but clearly has its roots in the tradition of Louis Pasteur, Robert Koch and Paul Ehrlich. These giants of medicine performed scrutinising clinical observations which were complemented by laboratory analyses of patient samples for further study of etiology, host factors and immune response. Our group is interested in this kind of translational research with a clear focus on virus complications. The approach is unspectacular and traditional: Clinical observations suggesting a role for a virus are corroborated by improved viral diagnostics on a qualitative and quantitative level in the accredited diagnostic laboratory. In the research laboratory, we further characterize viral determinants in clinically relevant host cells to identify key components of viral infection, potential targets of antivirals and informative immune responses for monitoring, vaccines design, or adoptive T-cell transfer. Together with the improved diagnostics, these insights can be taken back to the clinics and improve screening, management and ultimately prevention of viral diseases.

Figure 1: The Institute of Medical Microbiology of the University of Basel

More clinical demand: Clinical virology has been revolutionized by the ability to quantify viral genomes in body fluids and tissues with unparalleled analytic sensitivity and specificity. Moreover, genotypic information is obtained from fragment polymorphisms, hybridization assays and viral gene sequencing. In fact, viral loads, genotyping, resistance testing and receptor tropism are routine determinants for optimal treatment decisions in the management of HIV-1, hepatitis B and hepatitis C virus infection. We are also working on characterizing the "virobiome" of circulating viral majority species and their changes within the general population, populations at risk as well as within individual patients over time. While the closeness to the clinics provides our key translational research opportunities, clinical virology time is nowadays challenged by a paradigm shift following the swine flu pandemic in 2009. Here, clinical virology moved from *"nice-to-know"* addition to a *"must-have"* emergency diagnostic demanding a *"7-days-a-week-NAT"* with a *"24-hour-TAT"* (i.e. nucleic acid testing; turn-around-time), to permit effective infection control as well as timely therapy decisions.

In the Institute of Medical Microbiology, which is located in a partly renovated building from the 1470s (Figure 1), more than 3600 tests for swine flu were performed during 2009 in the quality controlled environment of our accredited and certified diagnostics laboratory (ISO-EN17025). These urgent diagnoses were carried out in addition to the usual standard diagnostic routine tests we run and were carried out without extra staff. The challenge was met on three levels:

– Technically, by being the first after the National Reference Laboratory in Geneva to develop an impressively

robust, sensitive, specific and quantitative in-house swine flu NAT in the first week of May 2009 which allowed us to diagnose the second case of swine flu infection in Switzerland;

– Structurally, by installing laboratory space dedicated to swine flu and respiratory virus diagnostics, initially in the biosafety level 3 environment with gloves, goggles, and full gowning, and then in the standard biosafety level 2;
– Personally, through an unparalleled dedication of the team which cannot be admired enough.

Now that this has become the new standard for clinical virology, and in face of the expected DRGs in the hospitals, this high professional level needs to be embedded in more appropriate facilities and space, with better laboratory informatics to administrate the work load and to effectively deliver the "NAT" results with shortest "TAT" to the clinics.

More viruses in question: Although the swine flu A/H1N1 pandemic in 2009 was clinically less severe than expected, there remains the threat of another influenza pandemic e.g. of a bird flu derivative e.g. A/H5N1. In the aftermath of SARS in 2003, 3 new coronaviruses have been detected in respiratory samples, but their primary role in clinical disease is not clear, yet. Our swine flu results in Basel indicated that there were at least three phases of the pandemic: The initial arrival phase with a flat peak which lasted till the end of July and a A/H1N1v rate of 18%, a second phase of low-level transmission throughout the warmer summer season with a rate of below 5%, and the third phase with a high positive rate of up to 60% during the autumn and winter of 2009 (Figure 2). Using a multiplex PCR to identify 16 respiratory pathogens including respiratory syncytial-(RSV),

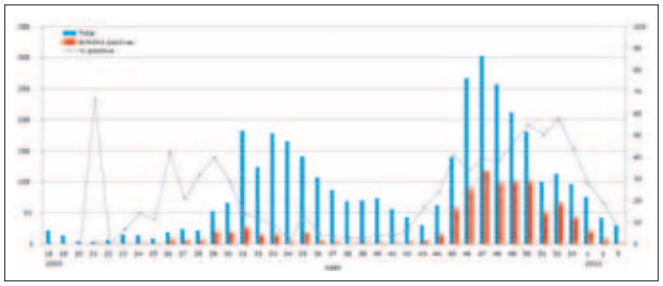

Figure 2: Diagnostic results of the swine flu A/H1N1v pandemic at the IMM in 2009. Blue: total number of tests per week; red: number of A/H1N1/v positives; line: percent positives.

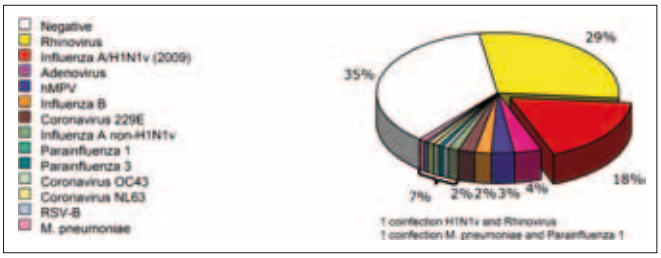

Figure 3: Comprehensive NAT for respiratory infectious agents during the first phase of the swine flu pandemic in 2009.

human metapneumo-(hMPV), parainfluenza (PIV1-4), corona-, adeno, and rhinoviruses in addition to Influenza A and B, new A/H1N1v ("swine flu"), we found that rhinovirus infections were the most prominent other cause of viral respiratory tract infection detected in up to 30 percent, while another 20% were attributable to miscellaneous viruses (Figure 3) (2). In fact, rhinoviruses seemed to compete for susceptible hosts which could be called "viral interference" and might result from interferon production. These results have scientific and epidemiologic implications, but also impact on (in-) appropriate antibiotic or anti-influenza therapies, outpatient management and hospital admission practices. However, the expanding number of new viral agents is not limited to the respiratory tract. There are currently at least 8 human herpes viruses and 5 human parvoviruses. Until 2007, only 2 human polyomaviruses (huPyV) were known, BK virus (BKV) and JC virus (JCV). Since then, 6 new human polyomavirus have been identified. Most of these agents seem to be well adapted to the human host as suggested by the high seroprevalence rates ranging from 50% to more than 90% in the general healthy po-pulation. However, they cause significant organ disease and cancer in immunocompromized hosts.

More patients at risk: HIV-AIDS, SARS and Swine Flu dramatically illustrate the vulnerability of "new viruses" attacking the general human population. Clearly, virus infections are even more severe when the immune system of the infected host is compromised in its response. Over the past 2 decades, the number and diversity of patients at risk for viral complications has been increasing due to an increasing number of conditions with acquired and iatrogenic/therapeutic immune dysfunction. In addition to HIV-1 infection, there are more patients with solid organ transplantation (SOT) or hema-

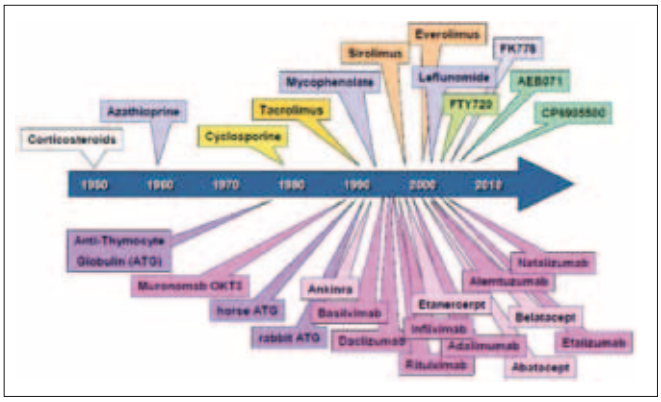

Figure 4: Immunosuppressive agents over time (arrow): Above, small molecules; below, antibody preparations.

topoietic stem cell transplantation (HSCT), and autoimmune disorders treated with modern immunosuppressive and/or immunomodulatory drugs.

While many of these new drugs are small molecules attempting to targeting activation and proliferation functions of immune cells, others are monoclonal antibodies specifically blocking and/or to depleting immune cells with the corresponding target molecules (Figure 4). Although generally increasing the "net state of immunosuppression", some of these drugs appear to disproportionally increase the risk of one virus over another suggesting that some pathophysiological function specific to virus replication or containment might be affected. It is therefore of interest to characterize the presence of specific determinants of the affected patients, the affected organs and the viruses in question, as well as the modulators of this "ménage-à-trois" (Figure 5). It is clear that this interaction is significantly perturbed by transplantation procedures where viruses, host cells and immune effectors are brought together in an allogenic constellation under an umbrella of initially intense immunosuppressive induction conditions followed by often life-long maintenance immunosuppression.

More defined viral risk management: Respiratory syncytial virus (RSV) is a common infection during childhood with severe disease only occurring in neonates. However, RSV may cause a decline in respiratory function, viral pneumonia and death in patients after lung transplantation and after allogenic HSCT. In fact, progression from upper to lower respiratory tract infection has been associated with mortality rates as high as 50%. While the "net state of immunosuppression" and the specific antiviral immunity seem to be key risk factors, RSV diagnosis was often late due to insensitivity of the rapid antigen test and the 3–5 days duration of the more sensitive cell culture. To permit an early, sensitive and specific diagnosis, we adopted RSV NAT for these patients and developed a classification denoted either severe immunodeficiency (SID) or moderate immunodeficiency (MID) according to clinical and laboratory markers (11). We found that HSCT patients with SID were more likely to shed higher RSV loads in respiratory secretions, were symptomatic for longer (Figure 6) and at higher risk for RSV pneumonia and death (11). For SID patients, more aggressive interventions seems to be warranted which, in the absence of definitive studies with better drugs, consisted of oral ribavirin, intravenous immunoglobulin and a monoclonal antibody to the RSV F-protein for SID patients. For influenza A and B which can be inhibited by neuraminidase inhibitors, we found higher influenza viral loads and prolonged shedding for more than 3 weeks in patients with SID as compared to those with MID, despite oseltamivir therapy (10). Further independent studies are needed to evaluate the role of SID criteria and the potential role more specific immunoassays.

Cytomegalovirus (CMV) is a human herpes virus that infects 40–70% of the general population, and is the most significant viral pathogen after SOT and HSCT causing organ-invasive disease as well as indirect immunological damage to grafts. The current antiviral options have side-effects such as bone marrow toxicity, electrolyte

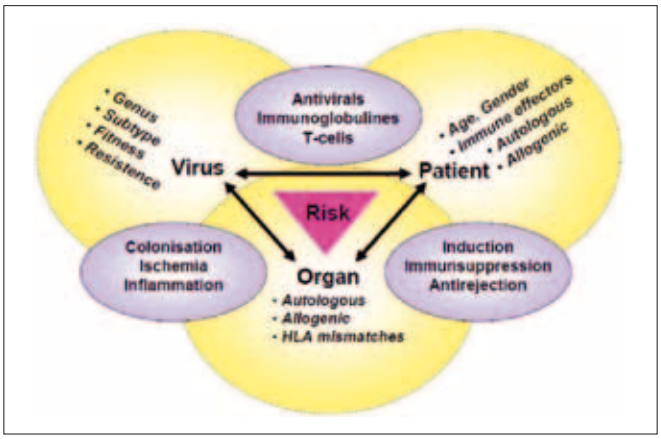

Figure 5: Determinants (yellow area) and modulators (small blue) of viral diseases.

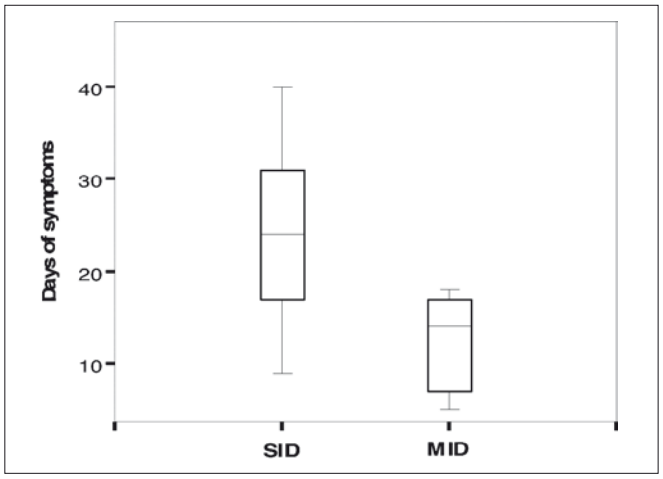

Figure 6: RSV replication and symptoms in haematological and HSCT patients. SID, severe immunodeficiency; MID, moderat immunodecifiency (p<0.05).

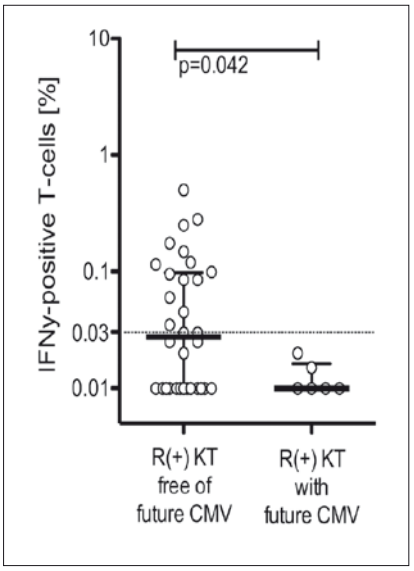

Figure 7: CMV-specific T-cell frequency in kidney transplant (KT) patients with or without future CMV replication and genotypic ganciclovir resistance.

imbalance and nephrotoxicity, and possibly of antiviral drug resistance. In kidney transplant patients, we observed that the overall CMV-specific T-cell responses were significantly lower and undetectable compared to patients without ongoing viremia. More importantly, kidney transplant patients without ongoing CMV viremia were protected from CMV replication for the following 8 weeks if CMV pp65-specific CD4-Tcell responses were above 0.03% (Figure 7). On the other hand, CMV-seropositive kidney transplant patients without detectable CMV-specific T-cells in the peripheral blood were at increased risk for viremia and ganciclovir resistance. Thus, assessment of virus-specific cellular immune responses has the potential to evaluate the risk of viral disease and drug resistance development in transplant patients.

More polyomavirus diseases: Currently, 4 of the 8 known human PyV are known to cause significant diseases in immunocompromized patients. BK virus (BKV) is linked to polyomavirus-associated nephropathy after kidney transplantation and hemorrhagic cystitis after HSCT. In Basel, the first cases of nephropathy were diagnosed in 1996 in kidney transplant patients treated with higher doses of tacrolimus. Meanwhile, BKV nephropathy is found in up to 10% of patients around the world. In addition to a detailed characterization of the clinical and pathological presentation, we established that kidney transplant patients progress from by high-level BKV viruria with decoy cell shedding to BKV viremia with plasma BKV loads increasing to more than 10'000 genome equivalents followed by histologically defined nephropathy (6, 13). Based on these results (Figure 7), screening kidney transplant patients for increasing plasma BKV loads is currently recommended by international guidelines to identify kidney patients at risk before overt disease and failing transplant function (7). We could show that reducing immunosuppression is followed by declining plasma BKV loads, increasing BKV-specific T-cells in the peripheral blood and clearance of nephropathy (1). To better understand the role of tacrolimus, we participated in an international 1:1 randomized-controlled trial comparing tacrolimus with cyclosporine in 682 de novo kidney transplant recipients. We found that BKV viremia is more frequent and higher in patients receiving tacrolimus when compared to cyclosporine at month 6 and 12 post-transplant (8). Kinetic

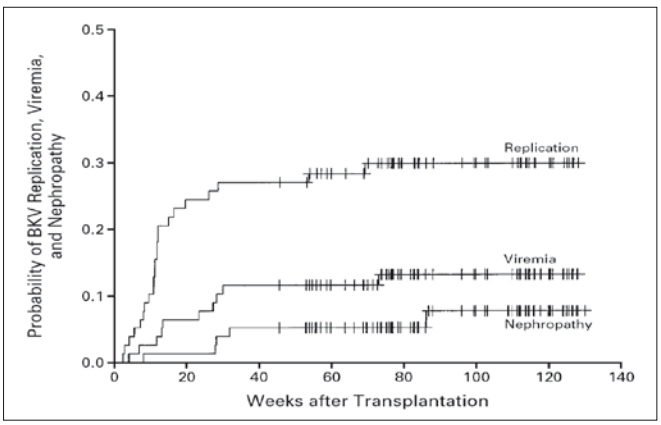

Figure 8: BKV viruria and viremia precede the diagnosis of BKV nephropathy in kidney transplant recipients.

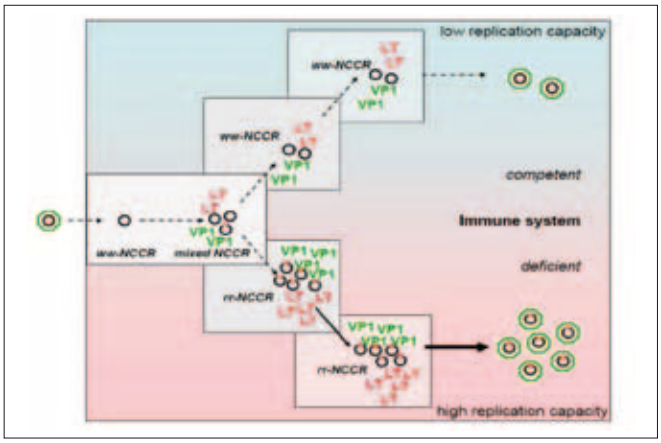

Figure 9: Genotypic polyomavirus variants with increased early gene expression (LT, large T-antigen, red) and higher replication capacity are emerging in immunodeficient patients.

studies of patients undergoing allograft nephropathy indicates a short-half life of plasma BKV in the order of <2 h and a high turnover rate (3). *In silico* modelling indicated a 2-compartment replication model where clearance of BKV viremia and nephropathy, more than 80% curtailing of BKV replication is needed. To date there are no antivirals of proven clinical efficacy, but our recent *in vitro* study suggests that the lipid derivative of cidofovir may be more 400-fold more efficacious than the parent drug cidofovir in interrupting BKV replication with an EC_{90} of 0.31 uM in renal tubular epithelial cells (14). Characterisation of the BKV non-coding control region demonstrated the emergence of genetic variants characterized by rearrangements, 20-higher plasma viral loads and more advanced histological allograft pathology (5). These rearrangements are sufficient to activate early gene expression and increase BKV replication in vitro (5). Thus, a poor antiviral immunity does not determine the emergence of more virulent BKV genotypes, but also more pathology. One of the regulators of polyomavirus replication appears to be the BKV agnoprotein which associates with lipid droplets (15) and may be critical in virus release and the avoidance of host immune recognition (12).

Polyomavirus JC virus (JCV) causes progressive multifocal leukoencephalopathy (PML) in patients with profound immunodeficiency including in HIV-AIDS, haematological malignancy, and in autoimmune disorders treated with modern immunosuppressive drugs (9). In a clinical study, we identified close to 200 cases with PML in the Swiss HIV Cohort Study and found a significant reduction in the number of cases after the availability of modern HIV therapy in 1996. The average PML-attributable mortality was 70 days, but mortality was significantly reduced for patients started on HIV-suppressive therapy. Our immunological studies indicated that compared to non-survivors, PML survivors had significantly higher antibody levels and higher JCV-specific T-cell responses at the time of diagnosis whereas no difference was seen regarding CMV-specific T-cells in these patients. The data suggest that the presence of specific deficits in the JCV-specific immune repertoire rather than the overall low CD4 cell count as a determinant for outcome. Therefore, raising JCV-specific T-cells from healthy donors *in vitro* using the peptide antigens described as an adjuvant therapy may be an ultimate option in the setting of HSCT, as described in a case study. Similar to BKV, JCV genomes in PML are also rearranged and increase JCV replication rate *in vitro* in primary human glia derived astrocyte cells compared to the archetype JCV found in urine (4). The archetype JCV, however, could be significantly activated by HIV-*tat* expression suggesting that HIV infection in the brain could be critical first step in JCV-PML. Thus, activation of viral replication and profound immunodeficiency synergize in the onset of polyomavirus diseases which are further accelerated by genotypic variants of higher replication rate and virulence.

More studies needed: Although the basic science aspect of the "Clinical & Transplantation Virology" research may not be so fundamental, our small increments in knowledge actually have the potential to translate fairly rapidly in clinical practice. In fact, several of our observations have been included in the clinical guidelines of national and international medical societies. It is clear that our approach is multidisciplinary and enjoys the collaboration with a variety of colleagues from Infectious Diseases and other disciplines in clinical medicine and basic science in Basel and beyond without whom this work would not have been possible.

Hans Hirsch

From the left:
First row: Andrea Glaser, Simone Neu, Julia Manzetti, Bryan Rupinski, Vroni del Zenero, Erika Hofmann, Alexis Dumoulin.
Second row: Hans Hirsch, Piotr Kardas, Rainer Gosert, Marion Wernli, Gunhild Unterstab.

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Notch Signaling in Hepatic Microcirculation and Chronic Liver Disease

Introduction

The focus of our group is angiogenesis and vascular remodeling in chronic liver disease and hepatocellular carcinoma. Chronic liver disease leads to profound changes of the sinusoidal vascular network with development of portal hypertension. The microvasculature in cirrhotic liver is remodeled and abnormal with vessels of varying diameter separated into micronodules. Several processes have been recognized that lead to vascular remodeling in the liver: On a cellular level resting stellate cells become activated and start to deposit matrix proteins, which will lead to formation of a basement membrane around the sinusoids. Liver sinusoidal endothelial cells (LSEC) become dysfunctional and deficient for production i.e. of the vasodilator nitric oxide. These changes will finally transform the low resistance vascular bed leading to portal hypertension with all its consequences such as variceal bleeding, formation of collateral vessels porto-systemic shunts and formation of ascites.

The role of LSEC signaling and sinusoidal vascular remodeling in the process of cirrhosis and portal hypertension is not completely understood. Under physiological conditions, LSEC are resting and highly differentiated cells showing unique morphology with fenestrations and a lack of a basement membrane. However, in chronic liver disease, LSEC become activated, start to proliferate, upregulate various arterial surface markers and lose their fenestrations, eventually leading to dedifferentiation and capillarisation of the hepatic microvascular bed.

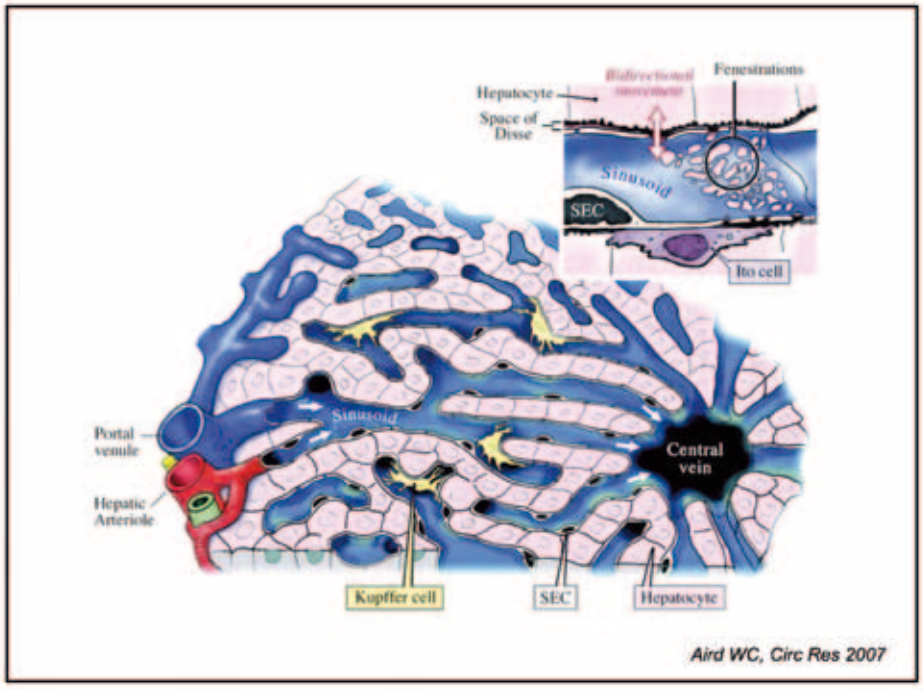

Figure 1:
Sinusoids and the structure of the hepatic microcirculation. Hepatic sinusoidal endothelial cells form a discontinuous lining, characterized by large membrane-bound, nondiaphragmed round cytoplasmic holes or fenestrae and poorly organized basement membrane. SEC indicates sinusoidal endothelial cells. Adapted from Aird WC, Circ Res 2007.

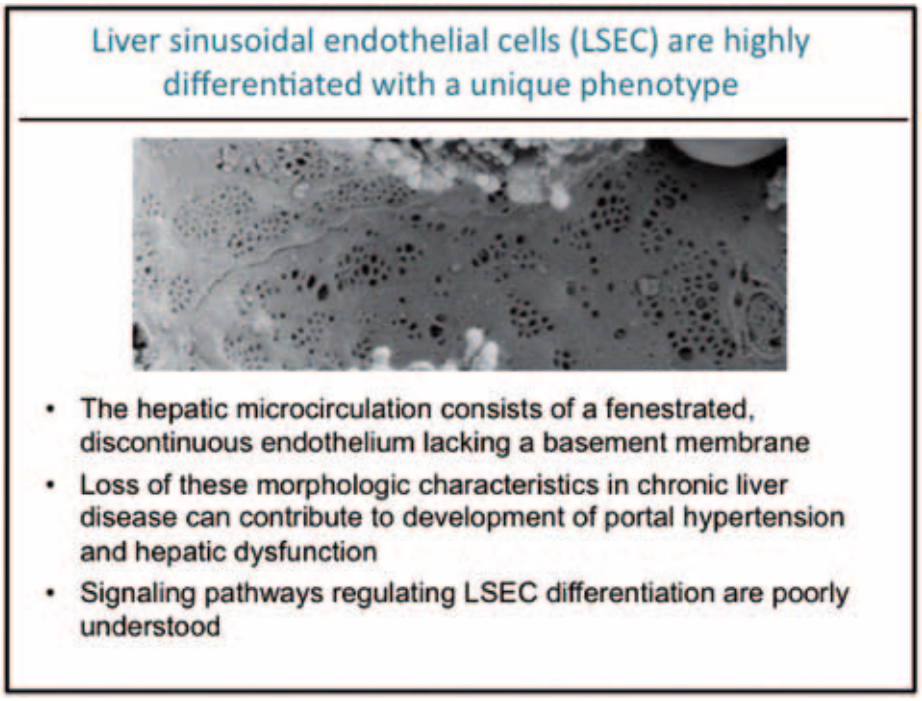

Figure 2:
Scanning electron microscopy showing normal liver sinusoidal endothelial cells with fenestrations.

A key signaling pathway in vascular differentiation and interendothelial cell interactions is Notch signaling. Notch signaling plays a pivotal role in embryonic vascular development and vascular differentiation. Notch1 receptor and its ligands Jagged and DLL are expressed in healthy adult liver. However, their function in liver is unknown. We have therefore developed animal models in order to study the hepatic microcirculation in different Notch knockout mice suffering from portal hypertension and liver cancer with active tumor angiogenesis.

Liver sinusoids – a unique microvasculature

The liver is the largest internal organ (2.5% of body weight) and receives 15% to 20% of the total cardiac output. It has a dual vascular supply where well oxygenated blood arrives via the hepatic artery (1/3 of hepatic blood flow) and poorlyoxygenated, but nutrient-rich, blood from the intestine arrives through the portal vein (2/3 of hepatic blood flow). Both vessels drain into the liver sinusoids, a unique microvasculature which consists of plates of liver sinusoidal endothelial cells (LSECs) between plates of hepatocytes, before plasma comes in contact with the liver parenchyma (Figure 1).

LSECs account for 20% of the total liver cells (an estimated 1 x 10^8 cells in adult humans) whereas hepatocytes represent the majority of liver cells (estimated 60% or 3 x 10^8 cells). LSECs have a unique phenotype in comparison to endothelial cells of other organs characterized by a fenestrated, discontinuous endothelium, which lacks an organized basement membrane (Figure 2).

Fenestrae are large (100 to 200 nm), non-diaphragmated cytoplasmic holes, which occupy 6% to 8% of the endothelial surface and occur at a frequency of 9 to 13/ μm2 (1). They are arranged in so-called sieve plates, which comprise 20 to 50 aggregated pores (approximately 0.1 µm in diameter). These sieve plates filter the plasma which is exchanged between the sinusoidal lumen and the space of Disse, defined as the perisinusoidal or subendothelial space separating the sinusoids from the adjacent hepatocytes (2).

Dedifferentiation of the hepatic microcirculation in chronic liver disease

Chronic liver disease leads to fibrosis with profound changes of the sinusoidal vascular network and development of portal hypertension. Portal hypertension, which is defined by elevated pressure in the portal vein above the normal values of 1–5 mmHg is the major cause of mortality in patients with advanced liver fibrosis and cirrhosis. Elevated portal pressure, especially if above the threshold of 12 mmHg, leads to serious complications such as oesophageal or gastric varices with

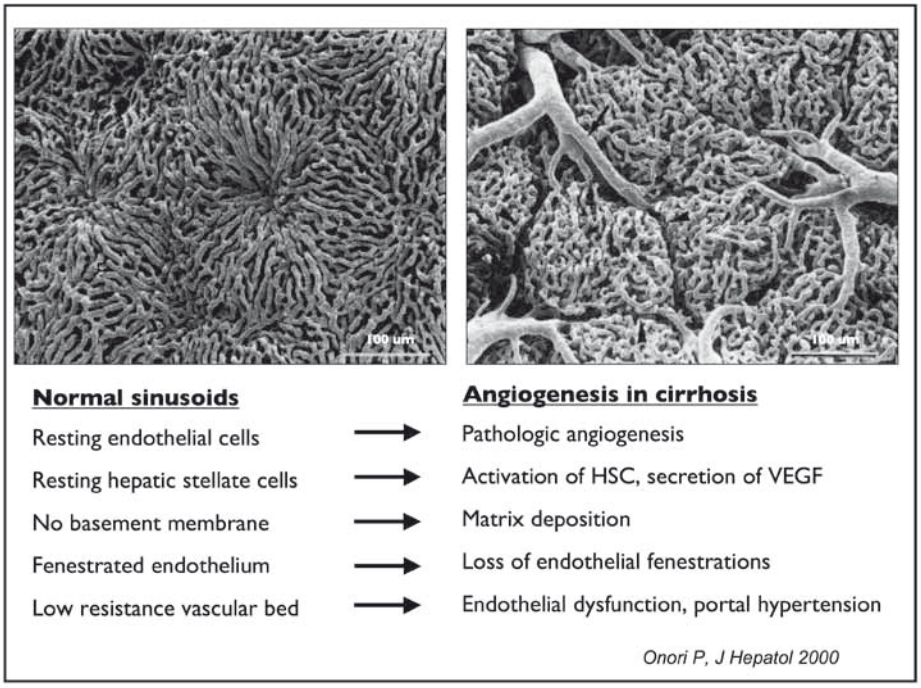

Figure 3:
Electron microscopy of vascular casts from normal rats (left) and rats after bile duct ligation (right), which leads to liver cirrhosis and vascular remodeling with abnormal vessels of varying diameter separated into micronodules. Adapted from Onori P, J Hepatol 2000.

massive gastrointestinal bleeding, ascites (accumulation of fluid in the abdominal cavity), hepatorenal syndrome and hepatic encephalopathy.

The architecture of hepatic microvasculature in the cirrhotic liver is transformed. This process of transformation, also called vascular remodeling, leads to distorted vessels of varying diameter separated into micro-nodules (Figure 3). Additionally, chronic liver disease also leads to angiogenesis, which is defined as the formation of new blood vessels from pre-existing vasculature. Several processes have been recognized as leading to angiogenesis and vascular remodeling in chronic liver disease: secreted growth factors (i.e. vascular endothelial growth factor) induce endothelial cell proliferation and hepatic stellate cells start to deposit extracellular matrix proteins such as collagen, which will lead to formation of a basement membrane around the sinusoids. Furthermore, hepatic sinusoidal endothelial cells lose

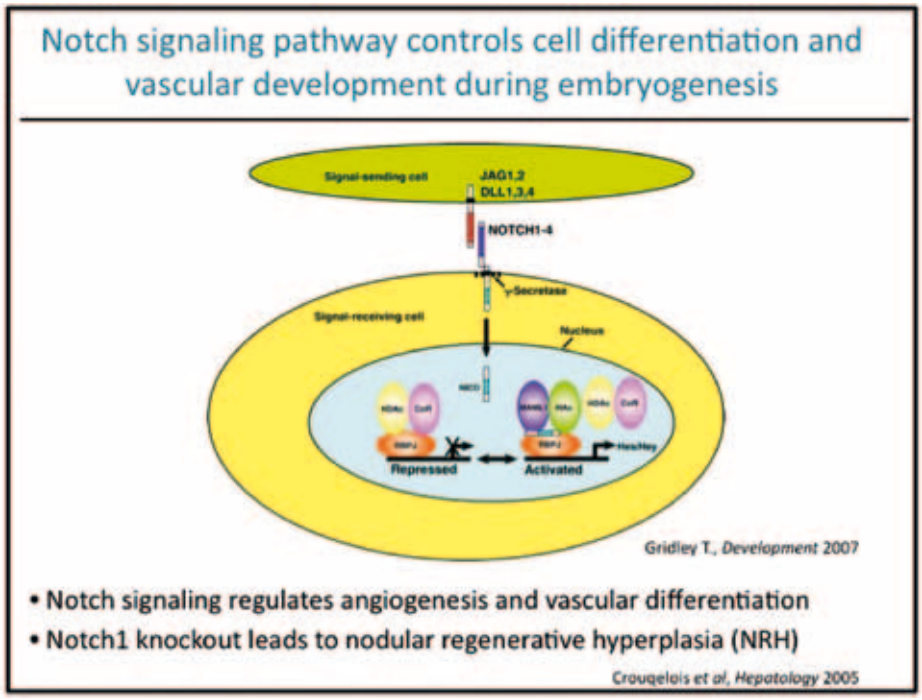

Figure 4:
Schematic representation of the Notch signaling pathway. Apapted from Gridley T, Development 2007.

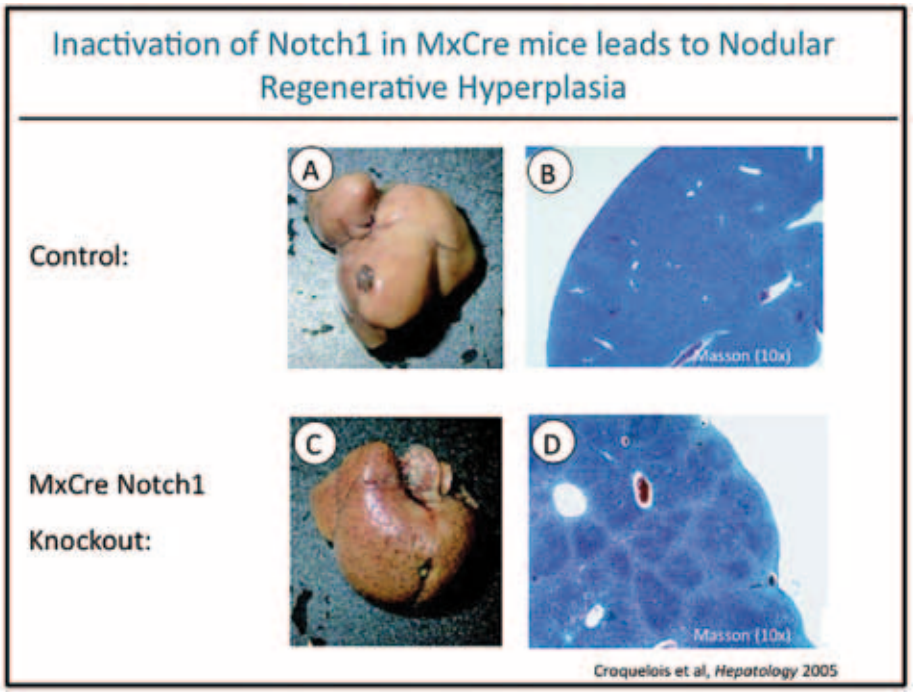

Figure 5:
Nodular regenerative hyperplasia in a mouse liver of MxCre Notch1 knockout mice. Adapted from Croquelois A, Hepatology 2005.

their fenestrations and become deficient in the production of the vasodilator molecule nitric oxide leading to increased hepatic stellate cell contractility. The sum of these processes results in remodeling and vasoconstriction which contribute to increased hepatic vascular resistance and portal hypertension.

Although hepatic stellate cell contractility and matrix deposition are well established in the process of cirrhosis and portal hypertension, the role of endothelial cell dysfunction and sinusoidal remodeling is less understood. Interaction between pericytes and endothelial cells as well as between neighbouring two endothelial cells is a central process in the regulation of angiogenesis, vascular remodeling, stabilization and maintenance of blood vessels. Failure of such interactions result in severe cardiovascular defects as described in several genetic mouse models.

Notch signaling

A key signaling pathway in inter-endothelial cell cross talk is the Notch signaling. The Notch pathway is a signal transduction pathway which is essential for cellular proliferation, specification and differentiation. Notch signaling mediates intercellular communication through membrane-bound receptors (Notch-1, -2, -3, -4) and ligands (Jagged-1, -2 and Delta-like-1, -3, -4) (Figure 4).

Notch-1 and its ligand Jagged-1 are expressed in normal liver and have been detected in hepatocytes, hepatic sinusoidal endothelial cells and biliary epithelial cells. However, the function of Notch signaling in the liver is poorly understood. Markus Heim and co-workers have found that inactivation of Notch-1 induces hepatocyte proliferation and leads to a specific pathology termed nodular regenerative hyperplasia of the liver (Figure 5).

Nodular regenerative hyperplasia – A model to study the liver microcirculation

Nodular regenerative hyperplasia (NRH) is a human disease characterized by proliferation of hepatocytes and nodular transformation of the liver parenchyma in the absence of collagen deposition, which is in contrast to liver cirrhosis. NRH can be complicated by portal hypertension, which is a serious and potentially live threatening complication of NRH. The etiology of NRH is unclear; several clinical reports suggest that this condition is related to injury of the liver endothelial cells.
Surprisingly, Markus Heim and co-workers have found NRH in Notch1 KO mice (Figure 5). However, the pathogenesis remained unclear. Our first hypothesis, that the nodular transformation of the liver in these mice is driven by Notch1 in the hepatocytes, has been proven wrong since knockout of Notch1 in hepatocytes only (Notch1 lox/lox crossed with AlbCre+/– mice) showed

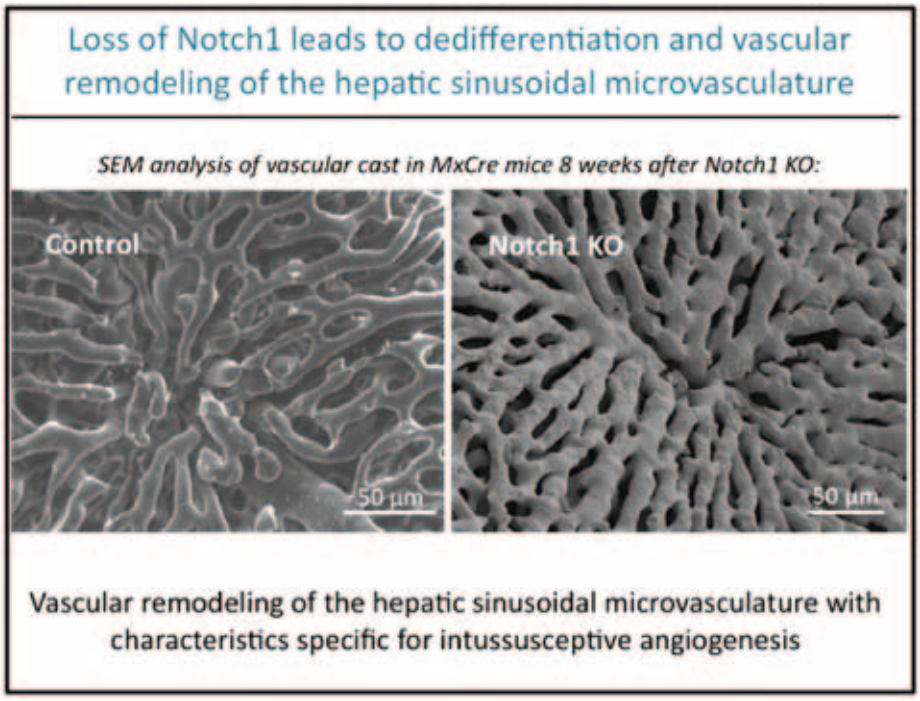

Figure 6:
Vascular remodeling in Notch1 KO mice as assessed by vascular casting in scanning electron microscopy.

a normal phenotype. This finding further supported the idea that Notch1 in LSEC might be the driver of this remodeling process. We are therefore currently exploring our animal model of NRH in order to study the function of Notch1 in the hepatic microcirculation. In collaboration with Valentin Djonov and Ruslan Hlushchuk at the University of Bern we are, as a first step, analyzing the hepatic microvasculature by corrosion casting of Notch1 KO (MxCre Notch1 lox/lox mice as a tissue-unspecific conditional KO mouse model) and histological analyses.

We found a persistently increased proliferation rate of LSECs in MxCre Notch1 KO mice. Scanning electron microscopy of vascular casts showed that loss of Notch1 leads to dedifferentiation and dramatic vascular remodeling (Figure 6) of the hepatic sinusoidal microvasculature with increased branching and diameter as well as active intussusceptive angiogenesis (Figure 7). MxCre Notch1 KO mice developed portal hypertension and upregulated endothelial CD34 as marker of capillarisation further supporting the hypothesis that NRH is an endotheliopathy.

Based on our current results we conclude that Notch1 signaling is required for vascular homeostasis of hepatic sinusoids by inducing quiescence and differentiation of LSEC in adult mice. Disruption of Notch1 pathway leads to LSEC proliferation, vascular remodeling, intussusceptive angiogenesis and portal hypertension. The lack of phenotypic changes in hepatocyte-specific Notch1 KO mice suggests that the development of NRH in our model is secondary to vascular remodeling induced by loss of Notch1 signaling in LSEC.

Notch Function in Tumor Angiogenesis of Liver Cancer

In a separate project, we are investigating the role of Notch1 signaling in the development of liver cancer. Growth of liver cancer (hepatocellular carcinoma, HCC) relies on formation of new blood vessels in order to receive an adequate supply of oxygen and nutrients. The acquisition of the capacity to stimulate angiogenesis („angiogenic switch“) is an important step in the tumoral development and HCC progression. HCC is a hypervascular tumor and intratumoral microvessel density correlates with patient mortality. The Notch ligand Dll4 is prominently expressed in tumor blood vessels in a VEGF-dependent fashion. Blockade of Dll4-Notch signaling with the Dll4/Fc antagonist, anti-Dll4 antibodies, or gamma-secretase inhibitor promotes endothelial sprouting and thereby increases vascular density in xenograft tumor models in mice. Surprisingly, inhibition of Notch signaling with these strategies lead to significantly smaller tumors compared with controls. The analysis

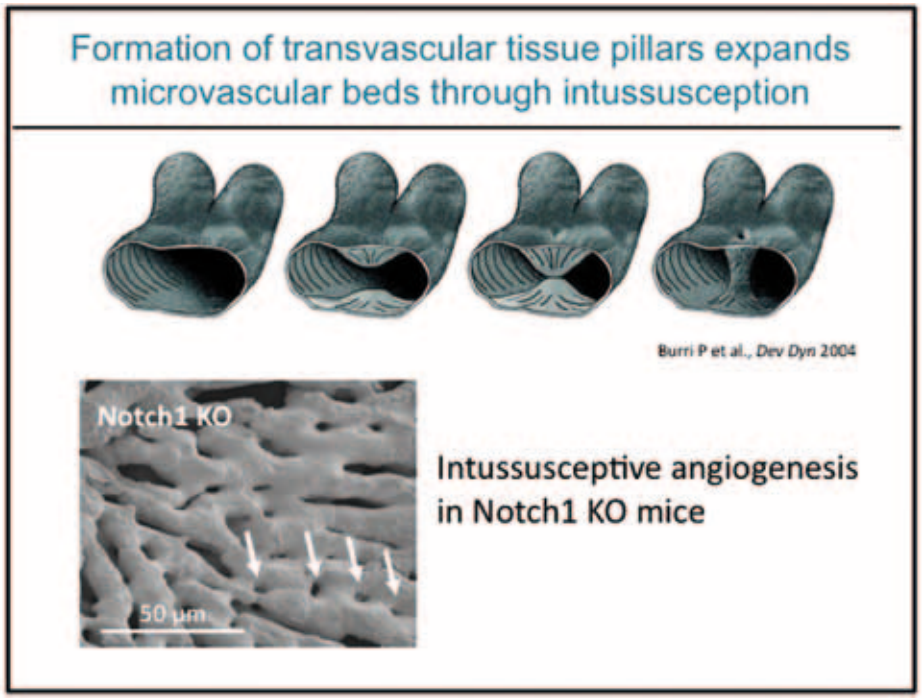

Figure 7:
Cartoon of intussusceptive angiogenesis, adapted from Burri P, Dev Dyn 2004 (Top). Vascular cast in Notch1 knockout mouse showing features of intussusceptive angiogenesis (Bottom).

of blood vessel showed that these vessels were poorly functional leading to increased hypoxia, poor perfusion and reduced tumor growth. In this project, we intend to study the role of Notch1 in hepatocarcinogenesis and tumor angiogenesis by using the well established diethylnitrosamine HCC model in different Notch1 KO mice with selective knockout of Notch-1 in hepatocytes or LSEC.

Outlook

Using liver biopsies and tissue microarrays from patients suffering from portal hypertension (i.e. NRH and other chronic liver diseases) or liver cancer we are ultimately analyzing the role of the Notch pathway in human liver disease in a translational study. This is in collaboration with Luigi Terracciano and Luigi Tornillo at the Institute of Pathology, University of Basel and might be of clinical relevance since the first drugs targeting Notch signaling are being tested in Phase I/II studies.

David Semela

Acknowledgement: We would like to thank the Hepatology group of Markus Heim for their great support and fruitful discussions. Besides Sonja Rothweiler, also Michael Dill performed many of the described experiments. We are indepted to Luigi Terracciano & Luigi Tornillo for assistance with light microscopy and Valentin Djonov & Ruslan Hlushchuk for access and assistence with scanning electron microscopy.

David Semela und Sonja Rothweiler

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

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

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

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

Deadline for the next issue is January 31, 2011.

Nature Methods nature methods 7, 893–895, 2010 IF 16,8

Dual RMCE for efficient re-engineering of mouse mutant alleles

M. Osterwalder[1], A. Galli[1,3], B. Rosen[2], W. C. Skarnes[2], R. Zeller[1] and J. Lopez-Rios[1]

Abstract:
We have developed dual recombinase-mediated cassette exchange (dRMCE) to efficiently re-engineer the thousands of available conditional alleles in mouse embryonic stem cells. dRMCE takes advantage of the wild-type *loxP* and *FRT* sites present in these conditional alleles and in many gene-trap lines. dRMCE is a scalable, flexible tool to introduce tags, reporters and mutant coding regions into an endogenous locus of interest in an easy and highly efficient manner.

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Neurology Neurology® 75, 403–410, 2010 IF 8.2

Th17 central memory T cells are reduced by FTY720 in patients with multiple sclerosis

M. Mehling[1], R. Lindberg[1], F. Raulf[3], J. Kuhle[1], C. Hess[2], L. Kappos[1] and V. Brinkman[3]

Abstract:
Objective: FTY720 is a sphingosine 1-phosphate (S1P) receptor modulator that showed efficacy in phase II and III clinical trials in patients with multiple sclerosis (MS). FTY720 inhibits lymphocyte egress from secondary lymphoid organs into the peripheral circulation, thereby reducing the number of circulating naïve and central memory T cells, but not effector memory T cells in blood. Little is known to which of these memory T-cell subsets interleukin 17 (IL-17)-producing T cells (Th17 cells) belong, which are considered to be key mediators of inflammation in MS, and how they are affected by treatment with FTY720. In this study, we determined the phenotype and frequency of Th17 cells in blood of untreated, FTY720-treated, and interferon-β (IFNβ)-treated patients with MS and healthy donors.

Methods: In a prospective observational study, circulating T cells were phenotypically characterized and Th17 cells enumerated in T-cell subsets ex vivo. Production of IL-17 upon activation and expression of the Th17-specific transcription factor RORC2 was assessed in vitro.

Results: Th17 cells were found primarily within central memory T cells in all study populations. FTY720 treatment reduced blood central memory T cells, including RORC2+ and IL-17-producing T cells, by >90%. FTY720 did not per se affect IL-17 production when added to activated T cells in vitro.

Conclusion: Phenotypic Th17 cells are defined by a central memory T-cell phenotype. FTY720 reduces these Th17 cells in blood. This is presumably because central memory T cells are retained by FTY720 in secondary lymphoid organs.

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Biomaterials Biomaterials 31, 8946–8952, 2010 IF 7,4

Bioreactor based engineering of large-scale human cartilage grafts for joint resurfacing

R. Santoro[1], A. L. Olivares[2], G. Brans[3], D. Wirz[4], C. Longinotti[5], D. Lacroix[2], I. Martin[1] and D. Wendt[1]

Abstract:
Apart from partial or total joint replacement, no surgical procedure is currently available to treat large and deep cartilage defects associated with advanced diseases such as osteoarthritis. In this work, we developed a perfusion bioreactor system to engineer human cartilage grafts in a size with clinical relevance for unicompartmental resurfacing of human knee joints (50 mm diameter × 3 mm thick). Computational fluid dynamics models were developed to optimize the flow profile when designing the perfusion chamber. Using the developed system, human chondrocytes could be seeded throughout large 50 mm diameter scaffolds with a uniform distribution. Following two weeks culture, tissues grown in the bioreactor were viable and homogeneously cartilaginous, with biomechanical properties approaching those of native cartilage. In contrast, tissues generated by conventional manual production procedures were highly inhomogeneous and contained large necrotic regions. The unprecedented engineering of human cartilage tissues in this large-scale opens the practical perspective of grafting functional biological substitutes for the clinical treatment for extensive cartilage defects, possibly in combination with surgical or pharmacological therapies to support durability of the implant. Ongoing efforts are aimed at integrating the up-scaled bioreactor based processes within a fully automated and closed manufacturing system for safe, standardized, and GMP compliant production of large-scale cartilage grafts.

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[5] Fidia Advanced Biopolymers srl, Italy

CLINICAL PHARMACOLOGY & THERAPEUTICS 95, 1389–1396, 2010 IF 7,0

Role of RAS Inhibition in the Regulation of Cu/Zn-SOD in the Cardiac and Peripheral Arterial Beds in Humans

G.M. Kuster[1,2], F. Nietlispach[2], W. Kiowski[3], R. Schindler[2], A. Bernheim[2], P. Schuetz[4], B. Mueller[5], N. G. Morgenthaler[6], F. Rüter[7], W. Riesen[8], H Rickli[9] and H. P. Brunner-La Rocca[2,10]

Abstract:
Inhibition of the renin–angiotensin system (RAS) improves hemodynamics and may ameliorate oxidative stress in heart failure (HF). Through activation of nicotinamide adenine dinucleotide phosphate oxidase, angiotensin II induces superoxide, which is primarily cleared by cytosolic copper–zinc superoxide dismutase (Cu/Zn-SOD). We examined the interdependency of hemodynamics and levels of Cu/Zn-SOD and oxidized low-density lipoprotein (oxLDL) in HF patients, using a randomized, double-blinded, crossover design to compare (i) the outcomes of single-agent therapy with either benazepril or valsartan alone vs. the combination thereof and (ii) the outcome of single-agent treatment with benazepril vs. single-agent treatment with valsartan. After each treatment, arterial (ART) and coronary sinus (CS) blood samples were collected. Cu/Zn-SOD and oxLDL levels were higher in CS samples than in ART samples. Furthermore, patients under combined treatment exhibited the highest CS levels of Cu/Zn-SOD, whereas there was no significant difference between the groups on either benazepril or valsartan alone. This finding suggests an augmentation of the cardiac antioxidative potential under more complete RAS inhibition. Cu/Zn-SOD and oxLDL levels correlated with measures of afterload rather than preload, which in turn suggests a beneficial effect of afterload reduction on oxidative stress in HF.

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Haematologica 95, 1389–1396, 2010 IF 6,4

Mannose-binding lectin levels and major infections in a cohort of very long-term survivors after allogeneic stem cell transplantation

M. Osthoff[1], A. Rovó[2], M. Stern[2], D. Danner[1], A. Gratwohl[2], A. Tichelli[2] and M. Trendelenburg[1]

Abstract:

Background: Life-threatening infections are a major cause of death after allogeneic stem cell transplantation. Complement Mannose-binding lectin is a key component of innate immunity. Functional deficiency of mannose-binding lectin due to genetic polymorphism is frequent. Previous reports showed conflicting results with respect to the influence of functional mannose-binding lectin deficiency on infectious risk after allogeneic stem cell transplantation. The aim of this study was to clarify the impact of low mannose-binding lectin levels on infectious risk in a unique cohort of very long-term survivors after stem cell transplantation.

Design and Methods: Incidence of major infections was evaluable in 43 out of 44 very long-term survivors (over ten years) and studied retrospectively in relation to mannose-binding lectin serum concentrations.

Results: Recipients with mannose-binding lectin levels below 1,000 ng/mL were at increased risk to suffer from one or more major infections (P=0.002) during entire follow up. Infectious susceptibility was increased after neutrophil recovery, particularly until 24 months (Hazard Ratio 3.4) with sustained effects afterwards (Hazard Ratio 2.9). Mannose-binding lectin serum concentrations below 1,000 ng/mL were independently associated with major infections after neutrophil recovery (P=0.009). In subgroup analyses occurrence of severe herpes virus infections in particular was associated with significantly lower mannose-binding lectin levels (P=0.02).

Conclusions: Our findings indicate that low mannose-binding lectin levels may predict markedly increased susceptibility to severe infections with sustained effects even late after allogeneic stem cell transplantation. Determinations of mannose-binding lectin status should therefore be included into pre-transplantation risk assessment.

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American Journal of Transplantation | American Journal of Transplantation | 9, 136–146, 2010 IF 6.4

BK Virus in Solid Organ Transplant Recipients

H. H. Hirsch[1,2], P. Randhawa[3] and the AST Infectious Diseases Community of Practice

Abstract:
The human polyomavirus BK (BKV) is linked to two major complications in transplant recipients, polyomavirus-associated nephropathy (PyVAN) (1–4) and polyomavirus-associated hemorrhagic cystitis (PyVHC) (5,6). PyVAN and PyVHC have been encountered in a variety of immunodeficient patients (7,8), but most cases of PyVAN arise in kidney transplant patients at rates of 1–10%, while PyVHC preferentially affects allogeneic hematopoietic stem cell transplant patients at rates of 5–15% (7,9). BKV has been less frequently associated with other pathologies, such as ureteric stenosis, pneumonitis, hemophagocytic syndrome, encephalitis, retinitis, multiorgan failure and polyomavirus-associated multifocal leukoencephalopathy (PyVML) (10–12), a complication of the central nervous system mostly caused by the closely related polyomavirus JC (JCV) (13). The objective of this section is to update previous recommendations (14) regarding diagnosis and management of BKV replication and PyVAN in solid organ transplantation (SOT) using the grading proposed by Gross et al. (15).

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American Journal of Pathology | 177, 829–839, 2010 IF5,7

Progressive Secondary Neurodegeneration and Microcalcification Co-Occur in Osteopontin-Deficient Mice

W. Maetzler[1], D. Berg[1], C. Funke[2], F. Sandmann[1], H. Stünitz, C. Maetzler and C. Nitsch

Abstract:
In the brain, osteopontin (OPN) may function in a variety of pathological conditions, including neurodegeneration, microcalcification, and inflammation. In this study, we addressed the role of OPN in primary and secondary neurodegeneration, microcalcification, and inflammation after an excitotoxic lesion by examining OPN knock-out (KO) mice. Two, four, and ten weeks after injection of the glutamate analogue ibotenate into the corticostriatal boundary, the brains of 12 mice per survival time and strain were evaluated. OPN was detectable in neuron-shaped cells, in microglia, and at the surface of dense calcium deposits. At this primary lesion site, although the glial reaction was attenuated in OPN-KO mice, lesion size and presence of microcalcification were comparable between OPN-KO and wild-type mice. In contrast, secondary neurodegeneration at the thalamus was more prominent in OPN-KO mice, and this difference increased over time. This was paralleled by a dramatic rise in the regional extent of dense microcalcification. Despite these differences, the numbers of glial cells did not significantly differ between the two strains. This study demonstrates for the first time a genetic model with co-occurrence of neurodegeneration and microcalcification, mediated by the lack of OPN, and suggests a basic involvement of OPN action in these conditions. In the case of secondary retrograde or transneuronal degeneration, OPN may have a protective role as intracellular actor.

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The Journal of Biological Chemistry doi/10.1074/jbc.M110.126748, 2010 IF 5,3

Ectosomes Released by Polymorphonuclear Neutrophils Induce a MerTK-Dependent Anti-Inflammatory Pathway in Macrophages

C. Eken*, P. J. Martin, S. Sadallah, S. Treves, M. Schaller and J. A. Schifferli

Abstract:
At the earliest stage of activation, human polymorphonuclear neutrophils release vesicles derived directly from the cell surface. These vesicles, called ectosomes (PMN-Ect), expose phosphatidylserine in the outer membrane leaflet. They inhibit the inflammatory response of human monocyte-derived macrophages and dendritic cells to zymosan A (ZymA) and LPS, and induce TGF-β1 release, suggesting a reprogramming towards a tolerogenic phenotype. The receptors and signaling pathways involved have not yet been defined. Here, we demonstrated that PMN-Ect interfered with ZymA activation of macrophages via inhibition of NFκB p65 phosphorylation and NFκB translocation. Mer receptor tyrosine kinase (MerTK) and phosphatidylinositol 3 kinase (PI3K) / Akt pathway played a key role in this immunomodulatory effect as shown by using specific MerTK blocking antibodies, and PI3K inhibitors LY294002 and wortmannin. As a result, PMN-Ect reduced the transcription of many proinflammatory genes in ZymA activated macrophages. In sum, PMN-Ect interacted with the macrophages by an activation of the Mer pathway responsible for down-modulation of the proinflammatory signals generated by ZymA.

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British Journal of Pharmacology BJP BRITISH JOURNAL OF PHARMACOLOGY 161, 393–404, 2010 IF 5,2

Effects of drug interactions on biotransformation and antiplatelet effect of clopidogrel *in vitro*

A. Zahno[1], K. Brecht[1], M. Bodmer[1], D. Bur[2], D. A . Tsakiris[3] and S. Krähenbühl[1]

Abstract:
Background and purpose: The conversion of clopidogrel to its active metabolite, R-130964, is a two-step cytochrome P450 (CYP)-dependent process. The current investigations were performed to characterize *in vitro* the effects of different CYP inhibitors on the biotransformation and on the antiplatelet effect of clopidogrel.

Experimental approach: Clopidogrel biotransformation was studied using human liver microsomes (HLM) or specific CYPs and platelet aggregation using human platelets activated with ADP.

Key results experiments: using HLM or specific CYPs (3A4, 2C19) revealed that at clopidogrel concentrations >10 μM, CYP3A4 was primarily responsible for clopidogrel biotransformation. At a clopidogrel concentration of 40 μM, ketoconazole showed the strongest inhibitory effect on clopidogrel biotransformation and clopidogrel-associated inhibition of platelet aggregation with IC_{50} values of 0.03 ± 0.07 μM and 0.55 ± 0.06 μM respectively. Clarithromycin, another CYP3A4 inhibitor, impaired clopidogrel biotransformation and antiplatelet activity almost as effectively as ketoconazole. The CYP3A4 substrates atorvastatin and simvastatin both inhibited clopidogrel biotransformation and antiplatelet activity, less potently than ketoconazole. In contrast, pravastatin showed no inhibitory effect. As clopidogrel itself inhibited CYP2C19 at concentrations >10 μM, the CYP2C19 inhibitor lansozprazole affected clopidogrel biotransformation only at clopidogrel concentrations ≤10 μM. The carboxylate metabolite of clopidogrel was not a CYP substrate and did not affect platelet aggregation.

Conclusions and implications: At clopidogrel concentrations >10 μM, CYP3A4 is mainly responsible for clopidogrel biotransformation, whereas CYP2C19 contributes only at clopidogrel concentrations ≤10 μM. CYP2C19 inhibition by clopidogrel at concentrations >10 μM may explain the conflicting results between *in vitro* and *in vivo* investigations regarding drug interactions with clopidogrel.

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European Journal of Immunology | European Journal of Immunology | 40, 3268–3279, 2010 | IF 5,2

Invariant natural killer T cells: Linking inflammation and neovascularization in human atherosclerosis

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Abstract:

Atherosclerosis, a chronic inflammatory lipid storage disease of large arteries, is complicated by cardiovascular events usually precipitated by plaque rupture or erosion. Inflammation participates in lesion progression and plaque rupture. Identification of leukocyte populations involved in plaque destabilization is important for effective prevention of cardiovascular events. This study investigates CD1d-expressing cells and invariant NKT cells (iNKT) in human arterial tissue, their correlation with disease severity and symptoms, and potential mechanisms for their involvement in plaque formation and/or destabilization. CD1d-expressing cells were present in advanced plaques in patients who suffered from cardiovascular events in the past and were most abundant in plaques with ectopic neovascularization. Confocal microscopy detected iNKT cells in plaques, and plaque-derived iNKT cell lines promptly produced proinflammatory cytokines when stimulated by CD1d-expressing APC-presenting α-galactosylceramide lipid antigen. Furthermore, iNKT cells were diminished in the circulating blood of patients with symptomatic atherosclerosis. Activated iNKT cell-derived culture supernatants showed angiogenic activity in a human microvascular endothelial cell line HMEC-1-spheroid model of in vitro angiogenesis and strongly activated human microvascular endothelial cell line HMEC-1 migration. This functional activity was ascribed to IL-8 released by iNKT cells upon lipid recognition. These findings introduce iNKT cells as novel cellular candidates promoting plaque neovascularization and destabilization in human atherosclerosis.

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Journal of Virology | Journal of Virology | 48, 10448–10456, 2010 | IF 5,1

Rearranged JC Virus Noncoding Control Regions Found in Progressive Multifocal Leukoencephalopathy Patient Samples Increase Virus Early Gene Expression and Replication Rate

R. Gosert[1], P. Kardas[1], E. O. Major[2] and H. H. Hirsch[1,3]

Abstract:

Polyomavirus JC (JCV) infects 60% of the general population, followed by asymptomatic urinary shedding in 20%. In patients with pronounced immunodeficiency, including HIV/AIDS, JCV can cause progressive multifocal leukoencephalopathy (PML), a devastating brain disease of high mortality. While JCV in the urine of healthy people has a linear noncoding control region called the archetype NCCR (*at*-NCCR), JCV in brain and cerebrospinal fluid (CSF) of PML patients bear rearranged NCCRs (*rr*-NCCRs). Although JCV NCCR rearrangements are deemed pathognomonic for PML, their role as a viral determinant is unclear. We sequenced JCV NCCRs found in CSF of eight HIV/AIDS patients newly diagnosed with PML and analyzed their effect on early and late gene expression using a bidirectional reporter vector recapitulating the circular polyomavirus early and late gene organization. The *rr*-NCCR sequences were highly diverse, but all increased viral early reporter gene expression in progenitor-derived astrocytes, glia-derived cells, and human kidney compared to the expression levels with the *at*-NCCR. The expression of simian virus 40 (SV40) large T antigen or HIV Tat expression in *trans* was associated with a strong increase of *at*-NCCR-controlled early gene expression, while *rr*-NCCRs were less responsive. The insertion of rr-NCCRs into the JCV genome backbone revealed higher viral replication rates for *rr*-NCCR compared to those of the at-NCCR JCV in human progenitor-derived astrocytes or glia cells, which was abrogated in SV40 large T-expressing COS-7 cells. We conclude that naturally occurring JCV *rr*-NCCR variants from PML patients confer increased early gene expression and higher replication rates compared to those of *at*-NCCR JCV and thereby increase cytopathology.

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Antimicrobial Agents and Chemotherapy 54, 4714–4722, 2010 IF 4,8

1-*O*-Hexadecyloxypropyl Cidofovir (CMX001) Effectively Inhibits Polyomavirus BK Replication in Primary Human Renal Tubular Epithelial Cells

C. Hanssen Rinaldo[1], R. Gosert[2], E. Bernhoff[1], S. Finstad[1] and H. H. Hirsch[2,3]

Abstract:
Antiviral drugs for treating polyomavirus BK (BKV) replication in polyomavirus-associated nephropathy or hemorrhagic cystitis are of considerable clinical interest. Unlike cidofovir, the lipid conjugate 1-O-hexadecyloxypropyl cidofovir (CMX001) is orally available and has not caused detectable nephrotoxicity in rodent models or human studies to date. Primary human renal proximal tubular epithelial cells were infected with BKV-Dunlop, and CMX001 was added 2 h postinfection (hpi). The intracellular and extracellular BKV DNA load was determined by quantitative PCR. Viral gene expression was examined by quantitative reverse transcription-PCR, Western blotting, and immunofluorescence microscopy. We also examined host cell viability, proliferation, metabolic activity, and DNA replication. The titration of CMX001 identified 0.31 μM as the 90% effective concentration (EC90) for reducing the extracellular BKV load at 72 hpi. BKV large T antigen mRNA and protein expression was unaffected at 24 hpi, but the intracellular BKV genome was reduced by 90% at 48 hpi. Late gene expression was reduced by 70 and 90% at 48 and 72 hpi, respectively. Comparisons of CMX001 and cidofovir EC90s from 24 to 96 hpi demonstrated that CMX001 had a more rapid and enduring effect on BKV DNA and infectious progeny at 96 hpi than cidofovir. CMX001 at 0.31 μM had little effect on overall cell metabolism but reduced bromodeoxyuridine incorporation and host cell proliferation by 20 to 30%, while BKV infection increased cell proliferation in both rapidly dividing and near-confluent cultures. We conclude that CMX001 inhibits BKV replication with a longer-lasting effect than cidofovir at 400x lower levels, with fewer side effects on relevant host cells in vitro.

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Tissue Engineering Part A **Tissue Engineering** 16, 2419–2427, 2010 IF 4,5

A Survey on Cellular and Engineered Tissue Therapies in Europe in 2008

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Abstract:
Cellular therapy is an evolving investigational treatment modality in regenerative medicine, but little published information is available on its current use. Starting from the established European group for Blood and Marrow Transplantation activity survey on hematopoietic stem cell transplantation, a joint committee of four major scientific organizations made a coordinated attempt to collect detailed information in Europe for the year 2008. Thirty-three teams from 16 countries reported data on 656 patients to a "novel cellular therapy" survey, which were combined to additional 384 records reported to the standard European group for Blood and Marrow Transplantation survey. Indications were cardiovascular (29%; 100% autologous), musculoskeletal (18%; 97% autologous), neurological (9%; 39% autologous), epithelial/parenchymal (9%; 18% autologous), autoimmune diseases (12%; 77% autologous), or graft-versus-host disease (23%; 13% autologous). Reported cell types were hematopoietic stem cells (39%), mesenchymal stromal cells (47%), chondrocytes (5%), keratinocytes (7%), myoblasts (2%), and others (1%). In 51% of the grafts, cells were delivered after expansion; in 4% of the cases, cells were transduced. Cells were delivered intravenously (31%), intraorgan (45%), on a membrane or gel (14%), or using three-dimensional scaffolds (10%). This data collection platform is expected to capture and foresee trends for novel cellular therapies in Europe, and warrants further consolidation and extension.

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Arthritis Research & Therapy doi:10.1186/ar2942, 2010 IF 4,3

Anabolic and catabolic responses of human articular chondrocytes to varying oxygen percentages

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Abstract:

Introduction: Oxygen is a critical parameter proposed to modulate the functions of chondrocytes ex-vivo as well as in damaged joints. This article investigates the effect of low (more physiological) oxygen percentage on the biosynthetic and catabolic activity of human articular chondrocytes (HAC) at different phases of in vitro culture.

Methods: HAC expanded in monolayer were cultured in pellets for two weeks (Phase I) or up to an additional two weeks (Phase II). In each Phase, cells were exposed to 19% or 5% oxygen. Resulting tissues and culture media were assessed to determine amounts of produced/released proteoglycans and collagens, metalloproteinases (MMPs), collagen degradation products and collagen fibril organization using biochemical, (immuno)-histochemical, gene expression and scanning electron microscopy analyses. In specific experiments, the hypoxia-inducible factor-1α (HIF-1α) inhibitor cadmium chloride was supplemented in the culture medium to assess the involvement of this pathway.

Results: Independent from the oxygen percentage during expansion, HAC cultured at 5% O2 (vs 19% O2) during Phase I accumulated higher amounts of glycosaminoglycans and type II collagen and expressed reduced levels of MMP-1 and MMP-13 mRNA and protein. Switching to 19% oxygen during Phase II resulted in reduced synthesis of proteoglycan and collagen, increased release of MMPs, accumulation of type II collagen fragments and higher branching of collagen fibrils. In contrast, reducing O2 during Phase II resulted in increased proteoglycan and type II collagen synthesis and reduced expression and release of MMP-13 mRNA and protein. Supplementation of cadmium chloride during differentiation culture at 5% O2 drastically reduced the up-regulation of type II collagen and the down-regulation of MMP-1 mRNA.

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Biochemical Pharmacology 80, 1736–1745, 2010 IF 4,2

Mechanisms of metformin action on glucose transport and metabolism in human adipocytes

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Abstract:

The mechanisms of metformin effects on glucose transport and metabolism were investigated in human adipocytes. Human preadipocytes obtained from surgical biopsies were differentiated in vitro into adipocytes and the effects of metformin on glucose uptake, glucose oxidation and the involved signaling pathways were analyzed. Metformin (1 mM, 24 h) increased glucose uptake 2.3 ± 0.2-fold ($p < 0.001$ vs. basal) in human adipocytes, without altering cell viability and oxygen consumption. Metformin did not alter GLUT-1 mRNA expression and protein content but increased GLUT-4 mRNA expression and cellular protein content, leading to increased GLUT-4 protein content in the plasma membrane. Neither basal nor insulin-induced phosphorylation of Akt at Ser-473 and AS160 (Akt substrate of 160 kDa) at Thr-642 were enhanced by metformin. Suppression of metformin-induced AMP-activated protein kinase (AMPK) activity by AMPKα1 silencing, however, reduced metformin-associated GLUT-4 expression and stimulation of glucose uptake. In addition, metformin induced glucose oxidation. In conclusion, activation of AMPKα1 without impairment of cell respiration is crucial for metformin-mediated increase in GLUT-4 protein content and glucose uptake in human adipocytes.

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Journal of the American Academy of Dermatology doi:10.1016/j.jaad.2009.11.013, 2010 IF 4,1

The immigration delay disease: Adermatoglyphia–inherited absence of epidermal ridges

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Abstract:
In the digital age, personal identification by fingerprints (epidermal ridges) has become more frequent and is often required for biometric passports. The more fingerprints are analyzed, the more variants in their formation are documented. Individuals completely missing fingerprints as an isolated finding are extremely rare. Only 4 kindreds have been described to date, with additional clinical features in most cases. We describe a female patient with missing epidermal ridges on the fingers, palms, toes, and soles as an isolated feature. Absent fingerprints, or adermatoglyphia, were inherited over 4 generations of her family in an autosomal dominant fashion. We present the clinical features of the index patient, and compare the case with previous reports in the literature. Because of problems in personal identification, this embryologic malformation caused the patient significant difficulties when traveling to other countries, which is why we name it the immigration delay disease.

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Nephrology Dialysis Transplantation 10.1093/ndt/gfq558, 2010 IF 3,3

Anti-C1q autoantibodies do not correlate with the occurrence or severity of experimental lupus nephritis

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Abstract:

Background:
In systemic lupus erythematosus patients, a strong association between the occurrence of antibodies against complement C1q (anti-C1q) and lupus nephritis can be observed. However, the predictive value of anti-C1q titres for a renal flare remains to be determined. Increasing titres of anti-C1q before the occurrence of clinical apparent nephritis might not only serve as a clinical parameter but also indicate a direct pathogenic mechanism of anti-C1q.

Methods:
The aim of this study was to analyse the occurrence of anti-C1q before the onset of experimental lupus nephritis in MRL/MpJ +/+ mice and to correlate anti-C1q titres with the type and severity of glomerulonephritis (GN) developing at advanced age.

Results: As judged by a number of morphological and immunological analyses, GN in MRL/MpJ +/+ mice resembled human lupus nephritis and occurred in variable degrees of severity. We also observed an abundant and early presence of anti-C1q. However, anti-C1q neither correlated with overall survival nor with any histological marker of severity of GN.

Conclusions:
The absence of a correlation between the presence of anti-C1q and the occurrence of experimental lupus nephritis contradicts the hypothesis that anti-C1q are pathogenic. However, different pathogenic mechanisms of experimental lupus nephritis and human proliferative lupus nephritis cannot be excluded.

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Neuroscience NEUROSCIENCE 170, 361–371, 2010 IF 3,2

Preservation of transendothelial glucose transporter 1 and P-glycoprotein transporters in a cortical slice culture model of the blood–brain barrier

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Abstract:
A variety of neurological diseases are characterized by disturbances of the blood–brain barrier (BBB) and its transporters. We recently introduced fibroblast growth factor treated cortical organotypic slice cultures of mice as a model for in vitro studies of the blood–brain barrier and have now further characterized the maintenance and function of transport-proteins typically expressed in the endothelium of cerebral blood vessels. The glucose transporter GLUT-1 is present in blood vessels of slice cultures derived from postnatal day 4 to 21 mice after 3 days *in vitro*. The endothelial multidrug resistance P-glycoprotein (P-gp) which is involved in the control of pharmacological substance transport across the blood–brain barrier is also maintained in blood vessels, most prominently in slice cultures derived from postnatal day 14 and 21 mice. To assess P-gp function, we tested rhodamine 123 transport in presence or absence of the P-gp inhibitor verapamil. Rhodamine 123-fluorescence accumulated rapidly in the vascular lumen both in acute slices and in slices cultured for 3 days *in vitro*. Our results provide evidence that endothelial transporters and their functional properties can be maintained in organotypic cortical slices cultures, thus making it an attractive model system for the study of the blood–brain barrier.

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Journal of Neuroimmunology 225, 184–189, 2010 IF 2,8

Gene expression profiling in nerve biopsy of vasculitic neuropathy

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Abstract:
To investigate molecular mechanisms of peripheral nerve vasculitis, gene expression patterns in archived frozen sural nerve biopsies from patients with vasculitic neuropathy were compared to control nerves by DNA microarray technology. There was a striking upregulation of mRNA of genes involved in immune system processes. Of special interest was the activation of immunoglobulin genes, such as IGLJ3, IGHG3, IGKC, and IGL, and of several chemokines, such as CXCL9 or CCR2. Genes involved in vascular proliferation or remodelling such as CXC31 and AIF were also upregulated. Among the downregulated genes were the Krüppel-Like Transcription Factors KLF2, KLF4 and the nuclear orphan receptor NR4A1 genes known to be involved in endothelial cell activation. Thus, this gene expression profile analysis revealed that in peripheral nerve vasculitis a prominent activation of immune response related genes as well as genes involved in vascular proliferation is taken place, while genes inhibiting endothelial cell activation are down regulated. These data point to interesting mechanistic clues to the molecular pathogenesis of vasculitic neuropathies.

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Dermatology 221, 135–136, 2010 IF 2,7

Spontaneous Fading of Reticular Pigmentation in Naegeli-Franceschetti- Jadassohn Syndrome

P. H. Itin[1] and B. Burger[1,2]

Abstract:
Naegeli-Franceschetti- Jadassohn (NFJ) syndrome is a rare symptom complex out of the spectrum of ectodermal dysplasia that affects the skin and its pigmentation, sweat glands, nails, hair and teeth (OMIM 161000). NFJ syndrome is inherited in an autosomal dominant fashion and is caused by mutations in the KRT14 gene localized on chromosome 17q11.2–17q21. The disease is allelic to dermatopathia pigmentosa reticularis [1]. Prevalence is roughly estimated to be 1 in 3 million.

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Tissue Engineering Part C **Tissue Engineering** 16, 11–21, 2010 IF 2,3

In Vitro and In Vivo Validation of Human and Goat Chondrocyte Labeling by Green Fluorescent Protein Lentivirus Transduction

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Abstract:
We investigated whether human articular chondrocytes can be labeled efficiently and for long-term with a green fluorescent protein (GFP) lentivirus and whether the viral transduction would influence cell proliferation and tissue-forming capacity. The method was then applied to track goat articular chondrocytes after autologous implantation in cartilage defects. Expression of GFP in transduced chondrocytes was detected cytofluorimetrically and immunohistochemically. Chondrogenic capacity of chondrocytes was assessed by Safranin-O staining, immunostaining for type II collagen, and glycosaminoglycan content. Human articular chondrocytes were efficiently transduced with GFP lentivirus (73.4±0.5% at passage 1) and maintained the expression of GFP up to 22 weeks of *in vitro* culture after transduction. Upon implantation in nude mice, 12 weeks after transduction, the percentage of labeled cells (73.6±3.3%) was similar to the initial one. Importantly, viral transduction of chondrocytes did not affect the cell proliferation rate, chondrogenic differentiation, or tissue-forming capacity, either *in vitro* or *in vivo*. Goat articular chondrocytes were also efficiently transduced with GFP lentivirus (78.3±3.2%) and maintained the expression of GFP in the reparative tissue after orthotopic implantation. This study demonstrates the feasibility of efficient and relatively long-term labeling of human chondrocytes for co-culture on integration studies, and indicates the potential of this stable labeling technique for tracking animal chondrocytes for in cartilage repair studies.

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European Journal of Dermatology EJD EUROPEAN JOURNAL OF DERMATOLOGY 20, 693–697, 2010 IF 2,2

Buschke-Ollendorff syndrome in a three-generation family: Influence of a novel *LEMD3* mutation to tropoelastin expression

B. Burger[1,2], D. Hershkovitz[3], M. Indelman[4], M. Kovac[5], J. Galambos[1], P. Haeusermann[1], E. Sprecher[6] and P. H Itin[1]

Abstract:
Buschke-Ollendorff syndrome refers to the concomitant occurrence of connective tissue nevi, composed of elastic fibers in most cases, with osteopoikilosis. This autosomal dominant inherited disorder is caused by mutations in the gene *LEMD3* on chromosome 12q14, which induces a rather heterogeneous clinical phenotype. Here, we report on the most proximal germline mutation found to date in the *LEMD3* gene, p.Val94fs, in a three-generation Swiss family. Quantitative RNA analyses in affected and non-affected skin tissue from the proband demonstrate a comparable nonsense-mediated decay of mutant *LEMD3* mRNA in both tissues\; however, different levels of tropoelastin expression suggest that additional factors are involved in the development of the cutaneous lesions.

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Graefe's Archive for Clinical and Experimental Ophthalmology 248, 1273–1278, 2010 IF 2,1

Primary cell culture of meningothelial cells—a new model to study the arachnoid in glaucomatous optic neuropathy

X. Xin[1,3], B. Fan[1,4], H. E. Killer[1,2], A. Neutzner[1], J. Flammer[1] and P. Meyer[1]

Abstract:
Background: In a previous report, we found that the occurrence and amount of meningothelial cell nests in the subarachnoid space are significantly increased in glaucomatous optic nerves compared to normals. In order to allow research into the role of meningothelial cells during diseases of the optic nerve, an in vitro model is necessary. For this purpose, we developed a culture method for porcine meningothelial cells from the arachnoid layer covering the optic nerve.
Methods: Meningothelial cells were scraped from the arachnoid layer of porcine optic nerves and cultured for 2–3 weeks until the cells formed a monolayer. To eliminate contaminating fibroblasts from the culture, cells were negatively selected using magnetic anti-fibroblast beads after the first passage. Cells were detached using 0.05% Trypsin-EDTA, incubated with anti-fibroblast beads, separated using a magnetic column and the flow-through was collected. The purified primary meningothelial cells were characterized by electron microscopy and immunocytochemistry using anti-glial fibrillary acidic protein (GFAP) and anti-keratan sulfate antibodies.
Results: Primary cells grew out after dissection and formed a monolayer within 2–3 weeks, which was composed of two morphologically different cell types, flattened cells with round nuclei and fibroblast-like cells with long processes. The fibroblast-like cells in the culture could be labelled and selected using anti-fibroblast microbeads. The second cell type did not bind to the anti-fibroblast beads, and upon immunocytochemistry showed a marked expression of both GFAP and keratan sulphate. In addition, examination of these cells by electron microscopy revealed morphological characteristics of meningothelial cells, including hemidesmosomes and cytoplasmatic filaments.
Conclusions: The technique described in this paper for the primary culture of meningothelial cells from the subarachnoid space of the optic nerve and using magnetic beads for the removal of fibroblasts is effective in obtaining a highly enriched meningothelial cell culture.

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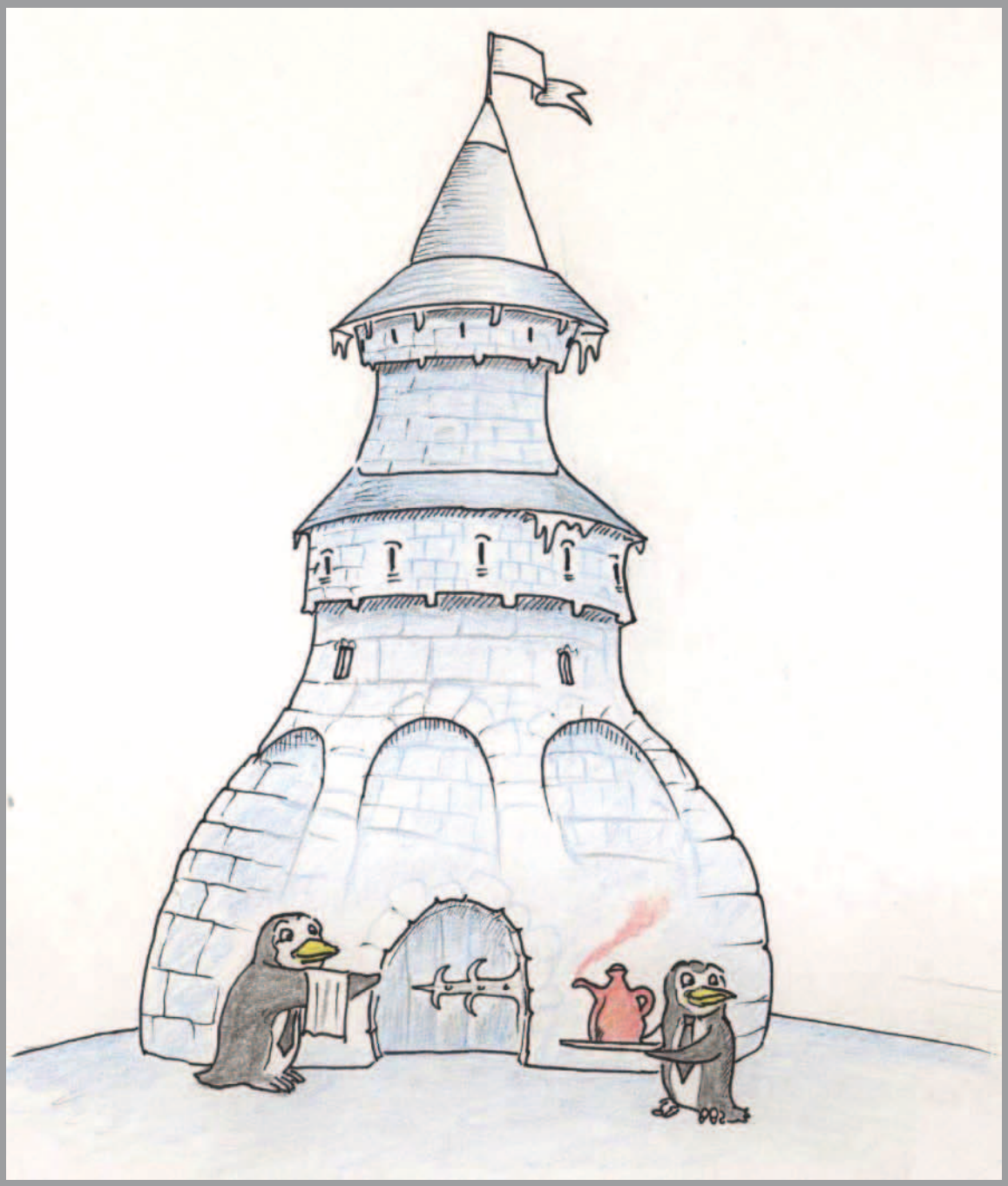


Thorsten Fritzius, Ice castle

Dissertationen

Seit dem 21. Oktober 2010 darf sich **Emmanouil Kyriakakis** von der Forschungsgruppe Signal Transduction (Departement Biomedizin USB) Herr Dr. nennen. Er befasste sich in seiner Dissertation mit dem Thema: „Travelling to Rome: inflammation, endoplasmic reticulum stress and angiogenesis during atherosclerotic development".

Habilitationen

Venia docendi an Andrea Barbero, Otmar Pfister und Rainer Gosert

Die Regenz der Universität Basel hat in ihrer Sitzung am 10. November 2010 Andrea Barbero von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin USB) die Venia docendi für Experimentelle Medizin, Otmar Pfister von der Forschungsgruppe Myocardial Research (Departement Biomedizin USB) für Kardiologie und Rainer Gosert von der Forschungsgruppe Transplantation Virology (Institut für Mikrobiologie) für Virologie erteilt. Sie sind nun befugt, den Titel eines Privatdozenten zu führen.

Beförderungen

Daniela Finke wird Ordinaria für Molekulare Medizin in der Pädiatrie

Daniela Finke von der Forschungsgruppe Developmental Immunology (Institut für Biochemie und Genetik) wurde zur Ordinaria für Molekulare Medizin in der Pädiatrie an der Medizinischen Fakultät der Universität Basel gewählt. Gleichzeitig ist sie zur Leiterin Forschung am Universitätskinderspital beider Basel (UKBB) ernannt worden.

Auszeichnungen

Posterpreis an Ulrike Hopfer und Sebastien Löffler

Am BioValley Science Day sind Ulrike Hopfer von der Forschungsgruppe Tumor Biology (Institut für Biochemie und Genetik) und Sebastien Löffler von der Forschungsgruppe Pediatric Immunology (Institut für Biochemie und Genetik) mit dem mit 1'700 CHF dotierten BioValley Poster Award ausgezeichnet worden.

Herzliche Gratulation an alle!

DEPARTEMENT BIOMEDIZIN USB

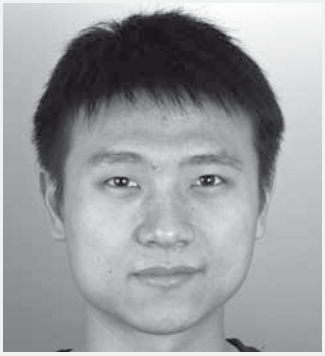
Fengfeng Cai
Gyn. Oncology

Artem Kalinichenko
Exp. Immunology

Martina Mitterhuber
Cardiovasc. Mol. Imaging

Karin Schmitter
Immunotherapy

Lena Wyss
Transplantation Immunology



Lei Fang
Gyn. Oncology

Arun Cumpelik
Immunonephrology

Andrea Felser
Clin. Pharmacology

Angeliki Thanasopoulou
Childhood Leukemia

Matteo Centola
Tissue Engineering

Bonnie Chen
Gyn. Oncology

INSTITUT FÜR BIOCHEMIE UND GENETIK

Maren Diepenbruck
Tumor Biology

INSTITUT FÜR PHYSIOLOGIE

Ruth Werthmann
Synaptic Plasticity

INSTITUT FÜR ANATOMIE

Amandine Duchesne
Developmental Genetics

Sandro Nuciforo
Developmental Genetics

Patric Schlenker
Developmental Genetics

Paola Valdivieso
Developmental Genetics

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Piotr Kardas
Transplantation Virology

Jacqueline Glaus
Serology

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN USB

Jan Rechsteiner, Tissue Engineering
Fabrizio Vinzens, Tissue Engineering
Agata Gorecka, Tissue Engineering
San Pun, Neuromuscular Research
Perrine Castets,
Neuromuscular Research

INSTITUT FÜR BIOCHEMIE UND GENETIK

Rafael Fritz,
Cell Migration and Neuritogenesis
Oliver Wirz, Developmental and Molecular Immunology
Natko Nuber, Developmental and Molecular Immunology
Alessandra Vigano, Developmental and Molecular Immunology

INSTITUT FÜR MEDIZINISCHE MIKRO-BIOLOGIE

Gabriele Tusch, Serology

INSTITUT FÜR PHYSIOLOGIE

Anja Harmeier, Synaptic Plasticity

Interne Wechsel:

DEPARTEMENT BIOMEDIZIN USB

Evangelos Panopoulos,
Oncology Surgery

Congratulations

Das DBM gratuliert ganz herzlich!

Kiara Mollé-Grisouard
Geboren am 2.9.2010

Elisa Jacquier
Geboren am 11.10.2010

Herzlich willkommen, allerseits!

Eleni Mallaun-Zahno
Geboren am 31.8.2010

Die Redaktion von DBM Facts wünscht allen ihren Leserinnen und Lesern schöne Weihnachten und ein gutes neues Jahr!

The Editorial team of DBM Facts wishes all its readers a Merry Christmas and a Happy New Year!

Zur Pensionierung von Alex N. Eberle

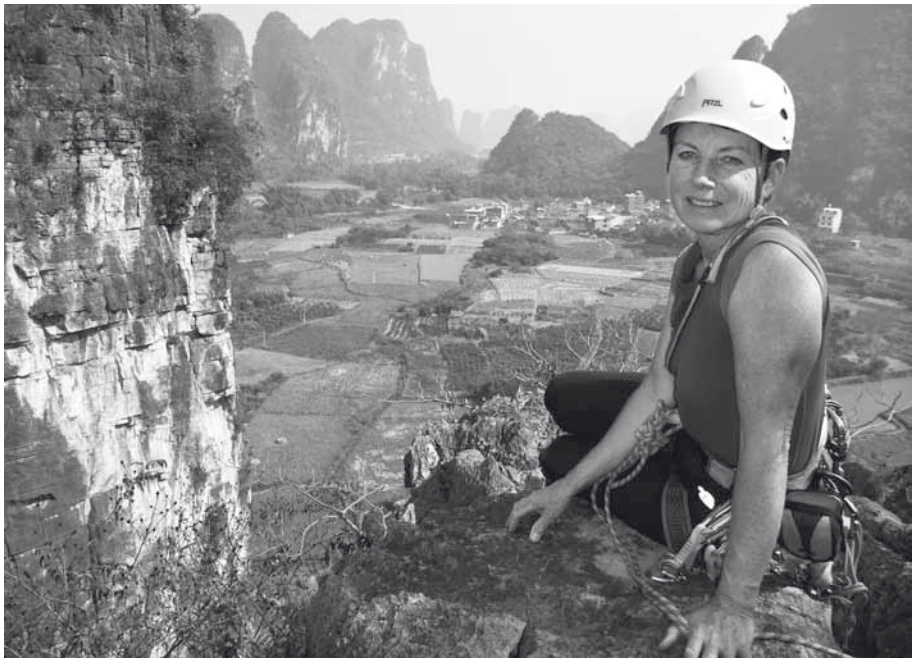
Per Jahresende verlässt Prof. Alex N. Eberle, ehemaliger Leiter des Departements Forschung (1992-1995 und 1997-2000) nach über 28 Jahren das USB. Er wird als «Vizerektor Entwicklung» weiterhin an unserer Universität tätig sein und mit dem USB in Kontakt bleiben.

Alex Eberle studierte Chemie und Biochemie an der ETH Zürich und hat sich danach in Peptidchemie und molekularer Biologie am MRC Laboratory of Molecular Biology, Cambridge (England) weitergebildet. Er kam 1982 an das Departement Forschung (DF) am damaligen Kantonsspital Basel und übernahm die Leitung eines neuen Forschungslabors für Endokrinologie. Sein Forschungsinteresse richtete sich auf die hormonelle Steuerung der Pigmentzellen der Haut (Melanozyten) und die Möglichkeit, diese Hormone gekoppelt an radioaktive Moleküle für die Therapie des «schwarzen Hautkrebses» (Melanoms) einzusetzen. Ein zweites Forschungsgebiet war die Regulation der Fettzellen (Adipozyten), mit interdisziplinären Ansätzen um die Ergebnisse für die Vorbeugung und Therapie der Adipositas anzuwenden. Als Dozent unterrichte er die Themen Pathobiochemie und Signaltransduktion. 1992 wurde Alex Eberle zum Extraordinarius in «Pathobiologie» (später umbenannt in «Experimentelle Endokrinologie») an der Medizinischen Fakultät der Universität Basel gewählt. Neben seiner Forschungstätigkeit fiel Prof. Alex Eberle durch sein strukturiertes Denken und sein ordnendes Prinzip auf und nach Weggang von Prof. Fritz Bühler 1992 wurde er Leiter des DF. Unter seiner Führung ist das DF gewachsen und hat an Autonomie gewonnen. Die Organisation und Erneuerung der Forschungsinfrastruktur und Informatik wurde zentralisiert und die Bedingungen für kompetitive Forschung wurden durch Anschaffung von Grossgeräten, die allen Forschungsgruppen zur Verfügung gestellt wurden, wesentlich verbessert. Prof. Alex Eberle war Ende der 90er Jahre auch an den Diskussionen beteiligt, die vorklinischen Institute zusammen mit dem DF zu einer Einheit zusammen zu führen, die zur Gründung des Departements für klinisch biologische Wissenschaften (DKBW) im Jahr 2000 geführt haben. Auch nach seinem Rücktritt als Leiter des DF blieb Alex Eberle interessiert an den Organisationsstrukturen. Er wurde Mitglied der universitären Planungskommission (PlaKo), zu deren Präsidenten er 2006 ernannt wurde. Seit 2009 ist Prof. Alex N. Eberle Vizerektor Entwicklung an der Universität Basel, eine Funktion, die er auch nach seinem Austritt aus dem USB weiter ausüben wird.

Mit Alex Eberle verliert das USB einen äusserst einsatzwilligen und beharrlichen Kämpfer für die universitäre Medizin, der sich stets durch Rücksichtnahme gegenüber Mitarbeitern auszeichnete und mir, als nachrückendem Leiter des Departements, ein wohlbereitetes Haus überlassen hat. Wir wünschen Dir, lieber Alex, viel Erfolg in Deiner weiteren Tätigkeit als Vizerektor Entwicklung und freuen uns auf gute Zusammenarbeit.

Radek Skoda

Auf zu neuen Gipfeln, Vreni!



Nach über dreissigjähriger Anstellung am Universitätskinderspital beider Basel verlässt Verena Jäggin ihren alten Arbeitgeber und damit das Departement Biomedizin per 31. Dezember 2010, um sich noch einmal einer neuen Herausforderung zu stellen. Nicht wie sonst, wenn sie wieder einmal von einer 7000er Bergbesteigung, einem Marathon durch die halbe Sahara oder einfach nur einer Innerschweizer Gletschertour, die für viele von uns der sportliche Höhepunkt der letzten fünf Jahre gewesen wäre, zurückgekehrt ist, sondern dieses Mal ist es beruflicher Natur. Verena zieht es nun Richtung Mattenstrasse, wo sie neu im Department of Biosystems Science and Engineering (D-BSSE), einer Abteilung der ETH Zürich, ihre langjährige Erfahrung als Facs-Operatorin einbringen wird.

Vom Beginn ihrer Tätigkeit am UKBB im Jahr 1979 bis zum Jahr 1989 pendelte Verena als Teamleiterin zwischen dem Hormonlabor und der Forschungsgruppe Endokrinologie des ehemaligen Basler Kinderspitals, in denen sie jeweils 50% ihrer Arbeitszeit verbrachte. Anschliessend wechselte sie zu 100% in die Forschungsgruppe Endokrinologie, in der sie 1992 Cheflaborantin wurde. Doch der Aktionsradius einer einzelnen Forschungsgruppe war Verena zu eng. Neue Gipfel galt es zu erklimmen und so wurde sie mit der Zeit je länger je mehr als Facs-Operatorin für das ganze Departement Ansprechpartnerin für das Cell sorting und die Flowcytometry. Im Jahr 2000 kam zu ihrem Aufgabenbereich noch die Institutszeitung DFacts, nun DBM-Facts, hinzu, die bis heute massgeblich auch Verenas Handschrift trägt.

Wie am Berg, so in der Ebene. Verena nahm es auch im Arbeitsleben sportlich. Leidenschaft, Aufopferungsbereitschaft, Verlässlichkeit, Willensstärke, bis hin zur Sturheit, die Fähigkeit, sich durchzusetzen, sich immer wieder neu zu motivieren und mit Begeisterung und Mut, neue Projekte in Angriff zu nehmen, zeichneten Verenas Tätigkeit und ihr Umgang mit uns aus.

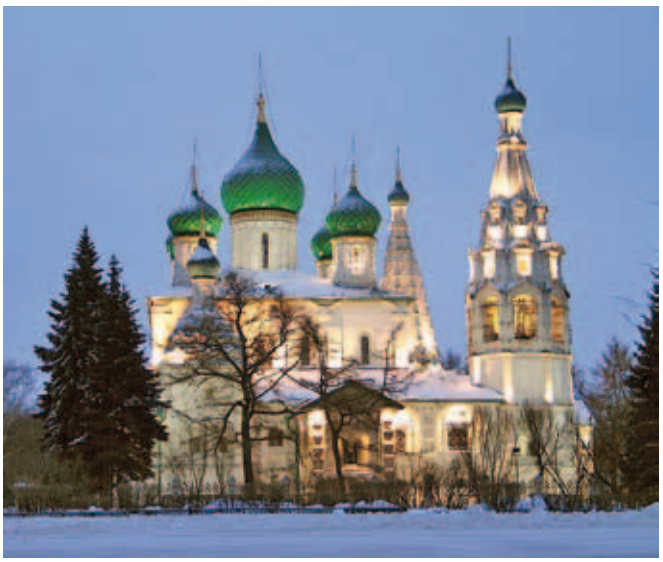
Stürmi Vreni, wir werden Deine positive Energie vermissen!

Heidi Hoyermann

Christmas in Russia

The Russian poet and Nobel prize winner Joseph Brodsky once said that if one wants to understand the key difference between Western and Eastern cultures one should look at their attitudes to two main Christian holidays. In a rationalistic and optimistic Western world it is Christmas, a celebration of the pure and simple joy of birth, which is the most important annual holiday. Russian Orthodox religion is closer to Eastern mysticism and places more emphasis on Easter, which symbolizes the miracle of resurrection and joy coming through suffering and tears. However, even while being less important in the religious sense, Christmas and New Year's Eve are still the most loved and widely celebrated feasts in Russia, and in this essay I would like to tell you how and when these celebrations are held.

The first comment people usually make when I say that I am going home for Christmas is "But you have Christmas on the wrong dates, right?" Indeed, in the Russian Orthodox church Christmas is two weeks later than in Europe. Let's see how the confusion was created and where the "wrong dates" come from. Until the XVI century Europe lived according to the Julian calendar that was introduced by Julius Caesar. The trouble with it was that the length of the calendar year did not exactly match the astronomical (solar) year and had an error of about 11 minutes which accumulated over the centuries, causing the date of Easter to gradually move away from the spring equinox. To cope with the problem the pope Gregory XIII signed a decree in 1582 introducing a new Gregorian calendar which had a slightly different day length and number of leap days to better match the solar cycle. The reform began by dropping 10 calendar days to revert to the correct date of the astronomical equinox. Russia did not follow the new system at that time and joined it only in the XX century; by that time it had to drop 13 days due to the further error accumulated in the old calendar since 1582. However, only the civil society adopted the new style and synchronized the calendar with the rest of Europe. The Orthodox church remained faithful to the old style, hence the shift in 13 days between the dates of many religious feasts including Christmas which is celebrated in Russia not on the 25th of December but on the 7th of January.



Church of Ilija the Prophet in Yaroslavl (Photo S. Tikhomirov)

Why did the Russian Orthodox church refuse to adopt the Pope's calendar? The reasons are many, including religious, political and cultural. The confrontation between Catholic and Orthodox churches started straight after the reform: the synod of the Orthodox bishops at Constantinople issued an anathema against the new calendar as falsifying true events of Christ's life as they are described in the Bible. In 1923 Russian Patriarch Tikhon tried to adopt the Gregorian calendar to synchronize the church events with the secular life in the Soviet Russia, but was forced to cancel his decree because people refused to change rituals which had lasted for generations. Also, it emerged that the Gregorian style destroyed some elements of the church calendar. For example, in the years when Easter is

late there is no room for the Peter and Paul's Fast which is important in the Orthodox tradition. So, whatever the reasons, the new style lasted for only 24 days, and now the Russian church is still 13 days behind Europe with celebrations.

I am not a religious person myself, so I am not in a position to judge whether this argument between the Orthodox and Catholic/Protestant branches of the Christianity creates any problems for the church-goers. However, other people who see Christmas simply as a main annual family feast and beautiful cultural tradition, definitely profited from the opposition, because Russians (who are always glad for a reason to party) now have four winter feasts while Europeans have only two.

We do not formally celebrate the 25th of December, but this day falls on the peak of a pre-holiday excitement with its nicely decorated streets and shop windows, shopping rush, corporate parties, searching for presents, decorating Christmas tree, making plans for the feast menu. All this, together with TV news showing feasts in Europe and the USA, with letters to and from foreign friends, marks the beginning of the holiday time.

On the 31st of December comes the main annual holiday in Russia, the New Year's Eve. This is the time when families meet together at the dinner table, drink sparkling wine, eat traditional meals like Russian Olivier salad or roasted goose with apples (see recipe), exchange presents, light fireworks in the snowy streets and wish each other all the best for the coming year.

On the 6th of January comes the Christmas Eve. In the olden days children and young people in villages gathered in little groups upon nightfall and wandered from home to home singing the "koliadki", Christmas ritual songs, under the windows and were given sweets and presents by hosts. Both the poor and the rich, and even tsars, participated in the celebrations. Christmas Eve is also a time when, according to beliefs, the dark forces are free to roam around and play bad tricks on people. All these rituals are described in a wonderful story by Nikolai Gogol "Christmas Eve" featuring witches flying on the broomstick in the night sky; the devil stealing the moon to prevent villagers from singing the koliadki; a very lazy and fat Cossack Patzuck who uses his magical powers to make dumplings jump from the plate directly into his mouth; and a village smith who is desperately in love with a beautiful girl and forces the devil to help his romantic plans.

Finally, on the 13th of January, comes the last holiday in the row, the "old New Year", i.e. the New Year eve according to the Julian calendar. While the "new New Year" is usually a day to spend together with the family at home, the "old New Year" is for going out, meeting friends and having fun at parties. On this day many Russian theatres organize the Kapustnik, literally translated as "cabbage festival". The program usually contains a mixture of jokes, sketches, well-known songs where the lyrics have been changed to tease the guests or make allusions to some recent social and political events. The scenario of the Kapustnik is only partly prepared in advance, and the main fun depends on free improvisation that makes the whole performance unique, unpredictable and, if actors are good, very funny. Originally the Kapustniks were simply informal gatherings of actors who came to big cities in winter in search for new contracts and spent evenings in little cafes, resting after a whole day's running between acting agencies, ordering the cheapest food (cabbage) and making jokes and little performances to entertain each other. Big theaters subsequently adopted

B. Kustodiev, Winter

this tradition, first organizing such informal feasts for the troupe, then making them public and using the collected money for actors in need. The most popular before the revolution were the Kapustniks at the Moscow Art Theatre headed by Stanislavsky and famous for staging Anton Chekhov's plays. The tickets for MAT Kapustniks were extremely difficult to get, and afterwards jokes and stories told at these events quickly spread over the city.

If you extend this row of holidays to the day of St.Tatjana, a patron of the Moscow State University and all Russian students, which is celebrated on the 25th of January and marks the end of the winter semester, you will see that winter feasts take the whole month. Thus, if you plan some business or scientific collaboration with Russia don't try to start it in January: most people are on holidays partying, going to theaters and concerts, lazying on the sofa in front of the TV screen with nice food and drink or skiing in Switzerland, and even those who must go to work are anyway not in a working mood.

If you happen to be in Russia at Christmas time and would like to see how this holiday is celebrated, it would be a nice idea to attend church service on the 6th of January. Even if you are not a believer, watching the colourful ceremony and listening to traditional choral music is a very interesting experience. The main service in Moscow is now held in the Cathedral of Christ the Saviour which was demolished after the revolution and recently reconstructed. True Moskovites do not like and in fact slightly despise this monstrously huge and kitsch building which dominates little streets and houses of the old city. It was built in the favourite architectural style of the ex-major and was precisely described by journalists as "Disney on anabolics". Better alternatives are the old Elokhovsky Cathedral or any of the many little churches still in the central part of the city. If you can spare a couple of days, I would recommend travelling to one of the ancient provincial towns, for example Yaroslavl which is located 250 kilometers northeast of Moscow at the confluence of the Volga and the Kotorosl rivers. Here you can experience the true Russian winter unspoiled by global warming or heavy Moscow traffic and rush. Take a stroll along the Volga embankment in complete silence violated only by snow creaking under your feet, let your eyes rest on quiet white open landscape with the only dark spots being ink-drawn silhouettes

Roasted goose with apples
1 goose
1–1 1/2 kg apples (green and sour, cut in 1/8 pieces, not peeled)
3–4 tbs sourcream, salt and pepper
Prepare the goose, staff it with apples. Sew up the vent, spread sourcream on top, sprinkle with salt and pepper and roast in the oven on the flat open baking tray for 2 hours at medium heat. Baste the bird with pan juices from time to time. During the last 1 hr – 40 min add potatoes (raw, peeled and cut in quarters) and more apple slices on the tray around the goose. Serve with red wine or, if you want to go Russian style, with sweet cranberry vodka.

River Volga in Yaroslavl (Photo D. Sirotkin)

of lime trees, visit beautiful churches, the outlines of which are brightly lit and float in the dark-blue winter sky. Also visit the local museum that has a small but brilliant collection of Russian art ranging from classical realism to modernism.

I would like to finish this article with a poem by Joseph Brodsky for whom the Christmas theme was very important and who tried to write one Nativity verse every year. I have chosen my favourite, which reflects best the anticipatory and slightly unreal atmosphere that one may sense while wandering through the cold and damp air in dark streets of old Moscow with its shimmering golden lights and black shadows of narrow passages, dying sounds of steps and voices, big snow flakes slowly falling on the pavement and feeling like icy wet stings on the lips.

And all the best to you and your families this holiday season!

Maria Filippova

CHRISTMAS BALLAD

I

There floats in an abiding gloom,
among immensities of brick,
a little boat of night: it seems
to sail through Alexander Park.
It's just a lonely streetlamp, though,
a yellow rose against the night,
for lovers strolling down below
the busy street.

II

There floats in an abiding gloom
a drone of bees: men drunk, asleep.
In the dark capital a lone
tourist takes another snap.
Now out onto Ordynka turns
a taxicab, with sickly faces;
dead men lean into the arms
of the low houses.

III

There floats in the abiding gloom
a poet in sorrow; over here
a round-faced man sells kerosene,
the sad custodian of his store.
Along a dull deserted street
an old Lothario hurries. Soon
the midnight-riding newlyweds
sail through the gloom.

IV

There floats in outer Moscow one
who swims at random to his loss,
and Jewish accents wander down
a dismal yellow flight of stairs.
From love toward unhappiness,
to New Year's Eve, to Sunday, floats
a good-time girl: she can't express
what's lost inside.

V

Cold evening floats within your eyes
and snow is fluttering on the panes
of carriages; the wind is ice
and pale, it seals your reddened palms.
Evening lights like honey seep;
the scent of halvah's everywhere,
as Christmas Eve lifts up its sweet-
meats in the air.

VI

Now drifting on a dark-blue wave
across the city's gloomy sea,
there floating by, your New Year's Eve –
as if life could restart, could be
a thing of light with each day lived
successfully, and food to eat,
– as if, life having rolled to left,
it could roll right.

(Translated by Glyn Maxwell)

ACHIEVE CLEAR MIND THROUGH YOGA

I discovered Yoga when I lived in New York City, and I immediately started to benefit from all the positive aspects of this ancient science. When most people think about Yoga, they immediately associate this word with some physical practices of stretching and stress release. Well, the Asana – the discipline of the body – is only one of the eight limbs of Yoga, and was primarily designed to facilitate the practice of Yoga – namely, the understanding and the complete mastery of the mind (Raja Yoga). Indeed, in the primary text – the Yoga Sutras (Sutra means 'thread') of Patanjali – the second Sutra gives the goal of Yoga:

Yogas citta vritti nirodhah – Yoga is the restraints of the fluctuations of the mind

Yoga is indeed meditation and is the art and science of systematically observing, accepting, understanding, and training each of the levels of ourselves, such that we can coordinate and integrate those aspects of ourselves and dwell in the direct experience of the center of consciousness. To start meditation you can 'simply' sit in an asana, in a posture that brings comfort and steadiness, and allows you to begin turning your attention inward. However, sitting in meditation can be challenging. You might feel anxious to get back to your thoughts and busy day. The mind certainly wanders very easily at the beginning; you can experience discomfort, such as your foot falling asleep, but remember that regular meditation can make your brain work better. I always think about meditation as a restart of my internal computer.

Neuroscientists interested in the effects of meditation are studying the brains of accomplished meditators. Both The Dalai Lama and John Kabat Zinn (the founder of the Stress Reduction Clinic) have participated in these studies. Plenty of anecdotal evidence shows that meditation and exercise reduce stress and anxiety, can help alleviate depression, and increase one's sense of well being. Scientists have shown that meditation has a profound effect on brain activity and the 'mind' can affect the brain. In other words, our minds actually influence brain development and structure. Generally, meditation slows brain waves and results in stress reduction that has both short and long term benefits. However, very experienced practitioners of meditation have increased the gamma waves (high frequency brain waves) both during and after meditation, particularly in the part of the brain (left pre-frontal cortex) associated with happiness and positive emotions, anti-depressant activity, and inhibition of fear/anxiety. Gamma waves are associ-

ated with attention, perception and learning. As such, meditation can work as an antidote to enhance learning, perception, nerve cell communication and mood. Some studies also show that consistent meditation keeps the brain healthier as it ages.

So how does one meditate? In the Yoga Sutras, Patanjali lists a variety of techniques that can lead to a meditative state. They include focusing on a single subject without variation, pranajama (control of the breath), subtle sense perception (e.g., passing of the breath in and out of the nostrils), reciting a mantra, or anything that is elevating. However, even if you have never practiced any of these techniques, it could be that you have already experienced a meditative state: it might have happened while you were walking in nature, making love, or looking into the eyes of a child. In these moments, all your worries and rambling thoughts loose their grip and allow you to just be in the present moment. However, practicing yoga can help achieve a meditative state on a more regular basis. The combination of the pranayama (breath control) and asana (discipline of the body) is a powerful tool for focusing and quieting the mind when you practice it with a clear mind. This is the goal during the yoga class, to quiet your mind and to focus on being in the moment, controlling the posture and your breath. The feeling of a yoga posture (asana) needs to be clear in the mind and happy in the heart.

"Clear mind is like full moon in the sky.
Sometimes clouds come and cover it, but the moon is always behind them.
Clouds go away, then the moon shines brightly.
So do not worry about clear mind: it is always there.
When thinking comes, behind there is clear mind.
When thinking goes, there is only clear mind..."

Zen master Seung Sahn

Before practicing yoga I was doing a lot of sport but most of the time I was pushing myself and my body to the limit and I was not taking care of myself. The status of happiness and serenity I reach after a yoga class is not comparable to any other physical practice. Yoga is a long path: if you accept yourself with your limits and you work on them, you always try to expand your limits and get comfortable in the posture through the breath. Yoga practice changed my way of perceiving myself and consequently others, so much so that I decided to deepen my practice. In New York City I also attended a teacher training Yoga in order to spread my joy for it. I now teach a beginner class at Syngenta and occasionally to friends and colleagues here at the University Hospital. If you are curious or you would like to try once I would be more than happy to have you in the class.

Namaste,

Anna Marsano

China-Tibet Abenteuer
Herbst 2010

Aus dem Tagebuch von Verena Jäggin

20.9.2010: In Peking vor dem Olympiastadion, dem „Bird's Nest", von links: Soledad (vom DBM begleitet uns bis Lhasa), Antoine, Noldi und Verena.

21.9.2010: Die Grosse Mauer (der 3 km lange Mauerabschnitt von Mutianyu).

22.9.2010: Blick auf die Verbotene Stadt

20.9.2010: Xi'an Bahnhof. Zum Glück waren immer nette Leute zur Stelle ...

23.9.2010: Oestlich von Xi'an, die Terrakotta-Armee, das Grab des Kaisers Jingdi.

23.9.2010: Am Endpunkt der Seidenstrasse in Xi'an, der „Drum Tower" in der Altstadt.

25.9.2010: Xining, am Westrand des Hochlands von Tibet, die Bevölkerung ein Gemisch aus Hui, Tibetern und Han-Chinesen.

26.9.2010: Die Tibet-Bahn hat bereits den 5220 m hohen Taggula-Pass überquert, wir nähern uns dem Transhimalaya und sind etwa 200 km von Lhasa entfernt.

26.9.2010: Zum ersten Mal sehen wir in weiter Ferne unser Hauptziel, den 7115 m hohen Nojin Tangla.

27.9.2010: Lhasa, 3700 m ü.M.

27.9.2010: Lhasa Tradition und Moderne: In China liegen sie noch beieinander ...

27.9.2010: Auf dem Platz des Jokhang Tempels im Zentrum von Lhasa.

28.9.2010: Der Potala-Palast auf dem Roten Berg (Hongshan) im Zentrum von Lhasa war bis 1959 die offizielle Residenz des Dalai Lama und der Sitz der Regierung Tibets.

30.9.2010: Ankunft im Base Camp (BC) auf 4700 m ü. M, ca. 25 km vom letzten Dorf entfernt und 100 km nördlich von Lhasa.

30.9.2010: Die letzten Häuser beim Base Camp. Getrockneter Yak-Mist wird als Windschutz und Brennmaterial verwendet (ein Yak ist ein (tibetischer) Grunzochse).

30.9.2010: Die Kinder bestaunen uns, nicht viele Fremde kommen in diese Gegend, vor 4 Jahren waren die letzten Bergsteiger hier.

2.10.2010: Bild links, unser Team am Berg, (vorne links nach rechts) Asu, unser Sherpa, Samdian, der Koch, Pu bu, ein Träger. (Mitte) Antoine, Tashi, der offizielle Begleitoffizier, er wartet hier im BC bis wir vom Berg zurückkommen, Verena, Awan, ein Träger (hinten) Zhawa, der Küchengehilfe, Noldi.
Bild rechts, unser Aufbruch Richtung Advanced Base Camp (ABC).

5.10.2010: Das Advanced Base Camp auf 5300 m ü. M, unser zu Hause für die nächsten 10 Tage.

5.10.2010: Der Nojin Tangla, 7115 m, in schönster Abendstimmung unterhalb vom Camp1.

9.10.2010: Nach 3 Tagen Akklimatisation im ABC sind wir auf 6ooo m aufgestiegen und haben Camp1 eingerichtet. Schon jetzt sehen wir es hat sehr viel Neuschnee und eine riesige Schneewächte die über unseren Köpfen hängt ... Jeden Morgen gibt es Neuschnee, die Tage sind oft neblig und es schneit weiter ...

9.10.2010: Wir steigen wieder auf Camp 1 hoch, noch 100 Höhenmeter weiter auf einen unbekannten Gipfel, belohnt werden wir mit einer wunderschönen Rundsicht, unser „Berg“ den Nojin Tangla (im Hintergrund) können wir von hier sehr gut beobachten und sehen, die Besteigung ist zu gefährlich, die Lawinengefahr zu gross, wir kehren um. Trotz allem, es war eine wunderschöne Zeit und Erfahrung in Tibet. Wir fahren zurück nach China.

Verena Widmer, Immunonephrology

Ich bin in Riehen mit drei älteren und einer jüngeren Schwester aufgewachsen.
Nach einer Lehre als Laborantin Richtung B in der J. R. Geigy AG, arbeitete ich sechs Jahre im Bereich Drug-Metabolismus in der mittlerweile fusionierten Ciba-Geigy AG.

Nach einem Sprachaufenthalt in England trat ich eine Stelle im Biozentrum in der Abteilung der Zell-Biochemie an. Die Arbeit war sehr abwechslungsreich: Zellkultur, Elektronenmikroskopie, biochemische Analysen, Antikörper-Herstellung und -Aufreinigung, was das Arbeiten mit Kaninchen und Mäusen bedeutete. Ein Projekt war der Entwicklung eines Meerschwammes (Microciona prolifera) gewidmet. Es war naheliegend, dies direkt am Meer zu tun. Unser Chef, Prof. M. M. Burger mietete jeden Sommer ein Labor am MBL. Das MBL (Marine Biological Laboratories) befindet sich in Woods Hole am Cape Cod, USA. Dort ist auch ein Ozeanographisches Institut ansässig. Ich hatte das Glück, etliche Male die Sommermonate am MBL arbeiten zu können. Die Labors waren dazumal sehr alt, hatten aber fliessendes Meerwasser, was für das Halten der Schwämme ideal war. Das Projekt war spannend und der Ort herrlich, direkt am Meer.

Ein kleines Dorf, das nur ein paar Einwohner hat, aber im Sommer von Wissenschaftlern bevölkert wird. Vom kleinen Hafen kann man die Fähren nach Marthas-Vineyard und Nantucket nehmen. Zwei wunderschöne Inseln und daher auch beliebte Ausflugsziele. Diese Zeit im Biozentrum war wirklich super. Die Arbeit war abwechslungsreich und spannend und die international «zusammengewürfelte» Gruppe war toll. Wir Laborantinnen von damals treffen uns heute noch regelmässig alle zwei Monate zu unserer «Hennen-Party».

Die Freizeit war ziemlich vom Sport geprägt. Joggen, Velofahren und Langlaufen waren unsere Favoriten. Irgendwann führte uns ein Freund in das alpine Bergsteigen und Klettern ein. Wir, mein damaliger Freund und späterer Mann und ich, waren begeistert davon. Im Frühling ging es zum Einklettern in die Calangues, Südfrankreich. Im Sommer verging wohl kein schönes Wochenende, ohne einen neuen Gipfel bestiegen zu haben. Korsika hatte es uns auch angetan, die Berge, das Meer, eine urchige Insel. Es war eine schöne und intensive Zeit. Dabei kam die Familienplanung etwas zu kurz. Der Wunsch, eine Familie zu gründen, wurde nun immer stärker. Dennoch frönten wir bald einem neuen Hobby, dem Gleitschirmfliegen. Eines der schönsten Erlebnisse mit dem Gleitschirm war auf Stromboli. Schon der Nachtaufstieg war speziell; ca. alle 10 Minuten hat der Stromboli eine Eruption. Was am Tage nur als Rauch sichtbar war, war nachts eine glühende Lavafontäne. Nach einem spektakulären Sonnenaufgang war dann das Dessert der Flug mit dem Gleitschirm zum Meer. Landung im schwarzen Sand. Unvergesslich!

Ja, dann wurde im Mai 1990 unsere Tochter Jasmin geboren. Ich habe aufgehört zu arbeiten und war ab jetzt Mutter und Hausfrau. Mit unserem VW-Bus verbrachten wir manches Wochenende in der Innerschweiz. Wir wanderten mit

Jasmin im Huckepack auf Berge im Voralpengebiet. Meistens war auch ein Gleitschirm dabei. Einer konnte runter fliegen, der andere fuhr mit Jasmin in der Gondel oder der Zahnradbahn. Wir genossen es!

Leider sollte dieses Glück nicht lange anhalten. Als Jasmin dreieinhalb Jahre alt war, starb mein Mann. Das Leben änderte sich schlagartig. Plötzlich war alles nur noch Erinnerung. Meine Familie und Freunde halfen uns sehr in diesen schwierigen Jahren. Ein emotionaler und ständiger Begleiter auf all unseren Reisen war und ist immer noch unser VW-Bus. Auch dieses Jahr brachte er uns mit seinen 22 Jahren sicher nach Sardinien und zurück.

Als Jasmin neun Jahre alt war, spielte ich wieder mit dem Gedanken zu arbeiten. Bald darauf wurde mir eine Stelle im Biozentrum, in der Zellbiologie bei Prof. W. Keller, angeboten. Es war ideal, ein 40% -Pensum und die Zeit konnte ich mir einteilen. Es war ein gutes Gefühl, wieder zu arbeiten. Ich war zuständig für die Zellkulturen unserer Abteilung. Es war, als wäre ich kaum weg gewesen. Die Arbeit sowie das Biozentrum waren mir noch sehr vertraut. Ich fühlte mich sehr wohl. Nach fast zehn Jahren wurde Prof. Keller pensioniert und die Abteilung aufgelöst.

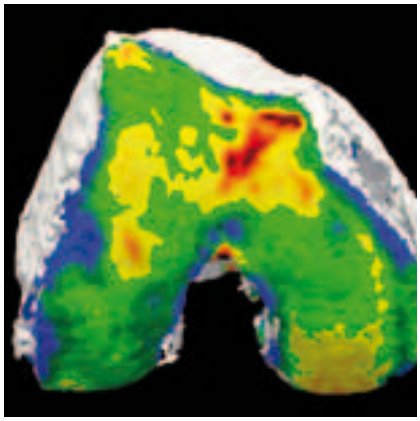
Ich überlegte mir, ob ich in meinem Alter wohl noch etwas finden würde. Eine Freundin erzählte mir von der freiwerdenden Stelle im Labor von Prof. J. Schifferli. Ich bewarb mich und konnte bald darauf die Arbeit beginnen. Sechs Monate lang war ich parallel dazu noch zu 25% im Biozentrum tätig. Diese neue Stelle war wirklich ein Glücksfall. Etwas Neues zu lernen und auch die Erfahrung einbringen zu können macht Spass. Dazu kommt noch, dass ich mich im Team sehr wohl fühle. So wohl, dass ich bereits ein zusätzliches Jahr angehängt habe. Obwohl ich mich kaum langweilen würde zu Hause. Ich musiziere in zwei Vereinen. Mit meiner Handharmonika bin ich seit meinem zehnten Lebensjahr aktiv in einem Verein und wirke dort auch in der Theatergruppe mit. Vor circa acht Jahren fing ich mit dem Querflötenspielen an und bin mittlerweile in der Binninger Blasmusik aktiv. Seit ein paar Jahren male ich auch gerne Bilder, aber es fehlt mir oft die Zeit dazu.

Sportlich hat sich Etliches geändert. Aus dem Joggen wurde Nordic walking, aus dem Bergsteigen Wandern. Neu entdeckt habe ich das Tango tanzen. Das Velofahren möchte ich wieder intensivieren.

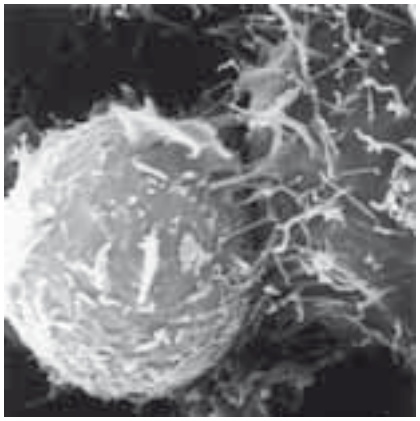
Meine Tochter wurde dieses Jahr 20 Jahre alt und hat ein Psychologiestudium angefangen.

VORSCHAU PREVIEW

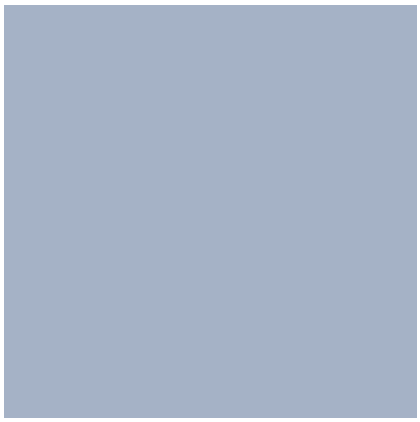
In der nächsten Ausgabe . . .

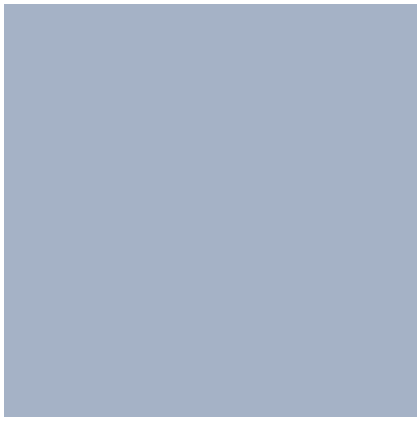


... führt Magdalena Müller-Gerbl uns in die Welt der Macroanatomy ein



... erläutert uns Alfred Zippelius die Herausforderungen der Cancer Immunology

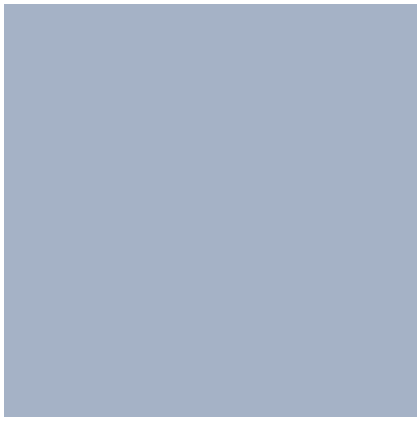


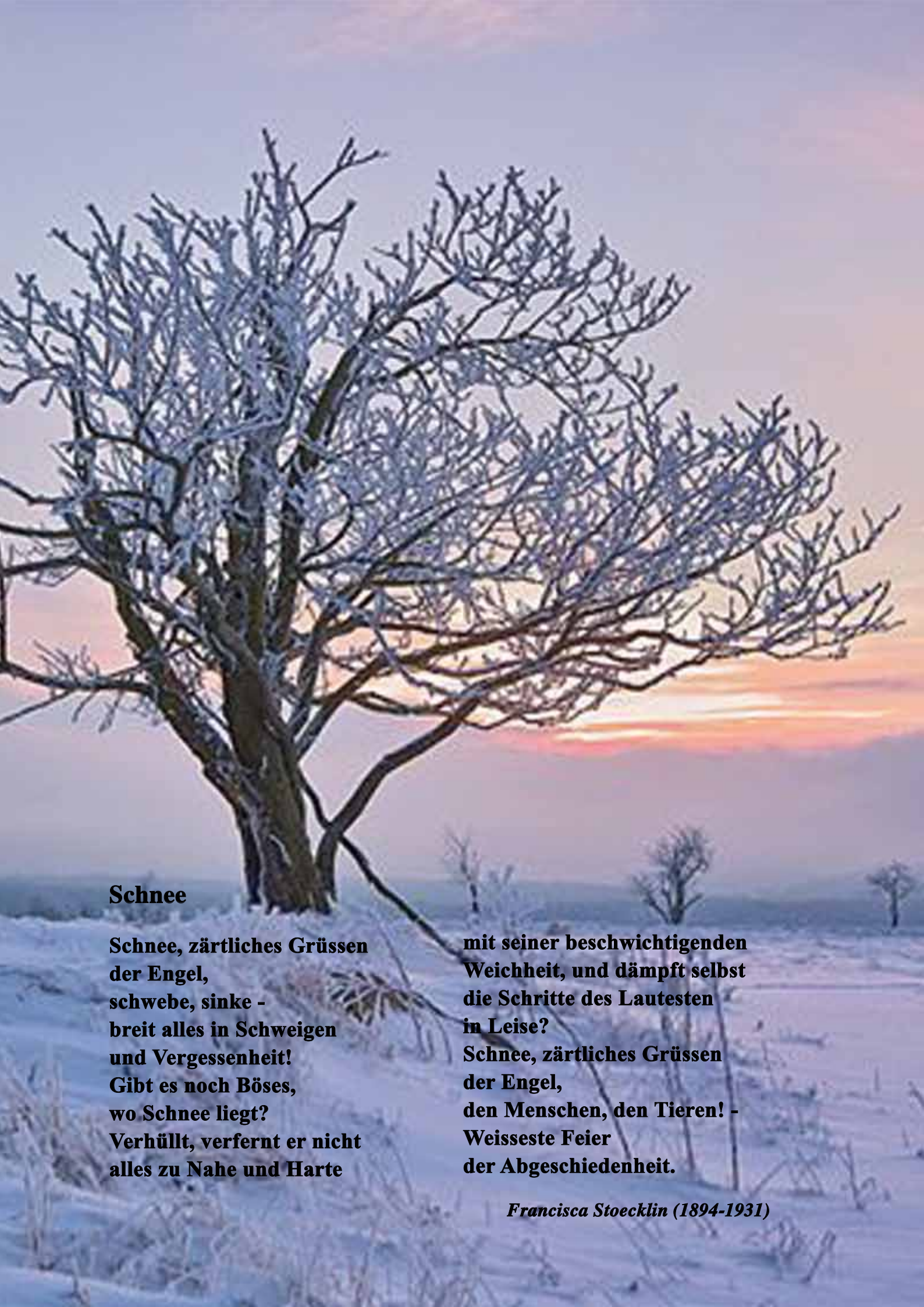


... nimmt uns Matteo Centola mit auf Tour durch die italienische Hauptstadt

... erfahren wir von Seddik Riad mehr über Aikido

... kochen wir mit Elham, Hojjat, Ramin und Zeinab iranisch





Schnee

Schnee, zärtliches Grüssen
der Engel,
schwebe, sinke -
breit alles in Schweigen
und Vergessenheit!
Gibt es noch Böses,
wo Schnee liegt?
Verhüllt, verfernt er nicht
alles zu Nahe und Harte
mit seiner beschwichtigenden
Weichheit, und dämpft selbst
die Schritte des Lautesten
in Leise?
Schnee, zärtliches Grüssen
der Engel,
den Menschen, den Tieren! -
Weisseste Feier
der Abgeschiedenheit.

Francisca Stoecklin (1894-1931)