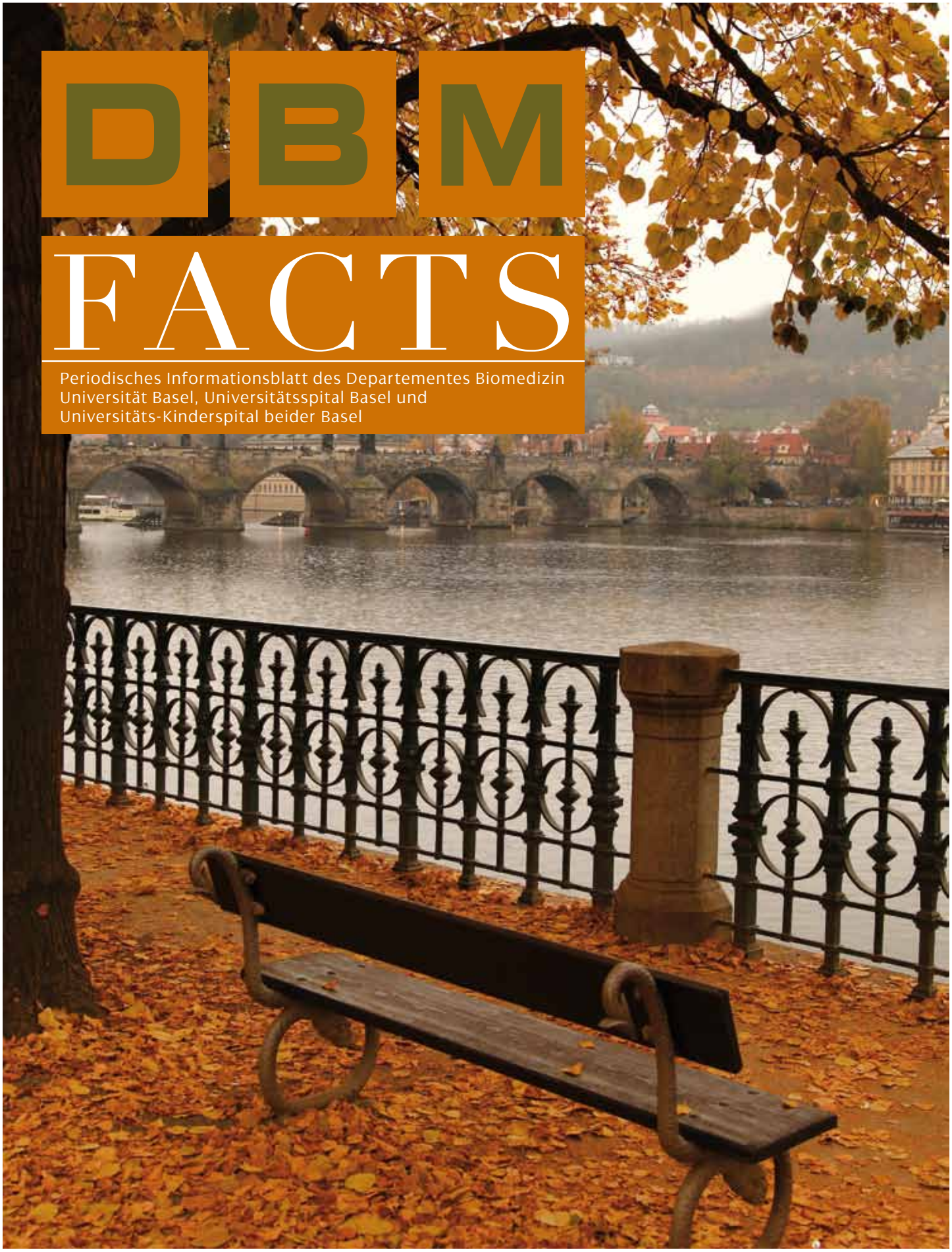
DBM FACTS

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



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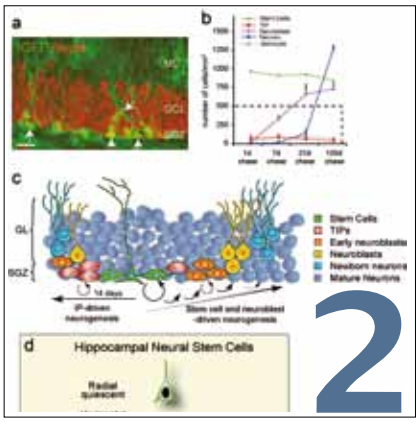

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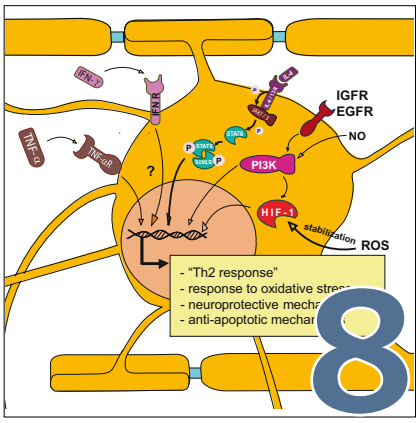

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EDITORIAL

Peter Meier-Abt
Head a.i.

Liebe Leserinnen und Leser

Während ich diese Zeilen für die Herbstausgabe der DBM Facts schreibe, geht meine Zeit am DBM zu Ende. Nach rund sechs Jahren im Rektorat der Universität Basel hatte ich in den letzten acht Monaten die Möglichkeit, wieder näher an die biomedizinische und klinische Forschung zu rücken. Es war eine tolle Erfahrung und so quasi eine Rückkehr in meine angestammte Umgebung. «Reisen bildet», wusste schon Friedrich der Grosse, manchmal müssen es nur ein paar hundert Meter sein, um Probleme aus einer anderen Perspektive wahrzunehmen und manches Verhalten besser zu verstehen. Tatsächlich ist es für die translationale Life Sciences Forschung der Universität Basel unabdingbar, dass universitäre Grundlagenforschung und klinische Forschung am Universitätsspital noch enger zusammenrücken. «An den Grenzflächen generiert sich bekanntlich das Leben».
Die nun verabschiedete neue Organisation des DBM zusammen mit der neuen Struktur der Medizinischen Fakultät (fünf Departemente) werden sicher mithelfen, bereits bestehende transdisziplinäre Netzwerke zu verstärken und neue Grenzüberschreitungen zu wagen. In die gleiche Richtung zielt das neu initiierte DBM Doktoratsprogramm, das in eine fakultätsübergreifende «Life Sciences Graduate School Basel» integriert werden soll. Hoffnung auf Entspannung besteht auch in der Raumplanung; der Umbau des 2. Stockes im DBM Hebelstrasse steht unmittelbar vor der Tür und die Chancen auf einen Zusammenzug aller DBM Häuser auf dem Schällemätteliareal sind mittelfristig intakt.
Ich möchte allen danken, die mich bei meiner Aufgabe in den letzten acht Monaten unterstützt haben, so dass ich das DBM wohlgeordnet an Radek Skoda zurückgeben kann. Ganz besonders gilt mein Dank der DBM-Leitung und dem DBM Stab für ihre aktive und stets transparente Mitarbeit. Ich wünsche dem DBM weiterhin viel Erfolg in der Zukunft. Ich werde seine Geschicke noch so gerne weiterverfolgen.
In dieser Ausgabe stellen uns Verdon Taylor (Neuronal Stem Cells) und Nicole Schaeren-Wiemers (Neurobiology) ihre Forschung vor (ab Seite 2). Handfest zur Sache geht es bei Mike Abanto und American Rugby (ab Seite 28), bevor uns Arun Cumpelik träumerisch in die «Goldene Stadt», seine Heimatstadt Prag, entführt. Dies und so manches mehr finden Sie nun in der vorliegenden Ausgabe.

Schöne Herbsttage und viel Freude bei der Lektüre!

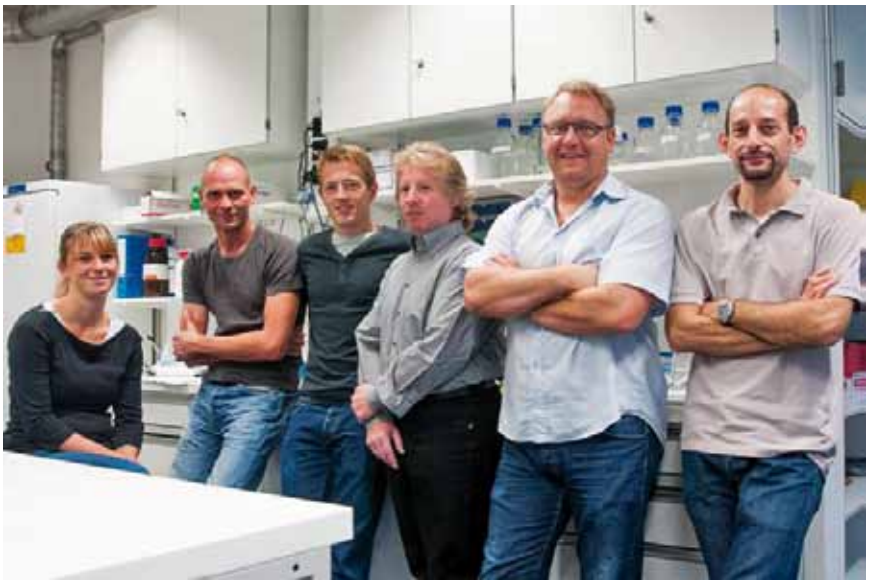
Dear Readers

As I write these lines for the autumn edition of DBM Facts, my time at the DBM is coming to an end. After almost six years in the rector's office at the University of Basel I have had the chance over the past eight months to once again get closer to biomedical and clinical research. It was a wonderful experience and almost like a return to my roots so to speak. Even Frederick the Great knew that "travel broadens the mind", sometimes it only needs to be a few hundred meters in order to see problems from a different perspective and to understand different attitudes. It is most definitely key for the translational life science research at the University of Basel that the university based basic research and the clinical research at the University hospital come ever closer together. "Life starts at the borders".
The newly adopted organisation of the DBM together with the new structure of the Medical Faculty (five departments) will most definitely help to strengthen the existing trans-disciplinary networks and overcome obstacles at the interface. The newly initiated DBM doctoral program, which is to be integrated into an inter-faculty Life Sciences Graduate School Basel, is a move in the right direction. There is also hope for more relaxation with regard to room planning; the renovation of the second floor of the DBM Hebelstrasse is imminent and the possibility of having all of the DBM houses gathered in the Schällemätteli area in the medium term is still intact.
I would like to thank all those who have supported me in my position over the past eight months, which enables me to pass a well ordered DBM back to Radek Skoda. In particular I would like to thank the DBM management and staff for their active and ever transparent cooperation. I wish the DBM every success in the future. I will continue to follow its story with interest.
In this edition Verdon Taylor (Neuronal Stem Cells) and Nicole Schaeren-Wiemers (Neurobiology) introduce their research to us (page 2). Mike Abanto gets straight to the point about American Rugby (page 28), before Arun Cumpelik brings us dreams of the "Golden City", his home town of Prague. This, and so much more can be found in this issue.

I wish you all wonderful autumn days and happy reading!

Brain Stem Cells: Not just controversial

When I started as a doctoral student here in Basel back in the 90's, I was told by a current member of the DBM *"Choose a question that fascinates you and always keep it in mind",* or words to that effect. Back then we were working with embryonic brain cells that could be cultured in suspension, passaged and differentiated into little "brain balls". Little did I know that what we were working with were, for all intents and purpose, stem cells of the brain. So I have been working with brain stem cells for 20 years, I will refer to them as neural stem cells from now on. Firstly, the term neural stem cell demands a definition and this is often confusing, conflicting and personal. In the lab we define neural stem cells as cells that retain the potential to divide and generate neurons and glial cells throughout the life of the organism. Coming back to the original advice, for a long time I have been fascinated by how the brain is formed and why diseases or trauma to the brain are so poorly repaired.



Left to right: Miriam Vogt, Dirk Junghans, Robert Beattie, Frank Sager, Verdon Taylor, Claudio Giachino (Missing on the picture: Dominik Herzog).

The human brain is arguably the most complex organ on earth. Billions of neurons are organized in a precise network to store and carry information between one another. It is amazing that this complex organ, which is essentially anatomically identical between individuals, is generated by a sheet of simple epithelial cells during embryogenesis. These so called neuroepithelial cells include the neural stem cells form a tube and become patterned. Those neural stem cells at the anterior of the neural tube will become the forebrain and those towards the back will generate the spinal cord. The type of neurons produced is dependent upon the location of the stem cell within the tube, and major mistakes in fate choice are not tolerated.

Generating the brain from neural stem cells

Generally speaking, you are born with the maximum number of neurons you are ever going to have and it is only down hill thereafter. During development, neural stem cells go through a period of expansion to increase their number, a period of producing neurons – neurogenesis – by dividing to generate two unequal daughters (one stem cell and one neuronal precursor) and a period of gliogenesis, generating the supporting cells of the brain. In most regions of the brain the switch to gliogenesis is at or around birth and is associated with the loss of neuron production. There are a few brain regions that are exceptions to this rule. For example, most neurons of the cerebellum are generated after birth but with time this structure also stops producing neurons. However, the lateral

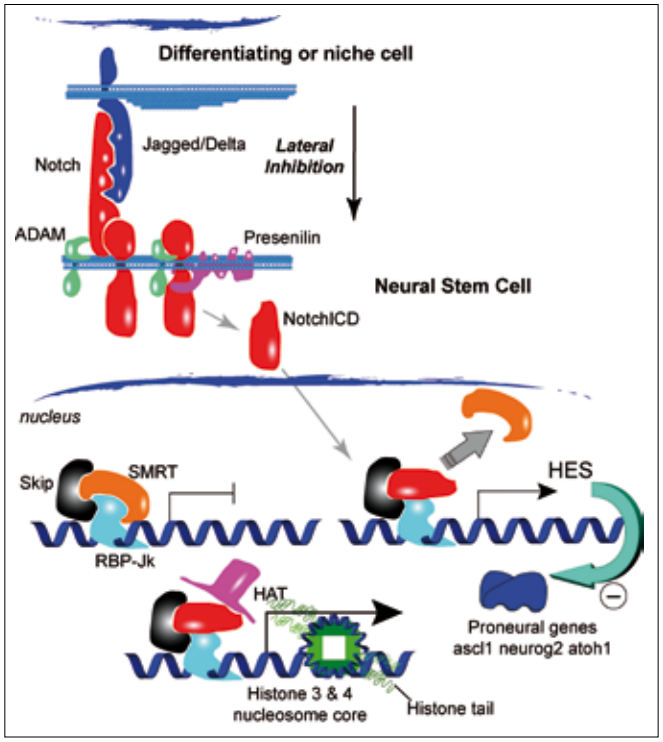


Figure 1: Notch signaling is a direct cell-cell communication system to regulate cell fate by lateral inhibition between cells. A differentiating or niche cell presents a transmembrane ligand of the Delta-like or Jagged families. Notch receptors are cleaved upon activation, first in the ectodomain by ADAM proteases and subsequently by the gamma-secretase containing a Presenilin. The Notch intracellular domain (NotchICD) contains signals that induce transport to the nucleus upon cleavage. In the nucleus, the NotchICD binds to the (recombination signal-binding protein Jκ) RBP-Jκ (CBF1 in humans) disrupting a transcriptional repressor complex which includes, RBP-Jκ, Silencing Mediator of Retinoid and Thyroid receptor (SMRT) and Ski-interacting protein (Skip) and recruits Histone acetyltransferases (HAT) to induce gene expression. Hes genes are a direct target of the Notch signal. Hes proteins are transcriptional repressors that bind to and inhibit expression of the proneural genes ascl1, neurog2 and atoh1, encoding transcription factors required for neuronal differentiation.

forebrain and the hippocampus in most mammals retain the ability to generate new neurons into adulthood. The lateral forebrain or subventricular zone generates many neurons which migrate and integrate into the central olfactory (smell) system. In the adult hippocampus, newly generated granule neurons form circuits involved in distinct forms of memory. In rodents, neural stem cells may have some degree of plasticity and controversial data suggest that resident stem cells may be able to adopt other fates and generate neurons outside the olfactory and hippocampal systems following certain types of brain injury. Therefore, adult neural stem cells are potentially important for disease and therapy.

Notch signaling in neural stem cell fate regulation

The mechanisms that guide stem cell fate and differentiation in the vertebrate central nervous system are poorly understood. Notchs are receptors for two families of five related transmembrane proteins, Delta-likes and Jaggeds. Thus, Notch signaling is a direct cell-cell communication system and an ideal niche pathway to control cell fate and decisions. Notch1 is one of four receptors in the Notch family and is expressed by stem cells of the vertebrate central nervous system. We addressed the role of Notch1 in the mammalian brain using a conditional gene ablation approach. Loss of Notch1 function results in premature onset of neurogenesis by neural stem cells during brain development. Notch1-deficient neural stem cells are unable to remain undifferentiated. Rather than undergoing the sequential phases of expansion, neurogenesis and gliogenesis, Notch1-deficient stem cells differentiate spontaneously thereby depleting the pool (Lutolf et al., 2002). Depletion of the stem cell population results in a loss of neurons and astrocytes which severely affects brain development. Hence, Notch1 signaling between neighboring cells is a key niche mechanism, controlling neural stem cell fate through a process of lateral inhibition, and blocking differentiation by inhibiting proneural gene expression (Figure 1).

Brain development is a balance between signaling and molecular degradation?

Having established that Notch signaling controls neural stem cell maintenance and differentiation during development, we were interested in the mechanisms. We performed a genome-wide transcriptome analysis of Notch1-regulated neural stem cell genes and uncovered a number of proteins involved in microRNA regulation of RNA stability and translation. Temporal regulation of embryonic neurogenesis is controlled by hypostable proneural transcription factors including Ngn2. Therefore, we looked in more detail at the role of the microRNA microprocessor in the control of neural stem cell differentiation (Knuckles et al., 2012). The RNAseIII Drosha and the RNA binding protein DGCR8 are key components of the microprocessor and play a crucial role in the initial stages of the biogenesis of most microRNAs. We inactivated the microprocessor

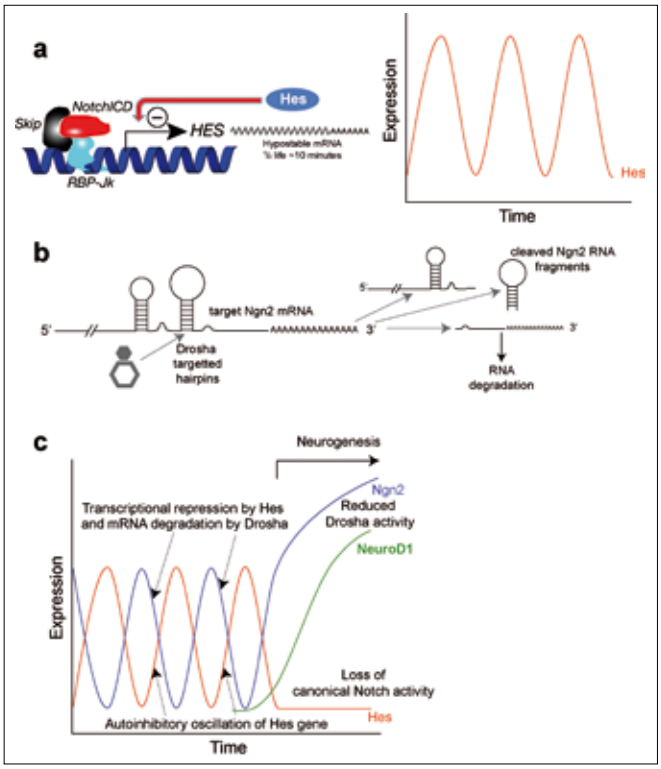


Figure 2: The miRNA microprocessor components Drosha and DGCR8 regulate neural stem cell differentiation by destabilizing proneural mRNAs. a. Hes expression and Notch signaling are oscillatory through a negative feedback loop and hypostable mRNAs and proteins. Hes proteins repress Notch signaling and their own gene expression. b. The microprocessor binds to hairpin loops in the mRNAs of the proneural genes including that of Neurogenin2 (Ngn2). Drosha cleaves the stem loops resulting in mRNA degradation. c. Notch signaling and proneural gene expression oscillate in anti-phase during neural stem cell maintenance. Notch signaling and the microprocessor compete in the regulation of neurogenesis. Loss of Notch activity reduces Hes expression, increases accumulation of proneural protein and activates the neurogenic differentiation cascade including the determination factor NeuroD1. Modified from (Knuckles et al., 2012).

in neural stem cells during development and found it plays an important role on neural stem cell maintenance. However, in contrast to an expected role via microRNA production, the microprocessor directly targets mRNAs of the proneural transcription factor Ngn2. The gene encoding Ngn2 *(neurog2)* is repressed by Notch signaling and a direct target of Hes proteins (Figure 1). Ngn2 is required for and induces differentiation of neural stem cells in the developing forebrain. But Notch signaling is not so straight-forward. Hes proteins are transcriptional repressors that block not only proneural gene expression but also expression of their own gene in an autoregulatory feedback loop (Figure 2). As the Hes encoding mRNAs and the proteins themselves are unstable – half-lives of only a few minutes – expression of these effectors of Notch signaling fluctuates (oscillates) even if the stem cell receives a constant activation of the Notch receptor. The dynamics in Hes expression are also seen in the expression of their targets the proneural genes whose mRNAs oscillate out of phase with those of the Hes genes. When we inactivated the microprocessor the levels of Ngn2 mRNAs no longer oscillated but stabilized due to the microprocessor normally degrading the Ngn2 mRNA (Figure 2b) (Knuckles et al., 2012). As a consequence, Ngn2 protein levels increased and the stem cells were forced into differentiation, overriding the Notch maintenance signal (Figure 2c).

Adult neural stem cells exist

Most tissues in our bodies are in a constant flux of cell turnover. Cells die or are shed and these are replaced throughout life by tissue-specific stem cells. Typical examples of this replenishment are the blood, skin and hair systems. Stem cells in these tissues sit in a niche that controls the rate at which they divide and differentiate to maintain the tissue. These stem cells can also become activated by injury and are recruited to repair the tissues. It was thought that the brains of mammals do not generate new neurons after birth and this together with the poor regenerative capacity of the brain was due to an absence of stem cells. Early in the 1990's evidence appeared that most adult vertebrates, including humans, generate neurons but the process is restricted to specific regions of the forebrain, the subventricular zone and the hippocampal dentate gyrus. So neural stem cells in the adult mammalian brain present somewhat of a conundrum. Over the last 2 decades we have made major advances in identifying cells with neural stem cell potential in the mammalian brain. We have some ideas about the function of these stem cells in rodents, replacing neuronal circuitry in the olfactory bulb and generating granule neurons in the dentate gyrus. The function of the new neurons in the olfactory and hippocampal system in rodents is to regenerate the circuitry that is continually turned-over. When neurogenesis in the subventricular zone is blocked, the sense of smell diminishes with time. So neural stem cells replace neurons throughout life but they are usually not used to repair most regions of the brain. The restriction

in function is likely controlled by the local environment or niche which supports the stem cells but also controls their potential.

How are adult neural stem cells controlled?

As in other somatic stem cell systems, neural stem cells are quiescent and proliferate only sporadically to produce more committed progeny. Neural stem cells in the postnatal mammalian brain self-renew and are a source of neurons and glia. To date, little is known about the molecular and cellular mechanisms regulating the maintenance and differentiation of these multipotent progenitors (Basak and Taylor, 2009). We showed that the Notch ligand Jagged1 is required by mitotic cells in the subventricular zone and stimulates self-renewal of multipotent neural stem cells (Nyfeler et al., 2005). Jagged1 expressing cells line the adult subventricular zone and are juxtaposed to Notch1 expressing stem cells. We demonstrated *in vitro* that Jagged1 acts through Notch1 to promote neural stem cell maintenance and multipotency. Conversely, reducing Jagged1/Notch1 signaling decreases the number of proliferating cells in the subventricular zone. Our findings suggested a central role for Jagged1 and Notch1 in the stem cell niche in the subventricular zone and that Jagged1 signaling is a pivotal mechanism for maintaining a population of neural stem cells in the postnatal brain.

In contrast to the quiescent stem cell theory, we recently found that some neural stem cells in the adult forebrain can be mitotically active over a long period of time. In addition, the subventricular zone contains regenerative stem cells that become activated following a lesion and have remarkable capacity to repair the structure. The molecular interplay controlling adult neural stem cells during neurogenesis and regeneration was not clear. Using conditional genetics and fate mapping we found that Notch signaling is essential for neurogenesis in the subventricular zone (Basak et al., 2012). However, we uncovered a surprising difference in Notch dependence between active neurogenic and quiescent neural stem cells that participate in regeneration of the subventricular zone (Figure 3). Both active and regenerative neural stem cells depend upon canonical Notch signaling. Loss of RBP-Jκ function and a total block of Notch signaling resulted in a loss of both active and quiescent regenerative neural stem cells. However, loss of Notch1 function results in a selective loss of active neural stem cells and a block in neurogenesis. In contrast, Notch1-deficient quiescent regenerative neural stem cells remain until induced to proliferate during regeneration or during ageing whereupon they become Notch1-dependent and fail to fully reinstate neurogenesis (Basak et al., 2012). Therefore, Notch1 is a key component of the adult sub-

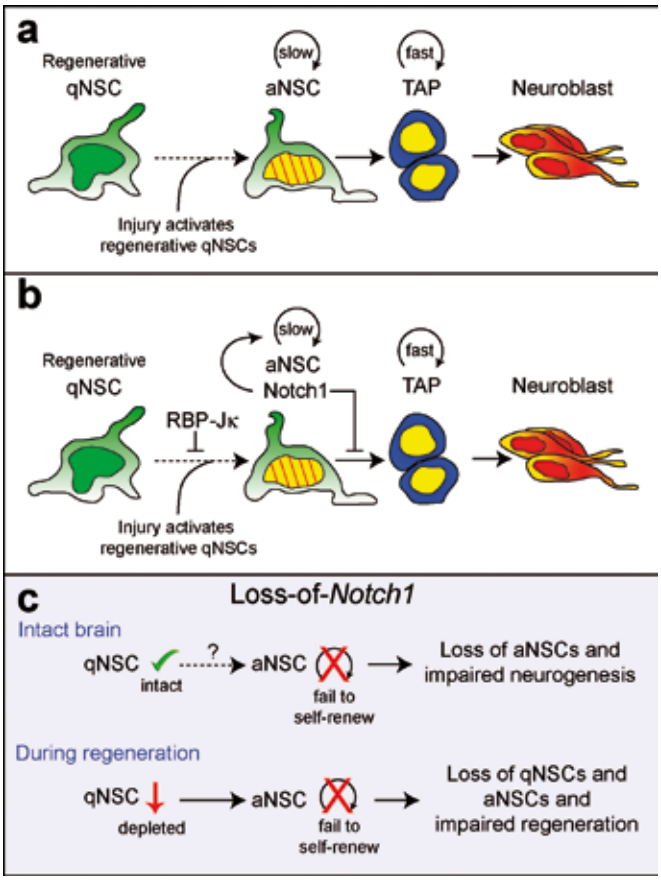


Figure 3: Notch signaling controls different stages of neural stem cell maintenance and differentiation in the adult subventricular zone. a. Continuous neurogenesis in the adult subventricular zone is maintained by active neural stem cells (aNSCs) which divide slowly (dashed yellow nucleus). aNSCs generate fast dividing transient amplifying progenitors (TAPs; blue with yellow nucleus) which give-rise to neuroblasts that migrate to the olfactory bulb and generate neurons. Regenerative neural stem cells are quiescent (qNSCs) and enter the cell cycle in response to injury. b, c. aNSCs depend upon Notch1 for maintenance, self-renewal and neurogenesis. In the absence of Notch1 aNSCs are compromised and lost. qNSCs depend upon RBP-Jκ but not Notch1 for maintenance. RBP-Jκ blocks cell cycle entry of qNSC. The selective loss of aNSCs following Notch1-deletion suggests an uncompensated role for Notch1 during homeostatic neurogenesis. In the absence of Notch1, activated neural stem cells fail to self-renew and effectively reinstate adult neurogenesis after lesion, resulting in a reduction in qNSCs and a loss of aNSCs. Slow/fast: Rate of cell division. Modified from (Basak et al., 2012).

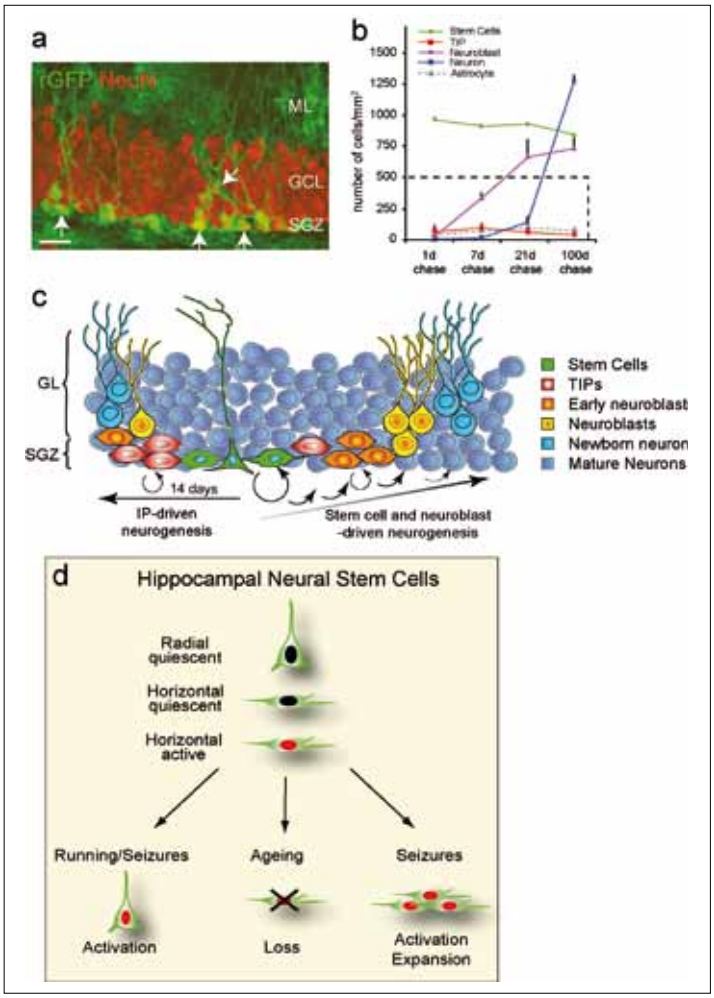


Figure 4: The hippocampus of adult mice contains multiple neural stem cell populations that are dynamic and respond to pathophysiological stimuli. a. The hippocampal dentate gyrus contains neural stem cells that generate new neurons (NeuN⁺, arrows) throughout life. The image show progeny (green) of neural stem cells 100 days after genetic labeling. b. Lineage tracing of neural stem cells and their progeny reveals intermediate cell types at different stages of differentiation. The number of stem cells remains constant over time. Stem cells generate transient intermediate progenitors (TIP) that rapidly produce neuroblasts that divide to increase the number of mature neurons generated. c. Scheme of intermediate progenitor (IP) and stem cell-driven homeostatic neurogenesis. Neural stem cells can be quiescent or mitotically active (circular arrow). In the IP driven model of neurogenesis, stem cells generate IPs through rare asymmetric cell divisions. IPs divide symmetrically to self-replicate before generating a pool of early neuroblasts. Early neuroblasts do not divide and give-rise to post-mitotic neuroblasts and newborn neurons. We have uncovered a stem cell and early neuroblast-driven mode of neurogenesis in the dentate gyrus. Active stem cells divide multiple times and generate IPs which rapidly produce highly mitotic, self-renewing early neuroblasts that increase and expand the precursor pool. GCL - granule cell layer, SGZ - subgranular zone. Modified from (Lugert et al., 2012). d. The dentate gyrus contains three stem cell populations; some with a radial process which are quiescent, some with horizontal processes that are quiescent and some with horizontal processes that divide frequently (active). These different stem cells behave differently to physical exercise, seizures and during aging. The active stem cells are lost with age causing a reduction in the number of new neurons that are generated. The quiescent stem cells can be reactivated in the brains of old animals to rejuvenate neuronal production. Scale bar in a = 20μm. Modified from (Lugert et al., 2010).

ventricular zone niche promoting maintenance of active neural stem cells and this function is compensated, potentially by another Notch, in functionally distinct quiescent neural stem cells.

Adult neural stem cells, heterogeneous and dynamic

New neurons are generated in the dentate gyrus of the adult hippocampus throughout life by neural stem cells within the subgranular zone niche. Hippocampal neural stem cells produce transient intermediate progenitors and neuroblasts that exit the cell cycle and differentiate into neurons. The precise dynamics of neuron production from neural stem cells in the adult hippocampus remained unclear due to technical limitations of lineage tracing. We found that Notch signaling is required for neurogenesis in the adult hippocampus. Loss of Notch signaling results in both a loss of stem cells and the production of new neurons. By tracing neural stem cells we showed that the production of neurons in the hippocampus is controlled not only at the level of the stem cells but also by proliferation of early neuroblasts (immature neuronal precursors) (Figure 4a). The formation of new neurons from stem cells in the adult dentate gyrus requires many days and weeks and the progeny of the stem cells pass through intermediate stages of differentiation (Figure 4b). Thus, the neurogenic process in the adult dentate gyrus takes much longer than had previously been predicted by viral labeling and cell birth-dating by marking proliferating cells with Thymidine analogues. The differences in characteristics of the cells at intermediate stages of the lineage potentially reflect their ability to respond to different environmental stimuli (Figure 4) (Lugert et al., 2012). These experiments resulted in a new model of neurogenesis in the adult hippocampus that involves a combination of stem cell and neuroblast-driven neurogenesis rather that intermediate progenitor expansion as the driving force of neuron production (Figure 4c).

Neurogenesis in the dentate gyrus is a plastic process, responsive to external stimuli. Using a reporter of Notch signaling we uncovered hippocampal neural stem cells with distinct radial and horizontal morphologies and functions (Basak and Taylor, 2007; Lugert et al., 2010). Within these pools of stem cells, subpopulations can shuttle between mitotic activities and quiescence. Radial and horizontal neural stem cells respond selectively to neurogenic stimuli. Physical exercise activates the quiescent radial population to proliferate and generate new neurons whereas epileptic seizures induce expansion of the horizontal stem cell pool, which may contribute to the pathology in human temporal lobe epilepsy (Lugert et al., 2010). Surprisingly, we observed that the age-related reduction in hippocampal neurogenesis correlates with a selective loss of the active horizontal neural stem cell pool and their transition to a quiescent state rather than a total loss of stem cells. These aged neural stem cells enter a quiescent state which is reversible and neurogenesis can be experimentally rejuvenated even in old mice (Lugert et al., 2010). The discovery of multiple neural stem cell populations with Notch-dependence but selective responses to stimuli and reversible quiescence has important implications for the mechanisms of adaptive learning and also for regenerative therapy (Figure 4d).

We continue to focus on the neural stem cell heterogeneity and the molecular mechanism controlling their differentiation and brain regeneration.

Acknowledgements

I would like to thank the current and past members of my lab. Without their hard work, determination and critical nature, and the helpful discussions in the lab, we would not have made the advances we have made.

Verdon Taylor

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Myelin, the essential nerve fiber insulation of higher vertebrates

The process of myelination represents a solution to a problem uniquely faced by higher order nervous system, namely accommodating a large number of rapidly conducting nerve fibers in a small space. This solution is remarkably effective; on average the volume of an unmyelinated axon must be 100 times greater than of a myelinated axon conducting impulses with the same velocity. We are using basic as well as clinical approaches for investigating the complex nature of the myelin membrane during myelination and in demyelinating diseases such as multiple sclerosis and primary demyelinating peripheral neuropathies.

From left to right: Lukas Enz, Monia Sobrio, Daniela Schmid, Nicole Schaeren-Wiemers, Melanie Gentner, Thomas Zeis

Introduction

The myelin sheath is a multilamellar plasma membrane structure that enwraps axons in the central (CNS) and the peripheral nervous systems (PNS) of vertebrates. Two specialized cell types – the oligodendrocytes in the CNS and the Schwann cells in the PNS – generate their spiral sheaths in a structurally similar but biochemical distinct way (Figure 1). The axon, conversely, regulates in a reciprocal fashion the myelinating cell during proliferation and initiation of myelination. Recent studies indicate that the functional role of oligodendrocytes as well as Schwann cells is not only to myelinate axons but also to maintain the functional integrity of the nerve fiber throughout its life. Still, a major question in myelinogenesis is to understand the tightly controlled reciprocal signaling mechanisms of axon-glia interaction during myelin formation and in maintenance. Although some of the axonal components, which are important in inducing myelination, have been identified, it is not known how the myelinating cell influences the axon and vice versa.

Myelinogenesis is a complex, developmentally regulated process involving the coordinated expression of genes coding for myelin proteins and for enzymes associated with the synthesis of myelin specific lipids. Each myelinating cell independently regulates myelin-specific genes, which are dependent on environmental cues unique to the central or peripheral nervous system. One of the major questions in myelinogenesis is to understand the molecular and cellular mechanisms regulating the coordinated expression and translocation of myelin constituents to the different compartments during development as well as in adulthood (Figure 2). Just recently, it emerged that molecular mechanisms known to be important for polarized sorting and trafficking in epithelial cells are also used in myelinating cells. The

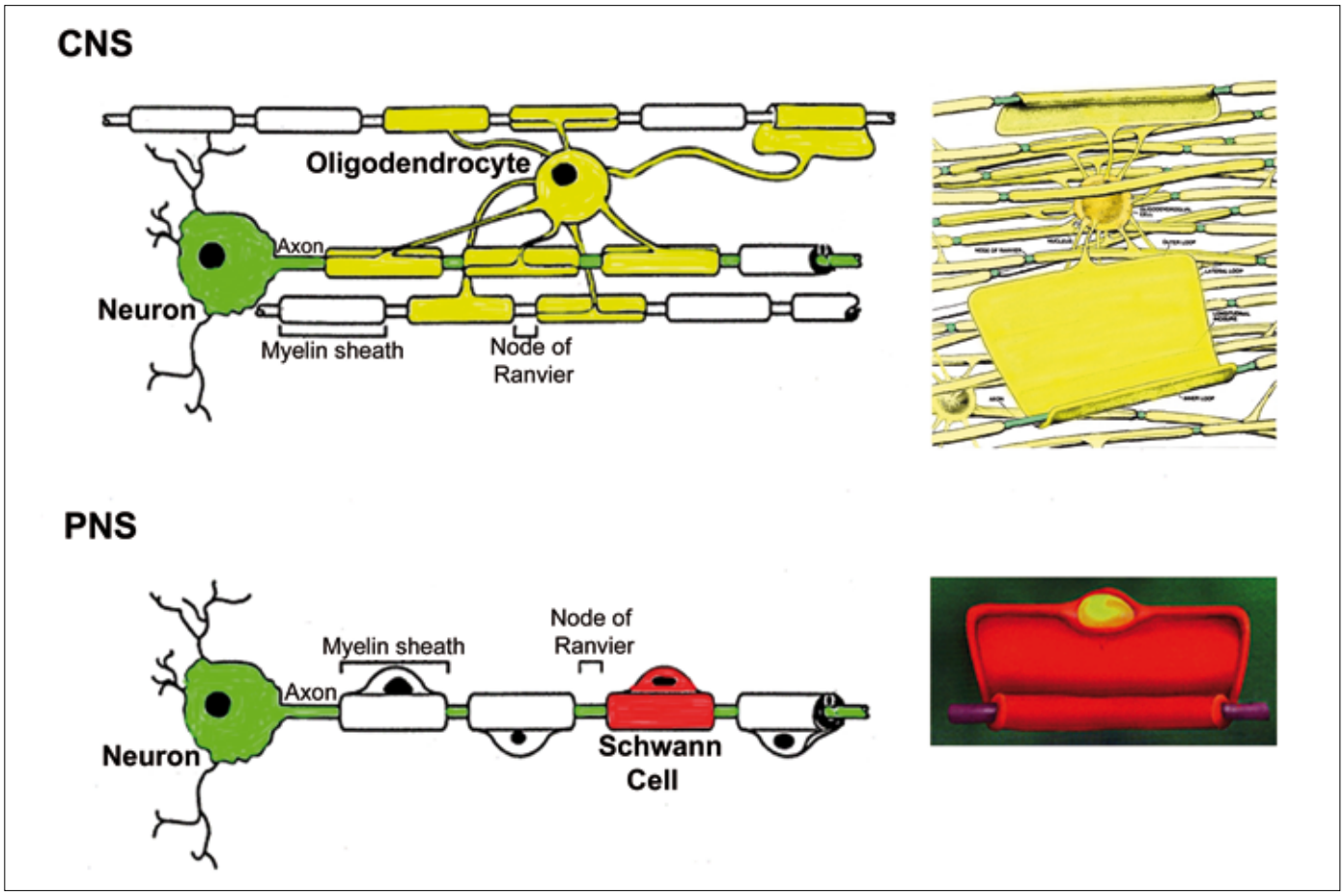

Figure 1: Schematic comparison between CNS and PNS myelination. Oligodendrocytes maintain several internodes of myelin in the brain and spinal cord, whereas one Schwann cell myelinates one internode. Oligodendrocytes are postmitotic and are not able to dedifferentiate; remyelination is carried out by progenitor cells. Schwann cells, however, dedifferentiate, proliferate and remyelinate upon demyelination.

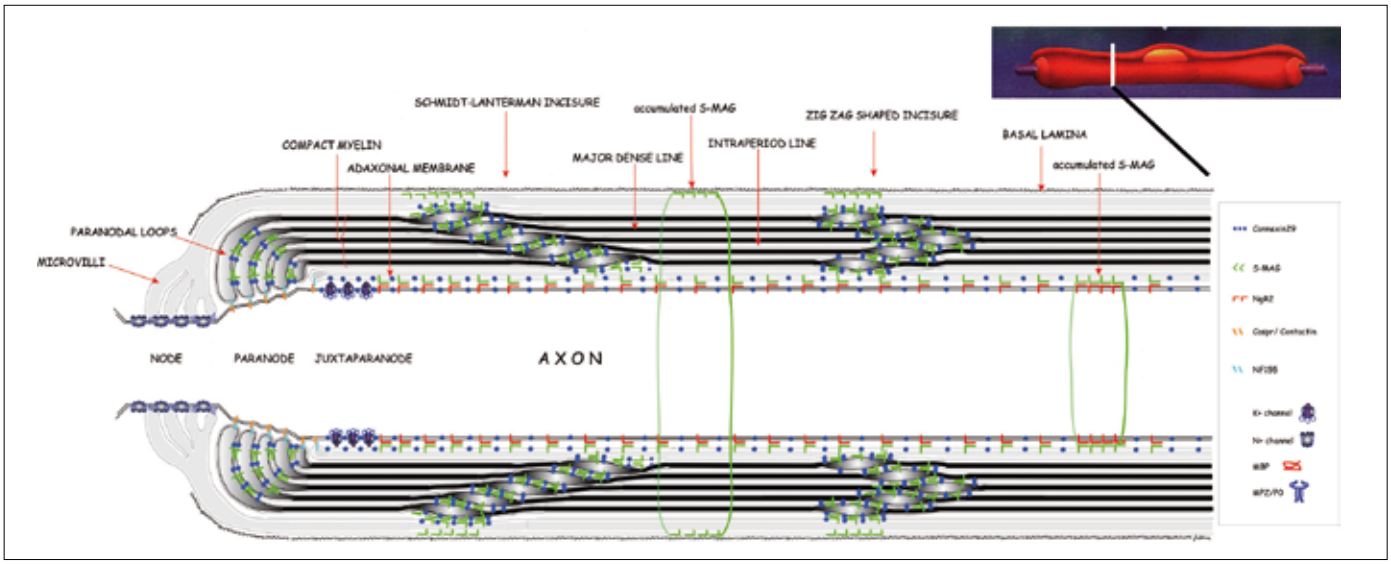

Figure 2: Schematic drawing of a typical myelin sheath of the PNS illustrating the different compartments of a myelin sheath and their specific components. A myelin internode of the PNS has a length of several hundred µm with the Schwann cell nucleus located in the center (from Erb et al., MCN 2006).

sorting and trafficking of proteins and lipids by membrane rafts, also called lipid rafts or detergent-insoluble glycolipid-enriched microdomains, have emerged as crucial regulatory mechanisms in polarized cells. In this regard, the myelinating cells are confronted with distinct challenges. Both cell types are specialized polarized cells that form the unique multi-layered plasma membrane structure myelin, which is separated into a number of subdomains with distinct protein and lipid compositions. Extraordinary amounts of membrane proteins and lipids have to be synthesized and both correctly transported and targeted by myelinating glia during myelination in development and regeneration. Many studies suggest that the transport of particular myelin components is targeted to the different myelin compartments by distinct lipid rafts in a highly regulated process. This process involves rafts that contain proteins guiding early development and rafts that are involved in the formation and maintenance of the myelin sheath. The fine-tuning of this complex structure is probably achieved by reciprocal interactions between myelinating cells and axons, which determine the degree of cellular polarization.

Oligodendrocytes are maintaining up to 50 internodes of myelin depending on the particular nerve fiber they ensheath. Repair mechanisms after CNS injury (such as traumatic brain injury, stroke and demyelinating lesions in MS) depend on the regenerative capacity of neurite outgrowth together with remyelination of nerve fibers. The molecular mechanisms of remyelination are currently of central interest in the field of MS, since only limited remyelination occurs. The question arises whether oligodendrocytes in MS are impaired to fulfill their function, because even the earliest changes leading to lesion formation and development are unknown. For this reason, we investigated possible molecular alterations in MS brain tissues.

Our current projects in the lab involve the characterization of the functional role of the lipid-raft protein MAL in axon-glia interaction and its role in primary demyelinating neuropathy CMT1A, and the endogenous neuroprotective mechanisms in MS. The knowledge of the selective function of the different components of the complex myelin structure is a prerequisite to understand the different mechanisms, which may damage myelin in MS and in primary demyelinating neuropathies leading ultimately to axonal degeneration.

MAL influences myelinogenesis and its maintenance

The Myelin and Lymphocyte protein MAL is a four transmembrane protein expressed in CNS and PNS myelin. Its functional role in the apical sorting and transport mechanisms of polarized epithelial cells, and its association with glycosphingolipids localized mainly in myelin membranes, suggest that MAL is involved in the formation, transport and/or maintenance of particular

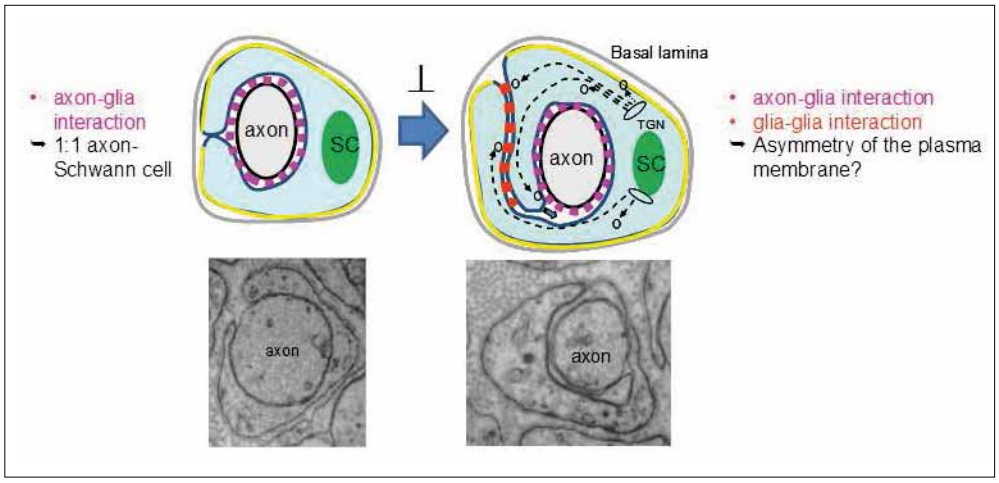

Figure 3: Initiation of myelination requires a switch of the plasma membrane from a sole axon-glia interaction to a glia-glia interaction on one side and an axon-glia interaction on the other side of the same membrane elongation. From our data we conclude that overexpression of MAL might influence this "polarization", possibly due to inhibition of the establishment of this particular asymmetry. Abbreviations: SC, Schwann cell nucleus; TGN, trans Golgi network

glycosphingolipid microdomains, the so-called "lipid-rafts", in specialized plasma membranes. In the CNS, we have identified that MAL plays an important role in axon-glia interaction in adult mice (Schaeren-Wiemers et al., JCB 2004). Lack of MAL resulted in structural as well as in molecular alterations resulting in disruption of axon-glia interaction at the node of Ranvier. These results demonstrated a critical role for MAL in the maintenance of CNS paranodes. In the PNS it seems that MAL does have a major influence on the onset of myelination and Remak bundle formation. Our detailed study on peripheral nerve development shows that MAL dosage influences p75 neurotrophin receptor (p75NTR) levels and, as a result, most probably the progress of myelination (Buser et al., EJN 2009). This is unexpected since MAL is considered to be a regulator of lipid raft-dependent protein transport processes but not a regulator of gene expression. However, our data point to a cascade of events which ultimately leads to reduced levels of p75NTR receptor and delayed myelination in MAL-overexpressing mice influencing the first step of wrapping (Figure 3).

Since polarized sorting and trafficking mechanisms require cytoskeletal components, a Yeast-two-Hybrid system analysis with the cytosolic N-terminal sequence of MAL was performed. Septin 6 was identified as an intracellular binding partner of MAL. Consequently, a comprehensive study of all Septins in CNS and PNS myelin was performed, elucidating which septin complexes are expressed by the myelinating cells (Buser et al., MCN 2009). Our data demonstrate that the septin cytoskeleton is an integral component of the myelin sheath, interacting with distinct myelin constituents, and therefore, septins represent intriguing candidates for membrane compartmentalization in myelin internodes (Figure 4).

Neuroprotective mechanisms in MS

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disease of the CNS with diverse clinical presentations and a heterogeneous histopathology. Currently, it is thought that MS is an autoimmune disorder directed against CNS antigens, which leads to inflammation and demyelination. A major characteristic of MS is the formation of inflammatory demyelinating lesions, areas of chronic demyelination and axonal damage (Figure 5). Demyelination occurs in the white and grey matter and can lead to chronic inactive demyelinated lesions or, if remyelination occurs, into remyelinating lesions, the so-called shadow plaques. Detailed histological analysis have been made to distinguish different tissue types in MS patients; normal appearing white matter (NAWM), actively demyelinating lesions, inactive demyelinated lesions and remyelinating lesions. Although these different tissue characteristics have been described, little is known about the molecular mechanisms of lesion formation, progression and conversion in MS. For this reason, we investigated possible molecular alterations in the so-called normal appearing white matter (NAWM) in MS brain tissues, and identified that the whole MS brain is in a subtle balance between neuroprotection and inflammation.

We performed a microarray study in which we compared the expression pattern of normal appearing subcortical white matter from MS and control patients. The genes

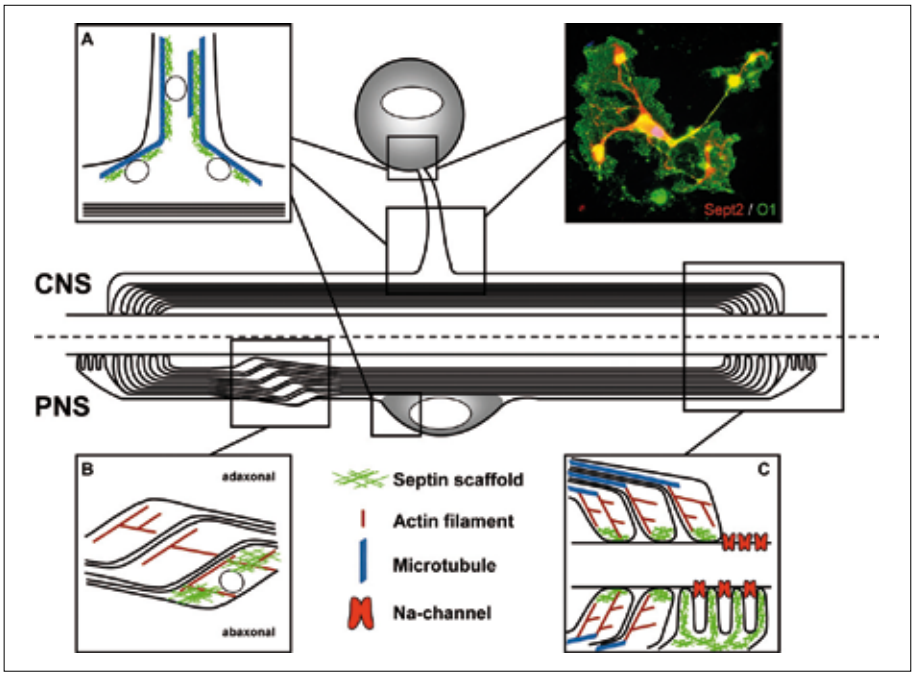

Figure 4: A schematic drawing that illustrates septin scaffolds identified in distinct subdomains of the myelin sheath. (A) The pool of septins in the perikaryon of Schwann cells as well as in the Cajal bands (not specially indicated) and the cytoplasm channels of the oligodendrocytes might have a role in sorting and targeting of myelin components to the emerging and adult myelin sheath. Furthermore, septin scaffolds are detected in the outer rim of the Schmidt-Lanterman incisures (B) as well as in the paranodal loops and the microvilli at the nodes of Ranvier (C) where they might contribute to subdomain formation and protein turnover (Buser et al., MCN 2009).

that were differentially expressed in MS patients indicate the occurrence of many endogenous neuroprotective mechanisms (Graumann et al., 2003), but also of oxidative stress and activation of the innate immunity (Zeis et al., Brain 2008). Our study revealed that the major transcription factor mediating ischemic preconditioning, namely HIF1α, is upregulated in oligodendrocytes of MS NAWM. Further, we identified that several components of the STAT6 anti-inflammatory signaling pathway are upregulated in oligodendrocytes as well. Our data showed that myelinating oligodendrocytes in MS have a rather activated or reactive phenotype ex-

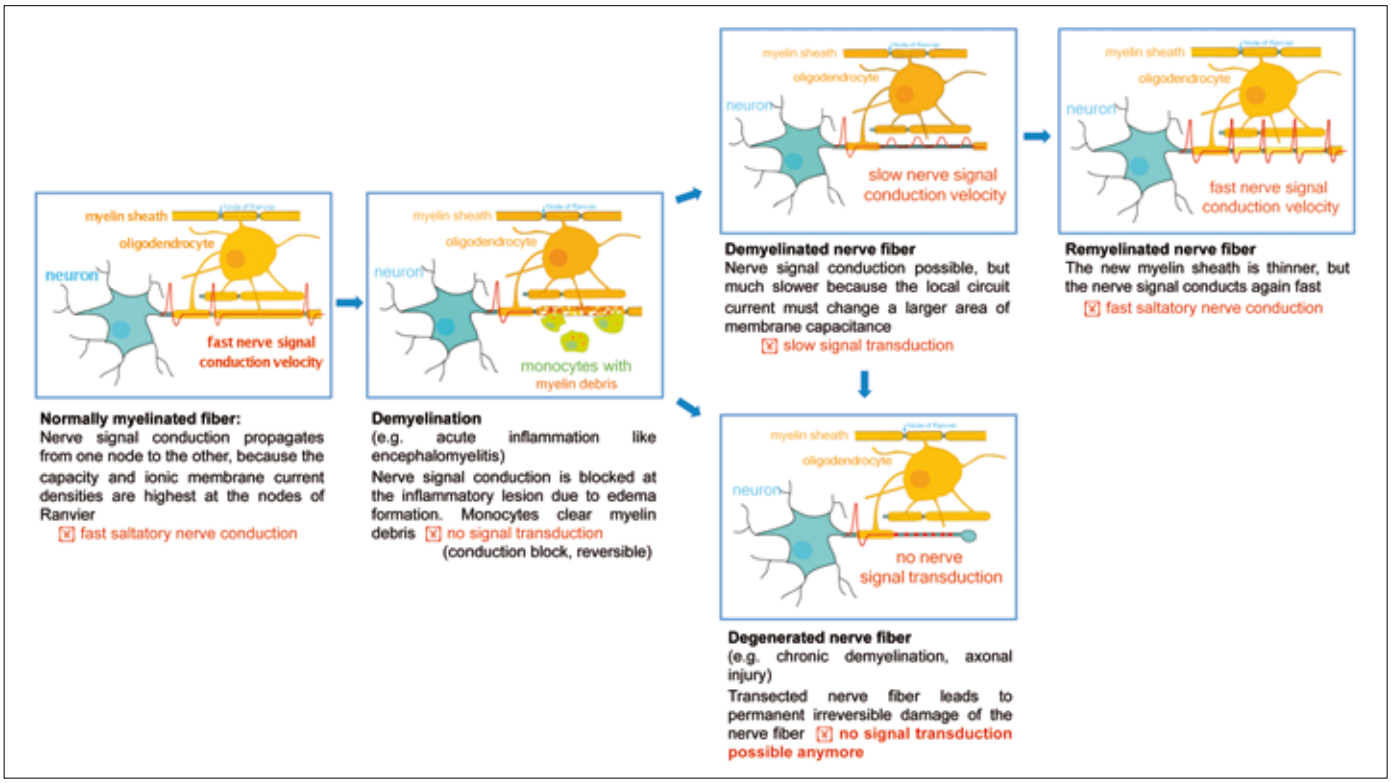

Figure 5: Mechanisms of demyelination and its consequence on signal transduction.

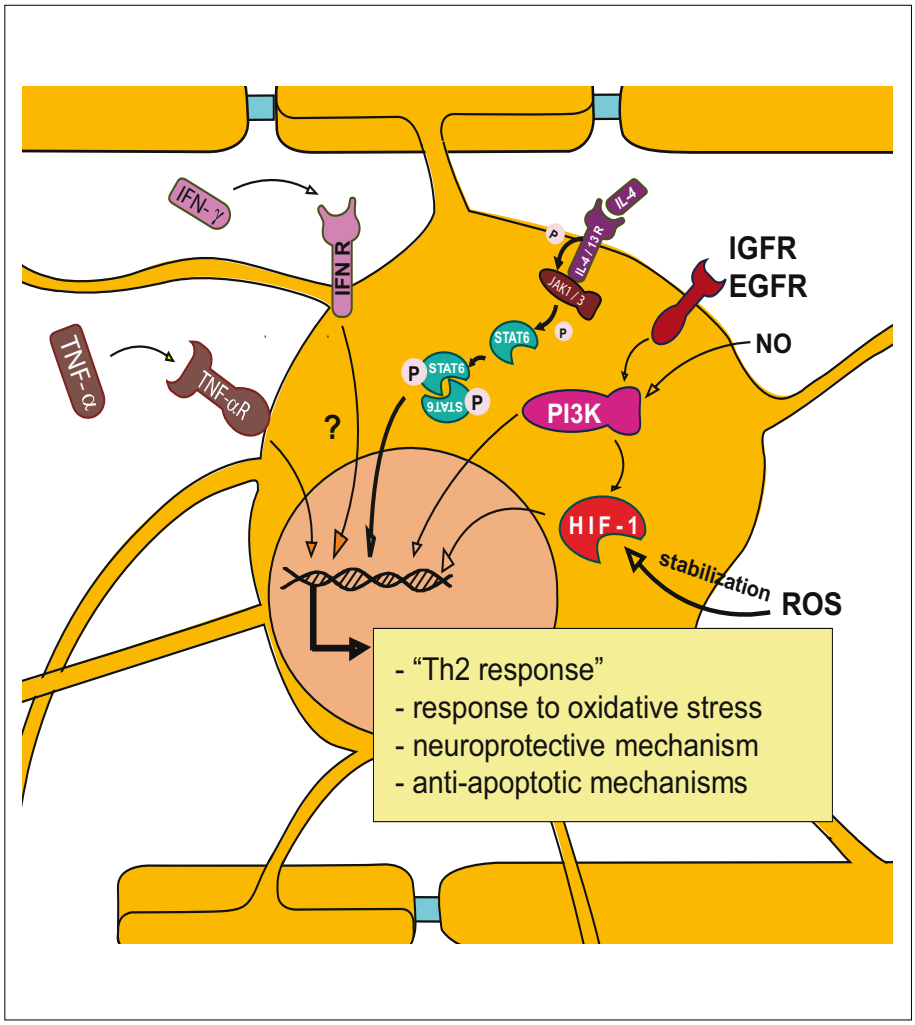

Figure 6: Reactive oligodendrocytes - pure defensive or actively modulating and shaping their cellular environment? Recent studies showed that oligodendrocytes can mount ischemic preconditioning mechanisms upon different stimuli. Treatment of oligodendrocytes with sub-lethal doses of IFN-γ and TNF-α led to the upregulation of genes involved in ischemic tolerance. Protective genes were also shown to be upregulated in oligodendrocytes after stimulation with growth factors (Balabanov et al., 2007). Furthermore, low-levels of RNS/ROS were reported to lead to a stabilization of HIF-1α which in turn activates the transcription of protective genes such as, for example, VEGFR, GLUT1 and 3. All these components have been identified in MS NAWM. Analysis of proteins expressed by oligodendrocytes revealed further that oligodendrocytes are able to express immune mechanisms-related proteins. We showed that members of the STAT6 signaling pathway, such as IL-4R, IL13R, JAK1 and STAT6, are expressed by oligodendrocytes. This might indicate an anti-inflammatory "Th-2"-like response by oligodendrocytes. Furthermore, treatment of oligodendrocytes with a sub-lethal dose of IFN-γ and TNF-α led to the secretion of chemokines such as CXCL10 (IP-10), CCL2 (MCP-1), CCL3 (MIP-1α) and CCL5 (Rantes), components, which were also identified in MS NAWM. Altogether, this indicates that oligodendrocytes might play an immune-modulating role MS.

pressing anti-inflammatory as well as neuroprotective components against oxidative stress (Figure 6). Our data introduce novel concepts of the molecular pathogenesis of MS in which oligodendrocytes are influencing innate immunity and are an active part in the formation of the immune privilege of the brain (Zeis and Schaeren-Wiemers, 2009). Consequently, we examined these molecular changes in an animal model of MS, namely experimental autoimmune mediated encephalomyelitis (EAE). Whereas examination of the cortical white matter revealed only minor changes, we identified a number of gene expression alterations in the cerebral cortex even though morphological and cellular alterations were not evident (Zeis et al., JNI 2008). One of the most striking observations was the downregulation of genes involved in mitochondrial function as well as a whole set of genes coding for different glutamate receptors. Our data demonstrate that although the MOG-induced EAE in DA rats is not appropriate to investigate alterations observed in NAWM in MS, it is a valuable model for MS to analyze alterations in long projecting neurons due to inflammatory-induced axonal injury. In parallel, we had the opportunity to study the altered expression pattern in a biopsy with subcortical white matter tissue of a patient suffering from the first disease exacerbation (Zeis et al., Brain Pathol 2009). This single case study suggests that many observed alterations in chronic MS may already taken place during the early phase of the disease.

Nicole Schaeren-Wiemers

Dissertationen

Seit dem 11. Mai 2012 darf sich **Constanze Baranek** von der Forschungsgruppe Cellular Neurobiology (Departement Biomedizin Pestalozzistrasse) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "The role of the proto-oncogene Ski in cortical development".

Mit der Doktorprüfung am 27. Juni 2012 schloss **Réjane Morand** von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin Hebelstrasse) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "Carnitine: analytical and physiological aspects".

Am 19. Juli 2012 stellte sich **Elia Piccinini** von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin Hebelstrasse) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "Engineered three-dimensional microenviroments as functional in vitro models of stromal tissues".

Am 29. August 2012 konnte **Lionel Nobs** von der Forschungsgruppe Cellular Neurobiology (Departement Biomedizin Pestalozzistrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Doktorarbeit mit dem Thema "The impact of Cyclin D1 on proliferating cells in the intact and injured mouse cortex".

Auszeichnungen

Primo Schär erhält Wissenschaftspreis der Stadt Basel

Primo Schär von der Forschungsgruppe Molecular Genetics (Departement Biomedizin Mattenstrasse) hat am 5. Juli 2012 für seine wichtigen Beiträge zum Verständnis der Stabilität der Erbinformation in normalen und Tumorgeweben den diesjährigen Wissenschaftspreis der Stadt Basel in Höhe von 20'000 CHF erhalten. Der Preis wird alljährlich und im Turnus der sieben Fakultäten Wissenschaftlern zuerkannt, die zur Universität Basel in Beziehung stehen und sich durch herausragende wissenschaftliche Leistungen hervorgetan haben.

Posterpreis der SGDV an Danielle Stegmann

Danielle Stegmann von der Forschungsgruppe Dermatology (Departement Biomedizin Hebelstrasse) hat im Rahmen der Jahresversammlung der Schweizerischen Gesellschaft für Dermatologie und Venerologie (SGDV) vom 30. August bis 1. September 2012 den Prof. U. W. Schnyder Poster-Preis für Genodermatosen erhalten. Der Titel ihres Posters lautete: "Aberrant splicing of *APC* in benign skin lesions of genetically confirmed FAP patients".

Herzliche Gratulation an alle!

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

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The Lancet Neurology THE LANCET Neurology Vol. 11 May 2012 IF23,4

Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study

Virginia Devonshire[1], Eva Havrdova[2], Ernst Wilhelm Radue[3], Paul O'Connor[4], Lixin Zhang-Auberson[5], Catherine Agoropoulou[5], Dieter Adrian Häring[5], Gordon Francis[6], Ludwig Kappos[3], for the FREEDOMS study group

Summary

Background Fingolimod 0·5 mg once daily is approved for treatment of relapsing multiple sclerosis (MS). In the phase 3, 2-year FREEDOMS (FTY720 Research Evaluating Effects of Daily Oral therapy in MS) study, fingolimod significantly reduced annualised relapse rates (ARRs) and the risk of confirmed disability progression compared with placebo. We aimed to investigate whether the beneficial treatment effect reported for the overall population is consistent in subgroups of patients with different baseline characteristics.

Methods We did subgroup analyses of ARRs (primary outcome) and confirmed disability progression (a secondary outcome) over 24 months in the FREEDOMS study, a randomised, double-blind study that included 1272 patients with relapsing-remitting MS who were assigned 1:1:1 to fingolimod (0·5 mg or 1·25 mg) or placebo once daily for 24 months. Subgroups were predefined, predefined and slightly modified, or defined post hoc, by demographic factors (including sex and age), disease characteristics (including baseline disability scores, relapse rates, and lesion parameters), and response to previous therapy (including analyses in patients eligible for fingolimod treatment according to the European label). Data were analysed by intention to treat. The FREEDOMS study is registered with ClinicalTrials.gov, number NCT00289978.

Findings Treatment with fingolimod 0·5 mg was associated with significantly lower ARRs versus placebo across all subgroups except for patients aged over 40 years. ARR ratios ranged from 0·76 (95% CI 0·54–1·09; p=0·13) in patients aged over 40 years to 0·29 (0·16–0·52; p<0·0001) in patients who had relapse activity despite receiving interferon beta during the year before study enrolment.

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[5] Novartis, Basel, Switzerland
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Nature Neuroscience | nature neuroscience | June 2012; doi:10.1038/nn.3139 | IF15,5

Drosha regulates neurogenesis by controlling Neurogenin 2 expression independent of microRNAs

Philip Knuckles[1,*], Miriam A Vogt[1,2,*], Sebastian Lugert[1,2], Marta Milo[3], Mark M W Chong[4,5], Guillaume M Hautbergue[6], Stuart A Wilson[6], Dan R Littman[4,7], Verdon Taylor[1,2]

Temporal regulation of embryonic neurogenesis is controlled by hypostable transcription factors. The mechanism of the process is unclear. Here we show that the RNase III Drosha and DGCR8 (also known as Pasha), key components of the microRNA (miRNA) microprocessor, have important functions in mouse neurogenesis. Loss of microprocessor in forebrain neural progenitors resulted in a loss of stem cell character and precocious differentiation whereas Dicer deficiency did not. Drosha negatively regulated expression of the transcription factors Neurogenin 2 (Ngn2) and NeuroD1 whereas forced Ngn2 expression phenocopied the loss of Drosha. *Neurog2* mRNA contains evolutionarily conserved hairpins with similarities to pri-miRNAs, and associates with the microprocessor in neural progenitors. We uncovered a Drosha-dependent destabilization of *Neurog2* mRNAs consistent with microprocessor cleavage at hairpins. Our findings implicate direct and miRNA-independent destabilization of proneural mRNAs by the microprocessor, which facilitates neural stem cell (NSC) maintenance by blocking accumulation of differentiation and determination factors.

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[*] These authors contributed equally to this work.

Stem Cells | STEM CELLS | 2012;30:1455–1464 | IF 7,7

Fibroblast Growth Factor-2 Maintains a Niche-Dependent Population of Self-Renewing Highly Potent Non-adherent Mesenchymal Progenitors Through FGFR2c

Nunzia Di Maggio[1,2], Arne Mehrkens[1,2], Adam Papadimitropoulos[1,2], Stefan Schaeren[1,2], Michael Heberer[1,2], Andrea Banfi[1,2,*], Ivan Martin[1,2,*]

Abstract

Bone marrow (BM) mesenchymal stem/stromal cells (MSC) are a heterogeneous population of multipotent progenitors currently under investigation for a variety of applications in regenerative medicine. While self-renewal of stem cells in different tissues has been demonstrated to be regulated by specialized microenvironments called niches, it is still unclear whether a self-renewing niche also exists for MSC. Here, we show that primary human BM cultures contain a population of intrinsically non-adherent mesenchymal progenitors (NAMP) with features of more primitive progenitors than the initially adhering colonyforming units-fibroblast (CFU-f). In fact, NAMP could generate an adherent progeny: (a) enriched with early mesenchymal populations (CD146+, SSEA-1+, and SSEA-4+); (b) with significantly greater proliferation and multilineage differentiation potential in vitro; and (c) capable of threefold greater bone formation in vivo than the corresponding CFU-f. Upon serial replating, NAMP were able to regenerate and expand in suspension as non-adherent clonogenic progenitors, while also giving rise to an adherent progeny. This took place at the cost of a gradual loss of proliferative potential, shown by a reduction in colony size, which could be completely prevented when NAMP were expanded on the initially adhering BM fraction. Mechanistically, we found that NAMP crucially depend on fibroblast growth factor (FGF)-2 signaling through FGFR2c for their survival and expansion. Furthermore, NAMP maintenance depends at least in part on humoral signals distinct from FGF-2. In conclusion, our data show a niche/progenitor organization in vitro, in which the BM adherent fraction provides a self-renewing microenvironment for primitive NAMP.

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Nature Communications | nature COMMUNICATIONS | 3:670; DOI: 10.1038/ncomms1670 IF 7,3

Homeostatic neurogenesis in the adult hippocampus does not involve amplification of Ascl1^{high} intermediate progenitors

Sebastian Lugert[1,2], Miriam Vogt[1,2], Jan S. Tchorz[3,4], Matthias Müller[4], Claudio Giachino[1,2], Verdon Taylor[1,2]

Neural stem/progenitor cells generate neurons in the adult hippocampus. Neural stem cells produce transient intermediate progenitors (type-2 cells), which generate neuroblasts (type-3 cells) that exit the cell cycle, and differentiate into neurons. The precise dynamics of neuron production from the neural stem cells remains controversial. Here we lineage trace Notch-dependent neural stem cells in the dentate gyrus and show that over 7–21 days, t he progeny of the neural stem cells progress through an Ascl1^{high} intermediate stage (type-2a) to neuroblasts. However, contrary to predictions, this Ascl1^{high} population is not an amplifying intermediate, but it differentiates into mitotic Tbr2^{+} early neuroblasts, which in turn expand the lineage. After 100 days, the majority of the neural stem cell progeny are neuroblasts or postmitotic neurons. Hence, the neural stem cells require many weeks to generate differentiated neurons. On the basis of this temporal delay in differentiation and population expansion, we propose that the neural stem cell and early neuroblast divisions drive dentate gyrus neurogenesis and not the amplification of type-2a intermediate progenitors as was previously thought.

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Clinical Pharmacology & Therapeutics | Clinical Pharmacology & Therapeutics | March 2012. doi:10.1038/clpt.2011.316 IF 6,0

Intranasal Midazolam: Pharmacokinetics and Pharmacodynamics Assessed by Quantitative EEG in Healthy Volunteers

M. Hardmeier[1], R. Zimmermann[1], S. Rüegg[1], M. Pflüger[1,2], S. Deuster[3], K. Suter[3], M. Donzelli[4], J. Drewe[4], S. Krähenbühl[4], P. Fuhr[1], M. Haschke[4]

The pharmacokinetics and pharmacodynamics of a highly concentrated cyclodextrin-based intranasal (i.n.) midazolam formulation containing the absorption-enhancer chitosan were studied in 12 healthy volunteers and compared with intravenous (i.v.) midazolam. The pharmacodynamic (pD) effects were assessed using quantitative electroencephalography (eeg). maximal plasma concentrations of 63 and 110 ng/ml were reached at 8.4 and 7.6 min after 3 and 6 mg i.n. midazolam, respectively. After 5 mg i.v. and 6 and 3 mg i.n. midazolam, the times to onset of significant eeg effects in the β2 band (18–25 hz) were 1.2, 5.5, and 6.9 min, respectively, and the times to loss of response to auditory stimuli were 3.0, 8.0, and 15.0 min, respectively. A sigmoid maximum-effect (E_{max}) model indicated disequilibrium between plasma and effect-site concentrations, with equilibration half-lives of 2.1–4.8 min. The observed pharmacokinetic–pD (pK–pD) properties suggest that i.n. midazolam deserves to be evaluated as an easy and noninvasive method of administering a first benzodiazepine dose, e.g., in out-of-hospital emergency settings with no immediate i.v. access.

Intranasal (i.n.) administration of benzodiazepines has been studied for use in sedation before diagnostic/painful procedures[1,2] and for emergency treatment of persistent or repetitive seizures in pediatric and adult patients.[3,4] Persistent or repetitive seizures are neurologic emergencies that require immediate and effective pharmacologic intervention to reduce seizure duration and associated morbidity and mortality.[5] Given that many of these seizure episodes occur in an out-of-hospital setting, prehospital treatment with intravenous (i.v.) lorazepam, is performed routinely (by paramedics, for example) and has been shown to be safe and effective.[5,6] However, i.v. administration of benzodiazepines in the prehospital setting requires medically trained personnel, and safe i.v. drug administration in a convulsing patient may be technically challenging.[7]

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Cardiovascular Research | Cardiovascular Research | (2012) 93, 498–507 | 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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The FASEB Journal | The FASEB Journal | 26, 2486–2497 (2012) | IF 5,7

Therapeutic angiogenesis due to balanced single-vector delivery of VEGF and PDGF-BB

Andrea Banfi[1,2,3], Georges von Degenfeld[1], Roberto Gianni-Barrera[2,3], Silvia Reginato[2,3], Milton J. Merchant[1], Donald M. McDonald[4,5,6], Helen M. Blau[1]

Abstract

Therapeutic angiogenesis by delivery of vascular growth factors is an attractive strategy for treating debilitating occlusive vascular diseases, yet clinical trials have thus far failed to show efficacy. As a result, limb amputation remains a common outcome for muscle ischemia due to severe atherosclerotic disease, with an overall incidence of 100 per million people in the United States per year. A challenge has been that the angiogenic master regulator vascular endothelial growth factor (VEGF) induces dysfunctional vessels, if expressed outside of a narrow dosage window. We tested the hypothesis that codelivery of platelet-derived growth factor-BB (PDGF-BB), which recruits pericytes, could induce normal angiogenesis in skeletal muscle irrespective of VEGF levels. Coexpression of VEGF and PDGF-BB encoded by separate vectors in different cells or in the same cells only partially corrected aberrant angiogenesis. In marked contrast, coexpression of both factors in every cell at a fixed relative level via a single bicistronic vector led to robust, uniformly normal angiogenesis, even when VEGF expression was high and heterogeneous. Notably, in an ischemic hindlimb model, single-vector expression led to efficient growth of collateral arteries, revascularization, increased blood flow, and reduced tissue damage. Furthermore, these results were confirmed in a clinically applicable gene therapy approach by adenoviral-mediated delivery of the bicistronic vector. We conclude that coordinated expression of VEGF and PDGF-BB via a single vector constitutes a novel strategy for harnessing the potency of VEGF to induce safe and efficacious angiogenesis.—Banfi, A., von Degenfeld, G., Gianni-Barrera, R., Reginato, S., Merchant, M. J., McDonald, D. M., Blau, H. M. Therapeutic angiogenesis due to balanced single-vector delivery of VEGF and PDGF-BB.

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Constitutive Notch2 signaling in neural stem cells promotes tumorigenic features and astroglial lineage entry

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Recent studies identified a highly tumorigenic subpopulation of glioma stem cells (GSCs) within malignant gliomas. GSCs are proposed to originate from transformed neural stem cells (NSCs). Several pathways active in NSCs, including the Notch pathway, were shown to promote proliferation and tumorigenesis in GSCs. Notch2 is highly expressed in glioblastoma multiforme (GBM), a highly malignant astrocytoma. It is therefore conceivable that increased Notch2 signaling in NSCs contributes to the formation of GBM. Here, we demonstrate that mice constitutively expressing the activated intracellular domain of Notch2 in NSCs display a hyperplasia of the neurogenic niche and reduced neuronal lineage entry. Neurospheres derived from these mice show increased proliferation, survival and resistance to apoptosis. Moreover, they preferentially differentiate into astrocytes, which are the characteristic cellular population of astrocytoma. Likewise, we show that Notch2 signaling increases proliferation and resistance to apoptosis in human GBM cell lines. Gene expression profiling of GBM patient tumor samples reveals a positive correlation of Notch2 transcripts with gene transcripts controlling anti-apoptotic processes, stemness and astrocyte fate, and a negative correlation with gene transcripts controlling proapoptotic processes and oligodendrocyte fate. Our data show that Notch2 signaling in NSCs produces features of GSCs and induces astrocytic lineage entry, consistent with a possible role in astrocytoma formation.

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Tissue Engineering | Tissue Engineering | Part C Volume 18, Number 4, 2012 | IF 4,6

Generation of Human Adult Mesenchymal Stromal/Stem Cells Expressing Defined Xenogenic Vascular Endothelial Growth Factor Levels by Optimized Transduction and Flow Cytometry Purification

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Adult mesenchymal stromal/stem cells (MSCs) are a valuable source of multipotent progenitors for tissue engineering and regenerative medicine, but may require to be genetically modified to widen their efficacy in therapeutic applications. For example, overexpression of the angiogenic factor vascular endothelial growth factor (VEGF) at controlled levels is an attractive strategy to overcome the crucial bottleneck of graft vascularization and to avoid aberrant vascular growth. Since the regenerative potential of MSCs is rapidly lost during *in vitro* expansion, we sought to develop an optimized technique to achieve high-efficiency retroviral vector transduction of MSCs derived from both adipose tissue (adipose stromal cells, ASCs) or bone marrow (BMSCs) and rapidly select cells expressing desired levels of VEGF with minimal *in vitro* expansion. The proliferative peak of freshly isolated human ASCs and BMSCs was reached 4 and 6 days after plating, respectively. By performing retroviral vector transduction at this time point, > 90% efficiency was routinely achieved before the first passage. MSCs were transduced with vectors expressing rat $VEGF_{164}$ quantitatively linked to a syngenic cell surface marker (truncated rat CD8). Retroviral transduction and VEGF expression did not affect MSC phenotype nor impair their *in vitro* proliferation and differentiation potential. Transgene expression was also maintained during *in vitro* differentiation. Furthermore, three subpopulations of transduced BMSCs homogeneously producing specific low, medium, and high VEGF doses could be prospectively isolated by flow cytometry based on the intensity of their CD8 expression already at the first passage. In conclusion, this optimized platform allowed the generation of populations of genetically modified MSCs, expressing specific levels of a therapeutic transgene, already at the first passage, thereby minimizing *in vitro* expansion and loss of regenerative potential.

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Tissue Engineering | Tissue Engineering | Part A Vol. 18, Numbers 3 and 4, 2012 IF 4,6

Response of Human Engineered Cartilage Based on Articular or Nasal Chondrocytes to Interleukin-1β and Low Oxygen

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Previous studies showed that human nasal chondrocytes (HNC) exhibit higher proliferation and chondrogenic capacity as compared to human articular chondrocytes (HAC). To consider HNC as a relevant alternative cell source for the repair of articular cartilage defects it is necessary to test how these cells react when exposed to environmental factors typical of an injured joint. We thus aimed this study at investigating the responses of HNC and HAC to exposure to interleukin (IL)-1β and low oxygen. For this purpose HAC and HNC harvested from the same donors ($N = 5$) were expanded *in vitro* and then cultured in pellets or collagen-based scaffolds at standard (19%) or low oxygen (5%) conditions. Resulting tissues were analyzed after a short (3 days) exposure to IL-1β, mimicking the initially inflammatory implantation site, or following a recovery time (1 or 2 weeks for pellets and scaffolds, respectively). After IL-1β treatment, constructs generated by both HAC and HNC displayed a transient loss of GAG (up to 21.8% and 36.8%, respectively) and, consistently, an increased production of metalloproteases (MMP)-1 and -13. Collagen type II and the cryptic fragment of aggrecan (DIPEN), both evaluated immunohistochemically, displayed a trend consistent with GAG and MMPs production. HNC-based constructs exhibited a more efficient recovery upon IL-1β withdrawal, resulting in a higher accumulation of GAG (up to 2.6-fold) compared to the corresponding HAC-based tissues. On the other hand, HAC displayed a positive response to low oxygen culture, while HNC were only slightly affected by oxygen percentage. Collectively, under the conditions tested mimicking the postsurgery articular environment, HNC retained a tissue-forming capacity, similar or even better than HAC. These results represent a step forward in validating HNC as a cell source for cartilage tissue engineering strategies.

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REVIEWS

Nature Reviews Neuroscience | nature REVIEWS NEUROSCIENCE | June 2012, Volume 13 IF 30,4

Regulation of neuronal $GABA_B$ receptor functions by subunit composition

Martin Gassmann and Bernhard Bettler

Abstract

$GABA_B$ receptors ($GABA_B$Rs) are G protein-coupled receptors for GABA, the main inhibitory neurotransmitter in the CNS. In the past 5 years, notable advances have been made in our understanding of the molecular composition of these receptors. $GABA_B$Rs are now known to comprise principal and auxiliary subunits that influence receptor properties in distinct ways. The principal subunits regulate the surface expression and the axonal versus dendritic distribution of these receptors, whereas the auxiliary subunits determine agonist potency and the kinetics of the receptor response. This Review summarizes current knowledge on how the subunit composition of $GABA_B$Rs affects the distribution of these receptors, neuronal processes and higher brain functions.

Neuronal activity results from the interplay between synaptic excitation and inhibition. In the brain, excitation is mainly generated by the neurotransmitter glutamate, which activates postsynaptic cation-permeable AMPA-type receptors (AMPARs), kainate-type receptors and NMDA-type receptors (NMDARs). By contrast, inhibition is mainly generated by the neurotransmitter GABA, which activates postsynaptic anion-permeable $GABA_A$ receptors ($GABA_A$Rs). These ionotropic receptors all produce fast (<10 ms) synaptic conductances. Glutamate and GABA also activate metabotropic glutamate receptors (mGluRs) and $GABA_B$ receptors ($GABA_B$Rs), respectively, which are coupled to G proteins and influence synaptic transmission over a slower timescale (sub-seconds to minutes). $GABA_B$Rs activate $G\alpha_{i/o}$-type G proteins, which inhibit adenylyl cyclase via $G\alpha_{i/o}$ and gate ion channels via $G\beta\gamma$[1–4]. Presynaptic $GABA_B$Rs are present at inhibitory and excitatory terminals, where they function as auto- and heteroreceptors, respectively. Released GABA can feed back onto $GABA_B$ autoreceptors and inhibit further release of GABA from a terminal. GABA can also spill over to neighbouring excitatory terminals and activate $GABA_B$ heteroreceptors that inhibit the release of glutamate. Postsynaptic $GABA_B$Rs open G protein-activated inwardly rectifying potassium channels (GIRKs; also known as inwardly rectifying K^+ Kir3 channels), which inhibit neuronal activity by local shunting and generate slow (100–500 ms) inhibitory postsynaptic potentials (IPSPs) that hyperpolarize the membrane.

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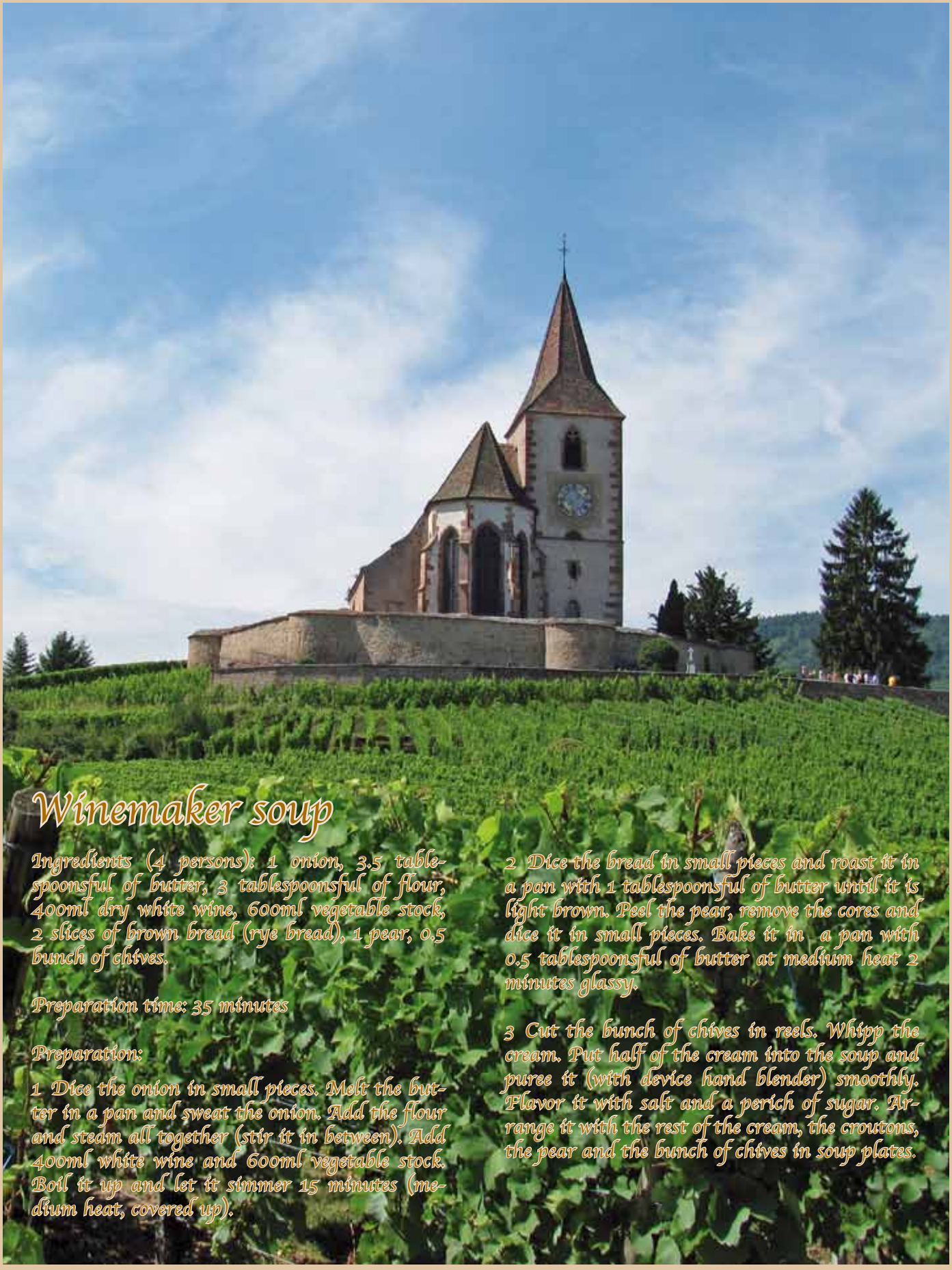

Winemaker soup

Ingredients (4 persons): 1 onion, 3.5 tablespoonsful of butter, 3 tablespoonsful of flour, 400ml dry white wine, 600ml vegetable stock, 2 slices of brown bread (rye bread), 1 pear, 0.5 bunch of chives.

Preparation time: 35 minutes

Preparation:

1 Dice the onion in small pieces. Melt the butter in a pan and sweat the onion. Add the flour and steam all together (stir it in between). Add 400ml white wine and 600ml vegetable stock. Boil it up and let it simmer 15 minutes (medium heat, covered up).

2 Dice the bread in small pieces and roast it in a pan with 1 tablespoonsful of butter until it is light brown. Peel the pear, remove the cores and dice it in small pieces. Bake it in a pan with 0.5 tablespoonsful of butter at medium heat 2 minutes glassy.

3 Cut the bunch of chives in reels. Whipp the cream. Put half of the cream into the soup and puree it (with device hand blender) smoothly. Flavor it with salt and a perich of sugar. Arrange it with the rest of the cream, the croutons, the pear and the bunch of chives in soup plates.

Foto: Eglise fortifiée de Hunawihr, Eric Spaety

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Congratulations

Das DBM gratuliert ganz herzlich!

Jan Bernasconi
Geboren am 05.08.2012

Jeremy Sinnreich-Filipowicz
Geboren am 08.08.2012

Herzlich willkommen, allerseits!

Lisa Schmaler Angevaare
Geboren am 30.08.2012

Tasuku Sato Mochizuki
Geboren am 02.08.2012

für Deine Liberalität

für die angenehme und effiziente Zusammenarbeit

für Deinen Humor

Danke, Peter!

für Deine Wertschätzung

für Deine Visionen

für die stets fröhliche Stimmung

Welcome back, Radek!

Welcome to Prague
Vítejte v Praze

In any travel survey Prague effortlessly slips in to the top 10 of the most visited European destinations. The reason for this is simple. With its narrow cobbled streets and a skyline of steeples, Prague is one of Europe's most enchanting cities. Home to approximately 1.5 million people, the Czech capital is very compact, so you can see a lot in a relatively short space of time.

Prague has a unique landscape. While many cities claim to have been built on 7 hills, Rome being the most well known, Prague is located amongst 9 hills, which makes for a spectacular view. The city's dominant feature is the Prague castle complex (Hradcany) overlooking the river and is best appreciated from the Petrin hill facing it. The highlight of the castle is the gothic St. Vitus cathedral. Other notable attractions include the Golden Lane, where alchemists turned base things to gold, and the Castles terrace gardens facing the river.

The Vitava River meanders through Prague and is spanned by 17 bridges. The most impressive of them is the Charles Bridge. Build in 1357 it was the first bridge connecting the Mala Strana with the Old Town and became one of the main trade routes between eastern and western Europe. The bridge is made of 16 gothic arches and is lined by an alleyway of 30 baroque statues with towers at each end. The 30th statue is that of St. Kosma and Damien,

who are believed to be patrons of medicine. Prior to their state exams, medical students go there to pray for a good outcome. If it's luck that you seek, touching the brass relief of St. Jan Nepomuk is believed to help.

Crossing the bridge to the right bank you will notice a statue of Charles IV and two baroque churches St. Francis and St. Salavator next to Klementinum, the library. Extending from the bridge is Charles Street, which will take you to the old town, known locally as Stare Mesto. Prague's old town is one of the most charming in Europe. The focal point of the area is the old town square, which is always bustling with people and is also full of cafés and restaurants. Branching off the square is a series of quaint narrow cobbled streets. One of the most popular things to do in the old town is to catch the procession of the 12 apostles, which happens at the astronomical clock every hour. You are allowed to climb up the tower and once at the top you will be rewarded by a stunning view of Prague's old town's countless roof tops. The St. Nicholas church is located behind the clock tower and at the center of the square there is the statue Jan Hus (Christian reformist).

Prague's repertoire doesn't however stop with its architecture. Between the National Theatre, State opera, Estate Theatre and Rudolfinum the classical music lover is bound to find his niche. The annual Prague spring autumn classical music festivals are sold out well in advance so plan ahead if you wish to attend.

The Laterna Magica shows are an intricate blend of film, ballet and black theatre. Its origin lies in the 58' Expo in Brussels. Parallel projections onto multiple screens allow seamless transitions between individual theatrical and film elements. The Magical Circus, a folk music inspired show created by Evald Schorm, is running uninterrupted since the 60's and is a piece you should not miss.

The historic cafes in Prague are often in the blind spot of the generic tourist. Hence they are the perfect place to sit back, avoid the crowds and blend in with the locals. There are many cafes, but some stand out.

The Café Louvre, on Národní Avenue, is an elegant, spacious art nouveau café established in the early 1900 and was one of the first of its kind in Prague. Deemed as too "bourgeois" the café was actually closed during communist times and reopened in 1992. The café itself is actually on the first floor and exudes style and elegance. Café Louvre however does not only impress with its style, but follows up with substance as well. The café serves excellent Czech pastries and a selection of classical Czech dishes done well! In their time, the likes of Kafka, Capek and Einstein were frequent flyers in café Louvre.

Another famous Czech café is Slavia, located at the corner of Narodni Avenue, opposite the National Theatre. Facing the river, its large plate glass windows offer a breathtaking view of the Prague castle. Just like café Louvre, it is one of the great pre-war cafes. Unlike Louvre though, Slavia is designed as an Art Deco café and has its own distinctive aesthetic. It took me some time to figure out the differences between the two styles – art deco is more streamlined, the emphasis is on modern materials and texture, art nouveau often features heavily embellished natural motifs, it loves its curls and semicircles, noticeable especially on railings. Being across the street from Laterna Magica, where the Civic Forum held its meetings during the Velvet Revolution, it was closely associated with the dissent. In fact, there is table in the far corner of the café under the painting of "the absinthe drinker" that was rumoured to be permanently reserved for Vaclav Havel (Czech dissident, playwright president). Slavia has also a reputation of serving one of the best apple pies in Prague. Under the café, there is a newly reconstructed club, where students from the neighbouring film academy often hang out.

Also well worth a visit are the Grand Café Orient in the cubist House of the Black Madonna and

the luxuriant, though not the original, Café Savoy across the river from Slavia.

Most of Prague's old cafés have at least three things in common: modern architectural style, decent food and a historical context (or at least a famous alumnus). The best thing is that as long as you order a coffee or two, you will be allowed to idle at your leisure without feeling under pressure to pay up and leave.

A word of advice: schedule 4–5 days when visiting Prague. When in Prague try to walk everywhere, rather than taking the trams. This will allow you to better appreciate the city's architectural marvels. The city's charms can occasionally be obscured by too many tourists and tacky commercialism, so avoid the mistakes made by the overzealous tourist. Instead schedule small trips every day to gradually get to know the city. Prague is best seen early morning and evening. The city is calm, less crowded and you are likely to take your best pictures at twilight anyway. Don't be shy to talk to the locals. They may look reserved at first, but tend to be helpful and may give you a good tip as to what's going on in the city at the moment. Make your Prague visit memorable.

Arun Cumpelik

Café Louvre
Národní 22, Prague 1

Café Slavia
Smetanovo nábřeží 1012/2, Prague 1

Café Savoy
Vitezna 5, Prague 5

Grand Café Orient
Dům u Černe Matky Boži
Ovocný trh 19, Prague 1

Laterna Magika
Národní 4, Prague 1

National theater
Národní 2, Prague 1

Rugby for scientists: questions, correlations, and thought

Exhibit A: Large bodies in small shorts. B: Unintelligible rules for simplistic brutality. C: Beer. If any of these images neatly fits inside your conception of rugby, then you are guilty. Worse than committing the crime of stereotyping is missing out on the weird, the wonderful, and the more curious aspects of rugby.

Maybe you think the only weird and curious things about rugby is why anyone would play it, and maybe you think that people who indulge in rugby are "wonderful", just like insane people are "special". Before you go back to that insufferable gel, that masochistic manuscript, that ageless donut that has been on your desk for longer than you can remember, please consider this: rugby is interesting.

The slickest way into the world of rugby is through the questions it poses. "Does size matter?" is a deeply philosophical question which many of you may have pondered without the aid of rugby. You don't need to be a quantum physicist to appreciate this; the size question is an import one handed down (or up) from one small philosopher to the next over the ages. Next we will meditate on cause and correlation in rugby. Cause and Correlation is not just the much awaited Jane Austin novel marketed to scientists. It is the bread and butter for scientific rumination. I'm telling you, rugby is worth chewing on. And if these exciting topics don't whet your scientific palate, let me ask you this question (which I know keeps most scientists up at night): Do you feel fat and lazy, and is there something to be done about it? For this introductory tour we will prod rugby from a comfortable perspective and with a sciency stick. Along the way I'll point out the contrarian origin of rugby and show you that rugby is more famous for its scientists than its thugs. By the end you will all think rugby is a safe and valuable exercise.

About size. Standing at 5ft 7inches (1.7m), weighing 11 stone (76kg), he might be a small, slightly malnourished grad student at the DBM. A small man from a small valley in Wales, a country whose astonishing zealotry for rugby is only surpassed by its astonishing sheep to man ratio (SMR) (- and i'll come back to this). Yes, a small man whose shorts are relatively big. Put him in a lab coat, he would walk by you unnoticed. That is Shane Williams, best rugby player in the world 2008, one of the greatest of all time, rebel against rugby stereotypes.

Jonah Lomu on the other hand is your average rugby stereotype, multiplied by 7. He is enormous. He is fast. He is tough to defend against in rugby, or even a heated game of scrabble. I'll remind you that momentum (ρ) equals mass (m) multiplied by velocity (v) (ρ=mv), and force is proportional to momentum over time. Jonah is a force to reckon with. 1.96m, 125kg, runs the 100 meters in 10.4 seconds (near Olympic speed).

Comparing Lomu to Williams one is forced to consider the size question. Does size matter, or is it how you use it? Is it better to have a Williams or a Lomu on your team? How size matters in rugby is unpredictable – there is an exception to every rule, and the rules change with every circumstance. Many different sizes and shapes are there in rugby, and their interaction creates color and tension in the game. Williams and Lomu played the same position, and when players of such stature line up against each other, magic happens. Ok, sometimes the small guy gets squished like a bug – but it's a very magical squishing.

Jonah Lomu

Rugby is not only richly painted by diverse sizes; it has a unique character derived from its odd history. The game originated

at an English school called Rugby, sometime back around 1750. Now listen, this was the dark ages of sports. Balls were artlessly hit, kicked, or hacked (think of the monolith in Kubrik's 2001, and add a ball). It wasn't just absence of elegance; something more was lacking from sport. With the type of revelation only known to Euclid or Newton, one William Web Ellis (legend has it) did not savagely kick or hit a ball whilst all others around him did. He ingeniously picked it up, nestled it in his bosom, and began to run (cue the music from «Also sprach Zarathustra»). And so Ellis begat rugby.

Modern rugby has evolved. Rugby (*) was an amateur sport that turned professional in the mid 1990s, and it will be Olympic in 2016. Early professional, and all amateur rugby players had a career – and many of them were scientists. Welsh rugby legend, JPR Williams, was a noted orthopaedic surgeon. Albert Fert was a decent rugby player, not an all time great, and not even an international, but he compensated for his mediocre rugby with the 2007 Nobel prize for physics. The current French captain and 2011 best player in the world, Thierry Dusautoir, has a degree in chemical engineering. I'll leave it to you to wonder why rugby is so miscible with scientists while things like fashion are not.

Walk around any rugby club, professional or local, and you will find people of every profession, from scientists to builders and on. And this is what I like about rugby. It requires and thrives on diversity, diversity in intellect, character, body morphology, strength, agility, and speed. Rugby is inviting to a large range of people. You need tall skinny people, short fat ones, and vice versa. You have people who can look up and think spontaneously, and others to trundle forward according to plan. There is some selection; you have to be a certain type to play, but this is analogous to the selection required to work in science, which also invites diverse people.

Cause and correlation. England is populated with the most rugby players in the world (2.5 million), about 20 times more players than in New Zealand (130,000). There is also more money etc. so one might be tempted to think that winning correlates with the population of players, but that would be too simple. In fact, the factor of 20 normalizes the magnitude of disappointment English fans feel when they lose to the Kiwis – and there's the reciprocal for New Zealander's smiles after winning. Could there be an inverse correlation between winning and population,

In the middle: Shane Williams

and what about the other countries of comparable rugby populations? New Zealand and Wales are historically the best teams, and they have near the smallest populations of players. Namibia and Georgia are even smaller, but they are terrible, relatively speaking. So what is so special about New Zealand and Wales? After much research (**), I have isolated the sole variable specific to these countries: exorbitant SMRs (high sheep to man ratios). Let's hope that is only a correlation. Nonetheless, rugby fans not from Wales or New Zealand seem more than eager to suggest causality- even the scientists.

Finally, the real introduction to rugby is watching or playing. Watching is easy: 1) sit in front of TV, and 2) apply food or beverage liberally to mouth area. Now I am going to convince you that playing rugby is not out of the question, and is perhaps healthier than watching. The fastest growing sport in America, for men and women, is called "touch rugby" or "flag rugby", involving no tackling or violence. You can learn and play this in Basel. If you do, you will be surrounded by expats and Swiss, and many of them will be in Pharma. Perhaps more importantly, you will get fit with a low risk of injury, and a high probability of fun. In conclusion, and with reference to the eternal size question, I'd suggest the following slogan for rugby in Basel: Smaller bum, bigger network.

Michael Abanto

* I refer to rugby union, my favorite. There are many types of rugby. Union has 15 players per side, league 13, sevens 7, and so on. I prefer union. 7s will be the Olympic sport.

** I googled it.

Marc Bichsel neuer IT-Supporter

Seit dem 1. September 2012 verstärkt Marc Bichsel das DBM IT-Team. Marc ist am DBM Hebelstrasse beheimatet, wird aber auch die anderen Häuser bei Bedarf unterstützen. Marc ist gelernter Informatiker, hat aber auch schon andere Berufsbereiche kennengelernt. Von 2011 auf 2012 hat er nur ein wenig die Buchstaben vertauscht: Von der UBS zu uns ans USB. Marc ist nicht mit seinem berühmten Namensvetter verwandt, ist in seiner Freizeit leidenschaftlicher Tennislehrer und -schüler, denn noch besser werden kann man ja bekanntlich immer, und freut sich auf die Herausforderungen, die auf ihn warten. Wir wünschen Marc einen guten Start und viel Freude am DBM!

Heidi Hoyermann

IT News

All Unibas email accounts at the DBM are currently being migrated to a new exchange server.

This will bring the following benefits:

- *Consolidated use of the calendar*
- *A proxy for editing the calendar*
- *A proxy for emails*
- *Automatic replies and forwarding of mails will be directly configurable through programs like Apple Mail for example*
- *A new webmail interface https://mail.unibas.ch/owa will replace the old http://webmail.unibas.ch*
- *It will be possible to include an address book with all the email addresses at the University*
- *A central backup of all mails*
- *Deleted mails will be recoverable*

If your email account has not yet been migrated, please note the following:

1. *The URZ will send you an email a week before the migration in order to inform you of the changes.*
2. *On the day before the changeover you will receive another mail with the request not to send any mails between approximately 07:00–11:00 the following day.*
3. *When the migration has been successfully completed you will receive a mail which will detail what you must change in your email program in order to continue to access your mails as normal*

If you wish to use all of the new functions then you will need to set up your email account again. You can find out what is necessary for this and how exactly it works by either accessing the information on our server http://gadget.dfusb.unibas.ch or by contacting your IT personnel.

Im Moment werden am DBM alle Unibas Email Accounts auf den neuen Exchange Server migriert.

Dies bringt folgende Möglichkeiten mit sich:

- gemeinsame Nutzung von Kalendern
- Stellvertretung für die Kalenderbearbeitung
- Stellvertretung für Mails
- Automatische Antwort und Weiterleitung aus zB Apple Mail direkt konfigurierbar
- Neues Webmail Interface https://mail.unibas.ch/owa ersetzt das alte http://webmail.unibas.ch
- Adressbuch mit allen Email Adressen der Universität einsetzbar
- Zentrale Sicherung aller Mails
- Wiederherstellung von gelöschten Mails möglich

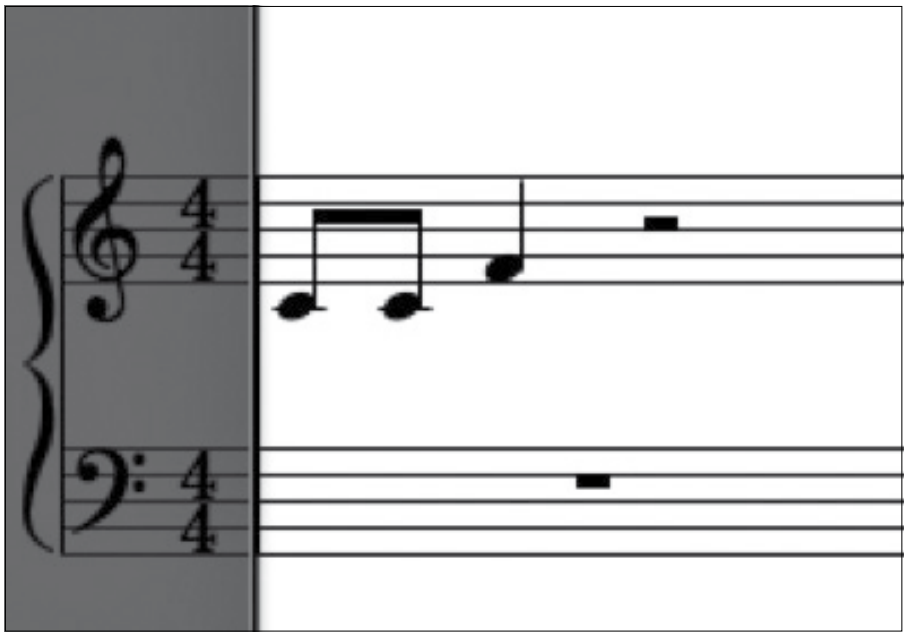
Falls Ihr Email Account noch nicht migiert wurde, beachten Sie bitte Folgendes:

1. Das URZ wird eine Woche vor der Migration ein Mail an Sie schicken, in welchem die Umstellung angekündigt wird.
2. Am Tag vor der Umstellung erhalten Sie nochmals ein Mail mit der Aufforderung, am nächsten Tag keine Mails von ca. 0700–1100 zu versenden
3. Wenn die Migration erfolgreich war, erhalten Sie ein Mail mit der Information, was Sie an Ihrem Mail Programm ändern müssen, um weiterhin wie gewohnt arbeiten zu können.

Wenn Sie alle neuen Funktionen verwenden wollen, so sollten Sie Ihren Email Account neu aufsetzen. Was dazu notwendig ist und wie das genau funktioniert, können Sie entweder auf unserem Server http://gadget.dfusb.unibas.ch erfahren oder wenden Sie sich an Ihren Informatiker vor Ort.

Apart from IT...

In this issue of DBM-FACTS you can find out what an IT-guy does when he's not at a computer.



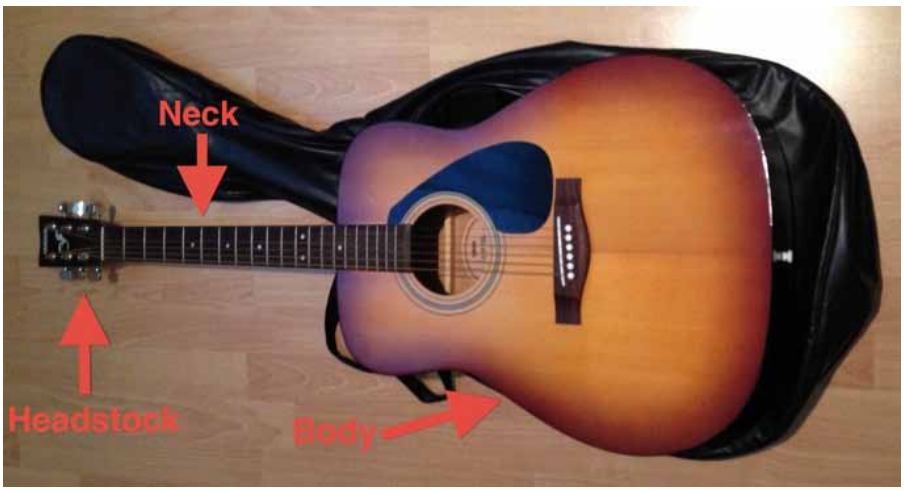
I could lose myself for hours playing guitar. I began playing guitar when I was eight years old. At that time I started playing in the Music school in Gelterkinden. I learned the basics there and I played my first songs. Of course I started playing slow and easy songs. The basic knowledge also involved reading and writing notes.

A simple example of musical notation:

After a while I joined an ensemble, where I played in a group with other guitarists. Shortly after that I gave my first public performances. In the beginning I started learning to play on an acoustic guitar. My first guitar was a bit smaller than usual and had three strings of nylon and three strings of steel. The nylons strings are made so that you can push the strings down more easily at the beginning. This helps avoid getting cramps in your hand.

Design of an acoustic guitar:

While playing guitar one or more strings are usually hit or picked with one hand. With the other hand you can push down a string onto the neck, which reduces the length of the string. Reducing the length of the string will result in raising the note. The hollow body amplifies the note, so that the guitar sounds loud. So the way in which a guitar produces music can be explained by physics rather than magic. After seven years I changed my teacher and I went to a music producer who had completely different experiences in music. I moved from someone who taught in an academic manner to someone who taught more artistically. At this time I needed a bigger guitar as I had also grown. This would



have been the one pictured above. This new guitar only had strings of steel. After two years playing on that guitar, I was ready for an electric guitar on which I then learned a lot of new stuff.

E-guitar: different to an acoustic guitar

Unlike an acoustic guitar the tune is generated in a completely different manner. The pickups, as their name suggests, pick up the note. The pickups contain permanent magnets, which are wrapped in conductors. Here again we have a little bit physics. Because of the vibrating strings the pickups turn into electro-magnetic transducers. This means that electricity is being produced. But this electricity is very weak. That is why an amplifier (amp) is needed to convert the electricity into a note and amplify it. The amp looks like a speaker but with an input for the cable that connects from the output connector (or output jack) of the guitar. With Apple's program GarageBand you can connect the guitar to a Mac, for example, which takes over the part of the amp. With the pickup selector switch you can choose which pickups (magnets) are picking up the vibrating strings. With the control knobs you can set the volume and accentuate the high and low notes.

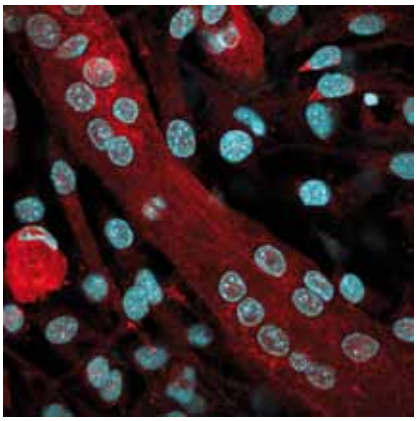
To date I have learned all of the following techniques for playing music on the guitar: vibrato, flageolett, hammer-on, pull-off, bending und glissando.
I have also learned a number of different music styles such as rock-'n'-roll, reggae, Arabic music, phrygian dominant music (Spanish and Jewish), as well normal rock, classic ballades...

Is it any wonder I can lose myself for hours when playing guitar.

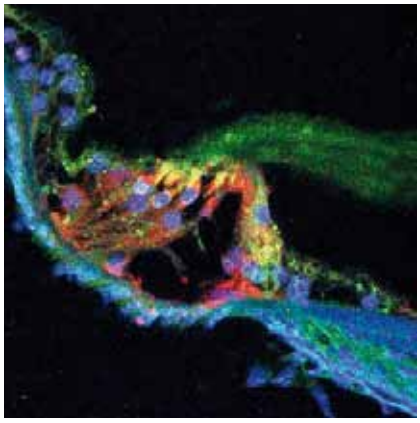
Ilija Lujic

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



. . . erfahren wir von Susan Treves, was Perioperative Patientensicherheit bedeutet



. . . führt uns Daniel Bodmer in die Innenohr-Forschung ein

. . . feiern wir mit Karoliina Pelttari Finnische Weihnachten

... gehen wir mit Yvonne Fink auf die Piste in ihrer Heimat Davos

. . . machen wir mit Charles Hemion einen Ausflug in die Welt der klassischen Musik

O trübe diese Tage nicht

O trübe diese Tage nicht,
Sie sind der letzte Sonnenschein,
Wie lange, und es lischt das Licht
Und unser Winter bricht herein.

Dies ist die Zeit, wo jeder Tag
Viel Tage gilt in seinem Wert,
Weil man's nicht mehr erhoffen mag,
Dass so die Stunde wiederkehrt.

Die Flut des Lebens ist dahin,
Es ebbt in seinem Stolz und Reiz,
Und sieh, es schleicht in unsern Sinn
Ein banger, nie gekannter Geiz;

Ein süßer Geiz, der Stunden zählt
Und jede prüft auf ihren Glanz –
O sorge, dass uns keine fehlt,
Und gönn' uns jede Stunde ganz.

Theodor Fontane (1845)