DBM FACTS

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Biomarkers, regulators and effectors of low-grade glioma invasion | Survival, proliferation, deletion: ask the lymph node stroma! | Wien ist anders

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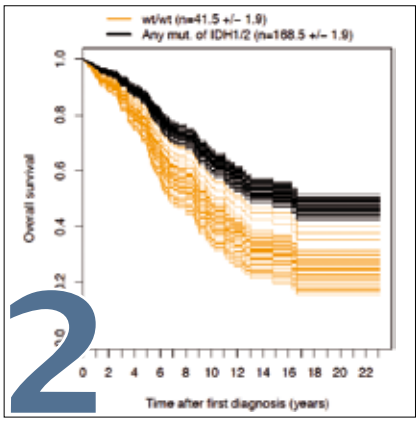
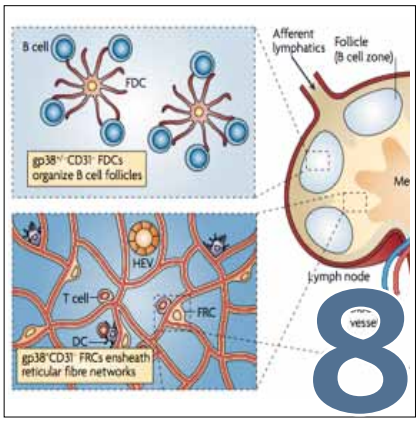


Biomarkers, regulators and effectors of low-grade glioma invasion
from Luigi Mariani



Survival, proliferation, deletion: ask the lymph node stroma!
from Simona Rossi Girard

Triathlon
from Brynn Kvinlaug

Wien ist anders
von Denise Berger

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EDITORIAL

Peter Meier-Abt
Head a.i.

Liebe Leserinnen und Leser

Was gibt es Neues zu berichten? Nur Positives! Am 1. Juli 2012 nimmt Viola Heinzelmann ihre Tätigkeit als leitende Ärztin in der Frauenklinik und Forschungsgruppenleiterin am DBM auf. Die Berufungsverhandlungen mit Prof. O. von Bohlen sind im Gange, der Berufungsbericht Professur Hämatologie/Stammzellbiologie wurde von der Fakultät akzeptiert. Die langen Wartezeiten am Mikroskop haben ein Ende: Michael Abanto verstärkt seit dem 1. Juni 2012 die Biooptik-Facility an der Hebelstrasse! Mit dem Aufbau der Bioinformatik an der Mattenstrasse hat Roland Ivanek angefangen! Allen viel Erfolg und ein herzliches Willkommen!
In der nun vorliegenden Sommerausgabe teilen uns Luigi Mariani und seine Mitarbeitenden die neuesten Erkenntnisse aus der Brain Tumor Biology mit (ab Seite 2), führen uns Simona Rossi und ihr Team in das Spiel der Immunoregulation ein (ab Seite 8), berichten wir von grossen Erfolgen (Seite 13) und davon, wie einfach und genial Forschung sein kann (Seite 14). Durchhaltevermögen anderer Art beweist Brynn Kvinlaug, die als Triathletin auch in der Freizeit nicht so schnell aufgibt (ab Seite 26). Das tut Denise Berger auch nicht, fordert ihre ehemalige Wahlheimat Wien doch den ganzen Menschen heraus (ab Seite 30). Und wem das noch nicht genug ist, der findet sicher unter den DBM Lesetipps den richtigen Zeitvertreib!
Viel Spass beim Lesen und schöne Ferien!

Peter Meier-Abt

Dear Readers

What news is there? Only positive news! On the 1st July 2012 Viola Heinzelmann will take up her position as senior physician at the women's clinic and as research group leader at the DBM. Appointment negotiations are underway with Prof. O. von Bohlen, the Professor of Haematology/Stem Cell Biology appointment report has been accepted by the faculty. The long wait time for microscopy should be coming to an end: since the 1st of June 2012 Michael Abanto has strengthened the bio-optic facility at Hebelstrasse! Roland Ivanek has begun with the installation of bioinformatics at Mattenstrasse! We welcome them all and wish them every success!
In this summer issue Luigi Mariani and his co-workers share the most up to date knowledge about brain tumor biology with us (page 2), Simona Rossi and her team introduce us to the Immunoregulation game (page 8), we report on great achievements (page 13) and how simple and brilliant research can be (page 14). Brynn Kvinlaug knows all about staying power, as a triathlete she does not stop, even in her free time (page 26). Denise Berger does not stop either, as Vienna, her former chosen place of residence, challenges a person as a whole (page 30). For those whom that is not yet enough, they are sure to find something to pass the time in the DBM book reviews! Happy reading and enjoy the holidays!

Peter Meier-Abt

Biomarkers, regulators and effectors of low-grade glioma invasion

Glioma progress by tumor cell invasion into adjacent brain tissue. The main goal of the Laboratory of Brain Tumor Biology is to understand mechanisms underlying tumor cell invasion. This involves the identification of biomarkers, genetic regulators, molecular networks and molecular effectors of tumor cell invasion that can ultimately be targeted to control glioma progression.

The group 'Brain Tumor Biology'. From left to right. Standing: Archana Ramadoss, Marie-Françoise Ritz, Gregor Hutter, Luigi Mariani, Jean-Louis Boulay. Sitting: Severina Leu, Cristóbal Tostado, Elisabeth Taylor. Missing on the picture: Martin Sailer

Introduction

Gliomas are among the deadliest malignancies, with a median survival varying between few months for the most frequent malignant grade IV glioblastoma (GBM), to over 20 years for the low-grade glioma (LGG). Given the extremely high resistance of tumor cells to chemo-/radiotherapy, conventional therapies have not significantly improved patient survival. In addition, the high invasive capacity of glioma cells into adjacent brain tissue compromises total surgical resection. Besides grading, glial tumors are classified into histologic subtypes based on morphologic and antigen expression features. The finding of chromosomal alterations and gene mutations allowed the identification of some glioma developmental pathways and refined classification into molecular subsets with various degrees of aggressiveness or responsiveness to current therapies.

The research of the Laboratory of Brain Tumor Biology, in close partnership with the Neurosurgery Clinic, focuses on glioma, and more specifically, on LGG. At the clinical point of view, we aim at defining biomarkers to classify LGG into molecular subsets to standardize treatment strategies. At a more basic level, we aim at identifying genetic regulators and molecular effectors of glioma cell invasion. For both purposes, we are collecting resected glioma biopsies of distinct grades and histologies directly in the operating room for further analytical and experimental purposes.

Genotyping low-grade gliomas

In collaboration with Stephan Frank (Pathology, UHBS), Stefanie von Felten (Clinical Trial Unit, UHBS), Istvan Vajtai and Erik Vassella (University of Bern).

Based on histology, LGG have been divided into three distinct subsets: diffuse astrocytoma (A), oligoastrocytoma (OA) and oligodendroglioma (OG). Molecular genetic and genomic analyses of LGG have identified four major alterations relevant to LGG development: *IDH* mutations and *MGMT* gene promoter methylation in nearly 80% of LGG, and TP53 mutations and 1p/19q allelic loss, each occurring in nearly 25% of LGG in a mutually exclusive manner. *IDH* genes encode isocitrate dehydrogenase that normally catalyzes the conversion of isocitrate into α-ketoglutarate (αKG) in the Krebs cycle. The muta-

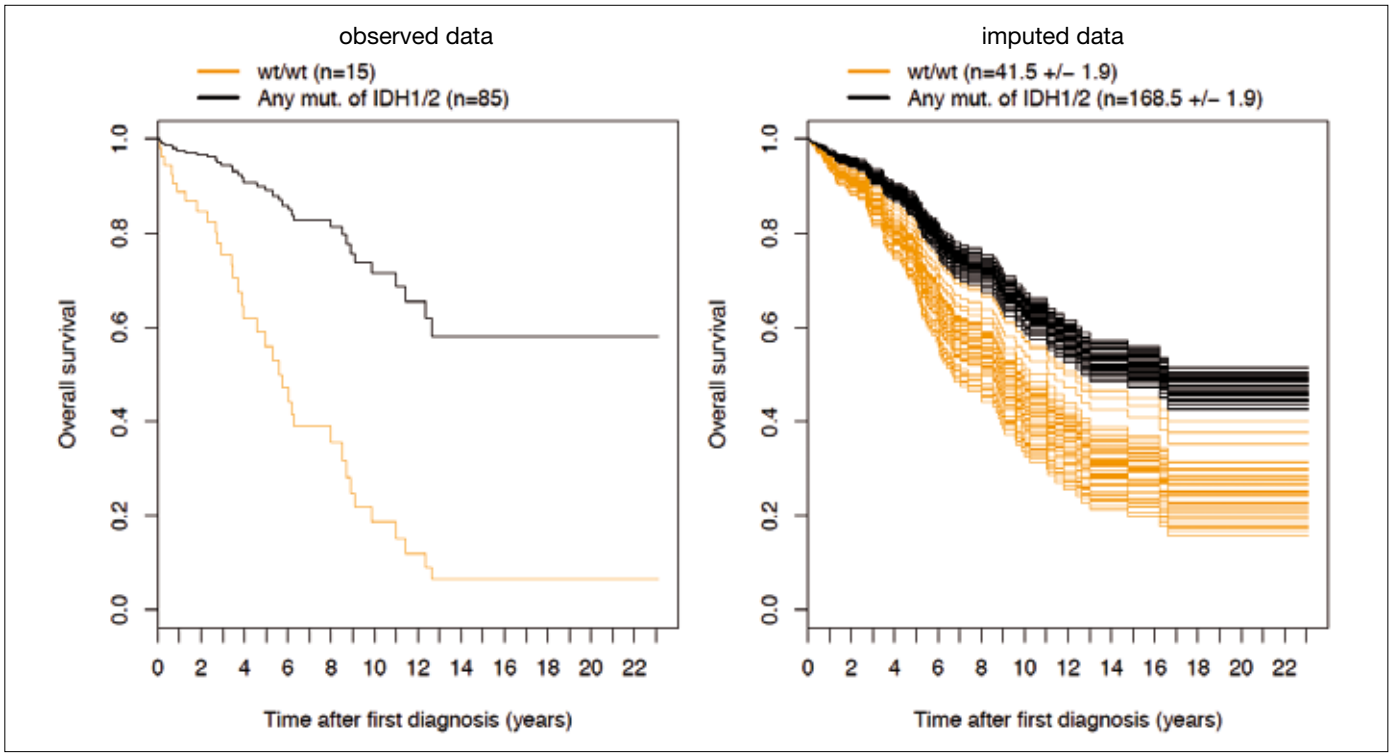

Figure 1. Association between IDH mutation and favorable outcome in LGG patients.

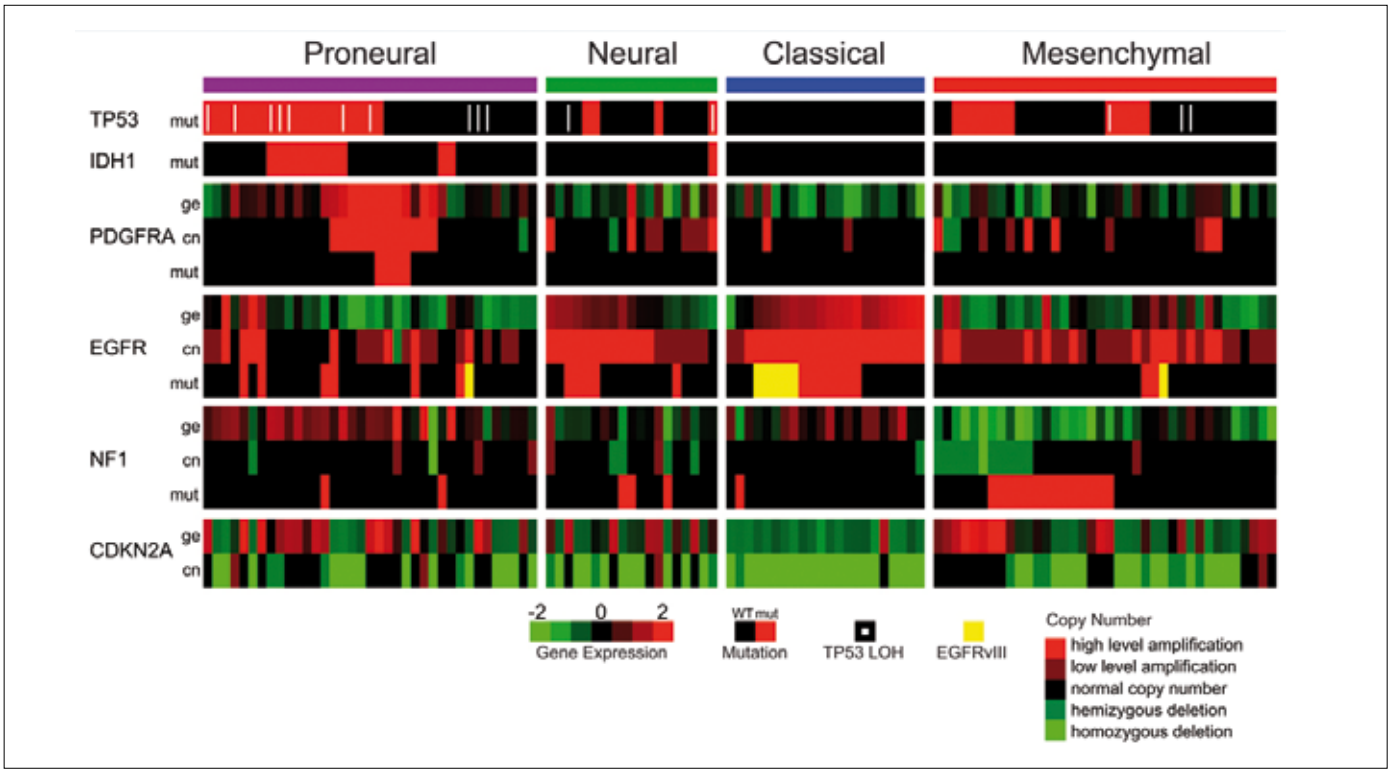

Figure 2. Glioma classification based on genomic and genetic data. From Verhaak et al., Cancer Cell (2010) 17:98.

tions create a novel catalytic function that converts αKG into 2-hydroxyglutarate (2HG). Accumulation of 2HG oncometabolite leads to genome-scale impaired DNA demethylation that results in extensive methylome and transcriptome remodelling, which includes methylation of the *MGMT* gene promoter. These are early events in the course of gliomagenesis and provide a molecular basis for the co-segregation observed between *IDH* mutation and *MGMT* methylation. Later, *TP53* mutations and 1p/19q allelic loss occur preferentially in A and OG, respectively. We are currently analysing the impact of these alterations on survival of >200 LGG in a retrospective study. In order to increase accuracy, missing data, a major issue in retrospective studies, is being compensated by multiple imputation.

Identification of novel biomarkers for gliomas

As depicted in Figure 2, glioma can be divided into 4 major molecular groups based on genomic, transcriptomic and proteomic/phosphoproteomic profiles: proneural (includes LGG with *IDH* mutation, *MGMT* methylation or *PDGFRA* amplification, derived anaplastic glioma and GBM), classical (GBM that contain *EGFR* amplification/mutation and *CDKN2A* loss), neural (GBM with additional *TP53* mutations), and mesenchymal (ultimate GBM developmental stage).

Upon surgical resection, we routinely extract DNA, RNA and protein from tumor biopsies. This material is used to attempt a systematic molecular classification of gliomas of all grades and histologies operated at the Neurosurgical Clinic. In cases where biopsies are taken from distinct areas of the tumor core and of the invasive rim at tumor periphery, variations in RNA expression between these distinct areas of the same tumor will be examined.

We are currently constructing a comprehensive, web-based glioma patient database containing personal (demographics, etiology, personal history); clinical (patient outcome, survival); MRI imaging (tumor size, location and infiltration grade), histopathological (tumor histology and WHO grade) and molecular annotations (genotyping, transcriptome, proteome and activated signal-

Histo	Grade	EGFR 7p11	CDKN2A 9p21	IL13RA2 Xq23	ERBB2 17q12	NF1 7q12 8M	PDGFRA 4q12	CKIT q12 .5M	PTEN 10q23	TP53 17p13	TRIM3 11p15	1p/19q	IDH1/2 q33 15q2	MGMT 10q26	
OG	II	2n	2n	2n	2n	2n	2n	2n	nd	nd	nd	no	R132H	low	Proneural
OG	II	2n	2n	2n	2n	2n	2n	2n	nd	nd	nd	no	R132H	low	Proneural
OG	II	2n	2n	2n	2n	2n	2n	2n	ret	ni	ret	no	R132H	yes	Proneural
OG	III	2n?	0n	2n	2n	2n	>4n	>4n	loh	ret	loh	no	R132C	nd	Proneural
GBM	IV	2n	0n?	2n	2n	nd	>4n	>4n	loh	loh	ret	no	wt	nd	Proneural
GBM	IV	2n	0n	2n	2n	2n	>4n	>4n	ni	loh	ret	nd	nd	nd	Proneural
GBM	IV	2n	0n	2n	2n	2n	2n	2n?	ni	ret	ret	no	wt	no	Proneural
GBM	IV	2n	0n	>4n	2n	2n	2n	2n	loh	ret	ret	no	wt	no	Proneural
GBM	IV	2n	0n	2n	2n	2n	2n	2n	loh	loh	ret	no	wt	no	Proneural
GBM	IV	2n	0n	2n	2n?	2n	2n	2n?	ni	ret	ret	no	wt	yes	Proneural
GBM	IV	2n	0n	2n	2n	2n	2n	2n	loh	loh	loh?	no	wt	97%	Proneural
GBM	IV	>4n	0n	2n?	nd	0n	>4n	nd	nd	nd	nd	no	wt	no	Neural
GBM	IV	>4n	0n	2n?	>4n	0n	>4n?	0n	nd	nd	nd	no	wt	nd	Neural
GBM	IV	>4n	0n	2n	2n	2n	>4n	2n	loh	ret	ni	no	wt	low?	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n	ret	ret	ret	no	wt	no	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n	loh	ret	ret	no	wt	no	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n?	ni	ret	ret	no	wt	no	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n	ni	loh	ret	no	wt	nd	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n	ni	ret	ret	no	wt	yes	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	2n	loh	loh	loh?	no	wt	nd	Classical
GBM	IV	>4n	0n	2n	2n	2n	2n	1n	ni	ret	ret	nd	wt	yes	Classical

Figure 3: Genotyping of tumor biopsies. Data obtained from real-time quantitative PCR (EGFR, CDKN2A, IL13RA2, ERBB2, NF1, PDGFRA, CKIT); loss of heterozygosity (PTEN, TP53, TRIM3); fluorescent in situ hybridization (1p/19q); pyrosequencing (IDH1/2) and sequencing of modified DNA (MGMT). ret = retention of both (polymorphic) alleles, loh = loss of heterozygosity (loss of one polymorphic allele), ni = non informative (no allelic polymorphism), nd = not done.

ing pathways). Classification of gliomas according to histologic, molecular and invasive features, will allow identification of novel glioma biomarkers, and hopefully identification of subgroups of glioma responsive to customized therapies.

Isolation and ex vivo culture of glioma cells from resected tumors

Parts of the resected tumors are also subjected to cell dissociation for *ex vivo* cell culture. Glioma cells are then grown *ex vivo* to establish long-term glioma stem cell and differentiation cultures. Whenever possible, biopsies are taken from distinct areas of the tumor core and of the invasive rim at tumor periphery to test their respective invasive behaviours. Further, putative glioma stem cells are xenografted orthotopically into the brains of immunocompromized mice to assess their tumorigenicity *in vivo*.

Molecular and genetic mechanisms of glioma invasion

We aim at identifying genetic determinants and molecular effectors of glioma invasion by comparing, on one hand, expression profiles of invasive *vs.* non-invasive tumors and, on the other hand, expression patterns of distinct areas within the same tumor.

Earlier data on genome-wide transcription analysis of invasive compared to non-invasive gliomas have indicated that tumor invasiveness is independent of a given histologic or a molecular subset. Indeed, the signature for invasiveness was associated with the differential regulation of a discrete number of genes only. Among those, we consistently found the gene for the mediator of glioma invasion BEHAB/brevican, and also the genes encoding transcription factors SOX2 and HEY1, suggesting a possible role for these genes in glioma invasion. Target genes for SOX2 and HEY1 encoding potential effectors of glioma invasion will be identified and tested for their capacities of altering glioma cell motility.

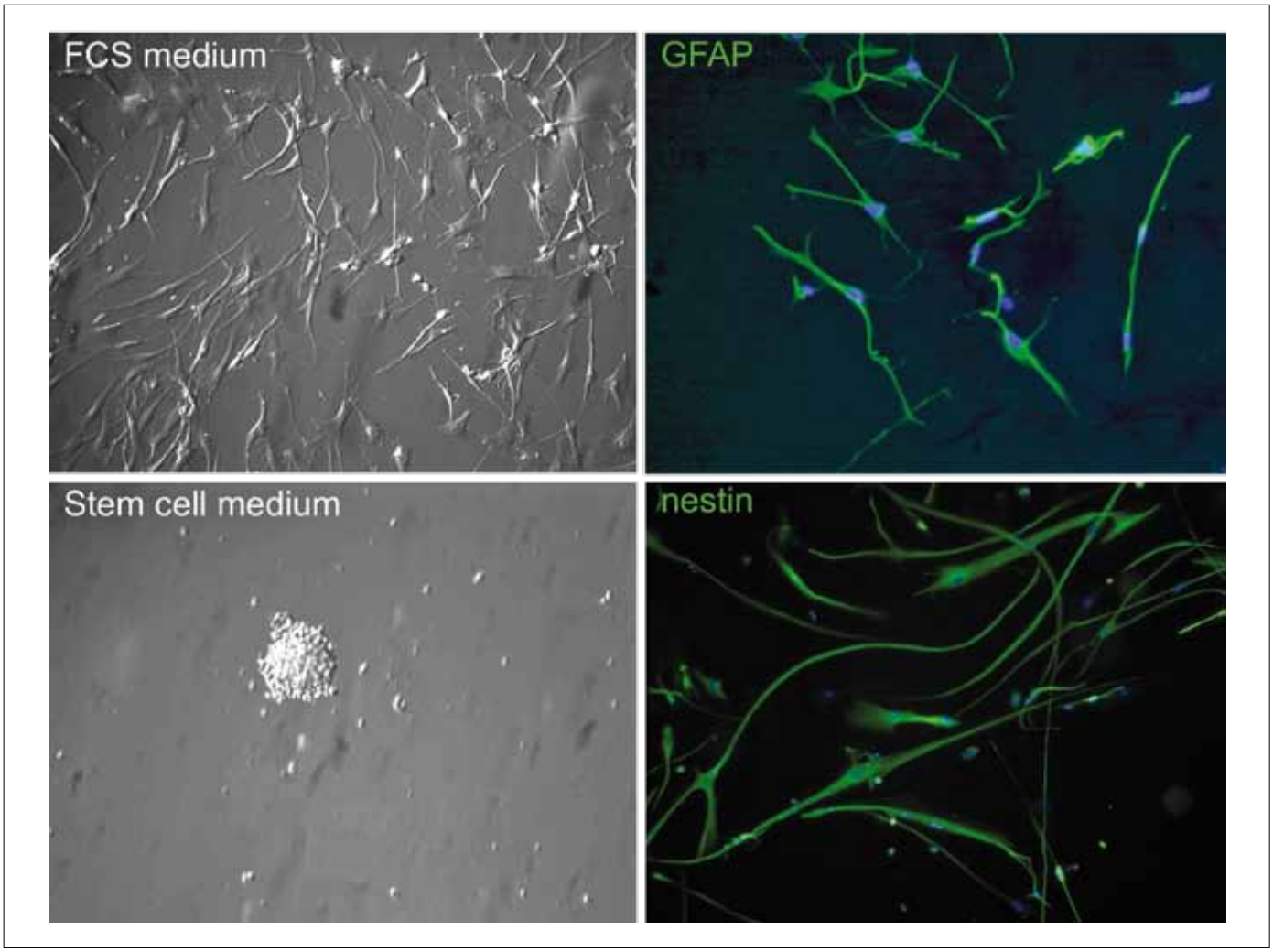

Figure 4. Human cells dissociated from a grade IV GBM expand as GFAP/Nestin-positive adherent cells in FCS-containing medium, or as floating spheres in stem cell medium.

As a complementary approach, identification of invasion genes also involves comparison of RNA levels between the invasive glioma cells located at the periphery of the tumor, and the non-invasive glioma cells embedded in the tumor mass. Genes showing significant differential expression between the distinct zones will be validated for their abilities in modulating glioma invasion. Results should provide clues on the molecular mechanisms of glioma invasion and designate potential targets for customized therapies to control glioma invasion.

In collaboration with Stephan Frank (Pathology, UHBS), Istvan Vajtai and Erik Vassella (University of Bern).
Some tumors, for which imaging data were available, could be graded for their invasion capacities by measurement of the thickness of the infiltration zone. Micro RNAs are being extracted from formalin-fixed paraffin-embedded tumors of known invasive properties, and micro RNA expression compared by micro-array hybridization.

Positional information and tumor invasion

Mechanisms of migration and invasion are also studied using rat embryonic neural stem cells (NSCs). These cells, when isolated from the embryonic cortex at E14.5 and put in culture in the presence of growth factors such as FGF, undergo a change from dorsal to ventral identity, as indicated by the expression of ventral genes and the inhibition of the expression of dorsal genes. After addition of bone morphogenic protein 4 (BMP4), dorsal genes are re-expressed, ventral genes repressed. Interestingly, NSCs also upregulate expression of sev-

eral genes, such as SPARC, TNC and HEY1, known to be expressed during tumor invasion (Figure 6). Moreover, these NSCs show migratory and invasive properties in several *in vitro* assays. The identification of the molecular pathways involved in this transition may help us to unravel the mechanisms inducing invasion and migration of normal NSCs but hopefully also of GBM tumor cells.

Luigi Mariani

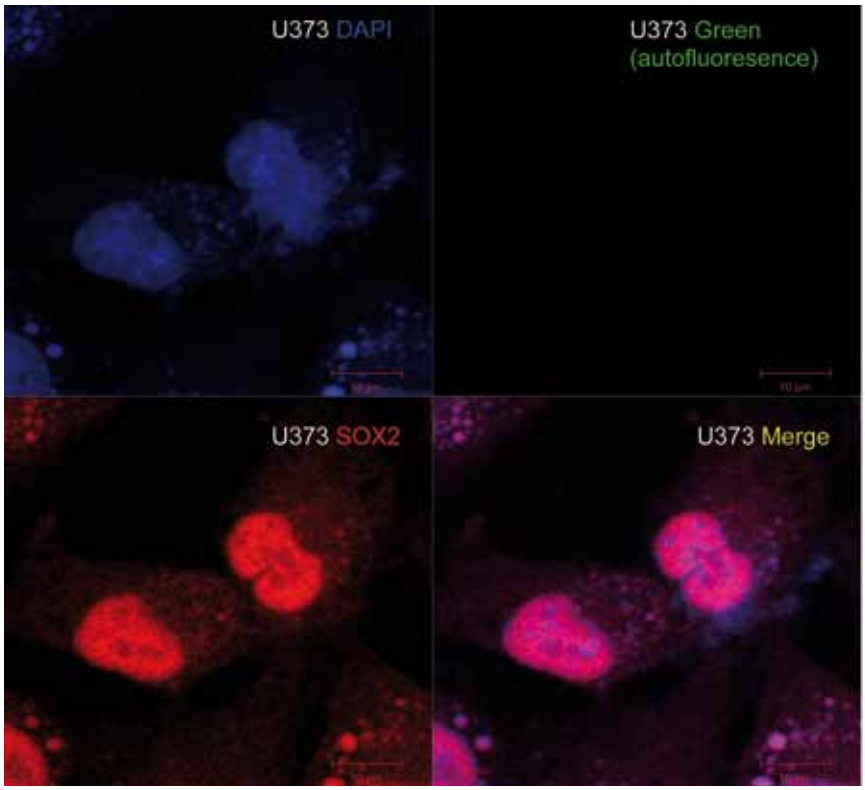

Figure 5. confocal SOX2 immunolabeling in U373 glioma cells

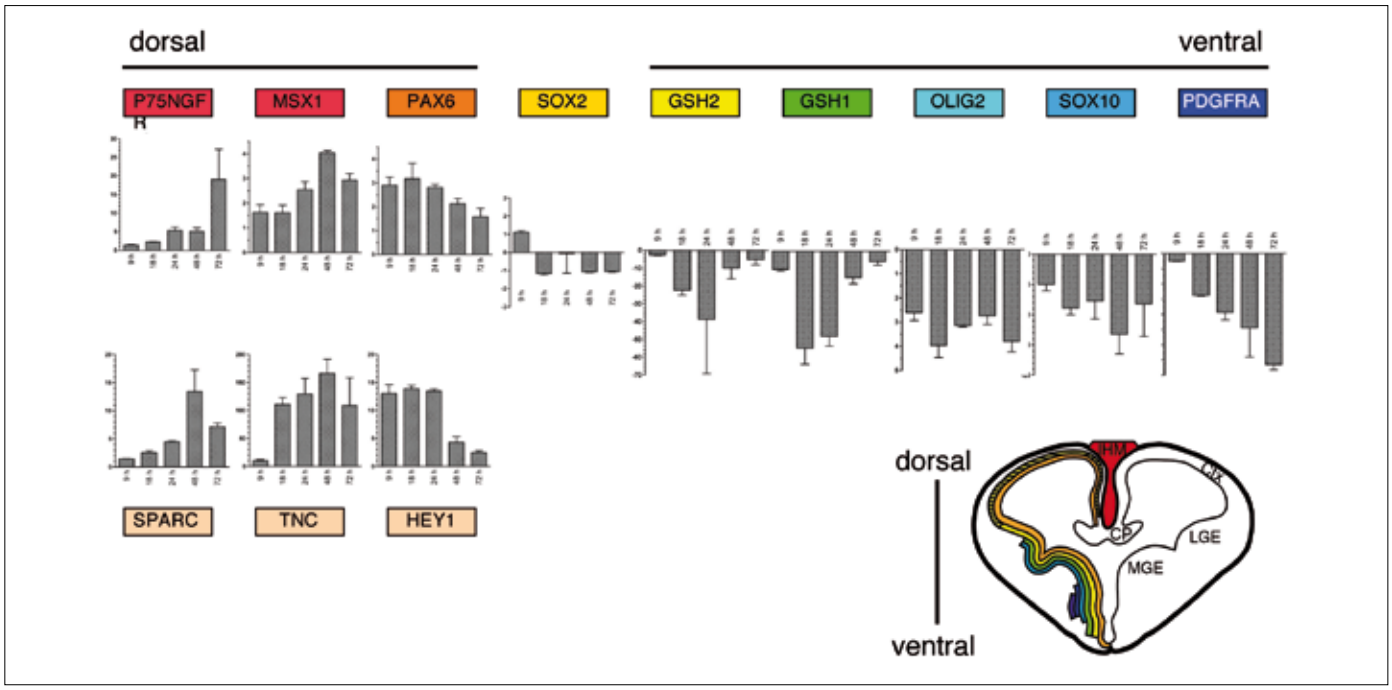

Figure 6: Gene expression according to dorso-ventral positional information in NSCs exposed to FGF followed by BMP4 in vitro. Schematic coronal section of rat embryonic brain.

Survival, proliferation, deletion: ask the lymph node stroma!

Transplantation and the immunoregulation game

From left to right: Maria Broggi, Nicolas Page, Simona Rossi Girard, Mathias Schmaler.

When we think about organ transplantation, the image of patients first waiting for a transplant and then taking medication for the rest of their life fills our imagination. The surgical and the immunological knowledge of the last 30 years have made it possible to live longer with an appreciably better quality of life. The goal in transplantation research is to be able to achieve graft tolerance by convincing the transplanted body that the organ or tissue received is not immunologically dangerous. How to convince the host immune system that the danger signals, the inflammation and the antigen that are flowing in the body are harmless? This is a hard job...
To dampen a graft-specific immune response, we first need to understand the starting point and how the environment modulates this immune response.

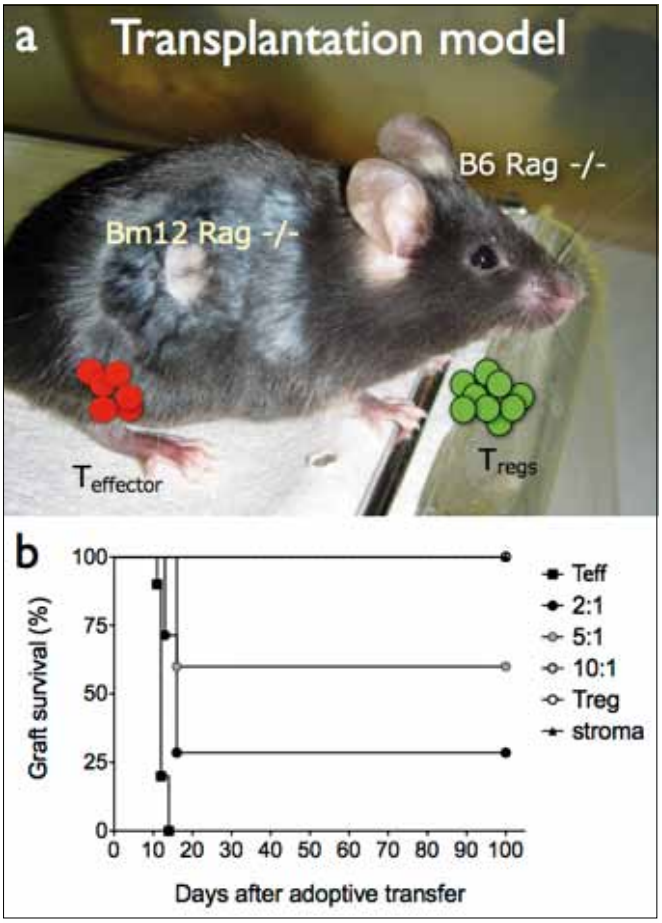

Fig. 1
a) Skin transplantation model.
b) Graft tolerance is dependent from the number of Tregs (10:1 means 10 Tregs per 1 Teff). Teff and Treg were adoptively transferred into the host twenty days after skin transplantation (day 0).

The players

More than 15 years ago a subset of T cells were described bearing immunosuppressive properties and those cells were called regulatory T cells (Tregs). Tregs are studied with great interest because they are selectively able to block the activation of T cells. The biggest problem for *in vivo* treatment with Tregs is the high number of cells needed to be transferred to achieve suppression of T cell activation. Currently the clonal expansion is achieved in culture and the cells are transferred into patients. Would it be possible to boost the suppressive activity or the number of Tregs directly *in vivo*? First we need to understand where Tregs get activated and where they preferentially exert their function. We take advantage of a skin transplantation model where the host mouse is empty of T and B cells and the skin donor harbours a mutation in the gene encoding the MHC class II molecules. We can modulate the outcome of transplantation by an adoptive co-transfer of alloreactive T cells (Teff) and Tregs (Fig. 1a-model, b-graft survival). The first observation is that the co-transferred Teff and Tregs reach and stay in the lymph node (Ln). When Teff are transferred alone in the host, they start to migrate in the grafted skin 9 days post-transfer leading to the skin-graft rejection. Since, in presence of Tregs, Teff stay in the Ln and their number only moderately increase, we concentrated our effort to understand what is happening in the Ln. The Ln is composed by several stroma cell subpopulations, mainly categorised in 4 groups following the surface expression of a glycoprotein responsible for the sticking of chemokines, called podoplanin or gp38 and CD31, also known as platelet endothelial cell adhesion molecule (PECAM-1) (Fig. 2, adapted from Turley SJ et Al. , Nat Rev Immunol, 2010). Vascular endothelial cells express CD31 (lymph: CD31+gp38+, blood: CD31+gp38-). The other cells, expressing only gp38 are known as fibroblastic reticular cells (FRC) and the cells negative for both markers (DN) were recently described to be pericytes-like-cells surrounding lymph and blood vessels. The stromal compartment provides the structure of the Ln and attracts and guides T cells and dendritic cells (DC) to favour their contact. Furthermore, the stroma cells of the Ln are producers of survival-, growth-factors, cytokines and chemokines that influence both T cells and DC. The recent knowledge on the active role

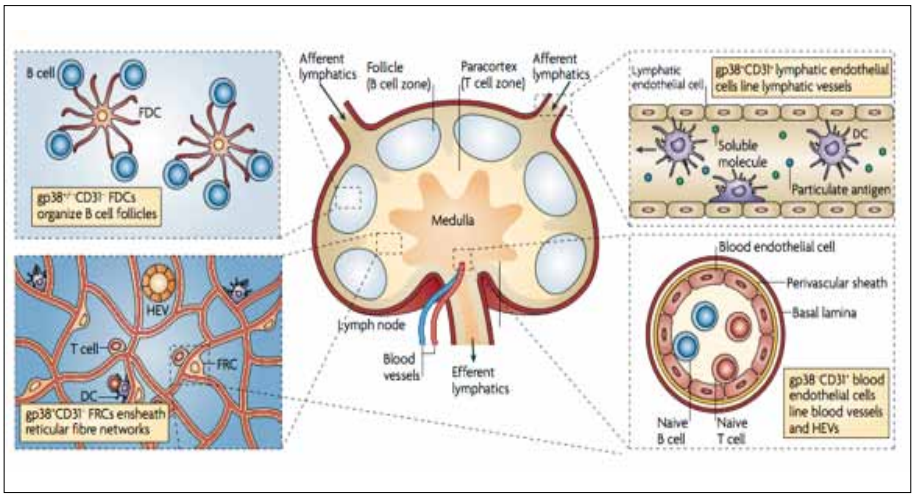

Fig. 2 Stromal cell populations and their location in the Ln. (Adapted from: Turley SJ, et Al., Nat Rev Immunol, 2010) Fibroblastic reticular cell (FRC) networks are found in T cell zones in the paracortex of the lymph node, where T cells and dendritic cells (DCs) encounter each other. Follicular dendritic cell (FDC) networks organise B cell follicles. Lymphatic endothelial cells form the afferent and efferent lymphatic vessels; they mediate the movement of leukocytes and lymph into the lymph nodes. Blood endothelial cells line blood vessels and form specialised structures known as high endothelial venules (HEVs), which are surrounded by a thick basal lamina and perivascular sheath.

of stromal cells in modulating the immune response, lead us to the idea that the environment where T cells get activated or inhibited by the presence of Tregs, can be conditioned to produce or abrogate the expression of survival factors and growth factor influencing the immune response.

The game

Transplanting a piece of tail skin expressing MHC class II molecules with a mismatch onto a recipient mouse is sufficient to induce an alloimmune response. Since our recipient mouse is Rag ko, a strain defined by the absence of T or B cells, we transfer different ratio of Tregs and Teff. Teff are monoclonal TcR transgenic cells that recognise and get activated by the MHC class II alloantigen expressed by the graft. Teff alloactivation, but not proliferation, is impaired by the presence of Tregs (Fig. 3a). To achieve tolerance we observed that the number of players in the lymph node field is determining the outcome: if more Tregs are in the lymph node then Teff (ratio > 1), a week after adoptive transfer, long term tolerance is achieved (Fig. 3b).

The field

T cells activation occurs in the Ln, where we can detect migration of donor Langerhans-DC expressing allo-MHC class II molecules. Our main research question is: are Tregs supported in their regulatory function by the Ln environment? The characterisation of this potential function of the Ln stroma can lead to the design of new therapeutic strategy that could modulate the suppressive capacity of Tregs.

First we wondered whether stromal cells can respond to activated T cells and if this is modulated by the presence of Tregs. Therefore, we isolated Ln stromal cells through enzymatic digestion and isolated them by cell sorting according to the expression of gp38 and CD31 (Fig 4a). Our group (not published) and others [1,2] showed that stroma cells are able to respond to IFN-γ produced by activated T cells by inducing the production of Nitric Oxide (NO) and, in turn, by inhibiting T cell

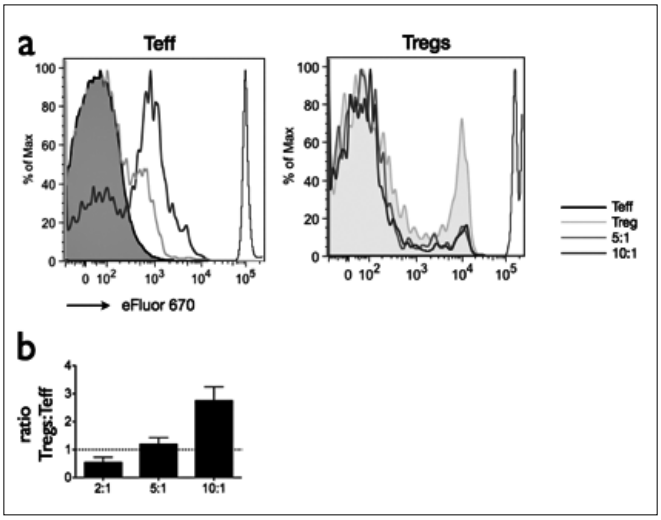

Fig. 3
a) Tregs do not stop, but delay proliferation of Teff upon antigen recognition (right panel). Also Tregs undergo proliferation (left panel).
b) The ratio between Tregs and Teff in the lymph node determines the transplant outcome. A ratio above 1 predicts tolerance.

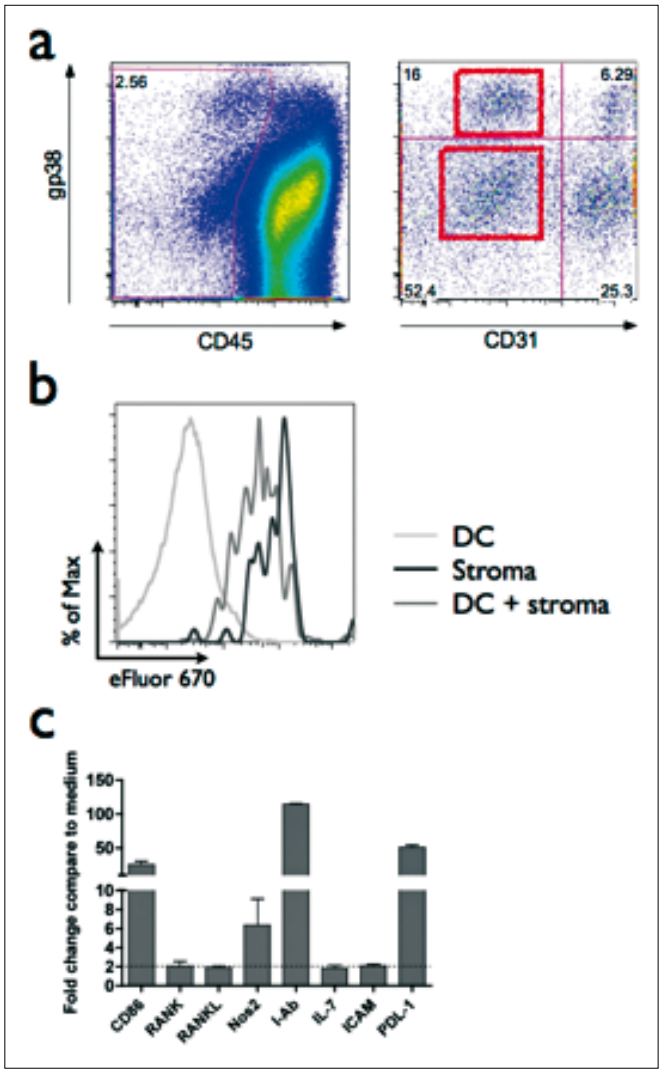

Fig. 4
a) Magnetic cell sorting strategy to isolate stroma cells. FRC are Gp38+CD31- and the DN population is negative for both markers. b) Stroma is able to inhibit the proliferation of DC-activated T cells. T cells were cultured with stroma only, stroma and DC 1:1 or only with DC and the proliferation was assessed after 7 days co-culture.

proliferation *in vitro* (Fig. 4b). IL7 production by stromal cells was upregulated as was RANKL, PDL1, MHC class II and CD86 (Fig. 4c), suggesting that the stroma might help the activation of T cells and control their activation status. In the presence of Tregs early in activation nothing happens. It seems that the message the stroma should get to be activated is missing. Indeed with high Treg numbers the IFN-γ in the lymph node is strongly reduced during activation. However, once tolerance is established, Tregs themselves start to transcribe IFN-γ. At the same time we detected an increased transcription of RANKL, PDL1, MHC class II and CD86 by stromal cells. The question that we currently aim to answer is whether the same factors can elicit different effects depending on the activation of T cells. A good candidate molecule produced by Ln stromal cells that could play an important role in helping Tregs survival and suppression is IL7 and the opportunity to collaborate with the group of Daniela Finke provides us with several tools to better define this potential mechanism. Indeed, during tolerance establishment *in vivo*, we observe a X-expression pattern of IL-7, suggesting a pleiotropic role of this cytokine depending on the presence of Tregs (Fig. 5a). To assess the effect of IL-7 on the suppressive capacity of Tregs we performed a suppression assay with or without mrIL-7 in which Teff were activated with anti-CD3/CD28 beads. In fact, we observed that the presence of mrIL-7 can substitute the presence of stromal cells in sustaining the suppressive capacity of Tregs (Fig. 5b). Furthermore, IL-7-conditioned Tregs showed an increased suppressive activity in co-culture with allo-activated Teff (Fig. 5c). The ongoing experiments *in vivo* will clarify the role of IL-7 in a more complex system. IL-7 is already being used in a clinical trial for bone marrow transplantation and correlations coming from patient data indicate that the Tregs pool can profit from this treatment. Can we convince the stroma to better sustain Tregs function? This is the challenge ahead of us and the main workers on this project are Maria and Mathias.

Other game, same players: outcome?

Transplantation of mismatch tissues or organs induces a sterile inflammation and the direct activation of T cells. What about inflammation induced by infection? Mathias is investigating the activation pattern of lymph node stroma cells during bacterial infections. Stroma cells express the TLR receptor family and therefore have the ability to respond to bacterial and danger pattern molecules (PAMPs). Indeed, stimulation with different PAMPs or TLR triggering molecules showed an activation pattern of the lymph node stroma, but the effect is not as dramatic as with IFN-γ stimulation. Usually, during bacterial infection, pro-inflammatory cytokines are released at the site of infection and, together with PAMPs, reach the Ln. The combination of cytokines and PAMPs

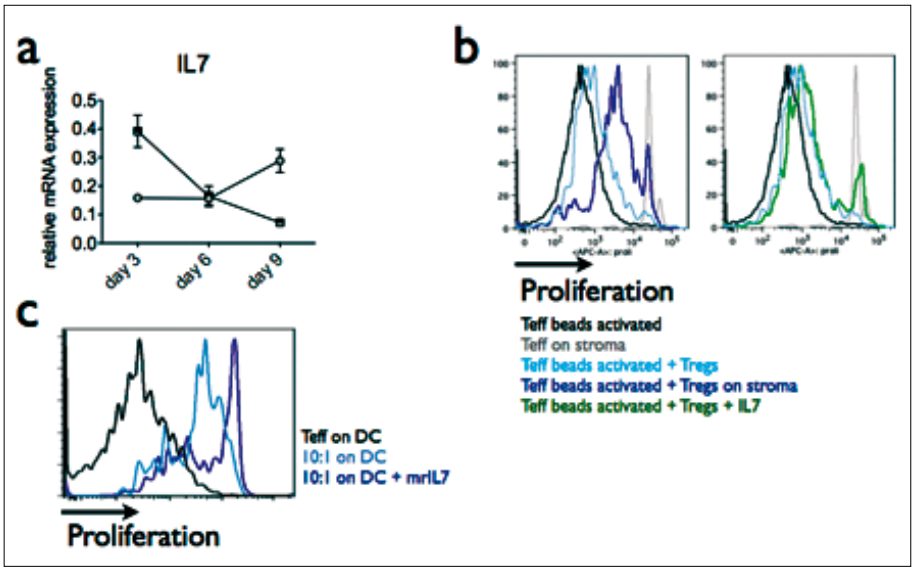

Fig. 5
a) IL-7 transcription is downregulated over time in lymph node stroma of mice transplanted and adoptively transferred with Teff (squares) and is upregulated over time in mice transplanted and adoptively transferred with Tregs:Teff at a ratio of 10:1 (circles).
b) Addition of IL-7 in co-culture can substitute the effect of stroma on ABM proliferation. Co-cultured performed for 3 days. T cells were activated with anti-CD3/28 beads and cultured in presence or absence of Ln stroma or 50 ng/ml rmIL-7.
c) IL-7 improves Tregs suppressive function in vitro. Proliferation of ABM cells in co-culture for 5 days with allogenic DC in presence or absence of Tregs.

increases the expression of ICAM, VCAM, cytokines and chemokines on the surface of stroma cells in the lymph nodes involving increased T cells recruitment. What is the role of stroma during infection? Sustaining T cell activation? Maintaining a structural integrity of the lymph node or helping Tregs dampen the cytokine storm? This research field is just at the beginning and we hope to soon better understand the role of the different players. Recently another group described the ability of lymph node stroma cells to clonally delete OT-I CD8 T cells in the context of the iFABP-tOVA model, where FRC were shown to be able to process ovalbumin and display OTI peptide on MHC class I molecules. Stroma cells delete in the periphery the autoreactive OVA cells[3]. A similar system for the CD4 T cells was never described.
During the evaluation of the ability of lymph node stroma cells to respond to TLR triggering, Nicolas observed *in vivo* and *in vitro* that TLR9 activation by immunostimulatory CpG oligodeoxynucleotides induced high level of MHC class II molecules at the surface of the lymph node stroma cells. In autoimmune diseases such as Systemic Lupus Erythematosous a defective clearance of dead and dying cells are known to contribute to its ethiopathogenesis. This defective clearance of apoptotic cells results in accumulation of apoptotic debris and necrotic DNA. Together with autoantibodies, necrotic DNA form DNA-containing immune complexes that will activate TLR9 signaling in dendritic cells. This excessive TLR9 activation drives production of IFN-γ, leading to an alteration of T and B-cell profiles, disruption of Treg networks, and exacerbates the clinical manifestation of lupus. In a lupus-prone mouse MRL/lpr, MHC class II expression is increased at the surface of Ln FRC (our own observation) and we are currently evaluating the cellular and molecular basis of this TLR9-mediated MHC class II expression in Ln stroma cells and its biological impact. We are especially interested in investigating the potential of Ln stroma cells to maintain peripheral tolerance by controlling the pool of autoreactive $CD4^+$ lymphocytes in a model of lupus.

Taken all together lymph node stroma cells are efficient players of the immunoregulation game. They can react to cytokines and microbial stimuli to sustain or down modulate the immune response. A better understanding of this cellular compartment will open new "regulatory" perspectives.

Acknowledgement
The Immunoregulation group would like to thank the sorting-facility for the incredible work performed with us, the animal care facility for their help and all the groups at the DBM that help us to "win" the game.

Simona Rossi Girard

Literature

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Otto Naegeli Preis 2012 an Markus Heim

Von links nach rechts: Markus Heim, H.J. Schürmann, Lars French. ***Foto: Vijay Shanker***

Markus Heim von der Forschungsgruppe Hepatology (DBM Hebelstrasse) hat am 24. April 2012 gemeinsam mit Lars French den mit 200'000 CHF dotierten Otto Naegeli Preis erhalten. Damit wurden zwei Experten ausgezeichnet, die mit ihrer translationalen biomedizinischen Forschung Grundlagen- und klinische Forschung miteinander verknüpfen. Markus Heim wurde für seine international anerkannte Forschung über die molekularen Mechanismen der Wechselwirkung zwischen dem Hepatitis C Virus und der Interferon-Signalgebung in der Leber geehrt. Er konnte mit seinem Team nachweisen, warum gängige Therapieansätze oft nicht den gewünschten Effekt erzielten. Der Otto Naegeli Preis wird alle zwei Jahre an herausragende Persönlichkeiten auf dem Gebiet der medizinischen Forschung verliehen.

Dissertationen

Mit der Doktorprüfung am 5. März 2012 schloss **Marco Osterwalder** von der Forschungsgruppe Developmental Genetics (Departement Biomedizin Mattenstrasse) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: «Genome-wide identification of Hand2 target regions in mouse embryos using dRMCE, a new genetic tool».

Am 29. März 2012 stellte sich **Michael Dill** von der Forschungsgruppe Hepatology (Departement Biomedizin Hebelstrasse) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: «Hepatitis C: Host-virus interactions and their impact on treatment of response».

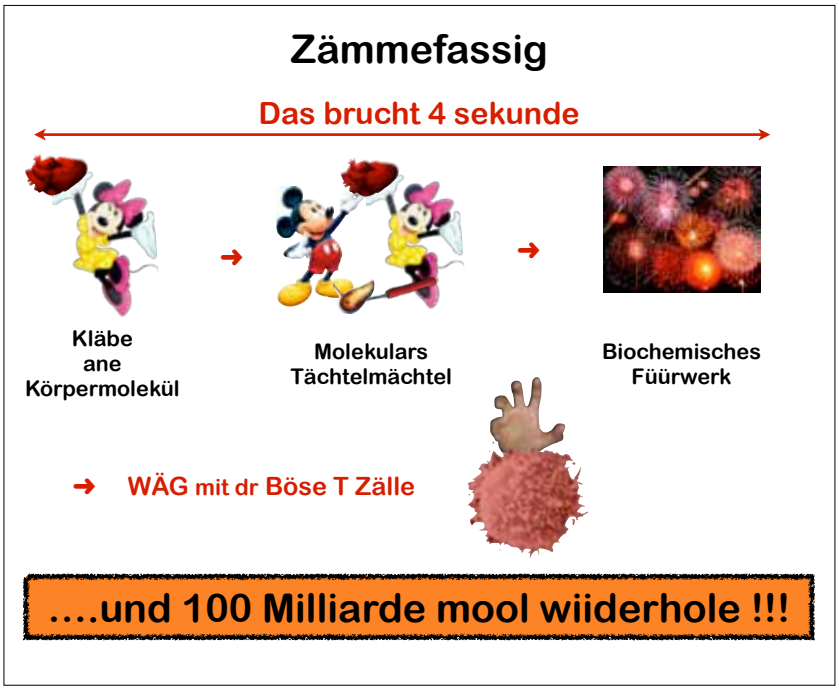
Venia docendi an Marianne Böni-Schnetzler

In ihrer Sitzung am 11. April 2012 erteilte die Regenz der Universität Basel Marianne Böni-Schnetzler von der Forschungsgruppe Diabetes Research (Departement Biomedizin Hebelstrasse) die Venia docendi für Endokrinologie, Diabetologie und Metabolismus.

Herzliche Gratulation an alle!

«Gute und sauböse Zelle»: Ed Palmer gewinnt Science Slam 2012

Ed Palmer von der Forschungsgruppe Transplantation Immunology (DBM Hebelstrasse) hat mit seiner Präsentation «Wäg mit de böse Immunzälle: E viersekündigs Tächtelmächtel und die Sach isch gritzt!» den von der Universität Basel und der Fachhochschule Nordwestschweiz getragenen Science Slam gewonnen. In dem Wettbewerb treten acht Wissenschaftler gegeneinander an und stellen in acht Minuten ihre Forschung auf unkonventionelle Weise vor. Wer diesen genialen Vortrag am 27. April 2012 verpasst hat, kann ihn auf dem Youtube-Kanal der Universität Basel nochmals anschauen. So unterhaltsam kann Wissenschaft ein!



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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 July 31, 2012.

Nature Immunology nature immunology Vol. 13 No. 5 May 2012 IF25,6

Peroxisome-derived lipids are self antigens that stimulate invariant natural killer T cells in the thymus

Federica Facciotti[1,5], Gundimeda S Ramanjaneyulu[1], Marco Lepore[1], Sebastiano Sansano[1], Marco Cavallari[1], Magdalena Kistowska[1,5], Sonja Forss-Petter[2], Guanghui Ni[3], Alessia Colone[4], Amit Singhal[4], Johannes Berger[2], Chengfeng Xia[3], Lucia Mori[1,4], & Gennaro De Libero[1,4]

The development and maturation of semi-invariant natural killer T cells (*i*NKT cells) rely on the recognition of self antigens presented by CD1d restriction molecules in thymus. The nature of the stimulatory thymic self lipids remains elusive. We isolated lipids from thymocytes and found that ether-bonded mono-alkyl glycerophosphates and the precursors and degradation products of plasmalogens stimulated *i*NKT cells. Synthetic analogs showed high potency in activating thymic and peripheral *i*NKT cells. Mice deficient in the peroxisomal enzyme glyceronephosphate O-acyltransferase (GNPAT), essential for the synthesis of ether lipids, had significant alteration of the thymic maturation of *i*NKT cells and fewer *i*NKT cells in both thymus and peripheral organs, which confirmed the role of ether-bonded lipids as *i*NKT cell antigens. Thus, peroxisome-derived lipids are nonredundant self antigens required for the generation of a full *i*NKT cell repertoire.

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Developmental Cell | Cell PRESS | 22, 837–848, April 17, 2012 IF13,9

GLI3 Constrains Digit Number by Controlling Both Progenitor Proliferation and BMP-Dependent Exit to Chondrogenesis

Javier Lopez-Rios[1], Dario Speziale[1,*], Dimitri Robay[1,5,*], Martina Scotti[3,*], Marco Osterwalder[1], Gretel Nusspaumer[2], Antonella Galli[1,6], Georg A. Holländer[2,4], Marie Kmita[3] and Rolf Zeller[1]

Summary

Inactivation of *Gli3*, a key component of Hedgehog signaling in vertebrates, results in formation of additional digits (polydactyly) during limb bud development. The analysis of mouse embryos constitutively lacking *Gli3* has revealed the essential GLI3 functions in specifying the anteroposterior (AP) limb axis and digit identities. We conditionally inactivated *Gli3* during mouse hand plate development, which uncoupled the resulting preaxial polydactyly from known GLI3 functions in establishing AP and digit identities. Our analysis revealed that GLI3 directly restricts the expression of regulators of the G_1–S cell-cycle transition such as *Cdk6* and constrains S phase entry of digit progenitors in the anterior hand plate. Furthermore, GLI3 promotes the exit of proliferating progenitors toward BMP-dependent chondrogenic differentiation by spatiotemporally restricting and terminating the expression of the BMP antagonist *Gremlin1*. Thus, *Gli3* is a negative regulator of the proliferative expansion of digit progenitors and acts as a gatekeeper for the exit to chondrogenic differentiation.

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Gastroenterology 2012; 142: 967–977 IF 12,0

Disruption of Notch1 Induces Vascular Remodeling, Intussusceptive Angiogenesis, and Angiosarcomas in Livers of Mice

Michael T. Dill[1], Sonja Rothweiler[1], Valentin Djonov[2], Ruslan Hlushchuk[2], Luigi Tornillo[3], Luigi Terracciano[3], Silvia Meili-Butz[1], Freddy Radtke[5], Markus H. Heim[1,4], David Semela[1,4]

Background & Aims: Notch signaling mediates embryonic vascular development and normal vascular remodeling; Notch1 knockout mice develop nodular regenerative hyperplasia (NRH). The pathogenesis of NRH is unclear, but has been associated with vascular injury in the liver sinusoids in clinical studies. We investigated the role of Notch1 signaling in liver sinusoidal endothelial cells (LSECs).

Methods: We studied *MxCre Notch1$^{lox/lox}$* mice (conditional knockout mice without tissue-specific disruption of *Notch1*); mice with hepatocyte-specific knockout were created by crossing *Notch1$^{lox/lox}$* with *Alb-Cre$^{+/-}$* mice. Portal vein pressure was measured; morphology of the hepatic vasculature was assessed by histologic and scanning electron microscopy analyses. We performed functional and expression analyses of isolated liver cells.

Results: *MxCre*-induced knockout of *Notch1* led to NRH, in the absence of fibrosis, with a persistent increase in proliferation of LSECs. *Notch1* deletion led to de-differentiation, vascular remodeling of the hepatic sinusoidal microvasculature, intussusceptive angiogenesis, and dysregulation of ephrinB2/EphB4 and endothelial tyrosine kinase. Time-course experiments revealed that vascular changes preceded node transformation. *MxCre Notch1$^{lox/lox}$* mice had reduced endothelial fenestrae and developed portal hypertension and hepatic angiosarcoma over time. In contrast, mice with hepatocyte-specific disruption of *Notch1* had a normal phenotype.

Conclusions: Notch1 signaling is required for vascular homeostasis of hepatic sinusoids; it maintains quiescence and differentiation of LSECs in adult mice. Disruption of Notch1 signaling in LSECs leads to spontaneous formation of angiosarcoma, indicating its role as a tumor suppressor in the liver endothelium.

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PNAS PNAS cgi/doi/10.1073/pnas.1108718109 IF 9,7

Protooncogene Ski cooperates with the chromatin-remodeling factor Satb2 in specifying callosal neurons

Constanze Baranek[1], Manuela Dittrich[1], Srinivas Parthasarathy[2], Carine Gaiser Bonnon[1,3], Olga Britanova[2], Dmitriy Lanshakov[2], Fatiha Boukhtouche[4], Julia E. Sommer[4], Clemencia Colmenares[5], Victor Tarabykin[2], Suzana Atanasoski[1,3]

First insights into the molecular programs orchestrating the progression from neural stem cells to cortical projection neurons are emerging. Loss of the transcriptional regulator Ski has been linked to the human 1p36 deletion syndrome, which includes central nervous system defects. Here, we report critical roles for Ski in the maintenance of the neural stem cell pool and the specification of callosal neurons. *Ski*-deficient callosal neurons lose their identity and ectopically express the transcription factor Ctip2. The misspecified callosal neurons largely fail to form the corpus callosum and instead redirect their axons toward subcortical targets. We identify the chromatin-remodeling factor Satb2 as a partner of Ski, and show that both proteins are required for transcriptional repression of *Ctip2* in callosal neurons. We propose a model in which Satb2 recruits Ski to the *Ctip2* locus, and Ski attracts histone deacetylases, thereby enabling the formation of a functional nucleosome remodeling and deacetylase repressor complex. Our findings establish a central role for Ski–Satb2 interactions in regulating transcriptional mechanisms of callosal neuron specification.

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European Cells and Materials CELLS & MATERIALS Vol. 23 2012 (pages 222-236) IF 9,6

Influence of *in vitro* maturation of engineered cartilage on the outcome of osteochondral repair in a goat model

S. Miot[1], W. Brehm[2,5], S. Dickinson[3], T. Sims[3], A. Wixmerten[1], C. Longinotti[4], A.P. Hollander[3], P. Mainil-Varlet[2], I. Martin[1]

Abstract

This study was designed to determine if the maturation stage of engineered cartilage implanted in a goat model of cartilage injury influences the repair outcome. Goat engineered cartilage was generated from autologous chondrocytes cultured in hyaluronic acid scaffolds using 2 d, 2 weeks or 6 weeks of pre-culture and implanted above hydroxyapatite/hyaluronic acid sponges into osteochondral defects. Control defects were left untreated or treated with cell-free scaffolds. The quality of repair tissues was assessed 8 weeks or 8 months post implantation by histological staining, modified O'Driscoll scoring and biochemical analyses. Increasing pre-culture time resulted in progressive maturation of the grafts *in vitro*. After 8 weeks *in vivo*, the quality of the repair was not improved by any treatment. After 8 months, O'Driscoll histology scores indicated poor cartilage architecture for untreated (29.7 ± 1.6) and cell-free treated groups (24.3 ± 5.8). The histology score was improved when cellular grafts were implanted, with best scores observed for grafts pre-cultured for 2 weeks (16.3 ± 5.8). As compared to shorter pre-culture times, grafts cultured for 6 weeks (histology score: 22.3 ± 6.4) displayed highest type II/I collagen ratios but also inferior architecture of the surface and within the defect, as well as lower integration with native cartilage. Thus, pre-culture of engineered cartilage for 2 weeks achieved a suitable compromise between tissue maturity and structural/integrative properties of the repair tissue. The data demonstrate that the stage of development of engineered cartilage is an important parameter to be considered in designing cartilage repair strategies.

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Biomaterials **Biomaterials** 33 (2012) 5085–5093 IF 7,8

Enhancing the biological performance of synthetic polymeric materials by decoration with engineered, decellularized extracellular matrix

Nasser Sadr[1,2,3], Benjamin E. Pippenger[1,2], Arnaud Scherberich[1,2], David Wendt[1,2], Sara Mantero[3], Ivan Martin[1,2], Adam Papadimitropoulos[1,2]

Abstract

Materials based on synthetic polymers can be extensively tailored in their physical properties but often suffer from limited biological functionality. Here we tested the hypothesis that the biological performance of 3D synthetic polymer-based scaffolds can be enhanced by extracellular matrix (ECM) deposited by cells in vitro and subsequently decellularized. The hypothesis was tested in the context of bone graft substitutes, using polyesterurethane (PEU) foams and mineralized ECM laid by human mesenchymal stromal cells (hMSC). A perfusion-based bioreactor system was critically employed to uniformly seed and culture hMSC in the scaffolds and to efficiently decellularize (94% DNA reduction) the resulting ECM while preserving its main organic and inorganic components. As compared to plain PEU, the decellularized ECM-polymer hybrids supported the osteoblastic differentiation of newly seeded hMSC by upregulating the mRNA expression of typical osteoblastic genes (6-fold higher bone sialoprotein; 4-fold higher osteocalcin and osteopontin) and increasing calcium deposition (6-fold higher), approaching the performance of ceramic-based materials. After ectopic implantation in nude mice, the decellularized hybrids induced the formation of a mineralized matrix positively immunostained for bone sialoprotein and resembling an immature osteoid tissue. Our findings consolidate the perspective of bioreactor-based production of ECM-decorated polymeric scaffolds as off-the-shelf materials combining tunable physical properties with the physiological presentation of instructive biological signals.

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The Journal of Neuroscience *The Journal of Neuroscience* April 18, 2012, 32(16):5654 –5666 IF 7,2

Neurogenic Subventricular Zone Stem/Progenitor Cells Are Notch1-Dependent in Their Active But Not Quiescent State

Onur Basak[1,*], Claudio Giachino[1,2,*], Emma Fiorini[3], H. Robson MacDonald[3], and Verdon Taylor[1,2]

The adult mammalian forebrain contains neural stem/progenitor cells (NSCs) that generate neurons throughout life. As in other somatic stem cell systems, NSCs are proposed to be predominantly quiescent and proliferate only sporadically to produce more committed progeny. However, quiescence has recently been shown not to be an essential criterion for stem cells. It is not known whether NSCs show differences in molecular dependence based on their proliferation state. The subventricular zone (SVZ) of the adult mouse brain has a remarkable capacity for repair by activation of NSCs. The molecular interplay controlling adult NSCs during neurogenesis or regeneration is not clear but resolving these interactions is critical in order tounderstand brainhomeostasisandrepair. Using conditional genetics and fate mapping, we show that Notch signaling is essential for neurogenesis in the SVZ. By mosaic analysis, we uncovered a surprising difference in Notch dependence between active neurogenic and regenerative NSCs. While bothactive and regenerative NSCs depend upon canonical Notch signaling, *Notch1*-deletion results in a selective loss of active NSCs (aNSCs). In sharp contrast, quiescent NSCs (qNSCs) remain after *Notch1* ablation until induced during regeneration or aging, whereupon they become Notch1-dependent and fail to fully reinstate neurogenesis. Our results suggest that Notch1 is a key component of the adult SVZ niche, promoting maintenance of aNSCs, and that this function is compensated in qNSCs. Therefore, we confirm the importance of Notch signaling for maintaining NSCs and neurogenesis in the adult SVZ and reveal that NSCs display a selective reliance on Notch1 that may be dictated by mitotic state.

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Cardiovascular Research | Cardiovascular Research | (2012) 93, 1–10 IF 6,0

T-cadherin attenuates insulin-dependent signalling, eNOS activation, and angiogenesis in vascular endothelial cells

Maria Philippova[1,*], Manjunath B. Joshi[1,*], Dennis Pfaff[1], Emmanouil Kyriakakis[1], Kseniya Maslova[1], Paul Erne[2], Thérèse J. Resink[1,*]

Aims

T-cadherin (T-cad) is a glycosylphosphatidylinositol-anchored cadherin family member. Experimental, clinical, and genomic studies suggest a role for T-cad in vascular disorders such as atherosclerosis and hypertension, which are associated with endothelial dysfunction and insulin resistance (InsRes). In endothelial cells (EC), T-cad and insulin activate similar signalling pathways [e.g. PI3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR)] and processes (e.g. angiogenesis). We hypothesize that T-cad is a regulatory component of insulin signalling in EC and therefore a determinant of the development of endothelial InsRes.

Methods and results

We investigated T-cad-dependent effects on insulin sensitivity using human EC stably transduced with respect to T-cad overexpression or T-cad silencing. Responsiveness to insulin was examined at the level of effectors of the insulin signalling cascade, EC nitric oxide synthase (eNOS) activation, and angiogenic behaviour. Overexpression and ligation of T-cad on EC attenuates insulin-dependent activation of the PI3K/Akt/mTOR signalling axis, eNOS, EC migration, and angiogenesis. Conversely, T-cad silencing enhances these actions of insulin. Attenuation of EC responsiveness to insulin results from T-cad-mediated chronic activation of the Akt/mTOR-dependent negative feedback loop of the insulin cascade and enhanced degradation of the insulin receptor (IR) substrate. Coimmunoprecipitation experiments revealed an association between T-cad and IR. Filipin abrogated inhibitory effects of T-cad on insulin signalling, demonstrating localization of T-cad-insulin cross-talk to lipid raft plasma membrane domains. Hyperinsulinaemia up-regulates T-cad mRNA and protein levels in EC.

Conclusion

T-cad expression modulates signalling and functional responses of EC to insulin. We have identified a novel signalling mechanism regulating insulin function in the endothelium and attribute a role for T-cad up-regulation in the pathogenesis of endothelial InsRes.

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Cardiovascular Research | Cardiovascular Research | (2012) 93, 454–462 IF 6,0

NOX2-derived reactive oxygen species are crucial for CD29-induced pro-survival signalling in cardiomyocytes

Berit I. Rosc-Schlüter[1], Stéphanie P. Häuselmann[1], Vera Lorenz[1], Michika Mochizuki[1], Federica Facciotti[2], Otmar Pfister[1,3], Gabriela M. Kuster[1,3]

Aims

The highly expressed cell adhesion receptor CD29 (b1-integrin) is essential for cardiomyocyte growth and survival, and its loss of function causes severe heart disease. However, CD29-induced signalling in cardiomyocytes is ill defined and may involve reactive oxygen species (ROS). A decisive source of cardiac ROS is the abundant NADPH oxidase (NOX) isoform NOX2. Because understanding of NOX-derived ROS in the heart is still poor, we sought to test the role of ROS and NOX in CD29-induced survival signalling in cardiomyocytes.

Methods and results

In neonatal rat ventricular myocytes, CD29 activation induced intracellular ROS formation (oxidative burst) as assessed by flow cytometry using the redox-sensitive fluorescent dye dichlorodihydrofluorescein diacetate. This burst was inhibited by apocynin and diphenylene iodonium. Further, activation of CD29 enhanced NOX activity (lucigenin-enhanced chemiluminescence) and activated the MEK/ERK and PI3K/Akt survival pathways. CD29 also induced phosphorylation of the inhibitory Ser9 on the pro-apoptotic kinase glycogen synthase kinase-3β in a PI3K/Akt- and MEK-dependent manner, and improved cardiomyocyte viability under conditions of oxidative stress. The ROS scavenger MnTMPyP or adenoviral co-overexpression of the antioxidant enzymes superoxide dismutase and catalase inhibited CD29-induced pro-survival signalling. Further, CD29-induced protective pathways were lost in mouse cardiomyocytes deficient for NOX2 or functional $p47^{phox}$, a regulatory subunit of NOX.

Conclusion

$p47^{phox}$-dependent, NOX2-derived ROS are mandatory for CD29-induced pro-survival signalling in cardiomyocytes. These findings go in line with a growing body of evidence suggesting that ROS can be beneficial to the cell and support a crucial role for NOX2-derived ROS in cell survival in the heart.

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European Respiratory Journal 2012; 39: 705–711 IF 5,9

Cigarette smoke inhibits lung fibroblast proliferation by translational mechanisms

N. Miglino[1], M. Roth[1], D. Lardinois[2], C. Sadowski[2], M. Tamm[1] and P. Borger[1]

Abstract:
Cigarette smoke is a major cause of chronic obstructive pulmonary disease (COPD) and emphysema. Although cigarette smoke represses cellular proliferation, the molecular mechanisms underlying this phenomenon are unknown. CCAAT/enhancer-binding proteins (C/EBPs) are key regulators of cell cycle progression, differentiation and pro-inflammatory gene expression, are regulated predominantly at the translational level and may be involved in the pathogenesis of COPD. The aim of this study was to assess the effect of cigarette smoke on proliferation and the expression and translational regulation of C/EBPα and C/EBPβ in nondiseased primary human lung fibroblasts.
Fibroblasts were exposed to cigarette smoke-conditioned medium (10% and 20% for 24 h). Proliferation was determined by [^{3}H]thymidine incorporation. Protein expression levels were determined by immunoblotting and translation was monitored using a translation control reporter system.
Cigarette smoke significantly reduced fibroblast proliferation and significantly upregulated fulllength C/EBPα and C/EBPβ proteins due to a shift in the translational control of *CEBPA* and *CEBPB* mRNAs. This shift involved the re-initiation of mRNA translation *via* the regulatory upstream open reading frame, which coincided with increased interleukin-8 release and a decrease in functional elastin level.
These findings provide a novel mechanism to understanding the tissue remodelling observed in the lungs of COPD patients.

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The Journal of Biological Chemistry jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol.287, Number 13, March 23, 2012 IF 5,3

Proteasomal Inhibition Restores Biological Function of Mis-sense Mutated Dysferlin in Patient-derived Muscle Cells*

Bilal A. Azakir, Sabrina Di Fulvio, Jochen Kinter, and Michael Sinnreich[1]

Dysferlin is a transmembrane protein implicated in surfacemembrane repair of muscle cells. Mutations in dysferlin causethe progressive muscular dystrophies Miyoshi myopathy, limbgirdle muscular dystrophy 2B, and distal anterior compartmentmyopathy. Dysferlinopathies are inherited in an autosomalrecessive manner, and many patients with this disease harbormis-sense mutations in at least one of their two pathogenicDYSF alleles. These patients have significantly reduced or absent dysferlin levelsin skeletal muscle, suggesting that dysferlin encoded by mis-sense alleles is rapidly degraded by the cellular quality control system. We reasoned that mis-sensemutated dysferlin, if salvaged from degradation, might be biologically functional. We used a dysferlin-deficient human myoblast culture harboring the common R555W mis-sense alleleand a DYSF-null allele, as well as control human myoblast cultures harboring either two wild-type or two null alleles. We measured dysferlin protein and mRNA levels,resealing kinetics of laser-induced plasmalemmal wounds, myotube formation, and cellular viability after treatment of the human myoblast cultures with the proteasome inhibitors lactacystin orbortezomib (Velcade). We show that endogenous R555Wmis-sense mutated dysferlin is degraded by the proteasomalsystem. Inhibition of the proteasome by lactacystin or Velcade increases the levels of R555W mis-sense mutated dysferlin. This salvaged protein is functional as it restores plasmamembrane resealing in patient-derived myoblasts and reverses their deficit in myotube formation. Bortezomib and lactacystin did not cause cellular toxicity at theregimen used.Our results raise the possibility that inhibition of the degradation pathway of mis-sense mutated dysferlin could be usedas a therapeutic strategy for patients harboring certain dysferlin mis-sense mutations.

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

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Hepatology

Ilona Król
Hepatology

Ronny Nienhold
Exp. Hematology

Sophia Thanei
Clin. Immunology

Rubén Lopez
Perioperative Patient Safety

Ori Rokach
Perioperative Patient Safety

DEPARTEMENT BIOMEDIZIN KLINGELBERG-STRASSE

Camille Viviani
Cellular Neurophysiology

Jan Schulz
Cellular Neurophysiology

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN HEBELSTRASSE

Maumita Bhattacharjee
Tissue Engineering
Silvana Bösch
Immunonephrology
Laura Binkert
Inner Ear Research
Alessia Ramseier
Inner Ear Research
Corinna Bildl
Animal Care
Sarah Dimeloe
Immunobiology
Marco Fischer
Immunobiology
Audrey Frachet
Signaling
Nicholas Sanderson
Clin. Neuroimmunology
Ondrej Stepanek
Transplantation Immunology
Sébastien Wieckowski
Cancer Immunology

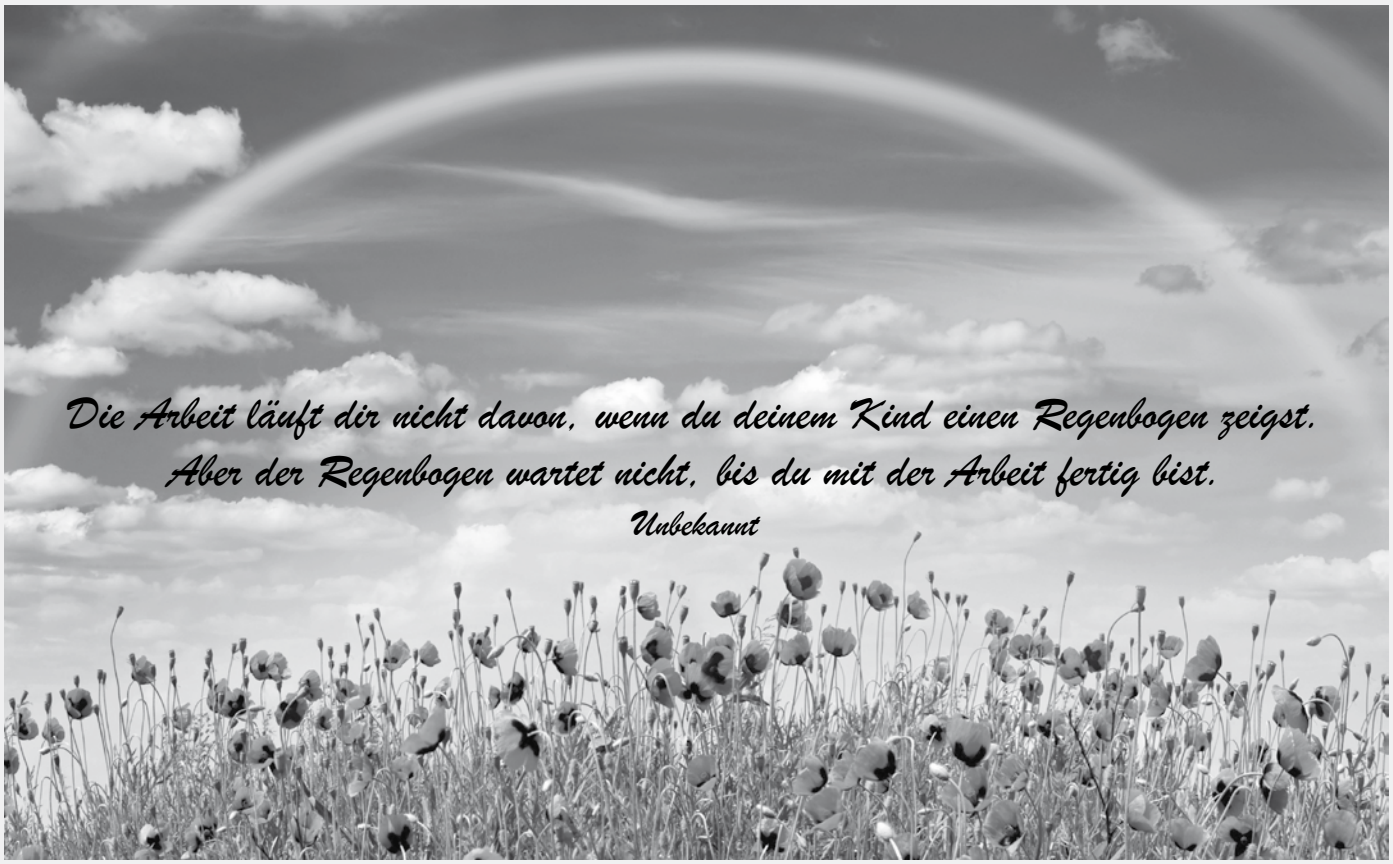
DEPARTEMENT BIOMEDIZIN KLINGELBERGSTRASSE

Liyi Li
Cellular Neurophysiology
Dieter Kunz
Synaptic Plasticity

Michael Abanto neuer Biooptiker

Am 1. Juni 2012 hat Mike Abanto seine Tätigkeit als Biooptiker am DBM Hebelstrasse begonnen. Mike hat an der Tufts University und der University of Utah in den USA studiert und anschliessend bei Pico Caroni am FMI promoviert. Die Mikroskopie ist sein Leben, man kann aber auch sehr gut mit ihm über Rugby (das er professionell betrieben hat), Klettern, Bergsteigen, Skifahren, Tauchen und was die Sportwelt sonst noch so hergibt philosophieren … Wir wünschen Mike viel Erfolg und Freude bei seiner neuen Tätigkeit!

Heidi Hoyermann



Congratulations

Das DBM gratuliert ganz herzlich!

Mats Fritz Karow
Geboren am 08.04.2012

Noah Pietro Miglino
Geboren am 18.04.2012

Levi Neumann
Geboren am 16.03.2012

Timothée Castets
Geboren am 12.03.2012

Herzlich willkommen, allerseits!

Triathlon

It is hard to believe, but triathlon was only included as an "official" Olympic sport in 2000. As the Olympics are fast approaching, so is the anticipation of the 2012 gold medallists. The first Olympic winners of the mens' and womens' triathlon events were Simon Whitfield of Canada and Brigitte McMahon of Switzerland. Their performances on that day were a result of years of steady training and racing; they made triathlon look easy. However, most people see a triathlon and underestimate its difficulty. The arduousness lies in optimising each component so that there is no weakness in any one of the three events, and once optimised the ability to race at threshold level (or the point just below puking, in layman's terms). Before I get into the specifics of triathlon I will give an overview of the general components of the sport first.

Triathlon consists of sequentially swimming, biking, and running without any breaks. The races range from 1–17 hours and there are four distances that competitors can participate in: a sprint distance (750 m swim, 20 km bike, 5 km run), Olympic distance (1.5 km swim, 40 km bike, 10 km run), half Ironman (1.9 km swim, 90 km bike, 21 km run), and full Ironman (3.8 km swim, 180 km bike, 42 km run). The momentary respite between events is called a transition and is known as the fourth stage of any triathlon. In the early development of a triathlete's career these periods act as a momentary pause to catch one's breath as the wetsuit is removed, the bike helmet is put on, and the shoes are changed. During the first couple of races of a triathlete's career several minutes are lost, but by the time a competitor reaches an elite level, the racer will have perfected the first transition down to approximately 50 seconds and the second transition to 35 seconds.

A race at the amateur level will begin either at 7 or 8 on a Sunday morning. This is primarily so that that the bike course can be completed on "quiet" roads, or at least roads with very few cars on them. Prior to a race there is a buzz at the headquarters. Competi-

Swim start of Ironman Canada

tors need to arrive at least 1.5 hours before the start to allow time to "check-in", attach race numbers to race belts and bikes, find the area in race transition for the bike, lay-out all equipment that will be needed for the race, fill-up water bottles, attach timing chips to ankles, put-on the wetsuit, and then wait. Waiting is by far the most difficult aspect as nerves can take over, but generally the moment of anxiety is fleeting as races begin on time. However, there was one occasion that a race that I participated in was delayed by two hours because of fog on the water, this was the Ironman.

The Ironman is the biggest of the triathlon events and as Ironman triathletes like to say "it is a long day at the office' since the race begins at 7 AM and finishes at midnight. Each event has a cut-off time; if one doesn't complete the section in the allotted time then the competitor is asked to discontinue. The 3.8 km swim is given 2 hours and 20 minutes, although most athletes will complete this in approximately one hour. The bike portion must be completed by 5 PM the same day, meaning if one is a good swimmer one can use the "extra" time to complete the bike portion. Generally, the 180 km cycle course is completed in 5-6 hours. The final 42.2 km marathon must be completed by midnight, or in the case of Ironman Switzerland, by 11 PM. The competitors crossing the line just before the cut-off time get as much cheering from the spectators as the race winners. I knew a competitor who crossed the line of Ironman France at 11:59:42 PM!

Preparations for these events usually begin up to a year in advance as one has to build up the training gradually. This is not only to prevent injury, but also to prevent mental burn-out from the sheer volume of training required. During this time one has to learn what it feels like to cope with tired muscles, constant hunger, and constant fatigue. In addition, it is important to practice "eating" while in constant motion. One might think that is a silly thing to practice, but funny things start to happen to the stomach after several hours of constant activity and finding foods/liquids/gels that do not give you a stomach ache is a feat in itself. In these types of races it is always important to keep "the tank topped-up" meaning that if you find yourself hungry or thirsty you are closer to dehydration than you think. You would be amazed how many competitors one sees after these races in the medical tents with i.v. drips attached to them!

The first time I participated in an Ironman was Ironman Canada in 2001. Triathlon was becoming more popular and entrance to these races was becoming difficult to obtain. I had travelled out the year before to cheer on my friends in the race of 2000 so that I could be in line for the sign-up for the following year. The race of 2000 was memorable primarily because the day had started with hot, bright sunshine, but by the time the competitors had cycled to the mountain summit there was snow and medical tents were set-up for hypothermia. Seeing these events unfold showed me that partaking in this type of event should not be taken lightly.

The start time of Ironman Canada 2001 was 7 AM sharp, but the race officials wanted competitors to be there for a 6 AM race briefing and a 6:30 AM "lock-in". This was a pen, by the water's edge, where the competitors waited for the sound of the canons to start the race. Transition set-up for these big events is done the day before, so on race morning all I had to do was pump my tires, prepare my energy drink bottles, and make sure the clothing that I needed after each event was ready. The atmosphere was electric as the two thousand competitors with their friends and supporters were all there. Music was blaring, the sun was shining, and the anticipation was building. All of the year's previous hard work was going to culminate in this race. It was going to be a good day!

Waiting for half an hour for the biggest race of your life is not easy, nor is it easy for the other 1999 competitors beside you. It is really important at the start of any Ironman to not swallow the lake water when there is a mass start. Can you guess why? The moment the canons sound a mob situation occurs. This is by far the scariest part of any Ironman because the more people around you in the water, the more kicking and punching that occurs. Goggles fly off, swimmers are pushed underwater; the whole process is scary. It is

Bike transition of Ironman Canada

important to keep calm and remain strong and always look for clear water. The buoys that signify the turn-around are usually at the other end of the lake and are difficult to find. Swimmers follow the feet of the person in front and this creates a massive vacuum that makes the swimming easier. Lifeguards in canoes signify the perimeter of the swim area. Reaching the turn-around point is also intense as many swimmers merge around one buoy. There are usually divers at these congestion points underneath the water to ensure that no one drowns. Once the congestion clears one just gets on with it and finishes swimming. By the time you see the shore you are ready for a change of activity.

Swimming continuously for over an hour can make one dizzy and at the exit of the swim there are people to help you keep your balance. First thing that many competitors do is guzzle a cola once the wetsuit has come off. This is not only for the sugar content, but the acidity does a pretty good job at killing anything that you may have swallowed in the water. You will never taste a cola as good as this in your life. Once changed, it is on to the bike for the next 5-6 hours.

The biggest problem with the 180 km bike course is boredom and coping with the numerous mood swings that one experiences while riding alone for many hours. At the beginning everything is new and invigorating because one is excited to be on the bike and not swimming! Unfortunately, by the fourth hour this novelty has worn-off. Your body hurts, you're tired of the food that you are snacking on, and you keep asking yourself "why am I doing this?" However, despite that, Ironman racing is a fantastic way to see a country and these bike courses have allowed me to see places of Canada, Switzerland, UK, and Austria that I never would have seen otherwise.

The last 20 km of the bike are generally the hardest, but in the case of Ironman Canada it was all downhill. We had three mountains to climb on that course and that had taken some of the monotony out of being on the bike for so long. I was riding slower than the men I had been training with, but several had to stop or drop-out because of bike mechanical issues that had been caused because of a vandal who decided to put tacks on the road. One has to be prepared not only for the proper functioning of your own body, but that of

Race winner of Ironman Canada

your bike as well. There are "feed" stations along the course consisting of bags that have been pre-packed by yourself for food that you may need at the halfway point of the bike. There is also a "mechanical" van that drives around the course, but with hundreds of competitors to look after it is often quicker to repair your own flats or broken chains.

Arriving into transition for the marathon is exciting. Like the swim, one is very happy to get-off the bike and have a change in activity. Crowds are cheering and this is usually the time when the first male pro is finishing the run. It is a bit disheartening when one sees the race winner finishing the marathon when one is just about to begin it. Like the biking section, the first half of the marathon is fun. There are lots of people around and one can usually pair up with other runners for support; this removes some of the boredom. In addition, the feeding stations along the run route also have tonnes of supporters to encourage the runners. In the case of Ironman Canada, the run was along a lake. It was an out-and-back so you could see exactly how close your nearest competitor was. When I started the marathon it was 35°C without any shade. It was imperative to be shielded from the sun, reapply sunscreen, and be constantly hydrated. The most difficult part was the last 10 km. I could smell greasy fries and all I wanted was to taste some. This was also the point at which I saw Sister Madonna Buder who is also known as the "Iron Nun". At the time she was a 71 year old multiple Ironman record holder for her age group and it was remarkable to see someone that age participating in this event.

By the last 2 km I heard the cheers of the crowd that spurred me on to finish the race. In Ironman it doesn't matter if you finished first or last; the crowd cheers each competitor the same. As I approached the last kilometre I saw my family and friends cheering me and heard the announcer say "Congratulations! You are an Ironman!" After crossing the finish line everyone is quickly given a medical check and then whisked away for a massage and pizza. The soreness and tiredness remains for a few weeks as well as the hunger, but in the end it is all worth it because you are an Ironman!

Brynn Kvinlaug

Wien ist anders

Es ist Freitag, 14.00 Uhr – endlich Wochenende, nichts wie raus aus dem Büro. Ich lasse in gutem Wiener Stil alles stehen und liegen – eine der ersten Fertigkeiten, die ich hier gelernt habe. Es gibt nichts, aber auch gar nichts, was nicht warten könnte bis Montag. Nur keinen Stress aufkommen lassen, das wird sich schon auch noch nächste Wochen ausgehen. Jetzt erst mal ins wohl verdiente Wochenende: Ausspannen, Geniessen. Eine Freundin aus der Schweiz hat sich angekündigt. Wir werden einige ihrer Lieblingsbeisln und -orte unsicher machen, auf jeden Fall viel essen und trinken, wir sind schliesslich in Wien, wo das zu (fast) jeder Tages- und Nachtzeit in über 4000 Lokalen in 23 Bezirken möglich ist.

Endlich ist der lang ersehnte Frühling da. Ich schlendre vom Büro in der Gonzagagassen durch den Tiefen Graben Richtung Freyung in der Wiener Altstadt zu einem meiner vielen Lieblingsschanigärten. Nach endlosen Winterwochen wolkenverhangenen Himmels sauge ich die Sonnenstrahlen dieses warmen Tages in mich auf. In der Trafik ums Eck kaufe ich die neueste Wochenausgabe des Falters für die Übersichtsliste mit dem Veranstaltungsprogramm der Stadt und die fachkundigen Artikel und Kommentare zu den neuesten Politskandalen.

Obwohl die Bedienung im Kaffeehaus im Schottenstift wie hier vielerorts nicht zu gebrauchen ist, lockt der ruhige Gastgarten im Hinterhof. Ribisel- und Mohntorten zählen zu den besten der Stadt, und das entschädigt fast für das schlamperte Personal. Ich sitze vor einer Melange mit Milchschaum anstelle des traditionellen Schlagobers und lese kopfschüttelnd im Falter über eine Staatsanwaltschaft, die der Bundesjustizministerin weisungsunterstellt ist; über im Ministerium liegen gebliebene oder verloren gegangene und dadurch verjährte Beweisakten im Zusammenhang mit brisanten Politikeraffären der letzten Jahre; über die Lockerung des Anti-Korruptionsgesetzes, damit Geschäftsgeschenke, wie Eintrittskarten zu den Salzburger Festspielen, wieder verschickt werden können; über die Forderung der Kritiker nach mehr Rechtsstaatlichkeit. Österreich ist eine Bananenrepublik, die mit Vorliebe Freunderlwirtschaft betreibt; und die Wiener betonen immer wieder, dass in ihrer Stadt der Balkan anfängt.

Spätestens jetzt bin ich reif für einen Almdudler, oder vielleicht doch eher einen Radler oder Aperol Spritz. Dafür schau ich, ob im Café Korb um diese Zeit noch ein Tisch zu ergattern ist. Auf jeden Fall

Hofburg

muss ein Schoko-Palatschinken her. Aber vorher könnte ich jetzt eigentlich noch einen Zwiebelrostbraten mit Nockerln und dazu ein Achterl Veltliner nehmen. Oder doch ein Gulasch mit Knödln, Eierschwammerln oder Fleckerln? Wiener Schnitzel geht eh immer.

«Wie wär's mit einem Eis beim Bortolotti in der Mariahilfer Strasse?», fragt meine Freundin, «Ich fahr mit einem City Bike rüber.» Sie sitzt im CAT auf dem Weg vom Flughafen Schwechat in die Stadt. Da ich draussen im 17. Bezirk wohne, logiert sie lieber in ihrer heiss geliebten grosszügigen Ferienwohnung, die eine Wiener Freundin von mir vermietet - eine traumhafte typische Wiener Altstadtwohnung mit Blick auf den Prater und das Riesenrad, ein Katzensprung vom Zentrum entfernt. «Wir könnten ausgiebig Shoppen, beim Café Ritter reinschauen, runter ins MuseumsQuartier, vielleicht ins Glazis, gehen. Und falls wir dann noch Lust haben, im Bohème am Spittelberg ein paar Arien reinziehen.» Das tönt nach einem gut Wienerischen Samstagsprogramm. Abends beglücken wir dann die Bonbonniere Bar, die Wein-Bar beim Rathaus und die Urania-Bar und enden auf dem Weg nach Hause im 2. Bezirk im Künstlerviertel um den Karmelitermarkt auf ein Fluchtachterl im Skopik & Lohn, bevor wir völlig erschöpft in die Federn sinken.

Da das sommerliche Wetter anhält, ist Auskatern im geräumigen Schanigarten des Café Dommayer angesagt – *die* Adresse für die besten Kuchenstücke in ganz Wien. Wir befinden uns im distinguierten teuren grünen 13. Aussenbezirk Hietzing – ein Dorf in der Stadt, wie eigentlich jeder Bezirk in Wien ein Dorf – ein Grätzel – mit ganz eigener Atmosphäre, typischen Bewohnern und Gepflogenheiten ist. In Hietzing trifft sich die Wiener High Society und wer gern dazu gehören möchte; man ist hier wer und zeigt es offenherzig mit viel Nerz und Klunkern. Ich verschlucke mich fast, als zwischen all den Schickimickis, dem Herrn Hofrat, der Frau Oberstudienrätin und dem Mag. Dr. XY, plötzlich die Literaturnobelpreisträgerin, Elfriede Jelinek, persönlich an unserem Tisch vorbeischwebt mit der ihr eigenen Eleganz, die so weit entfernt ist vom

Riesenrad

Wiener hoch gestylten Frauendurchschnitt. Meine Freundin erblasst ehrfürchtig und findet es einfach leiwand in dieser dörflichen Weltmetropole.

Kein Hietzing-Besuch ohne ein dunkles Seidel beim Brandauer. Wir schauen amüsiert zu, wie die Piefkes am Nachbartisch genüsslich eine der grössten Portionen Spare-Ribs der Stadt verzehren. Seit ich hier lebe hat sich mein Fleischkonsum mindestens verdoppelt und ist im Vergleich zu einem Wiener immer noch eher bescheiden. Am Nebentisch zur andern Seite jammern schlecht gelaunte Wiener über die Kürzung der Mindestsicherung. Tatsächlich gibt es jetzt anstatt 855 nur noch 773 Euro monatlich – das Ganze bei einer Armutsschwelle von 1'031 Euro und Arbeitslosigkeit von 9%. Meine Freundin kann das fast genauso wenig glauben wie die Tatsache, dass durch alle Bildungsschichten der durchschnittliche Gehaltsunterschied zwischen Männern und Frauen bis zu über 50% betragen kann. Zudem sitzen nur gerade 13% der Frauen in Führungspositionen mit Entscheidungskompetenzen. Und noch weniger glaubt sie, dass sie für den gleichen Job in der Schweiz mindestens das Doppelte bis fast Dreifache verdient.

In der Ausgangspassage des Brandauers locken die Schlossstubn und ein gutes Glasl Prosecco

direkt vom Fass. Weil das so spottbillig ist, bleibt es natürlich nicht bei dem einen. Amüsiert beobachten wir die aufgedonnerten Wasserstoffblondinen mit den Versace-Handtaschen auf den Barhockern, die sich von ihren ausgedehnten Shopping-Trips erholen und schon mal auf den Abend einstimmen. Im Verlauf der nächsten Stunden werden sich hier Szenen abspielen, die man sonst nur in Soap Operas zu sehen bekommt: Leute werden sich furchtbar betrinken, die Ladies werden auf ihren High Heels nur mit Mühe und wenig graziös zur Toilette schwanken. Paare werden sich formieren, unverhohlen anfangen, miteinander zu flirten und schliesslich zu knutschen, um sich kurze Zeit später neu zu formieren. Ganze Beziehungsdramen werden inszeniert, angestachelt von Neid und Rachegelüsten. Beste Freundinnen spannen sich die Männer gnadenlos vor der Nase aus. Der Speichelaustausch gewisser Personengruppen in dieser Bar kann an einem Abend enorm sein. Wiener Mann und Frau genieren sich wenig, man sieht das nicht so eng und nimmt es noch weniger ernst. Wien ist freizügig – nicht nur am stadteigenen FKK-Strand entlang der Donau.

Wir lassen den Tag mit einem Spaziergang im nahen wunderschönen weitläufigen Schlosspark von Schönbrunn ausklingen. Die Zeit reicht wieder einmal nicht fürs magische Palmenhaus und auch nicht für den Tierpark. Wir lassen den Abend ausklingen mit dem Blick über die Stadt vom Garten der Villa Aurora aus, vor uns auf den Tellern Cordon bleus mit griechischer und asiatischer Füllung, gefolgt von einem Kaiserschmarrn. Bald schon heisst es Abschied nehmen und in dem bin ich schon ganz gefühlsbetont wienerisch: Es geht fast nicht, es bricht mir das Herz. Fremde brauchen eine Weile, bis sie in Wiener Herzen aufgenommen werden, aber wenn sie mal drin sind, gibt es kein Entrinnen mehr. Mein Abschiednehmen dauerte nach zwei Jahren in Wien doppelt so lange als beim Wegzug von Basel von all meinen Freunden und Bekannten, die ich schon seit Urzeiten kenne. Spätestens seither weiss ich: Wien ist einfach anders!

Denise Berger

Rathaus

Texterklärungen und Anmerkungen:

Allgemeines:

etwas geht sich aus: etwas lässt sich (zeitlich) erledigen

Beisl: Kneipe

Wien hat 23 Bezirke, alle mit eigenem Bezirkswappen und Geschichte: www.wien.gv/at/bezirke/bezirkswappen; sie sind ungefähr kreisförmig im Uhrzeigersinn um die Stadtmitte angelegt, 21. und 22. Bezirk liegen über der Donau im Nordosten; die Nummern in der Postleitzahlmitte zeigen jeweils den Bezirk an: 1010 = 1. Bezirk, 1130 = 13. Bezirk etc.

Trafik: zu vergleichen mit unseren Kiosk-Läden, haben ein ähnliches Warenangebot; gibt es an vielen Strassenecken, oft direkt auch bei Eingängen der U-Bahnstationen auf der Seite (oft so klein, dass man sie fast übersieht). Dort bekommt man auch Parkscheine.

Falter: linksliberale Wochenzeitung mit detailliertem Veranstaltungsprogramm für Wien und Umgebung; sehr guter, hochstehender investigativer Journalismus, Mitbegründer und Chefredakteur: Armin Thurnher.

Schanigarten: vor den Gastronomiebetrieben auf dem Trottoir (Gehsteig) aufgestellte Tische und Stühle oder ein Gastgarten im Hinterhof; die verordnete Schanigartensaison läuft max. vom 1. März bis 15. November

Schlampert: österr. abwertend gebraucht für: nicht sorgfältig, ungenau, nachlässig

City Bike: www.citybikecard.at, es gibt viele über die Stadt verteilte Veloparkings mit Fahrrädern zum Ausleihen: 1. Stunde gratis, Tourist Card pro Kalendertag: 2 Euro; unbedingt sichere Fahrradrouten im Internet auskundschaften, da Radfahren in Wien ziemlich gefährlich sein kann. Die Autofahrer ignorieren Fahrradfahrer aus Prinzip - gilt übrigens auch umgekehrt.

Das Verwenden von akademischen Graden und Titeln jeglicher Art kaschiert im konservativ-bürgerlich geprägten, wenig demokratisch orientierten Österreich die eigene Mediokrität und befriedigt die Eitelkeiten und basiert wohl auf einem tief sitzenden Minderwertigkeitskomplex. Üblich ist die unlogische aufsteigende Reihenfolge, weil man keinen Titel weglassen möchte (Mag. Dr. XY) und die Verdopplung mit englischen Titeln am Schluss, wobei das für die so wichtige mündliche Anrede völlig ungeeignet ist. Gutes, durchaus realistisches und ernst gemeintes Beispiel: HR Univ.-Prof. Akad. Tourismusmanagerin Dr.phil. Maria Bauer, BSc MSc, will heissen: Frau Bauer ist Hofrätin, Universitätsprofessorin, hat einen Unilehrgang zur Tourismusmanagerin sowie ein Doktorratsstudium, Bachelor- und Masterstudium absolviert. Zaghafte Emanzipierungsversuche zeigen sich in den weiblichen Formen wie Mag[a]. für Magistra und Dr.[in] für Doktorin. Bachelor- und Masterabgänge sind trotz Bologna-Reform ganz frische «Babies» an den Universitäten und noch arg gewöhnungsbedürftig.

Leiwand: super

Piefke: abwertend gemeinte Bezeichnung für Deutsche, die in Österreich einen schweren Stand haben; im Vergleich dazu haben die Schweizer von vornherein einen Sympathiebonus und sind gern gesehen.

Kulinarisches:

Getränke:

• Almdudler: österr. Kräuterlimonade
• Radler: Biermischgetränk aus Bier und (Zitronen-)Limonade, bei uns Panaché genannt
• Aperol Spritz: erfrischender fruchtig-bitterer Aperitif-Likör, der mit Prosecco oder Weisswein gemischt wird
• G'spritzter: Wein und Sodawasser
• Achterl, Vierterl: Weinglasgrössen, als Fluchtachterl oder -vierterl wird das Glas vor dem Nachhause-Gehen bezeichnet
• Wiener Melange: wird traditionell in einem hohen Stielglas serviert und besteht zu zwei Dritteln aus starkem schwarzem Bohnenkaffee und zu einem Drittel aus heisser Milch. Die Milch darf aber nicht gekocht sein. Darauf kommt eine grosszügige Portion Schlagrahm (Schlagobers), die mit etwas feingemahlenem Kaffee bestreut wird.
• Seidel: kann sich auf Bier und Wein beziehen, etwa 0.354 Liter

Essen:

• Ribisel: Johannisbeere
• Palatschinken: Pfannkuchen mit verschiedenen Füllungen
• Eierschwammerl: Pilzsorte
• Knödl: geformte Teigkugeln aus verschiedensten Grundzutaten (z. B. zerquetschte Kartoffeln, altbackenes Brot, Quark, Grieß), die in siedendem Wasser gegart werden und als deftige Beilage, Suppeneinlage oder süße Nachspeise gegessen werden
• Fleckerl: Nudeln
• Nockerl: Spätzle
• Kaiserschmarrn: Pfannkuchenähnliche Süssspeise, serviert mit Zwetschkenrösta (=Pflaumenkompott)

Gelateria Paolo Bortolotti: bestes Eis der Stadt; entlang der Mariahilfer Strasse (Shopping-Strasse im 6. Bezirk) gibt es 3 Geschäfte, unbedingt das Mohneis probieren!

Restaurant Glacis im MuseumsQuartier oberhalb des MUMOK (Museum Moderner Kunst), Museumsplatz 1, 7. Bezirk (Neubau), Tel. 01 5265660; in diesem 7. Bezirk tummeln sich zwischen MuseumsQuartier, Spittelberg, Neubaugasse und Urban-Loritz-Platz die jungen Kreativen, Selbstständigen und Studierenden: Man nennt das Neubau-Grätzel der neuen Bourgeois Bohemians daher auch Boboville.

Edelbeisl Bohème, Spittelberggasse 19, 7. Bezirk (Neubau), Tel. 01 5233173, mit viel Opernmusik als Beschallung und signierten Starfotos an den Wänden

Beisl und Bar Skopik & Lohn, Leopoldsgasse 17, 2. Bezirk (Leopoldstadt), Tel. 01 2198977

Brandauers Schlossbräu, Am Platz 5, 13. Bezirk (Hietzing), Tel. 01 8795970

Beisl Villa Aurora: Wilhelminenstr. 237, 16. Bezirk (Otlakring), Tel. 01 489 33 33, durchgehend warme Küche, beste Cordon bleus der Stadt mit kreativen Füllungen. Der Ausblick über die Stadt lohnt sich.

Kaffeehäuser:

In Wiener Kaffeehäusern sitzt man für gewöhnlich lange und ausgiebig, studiert die aufliegenden Zeitungen, liest Bücher oder betätigt sich als Schriftsteller, ohne besonders viel konsumieren zu müssen. Neben viel Kaffee wird meist durchgehend traditionelle Wiener Küche serviert. Eine sehr kleine Auswahl:

Café im Schottenstift, Schottengasse 2, 1. Bezirk (Innere Stadt), Tel. 01 535155013

Künstlercafé Korb, Brandstätte 9, 1. Bezirk (Innere Stadt), Tel. 01 5337215

Café Ritter, Mariahilfer Strasse 73, 6. Bezirk (Mariahilf), Tel. 01 587 82 38

Café Dommayer, Dommayergasse 1, 13. Bezirk (Hietzing), Tel. 01 87754650

Bars:

Bar Schlossstubn, Am Platz 2, 13. Bezirk (Hietzing), Nähe Seitenausgang Schlosspark Schönbrunn - preiswertester guter Prosecco vom Fass, Glas 1.80 Euro

WIENO: Wiener Weinbar, neben Rathaus in Lichtenfelsgasse 3, 1. Bezirk (Innere Stadt), 60 Weine von 18 Wiener Winzern (es gibt Rebberge mitten in und um die Stadt herum, am besten unternimmt man eine Wanderung: http://www.wien.gv.at/umwelt/wald/freizeit/wandern/wege.html)

Bar Urania, Uraniastrasse 1, 1. Bezirk (Innere Stadt), Tel. 01 7133066

Pianobar Bonbonniere, Spiegelgasse 15, 1. Bezirk (Innere Stadt), Tel. 01 512 68 86, älteste Bar im Herzen von Wien mit Originalausstattung der 20er Jahre, mit Live-Klaviermusik

Buchtipp für politisch Interessierte: Michael Fleischhacker, «Politikerbeschimpfung», 176 Seiten, 22,00 Euro, ISBN: 978-3-902404-63-3

Anreise Flughafen-Stadtzentrum:

CAT: Mit Airport Shuttle direkt vom Flughafen Schwechat in 16 Minuten zur U-Bahnstation «Wien Mitte/Landstrasse», umsteigen auf U3 Richtung Ottakring zum Steffl (Stephansdom) für 9 Euro die Einzelfahrt. Wer trotzdem lieber mit dem Taxi fährt, ruft Josef Haager an: +43 664 785 28 64.

Empfohlene Unterkunft: preiswerte wunderschöne Ferienwohnungen von Susanne Tiefenbrunner direkt beim Prater, Ausstellungsstrasse 31, 1020 Wien,
Mobil-Tel. +43 699 195 80 151,
http://www.apartment.at/print/apartment/115

Urlaubslektüre

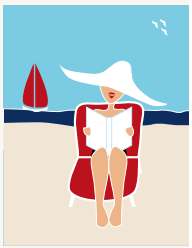
José Saramago: Das Zentrum

(Rowohlt, gebunden, 22.90 Euro)

Die ersten Zeilen höre ich mitten aus dem Buch heraus. Als mein Mann mir, der das Buch gerade liest, für mich völlig aus dem Zusammenhang gerissen, wenige Zeilen vorliest, in denen ein Hund mit einer unglaublichen Einfühlsamkeit in die Geschichte eingeführt wird. Später nehme ich mir das Buch und lese die erste Begegnung des alten Töpfers Cipriano Algor, der Hauptfigur des Buches, mit dem zugelaufenen Hund, der später Achado heissen wird, zu Ende. Ich bin elektrisiert von dieser Art des Erzählens, von dieser Kunstfertigkeit des Schreibens, fasziniert, wie Saramago es schafft, mich innerhalb von wenigen Zeilen, in die Hundehütte eines offenen Hofes einer kleinen Töpferei zu versetzen, in der der alte Cipriano Algor am Rande eines portugiesischen Dörfchens seinem Handwerk nachgeht. Keine Bange, dieses Buch ist nicht sentimental. Es ist auch keine dogmatische Auseinandersetzung des Marxisten Saramago mit dem Thema Arbeit. Es ist die einfühlsam erzählte Geschichte eines alten Töpfers, der seine Waren irgendwann nicht mehr dem hypermodernen Einkaufszentrum verkaufen kann, da Plastik besser als Ton zu sein scheint. Eines alten Töpfers, der sich auf seine Weise dagegen wehrt. Ein Buch nicht nur für den Portugalurlaub, sondern für alle, die nach den Ferien zurück in ihr «Zentrum» gehen.

Heidi Hoyermann

Kafka on the Shore



If you like fiction, fantasy, mystery, original ideas and an unpredictable plot, then you will probably enjoy Haruki Murakami's novel. You will enter into a unique dream-related atmosphere. *Kafka on the Shore* is an amazingly imaginative story comprising two distinct but interrelated plots, the life of a 15-year-old teenager Kafka and that of an old illiterate man, Nakata. Both characters have their own quest (or are they the same?), both are trying hard to escape their fate.

Kafka runs away from his father's house to escape an oedipal curse and to go in search of his mother and sister, while the police begin inquiring after him in connection with a brutal murder.

Nakata, who has experienced a strange traumatic event in his childhood, lost many of his mental faculties but in their place is able to talk to cats. He knows he has a mission, ignores which one, but when the time comes he will know exactly what to do.

In this novel, fishes fall from the sky, people collect cats' souls, WWII soldiers appear from forests, people commit murder and then are unsure if they committed it. Murakami mixes suspense, humour and refers all the time to both the real and the surreal so that you are not sure which world you are in.

Murakami's metaphoric writing is all about human condition and the (non)sense of life. As so, *Kafka on the Shore* poses more questions than he answers, creates more puzzles than he solves. And it is just fun! Let your imagination combine several of these riddles and finish the story any way you wish. Bon voyage!

Anne-Catherine Feutz

Room by Emma Donoghue

"Jack is five, and excited about his birthday. He lives with his Ma in Room, which has a locked door and a skylight, and measures eleven feet by eleven feet" (at just under 3 metres by 3 metres, that's small!) "He loves watching TV, and the cartoon characters he calls friends, but he knows that nothing he sees on screen is truly real – only him, Ma and the things in Room. Until the day Ma admits that there's a world outside."

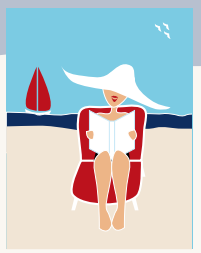
Having read the above blurb on the back of the book, I decided that this was not a book I would ever want to read. So what if it was a runner up for the Mann Booker prize (the UK's major book award) in 2011? It looked as if it was going to be 320 pages on a horrible theme that I would find far too distressing. Yet I did read *Room* and now I'm recommending it to you as a summer read, and even an on the beach read! I was "persuaded" to try the first couple of chapters and keep an open mind, and I reluctantly agreed.

Once I started reading, I wanted to finish the book in one sitting. It made me smile, then made me weep and then made me smile again. I was devastated and then uplifted and can't remember when a book last took me on such a rollercoaster ride. It's also written in straightforward English sentences and so just flowed along. "When it's over you look up: the world looks the same but you are somehow different and that feeling lingers for days," commented one reviewer and she's absolutely right.

Written in Jack's voice, *Room* is the story of a mother and son whose love lets them survive. As it's difficult to say much else without spoiling the plot, I'll just say "this is definitely one you should read."

Hilary Ireland

Have you been to Hyperion?



Dear DBM reader, let me start with a question. Do you like books AND science fiction? Are you desperately looking for a sense of wonder, that precious feeling invoked by the sudden understanding of new concepts & ideas? If your answer is YES, than I may have the right book for you. It is the classic novel Hyperion written by Dan Simmons.

The story is set in a far-future galaxy where humanity is scattered across hundreds of worlds, following the "Big Mistake" which destroyed Old Earth, all connected by wormhole technology and united under the Hegemony. This vast empire is under threat by the Ousters, interstellar rebel humans mutated beyond recognition, who dwell free of and beyond the bounds of the Hegemony. On the eve of galactic war, the book follows the journey of seven pilgrims (the Priest, the Soldier, the Poet, the Templar, the Detective, the Consul, the Scholar and his little daughter) who are travelling on Treeship Yggdrasill to the distant planet Hyperion in order to visit The Time Tombs (ancients structures that move backwards through time), confront their deadly guardian (a mysterious creature known as The Shrike) and hopefully help to prevent the total destruction of human civilization. During the journey, the pilgrims tell the stories of their lives. Each tale has an extremely different mood and atmosphere, giving the entire book a beautiful, patchwork sort of feel. The stories contain first contact mission, military SF, literary symbolism, colonial rebellion, cyberpunk, hard-boiled detective story, a touch of horror, and beautifully written stories of personal tragedy. This is not a collection of unrelated tales. Far from it. After the first few stories you will start to see deeper patterns and sense the hidden forces coming together. You will witness the effects of one story on another and feel the storm gathering. And most of all, you will begin to understand that Hyperion is the one wild card which could shift the balance of mankind's fate one way or another, and somehow these pilgrims hold the key...

I have nothing left to say. See for yourself. Take this book, turn the first page and start your pilgrimage.

Lucia Kubovcakova

News from the DBM-iT

EndNote X5

Infolge der Kooperation zwischen der Uni und den USB kann EndNote als Lizenz für 30.00 CHF bezogen werden. Die aktuelle Version heisst X5 und ist für OSX 10.6/10.7 und für Windows7/Vista/XP verfügbar.

PRISM und FlowJo

Sobald wir unsere neuen iMac's erhalten, werden wir FlowJo und PRISM auf den öffentlichen iT Rechnern im 3.OG des ZLF installieren. Somit können dort auch diese beiden Programme benützt werden.
Weiterhin ist auch das gesamte Adobe Creative Suite installiert.

Umbauaktion

CD/DVD-Drives werden immer seltener benötigt. Gehören Sie auch zu den Benützern die nur einmal im Quartal eine CD lesen müssen? Dann haben wir etwas, das Sie sich anschauen oder bestellen sollten.

LMP Disk Doubler für MB & MacBook Pro

Einbau Kit um das optische Laufwerk durch eine 2. Harddisk oder SSD zu ersetzen

LMP Disk Doubler ist ein Konverter (Einbau-) Rahmen für MacBook und MacBook Pro Unibody, um anstelle des optischen Laufwerks eine zweite SATA Harddisk oder zusätzlich eine SSD einzubauen. Fast alle MacBook und MacBook Pro Unibody werden unterstützt.

Eine empfehlenswerte Konfiguration ist eine super schnelle SSD (500 MB/Sek. mit SATA 6 Gb/s SSD der neuesten Generation) mit einer standard Harddisk zu kombinieren. Oder die Kapazität durch zwei 1 TB Harddisk auf maximale 2 TB zu erweitern und eine Harddisk als Time Machine Backup zu verwenden. Auch eine Datenspiegelung mit dem Apple System Utility wird dadurch möglich.

Das ausgebaute DVD Laufwerk kann in ein preisgünstiges USB Gehäuse eingebaut werden. Damit steht das DVD Laufwerk auch nach Ausbau extern zur Verfügung.

Disk Doubler
Konverter (Einbau-) Rahmen

LMP Disk Doubler

- Konverter (Einbau-) Rahmen für weitere Harddisk oder SSD (2.5" SATA HDD/SSD, 9.5 mm Bauhöhe, ersetzt optisches Laufwerk)
- Alle MacBook und MacBook Pro Unibody Modelle (ab Late 2008)
- SSD 6 Gb/s (500 MB/Sek. Datendurchsatz) anstelle der Harddisk installieren und dann diese Harddisk anstelle dem optischen Laufwerk (nur SATA Anschluss der internen Harddisk hat 6 Gb/s Interface)
- Installations-Werkzeug im Lieferumfang enthalten.
- Der Einbau durch einen Apple Techniker dauert ca. 30 Minuten.

Gehäuse (5.25") für
DVD Laufwerk, USB 2.0

	Artikel	Enduser CHF 8% MWSt
LMP Disk Doubler, Einbau Kit für 2. Harddisk/SSD (2.5"; statt DVD Laufwerk) für alle MacBook & MacBook Pro Unibody	9414	**68.–**
LMP Gehäuse für DVD Laufwerk aus MacBook, MB Pro Unibody & Mac mini, USB 2.0	9413	**38.–**
LMP Disk Doubler Bundle, Kit für 2. HD/SSD (statt DVD) MacBook & MB Pro & externes USB-DVD Gehäuse [Art. 9414 & 9413]	9415	**98.–**

Zur Zeit können wir die aufgeführten SSD 2.5" Drives zu folgenden Preisen bestellen:

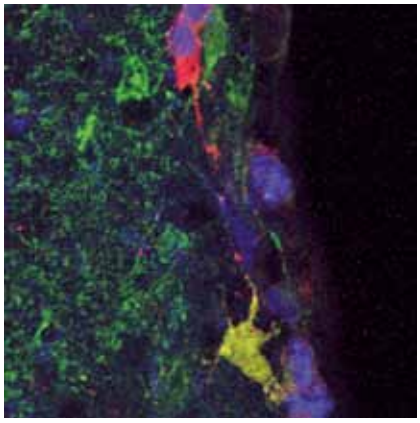
•120 GB OCZ Agility3 SSD MLC SATA, 6 Gb/Sek,, 500Mb/Sek.	130.00
•240 GB OCZ Agility3 SSD MLC SATA, 6 Gb/Sek,, 500Mb/Sek.	265.00
•480 GB OCZ Agility3 SSD MLC SATA, 6 Gb/Sek,, 500Mb/Sek.	635.00

Rechenbeispiel:
Sie wollen die interne bestehende HD weiterhin benützen und zusätzlich noch das interne DVD Laufwerk in ein externes USB2.0 Gehäuse umbauen lassen? Dann wählen Sie eine der obigen SSD Platten und addieren die 98.00 CHF dazu.

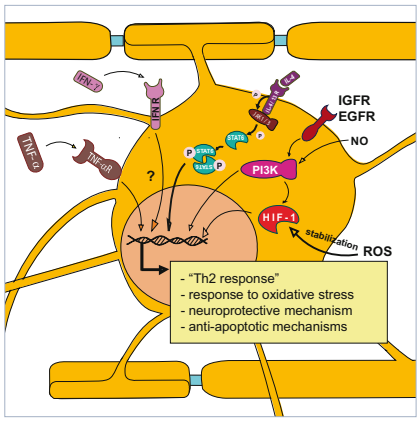
Sollten Sie Interesse an einer solchen Lösung haben, so fragen Sie uns einfach an. Anfagen bitte an niklaus.vogt@unibas.ch oder an ilija.lujic@unibas.ch mit dem Betreff "DiskDoubler Umbau".

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



. . . erfahren wir von Verdon Taylor mehr über Neuronal Stem Cells



. . . führt uns Nicole Schaeren-Wiemers in die Welt der Neurobiology ein

. . . entführt uns Arun Cumpelik in seine Heimatstadt Prag

... lernen wir mit Michael Abanto, worauf es beim Rugby ankommt

. . . lassen wir den Sommer Revue passieren mit den schönsten Fotos vom DBM Barbecue

Ausfahrt

Berggipfel erglühen,
Waldwipfel erblühen
Vom Lenzhauch geschwellt;
Zugvogel mit Singen
Erhebt seine Schwingen;
Ich fahr' in die Welt.

Mir ist zum Geleite
In lichtgoldnem Kleide
Frau Sonne bestellt;
Sie wirft meinen Schatten
Auf blumige Matten;
Ich fahr' in die Welt.

Mein Hutschmuck die Rose,
Mein Lager im Moose,
Der Himmel mein Zelt;
Mag lauern und kauern
Wer will, hinter Mauern;
Ich fahr' in die Welt.

Joseph Victor von Scheffel (1826–1886)