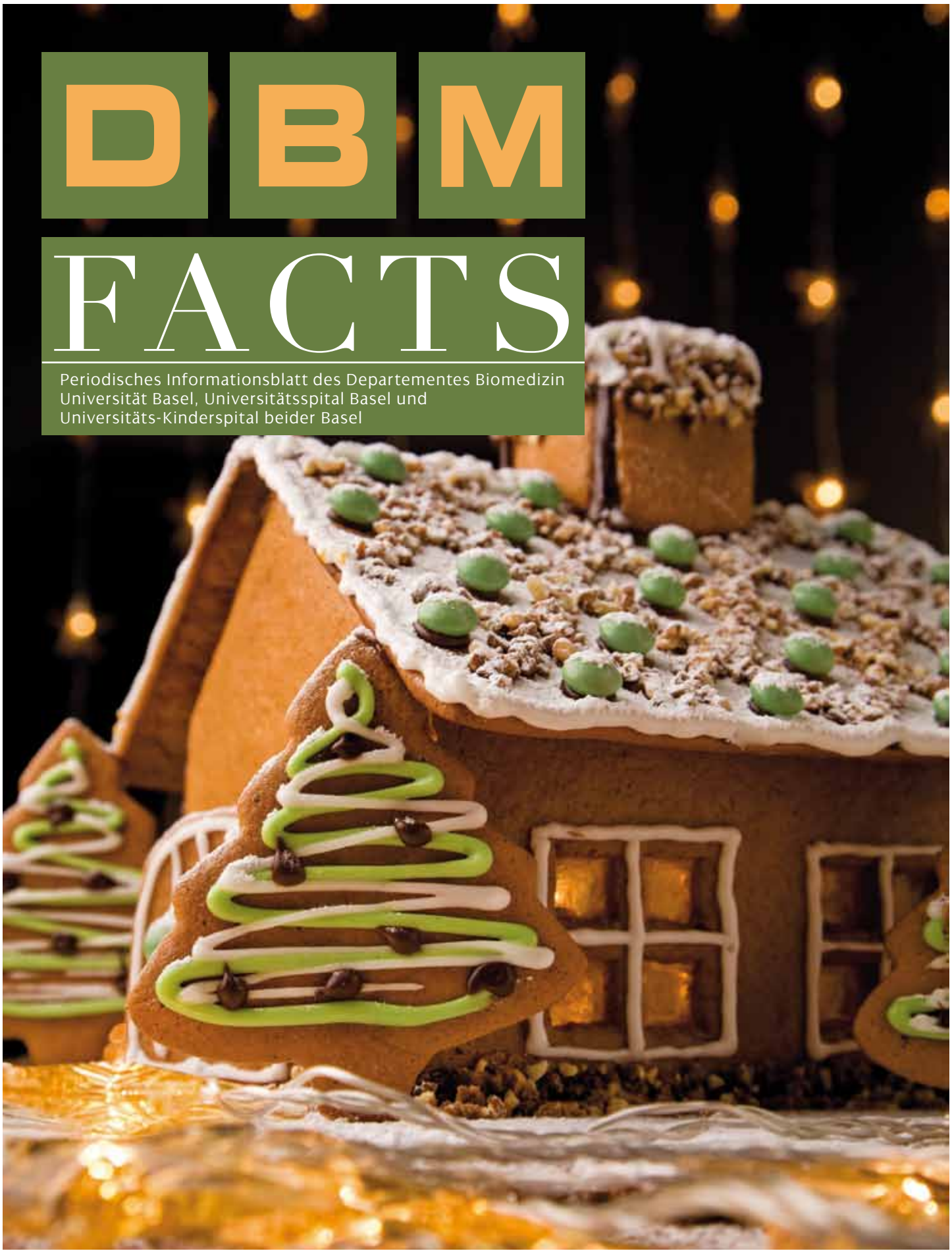
DBM FACTS

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



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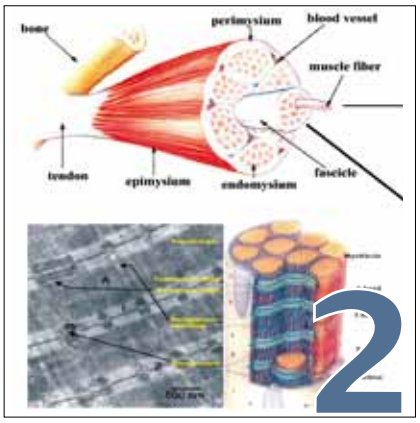
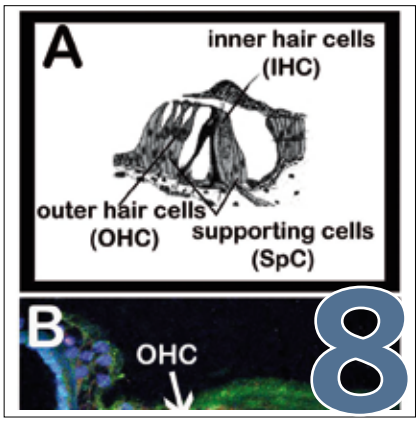


Skeletal Muscles, health and disease: a balance between Dr Jekyll and Mr Hyde
from Susan Treves and Francesco Zorzato



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Frank Neumann
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Titelfoto
Beautiful gingerbread house, Shutterstock

Druck
Morf Bimo Print AG, Binningen

Anschrift
Redaktion DBM Facts
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Universitätsspital Basel

UNI BASEL

EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Kaum wieder in Basel, neigt sich 2012 seinem Ende zu. Mein herzlicher Dank geht an Peter Meier-Abt für seine umsichtige Leitung des DBMs in den Monaten meiner Abwesenheit. Die Arbeit geht weiter: Der Umbau der Bibliothek im zweiten Stock zu Labors nimmt konkrete Gestalt an, die Planung des neuen DBMs auf dem Schällemätteliareal hat begonnen, die Research Days und der Besuch des Advisory Boards stehen schon vor der Tür.
Per 1. Januar 2013 wird die Medizinische Genetik vom UKBB an das USB und DBM wechseln. Sven Cichon wird die Leitung übernehmen. Seine Forschungsgruppe wird in der Mattenstrasse beheimatet sein, während die Dienstleistungslabors vorerst im Felix-Platter-Spital bleiben. Wir heissen alle Mitarbeitenden herzlich willkommen und wünschen viel Erfolg!
In der letzten Ausgabe dieses Jahres steht die wissenschaftliche Tätigkeit der Forschungsgruppen Perioperative Patient Safety und Inner Ear Research im Mittelpunkt. Susan Treves und Francesco Zorzato beschreiben, welchen Zusammenhang Mutationen in Proteinen, die Kalzium im Muskel regulieren, mit maligner Hyperthermie haben, während Daniel Bodmer und Soledad Levano die Signalübertragungswege untersuchen, die bei Hörvorgängen im Innenohr und bei Innenohrschwerhörigkeit eine Rolle spielen. Die neuesten Publikationen am DBM finden Sie ab Seite 16.
Wie man in Finnland Weihnachten feiert, wie liebenswert Davos sein kann, und warum nicht jeder Musikunterricht für Kinder tragisch enden muss, erfahren Sie ab Seite 32.
Ich würde mich freuen, Sie alle auf der DBM-Weihnachtsfeier zu sehen, an der auch der diesjährige DBM-Preis vergeben wird.

Schöne Festtage und einen guten Rutsch ins 2013!

Dear Readers

In Basel 2012 is already drifting towards its end. My sincerest thanks to Peter Meier-Abt for his prudent leadership of the DBM during my absence. The work continues: there are concrete plans in place for the conversion of the library on the second floor into lab space, the planning for the new DBM on the Schällemätteliareal has begun, the Research Days and the visit of the Advisory Boards are almost upon us again.
As of the 1st January the Medical Genetics department of the UKBB will move to the USB and the DBM. Sven Cichon will take over the leadership of this group. His research group will reside on Mattenstrasse while the service labs will, for now, remain in the Felix-Platter Hospital. We welcome all of the new staff and wish them every success!
In the last issue of this year the scientific practices of the research groups on Perioperative Patient Safety and Inner Ear Research are in the spotlight. Susan Treves and Francesco Zorzato describe the relationship between mutations in proteins that regulate calcium levels in muscles and malignant hypothermia, while Daniel Bodmer and Soledad Levano investigate the signal pathways that play a part in hearing in the inner ear and in inner ear hearing problems. The latest publications from the DBM can be found from page 16 on.
From page 32 on you can learn how Christmas is celebrated in Finland, how beautiful Davos can be and why not every child's music lesson must end tragically.
I hope to see you all at the DBM Christmas party where this year's DBM prize will be presented.

Happy holidays and a good slide into 2013!

Skeletal Muscles, health and disease: a balance between Dr Jekyll and Mr Hyde

From left to right:
Ori Rokach, Thierry Girard, Toshiaki Haraki, Marijana Sekulic, Francesco Zorzato, Mirko Vukcevic, Esther Schmid, Martine Singer, Anne-Sylvie Monnet, Rubén Lopéz, Albert Urwyler, Susan Treves, Antonio Teixeira

Introduction

All animals are characterized by their capacity to move and in order to do so have developed a specialized organ: skeletal muscle. Skeletal muscle constitutes approximately 40% of the total body mass, accounts for more than 30% of energy expenditure and is the major tissue involved in insulin-dependent glucose uptake. There are different kinds of skeletal muscles, located throughout the body, involved in different function (for example the diaphragm involved in breathing, leg and arm muscles involved in limb movement, back and neck muscles involved in posture) and biochemically subdivided according to their contraction velocities and expression of different protein isoforms (for example myosin heavy chain). These are: fast twitch muscles that fatigue rapidly, are poor in mitochondria are mainly anaerobic and are used for short bursts of intense exercise (such as sprinting and jumping); slow twitch muscles that are fatigue resistant, are rich in mitochondria, are mainly glycolytic and are used for endurance (such as marathons); the third category are the eye muscles, which are the fastest contracting muscles. Observing skeletal muscles by electron microscopy shows highly ordered structures underlying their high degree of specialization and sophistication. Muscle bundles are made up of many fibres and normally contain both fast twitch (type 2) and slow twitch (type 1) fibres at a ratio of about 50:50 under normal, non -pathological conditions (figure1).

Skeletal muscles communicate with other organs and tissues by releasing myokines, cytokines and hormones, and play an important role in maintaining our health and general well being. Indeed patients who are immobilized and require prolonged bed rest lose approximately 5–10% of their muscle mass per week and this results in a 20–30% decrease in muscle strength. Studies have shown that patients in the intensive care unit who lose muscle force have a more negative prognosis than patients who maintain muscle force. These results combined with the fact that exercise is generally "good for the health" indicate that muscle movement plays an important role in our general well being and "if we don't use our muscles, we lose them". In addition to sport physiologists, doctors working in the intensive care and endocrinologists, anesthesiologists also have a strong interest in the physiology of skeletal muscle, not only because patients are treated with neuromuscular blocking agents during surgery but also because of potentially adverse outcomes due to genetic predispositions such as Malignant Hyperthermia. The main focus of the anesthesia clinical research team is perioperative patient safety and skeletal muscle has been its major fo-

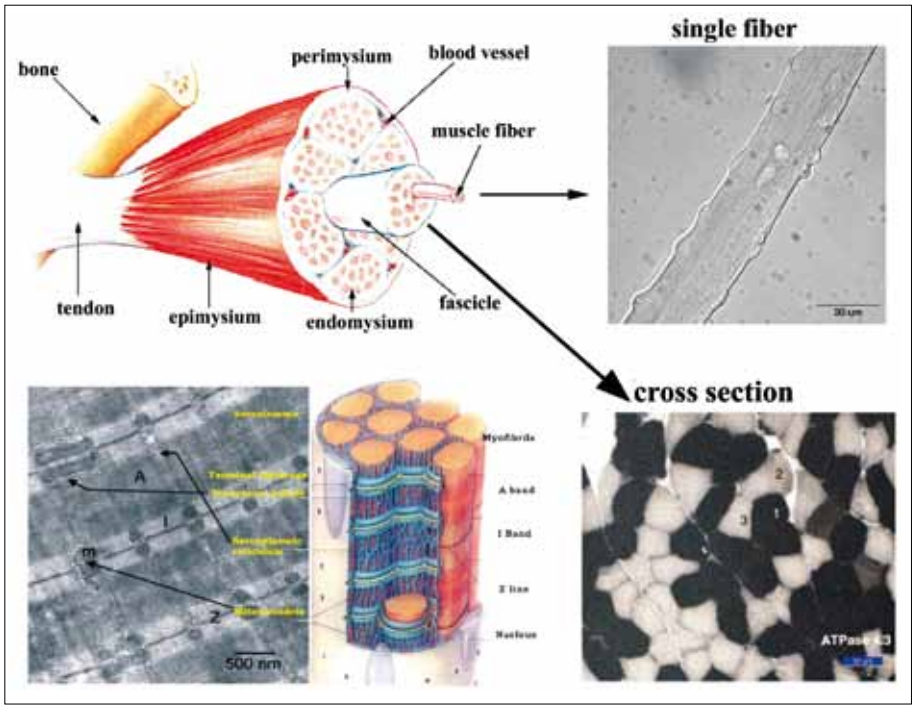

Figure 1: Structure of skeletal muscle.
Top left: schematic representation of skeletal muscle and its main constituents.
Top right: photomicrograph of a single isolated muscle fiber from mouse flexor digitalis brevis (FDB) muscle.
Bottom left: EM photomicrograph and schematic representation showing the highly ordered structure of muscle, contractile proteins and sarcoplasmic reticulum.
Bottom right: cross section of human skeletal muscle showing slow twitch (dark) and fast twitch (light) fibers.

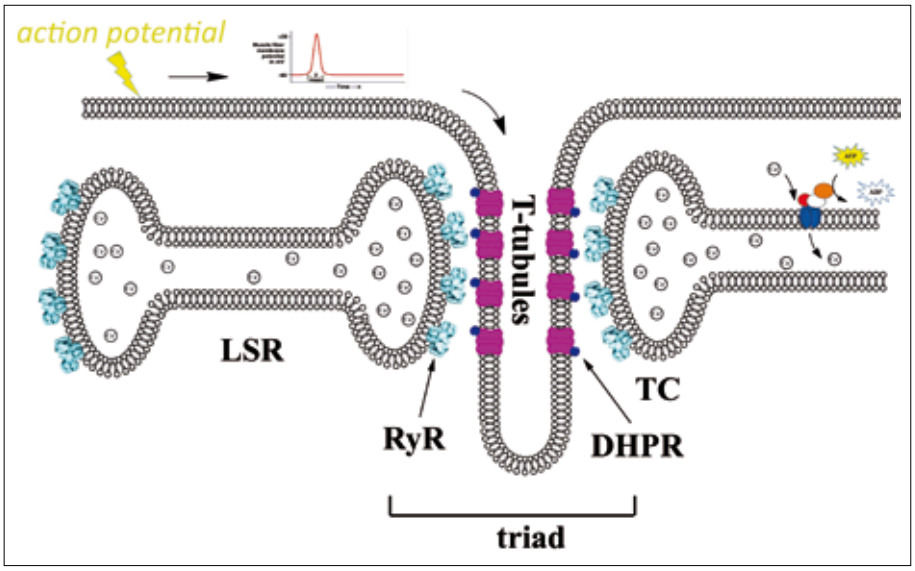

Figure 2: ***Schematic representation of the membrane components and main proteins involved in skeletal muscle excitation contraction coupling.***
In skeletal muscle the action potential is sensed by the dihydropyridine receptor, an L-type Ca^{2+} channel present on the transverse tubules, invaginations of the plasma membrane that penetrate deep in the muscle fibers. When they sense the change in voltage, DHPR undergo a conformational change and activate ryanodine receptor Ca^{2+} channels present on the sarcoplasmic reticulum terminal cisternae; this Ca^{2+} binds to tropomyosin and leads to contraction of the myofibers.

cus since the laboratory was established in 1986 as the first and still only Malignant Hyperthermia investigation unit in Switzerland.

Calcium homeostasis in striated muscles

But how is muscle movement achieved? Ca^{2+} is the key molecule underlying muscle contraction and sliding of the contractile proteins actin and myosin is dependent on the Ca^{2+} released from the sarcoplasmic reticulum (SR), an organelle constituting approximately 10% of the cell's volume and fully dedicated to uptake and release of Ca^{2+}. The SR can be structurally divided into two distinct portions: the terminal cisternae, which face the transverse tubules (an invagination of the plasma membrane) and the longitudinal sarcoplasmic reticulum, connecting two terminal cisternae (see figure 2). Depolarization of the plasma membrane of skeletal muscle leads to release of Ca^{2+} from the SR resulting in muscle contraction, by a process known as excitation-contraction coupling. Excitation-contraction coupling, the conversion of an electrical signal (depolarization) into a chemical gradient, occurs at the triad, a structure composed of the two membrane compartments, transverse tubules containing the voltage sensing dihydropyridine receptor (DHPR, an L-type Ca^{2+} channel) and terminal cisternae on which ryanodine receptor (RyR) Ca^{2+} release channels are localized (figure 2). The disposition of DHPRs and RyRs on their respective membranes is highly ordered and each RyR tetramer faces alternative rows of DHPRs. These two Ca^{2+} channels are the basic unit underlying excitation-contraction coupling but they do not function alone, rather they are macromolecular structures composed of a number of accessory proteins involved in their regulation. Because of the highly ordered structure of the excitation-contraction coupling machinery, this process is extremely rapid occurring in a time scale of mseconds. Figure 3 shows a representative linescan image of a mouse *flexor digitorum brevis* muscle fiber loaded with the Ca^{2+} indicator MagFluo-4 stimulated twice with an electric pulse of 15 V for 1 msec. As seen the kinetics of the Ca^{2+} transient are very fast, occurring within milliseconds.

Ryanodine receptors: Ca^{2+} release channel of skeletal muscle

The skeletal muscle RyR was first identified at the biochemical level in the 1980s and was named for its ability to bind the plant alkaloid *ryanodine*. Three RyR isoforms, encoded by separate genes sharing a high level of homology have been identified in mammalian tissues: RyR1 is the primary isoform expressed in skeletal muscle, is also expressed in some areas of the central nervous system, in some smooth muscle cells and in some haemopoietic cells. RyR2 is the predominant isoform in cardiac muscle and is also expressed in various regions of the brain whereas RyR3 has widespread tissue expression. The RyR is the largest known ion channel and forms a homotetrameric structure of

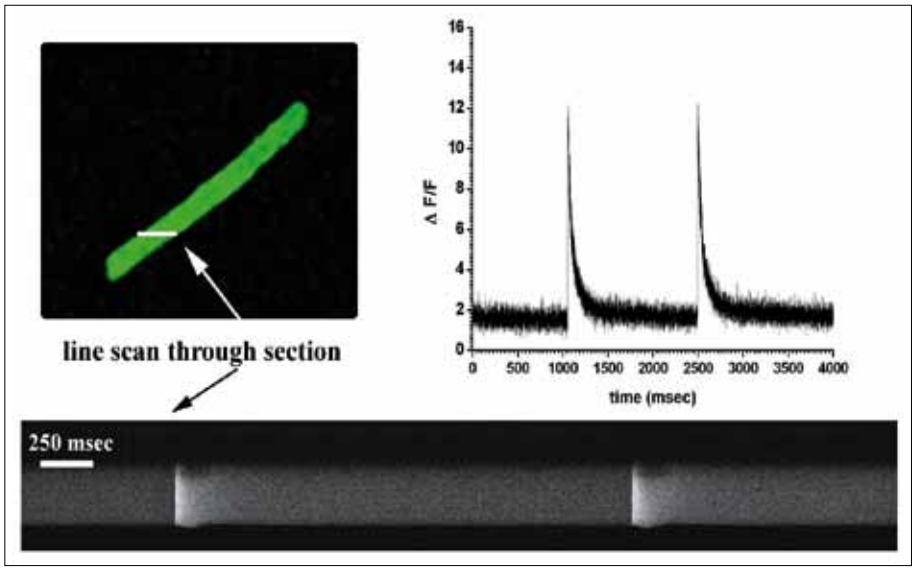

Figure 3: ***Calcium kinetics in a single FDB fiber.***
A. FDB muscle fibers was loaded with the Ca^{2+} indicator Fluo-4 and visualized with a Nikon A1R confocal microscope (20x objective). An optical section of the fiber was selected (white line) and imaging in real time resonant mode was performed on this section of the fiber, during electrical stimulation (2 pulses of 15 volts lasting 1 msec each).
B. Ca^{2+} transient elicited by the electrical stimulation and bottom image shows the linescan image through the selected region.

approximately 2.3 MDa. Each 565-kDa monomeric subunit consists of 5038 amino acids. Approximately four-fifths of the channel is made up of the large N-terminal cytoplasmic domain, which contains binding sites for a number of modulators. The C-terminal region contains the transmembrane domains and ion-conducting pore. RyR1 channels are characterized by a very large-conductance with moderate selectivity for divalent cations over monovalent cations. A number of accessory molecules such as calmodulin, S100 and FKBP12 binding protein can be found associated with the RyR1 and either stabilize or modify its function.

After it's cloning in 1990 it became apparent that mutations in *RYR1* are linked to Malignant Hyperthermia, a pharmacogenetic disorder of particular importance to anesthesiologists. Indeed it had been known amongst clinical anaesthesiologists that certain patients with anesthesia-related deaths in their families, developed a sudden life-threatening hypermetabolic disease not linked to their clinical condition, when they came into contact with trigger agents such as volatile anaesthetics and the muscle relaxant succinylcholine. After the first identification of a *RYR1* mutation in patients with malignant hyperthermia it is now known that mutations in *RYR1* are a major cause of muscle disease. Both dominant and recessive mutations have been identified throughout the *RYR1* coding sequence and are responsible for a wide range of muscle disorders including Malignant Hyperthermia, Central Core Disease, Multiminicore Disease, Centronuclear myopathy, Core-rod myopathy and Congenital Fiber Type Disproportion and King-Denborough Syndrome. Dantrolene, used in the emergency treatment of Malignant Hyperthermia, is currently the only clinically relevant drug for RyR1 disorders and drugs that address the chronic, often life-threatening muscle weakness associated with many RyR1 disorders are much needed.

How mutations in *RYR1* affect its function

For many years how mutations in *RYR1*, the gene encoding the *RyR1*, could be associated with diverse and at times opposing clinical phenotypes, remained a mystery. Indeed patients with Malignant Hyperthermia develop extreme muscle rigidity while patients with Core myopathies have weak, floppy muscles. We and several other groups have been investigating the functional impact of *RYR1* mutations associated with disease for the past decade. Our model system consists in obtaining the satellite cell population from small biopsies, expanding them into myoblasts in culture and finally differentiating them into multinucleated myotubes (figure 4A). Although not differentiate to the extent of fibres, myotubes express the proteins necessary for excitation-contraction coupling, namely the RyR1 and the voltage sensing DHPR.

Once multinucleated myotubes are visible, they are loaded with a fluorescent Ca^{2+} indicator such as fura-2 or fluo-4 and we assess their capacity to respond to

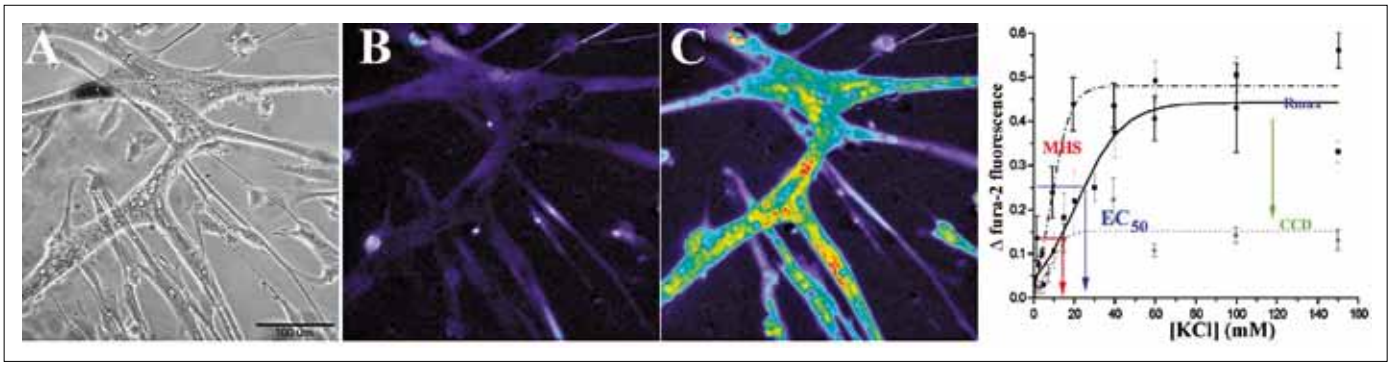

Figure 4: ***Analysis of Ca^{2+} homeostasis of human muscle cells.***
A. Photomicrograph of human muscle cells (20 x objective, bar indicates 50 µm).
B. Cells loaded with Fluo-4 and imaged under resting conditions and
C. after stimulation with 60 mM KCl.
D. Dose response curves to KCl of control cells (continuous line), cells from a patient with a RYR1 mutation leading to Malignant Hyperthermia (dash dot line) and cells from a patient with central core disease (dotted line).

pharmacological activation of RyR1 or depolarization, by monitoring the changes in cytoplasmic [Ca^{2+}] due to release of from the SR (figure 4 B-D) or Ca^{2+} influx. Research carried out on a number of different mutations has shown that most if not all *RYR1* mutations linked to malignant hyperthermia cause the RyR1 to become hypersenstitive to activation, that is the mutations shift the EC50 of agonists to lower concentrations, without affecting the total amount of Ca^{2+} released at maximal agonist concentration (figure 4 D), in other words, these mutations cause the channel to become pre-activated, and very little additional stimulation will cause maximal activation, leading to massive Ca^{2+} release. Most dominant mutations linked to Central Core Disease on the other hand, either lead to leaky channels, causing depletion of SR Ca^{2+} stores and consequently muscle weakness, or to uncoupled channels, whereby sarcolemmal depolarisation does not lead to Ca^{2+} release from the SR Ca^{2+} because the mutations affect the ability of the RyR1 to conduct Ca^{2+}. To discriminate between these two pathogenic hypotheses it is crucial to define the SR Ca^{2+} content in muscle cells from patients carrying *RYR1* mutations and we are currently investigating this issue as it is important in order to develop pharmacological strategies aimed at helping patients. As to Ca^{2+} influx, this is more prominent in myotubes from patients with Central Core Disease, indicating that the lack of Ca^{2+} release is partially compensated by Ca^{2+} influx from the extracellular environment. However these two mechanisms leading to an increase in the myoplasmic [Ca^{2+}] are not exactly the same since Ca^{2+} influx can cause the activation of membrane-associated enzyme complexes including nitric oxide synthase and calcineurin and these downstream events linked to Ca^{2+} dysregulation may be responsible for some of the pathophysiological changes seen in patients with core myopathies.

As to the recessive *RYR1* mutations seen in a number of patients with different phenotypes, the mutations do not seem to affect the function of the RyR1 at conducting Ca^{2+}, or its sensitivity to activation. A consistent finding has been a decrease in RyR1 protein content in the patients' muscle biopsy; thus in this case the weak muscle phenotype would be caused by the fact that little Ca^{2+} is released from the SR following depolarization, not because of a true defect in the RyR1 Ca^{2+} channel, but rather because few RyR1s are actually present. But what causes the decrease in protein expression is at the moment unknown and only a matter of speculation.

Other proteins of the sarcoplasmic reticulum

The past three decades have seen major advancements in our understanding the role of skeletal muscle sarcoplasmic reticulum proteins in excitation-contraction coupling. The use of genetically modified animal models has also taught us that few of these proteins, namely the ryanodine receptor, Cav1.1 and junctophillin, are essential however the minor protein components play an important role in the regulation of the excitation-contraction coupling machinery and the identification of mutations in genes encoding these

minor protein components linked to neuromuscular disorders will yield clues into their exact function. Using a biochemical and cellbiological approach linked to mass spec analysis our laboratory is also involved in the identification and functional characterisation of the complete array of proteins of the sarcoplasmic reticulum; we have so far identified four novel proteins: junctate, JP-45, SRP-27 and SRP-35 for all of which we have made animal models in which the protein is either over-expressed or knocked out. For some of these mice characterization of muscle functions have been already performed, but for others these still need to be carried out.

Conclusions and Outlooks

By analysing the functional effect of mutations we are starting to understand the primary mechanisms leading to muscle disease, but we are only glimpsing into the downstream events caused by the dysregulation of the second messenger "Ca^{2+}". Furthermore, for a number of patients no mutation in the *RYR1* has been found and the search for other culprits encoding proteins involved in Ca^{2+} regulation is underway. Finally, though mainly expressed in skeletal muscle, the RyR1 is also expressed in other tissues, including certain neurons and smooth muscle cells, as well as immune cells including dendritic cells and B-lymphocytes. Consequently *RYR1* mutations will not only affect muscle function, but also the function of other tissues. At present we are investigating the effect of a *RYR1* mutation linked to Malignant Hyperthermia in a mouse animal model knocked in for *RYR1* mutation; though the immune system of these mice is not severely affected, there are subtle differences that may imply that some gain of function mutations such as those linked to Malignant Hyperthermia may have given selective evolutionary advantage to their carriers in the pre-antibiotic era.

This research is also carried over to clinical problems and projects. Some of these are: molecular genetic diagnosis of malignant hyperthermia (Thierry Girard), the impact of anesthetic agents on skeletal muscle in patients with neuromuscular diseases (Oliver Bandschapp) and objective force assessment in unconscious patients on the intensive care unit (Hans Ginz). Clearly much remains to be done in this very exciting field.

Acknowledgements

We would like to thank the present and past members of the lab, the research assistants, clinicians, patients, funding agencies and even reviewers who have all contributed to this work and have helped us carry out our research in a critical and focused way.

Susan Treves and Francesco Zorzato

How much do we «hear» about Auditory Research?

The aim of the Inner Ear Research Laboratory is to gain a better understanding of the molecular processes occurring in the cochlea that might have relevance in elucidating the mechanism of hearing loss.

From left to right – front row: Soledad Levano, Cristian Setz. Back row: Alwyn Listyo, Yves Brand, Daniel Bodmer, Vesna Radojevic.

Introduction

Hearing loss has a huge impact on the affected individual as well as on society. It is estimated that 278 million persons worldwide suffer from disabling hearing loss. Up to 6 per 1000 infants suffer permanent hearing loss at birth or within the neonatal period (www.who.int). More than 50% of over-65s suffer from it, making hearing loss of adult onset one of the ten leading causes of disability-adjusted life years globally [1].

Inner ear

The complex architecture of the inner ear, named the labyrinth by early anatomists, houses the senses of hearing and balance. The main functions of the outer and the middle ear are transduction and amplification of sound, while the cochlea in the inner ear is the auditory sensory organ. The cochlea propagates mechanical signals as waves in fluid and membranes, and finally transduces them to nerve impulses. Its core component is the organ of Corti, which is distributed along the partition separating fluid chambers in the coiled tapered tube of the cochlea.

The organ of Corti contains 16000 hair cells in each cochlea. The outer hair cells of the organ of Corti are mechanically active, while the inner hair cells of the same organ convert the stimulus into neuronal impulses via afferent synapses to the dendrites of primary auditory neurons (spiral ganglion neurons).

Hearing loss causes

Hearing loss can be caused by damage to the external, middle or inner ear. Today, hearing loss caused by diseases of the external and the middle ear can be treated satisfactorily, while disorders affecting the inner ear cannot. Often, only prosthetic devices offer some help. For mild to moderate hearing loss conventional hearing aids are used, while for profound hearing loss cochlear implantation is the standard of care today. Loss of, or damage to hair cells and/or neuronal cells, which are the sensorineural elements of the inner ear, results in a so-called sensorineural hearing loss. However, the hair cells are the most vulnerable elements in the cochlea, and damage to them is the most common cause of sensorineural hearing loss. When the hair cells are lost from the adult organ of Corti, spiral ganglion dendrites retract and are possibly lost. Total loss of hair cells can result in degeneration of some cochlear neurons. Hair cell damage may result from a variety of causes, including genetic disorders, infectious diseases, overexposure to intense sound and certain drugs. As exposure to intense sound, drugs and diseases accumulates with aging, so the loss of sensorineural elements in the cochlea progresses with it, and many individuals experience noticeable hearing difficulty later in life.

Prevention of hearing loss?

Hearing loss due to sensorineural damage has been recognised for over a century and experiments to promote understanding of the phenomenon date from the early 1900s. Since cochlear hair cells of mammals, unlike those of fish and birds, do not regenerate [2], sensorineural hearing loss is often progressive and irreversible. Until recently, damage to cochlear hair cells and neurons has been regarded as an inevitable consequence of age, genetic conditions or exposure to certain environmental stimuli. This made avoidance of potentially harmful stimuli the primary means of protecting sensorineural structures. However, in the last few years, progress has been made in the understanding of hair cell damage. Our laboratory is studying different aspects of hair cell damage and death: we are investigating the somatostatinergic system in the inner ear, molecular aspects of age-related hearing loss, and we are employing the cre-lox system to generate inner-ear specific knock-out mice of genes involved in hair cell death. In addition, we are studying guidance-cues for spiral ganglion neurites, in order to enhance the interaction of these neurites with cochlear implant electrodes.

Somatostatin and their receptors in the mammalian cochlea

Somatostatins (SST) form a family of cyclopeptides that are mainly produced by normal endocrine, gastrointestinal, immune and neuronal cells, as well as by certain tumors. By binding to G-protein-coupled receptors (SSTR1-5) on target cells, SST act as neuromodulators and neurotransmitters, as well as potent inhibitors of various secretory processes and cell proliferation. Little

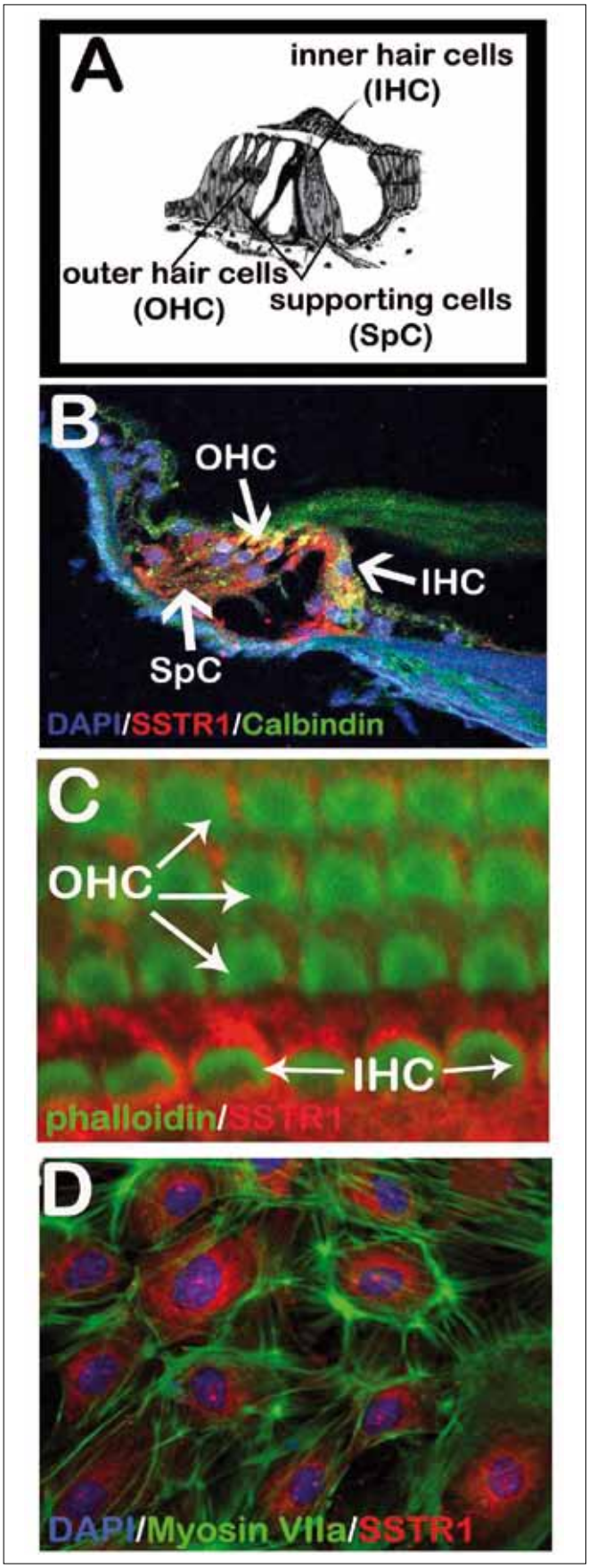

Figure 1. Expression of SSTR1. (A) The diagram of OC, B) Expression of SSTR1 in adult mouse cochlea, (C) explant of OC, (D) neurosensory cell culture.

is known about the expression and function of the somatostatinergic system in the mammalian cochlea. We analyzed the expression of SSTR1-SSTR5 in the immature and mature mammalian cochlea. The peak in the expression of SSTR1 and SSTR2 at mRNA and protein level is around the onset of hearing to airborne sound, at postnatal day 14 [3]. This suggests their involvement in the maturation of the mammalian cochlea. In immunohistochemical studies we demonstrated that the all five receptors are expressed in the outer (OHC) and inner hair cells (HCs) as well as in defined supporting cells of the organ of Corti (OC) in the adult mouse cochlea. A similar expression of the SST receptors in the inner and outer hair cells was found in cultivated P6 mouse OC explants and in cultivated neurosensory cells (Fig. 1) [4]. Interestingly, SST itself is not expressed in the mammalian cochlea, suggesting that SST reaches its receptors either through the blood-labyrinthine barrier from the systemic circulation or via the endolymphatic duct from the endolymphatic sac. In order to learn more about the regulation of SST receptors, we used mice with either a deletion of SSTR1, SSTR2 or SSTR1/SSTR2 (DKO). In SSTR1 knock-out (KO) mice, SSTR2 and SSTR5 were up-regulated and SSTR3 was down regulated while SSTR4 was not changed. In contrast, in SSTR2 KO mice, the expression pattern of all other receptors was not altered compared to wild-type mice. In DKO mice, SSTR5 was up-regulated, while SSTR3 and SSTR4 were down regulated. These findings provide evidence of a compensatory regulation in the mammalian cochlea as a consequence of a receptor subtype deletion. In addition, we observed reduced levels of phospho-Akt and total-Akt in SSTR1 KO and DKO mice as compared to wild type mice. Akt is likely to be involved in hair cell survival [3]. We know from previous studies that Akt is involved in hair cell survival [5]. Most importantly, we found improved hair cell survival in somatostatin analoge octreotide treated organ of Corti explants that had been exposed to gentamicin compared to those explants exposed to gentamicin alone (Fig. 2). These findings propose that the somatostatinergic system within the cochlea may have neuroprotective properties.

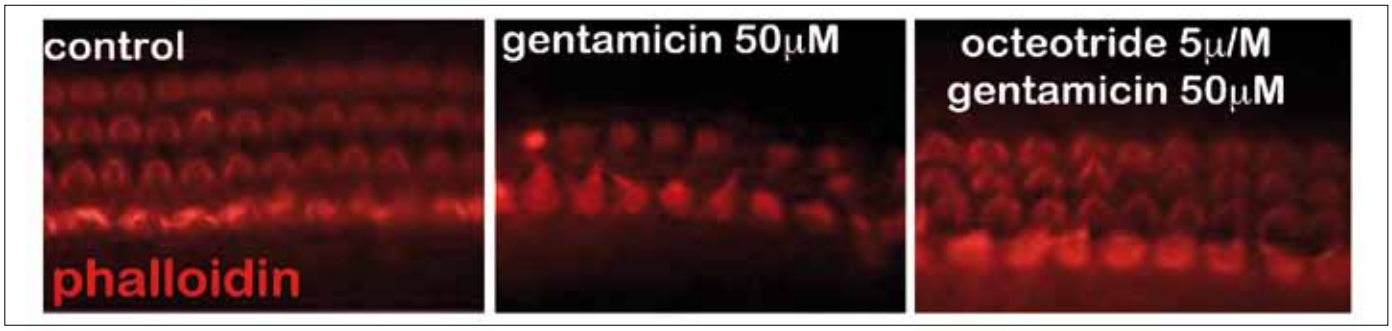

Figure 2. Effect of octreotide on gentamicin-induced hair cell damage. Photograph of phalloidin-labeled OC.

Age-related hearing loss: a molecular intrigue

Most of the molecular mechanisms related to age-related hearing loss, also known as presbycusis, are not known.

The inevitable deterioration in hearing ability that occurs with age is a multifactorial and polygenic process that can vary in severity from mild to substantial and poses an enormous humanitarian and economic challenge to our society. There are a number of pathophysiolological processes underlying age-related changes to functional components in the inner ear [6]. With increasing age, cochlear hair cells are lost together with neural elements and is thought to result in addition to age-related degeneration of the cochlea in cumulative effects of extrinsic damage (noise and other ototoxic agents) and intrinsic disorders (e.g. systemic diseases) [7].

In response to changes in the intracellular environment, mitochondria become producers of excessive reactive oxygen species and release prodeath proteins, resulting in disrupted ATP synthesis and activation of cell death pathways. Interestingly, cells have developed a defense mechanism against aberrant mitochondria that can cause harm to the cell. This mechanism involves selective sequestration and subsequent degradation of the dysfunctional mitochondrion before it causes activation of cell death. Induction of mitochondrial autophagy, or mitophagy, results in selective clearance of damaged mitochondria in cells. It has been demonstrated that in aging and some neurodegenerative disorders, mitochondria play a role in cell death by this process: autophagy [8].

Our first experiments are aimed at determining whether or not autophagy has a role to play in the aging cochlea.

The autophagy process is an evolutionarily conserved process, which is well known and is responsible for the degradation of components in the cytoplasm via the lysosomal pathway. Are autophagosomes formed in the inner ear? Which Atg (autophagy-related) genes play a role in age-related hearing loss?

Inner-ear specific knockout mice: Jak/Stat/Socs signaling pathway

The introduction of tissue specific knockout mice improves the research of those genes that were lethal in conventional knockout mice. Using the Cre-loxP systems to create inner ear specific knockout mice allows us to disrupt the gene of interest without disrupting the gene expression in other organs. An additional advantage of using the cre-loxP system is the possibility to monitor the time point of gene expression. In the last years, several floxed mice lines were created, while few cre mouse lines for ear specific genes are available [9]. One of these cre ear specific mice is the Tg(Atoh1-cre/

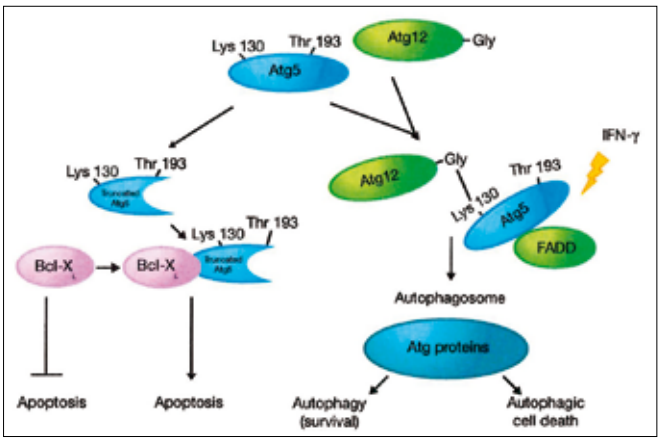

Figure 3. Atg5 and Atg12 in their role in autophagy and apoptosis. Together with other Atg proteins, Atg5-Atg12 contributes to the formation of the autophagosome, which sequesters cytoplasmic material before lysosomal delivery [20].

Figure 4. Cre-mediated recombination in hair cells of Atoh1-cre/ERT,R26R mice by beta-gal histochemistry. Mouse cochlea injected with vehicle (A) or tamoxifen (B). The arrows indicate the specific staining of the inner and outer hair cells [10].

ERT)1Sbk mouse. The cre activity is induced by tamoxifen and has been found in nearly 90% of cochlea hair cells (Fig. 4) [10]. Recently Jak/Stat/Socs signaling pathway has been shown to be involved in the inner ear hair cells damage and regeneration [11, 12]. Using the Atoh1-cre/ERT mice we will characterize those genes participating in this signaling pathway.

During hair cell damage genes participating in apoptosis or survival pathways are activated and it is assume that upon reaching a certain level of damage cell death is inevitable. Several agents, drugs (aminoglycosides, cisplatin) or aging processes could damage the hair cells by increasing the production of ROS (reactive oxygen species). ROS in the cochlea is mainly generated by NADPH oxidase isoform 3 (NOX3). Knockdown NOX3 attenuated cisplatin ototoxicity [13]. Stat1 phosphorylation has been observed in utricules exposed to cisplatin suggesting its participation in hair cell death [14]. Inactivation of NOX3 reduced Stat1 activation and siRNA mediated knockdown of Stat1 gene reduced the damage to hair cells against cisplatin-induced hearing loss [11]. A reciprocal regulatory mechanism between Stats proteins has been observed in Stat1-deficient. Recently it has been shown that transcient inhibition of Stat3 in adult zebrafish accelerated hair cell regeneration. This suggests that Stat3/socs3a pathway plays a key role in hair cell regeneration and could be a potential therapeutic target [12]. The conventional knockout mice Stat3 died early in embryogenesis, creating a tissue specific Stat3 knockout mice has allowed exploration of Stat3 function in adult tissues [15]. Currently we are collaborating with the group of Radek Skoda allowing us to get their valuable inputs and to learn their techniques.

Guidance-cues for spiral ganglion neurites and cochlear implant electrodes

The inner ear, with exquisite patterning of the sensory epithelium and precise projections of both afferent and efferent neurites into the organ of Corti, is a much-simplified example of the complex architecture that develops within the central nervous system. As such, it can serve as an experimental model with which to study the regulation of neural projections. The orderly projection of auditory neurons to the sensory epithelium of the cochlea is also the basis for multi-electrodes cochlear implants.

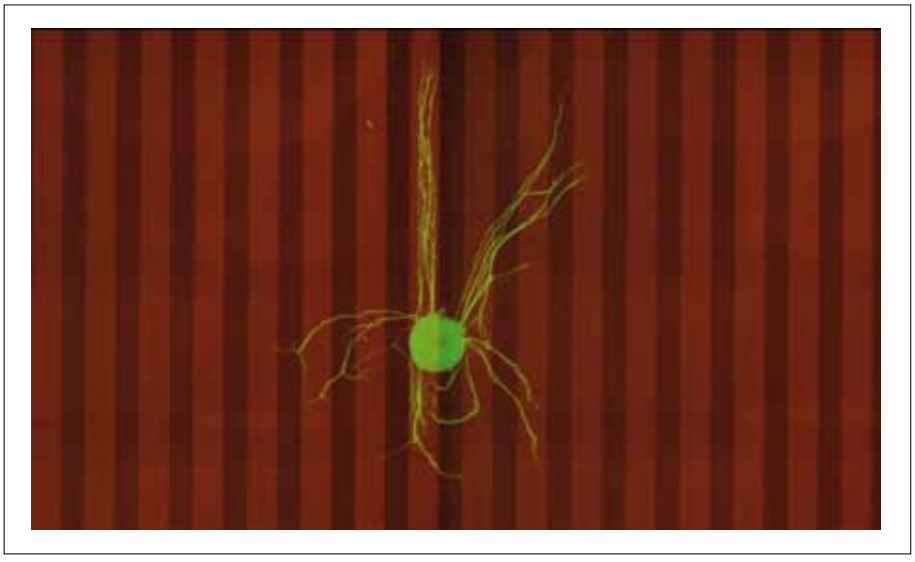

Figure 5. Netrin-4 coated stripes can serve as a guidance cue for spiral ganglion neurites. Scale bar 300 µm.

The cochlear implant is one of the most successful neural prostheses [16]. It can initiate or restore hearing in patients with sensorineural deafness, which is commonly caused by noise, age, ototoxic drugs, or inherited mutations and is the most common sensory deficit in developed countries among humans at any age [6]. With current implant designs, however, the effective number of frequency bands is inadequate for conversing in a noisy environment, grasping tonal and prosodic elements of speech, or listening to music [17]. A major reason for this functional deficit is the current spread over the considerable distance between the electrodes implanted in the scala tympani and their targets, somata of the spiral ganglion neurons in Rosenthal's canal. Minimizing this distance by promoting and guiding the growth of neuritis towards the electrodes could reduce the electrical interference and substantially improve the quality of hearing [18]. This would be a major improvement for the increasing number of implantees who became deaf post-lingually and are used to a higher fidelity of sound reception [19].

Several axon guidance factors have been identified in the central nervous system recently. However, little is known about axon guidance factors in the inner ear. Currently we are evaluating the role of netrins, the neural cell adhesion molecule L1 as well as the role of BDNF in spiral ganglion neurite survival and guidance (Fig. 5). The ultimate goal of is to increase our understanding of inner ear development and the molecular mechanisms of spiral ganglion neuron growth and the development of hair cell innervation. This may be useful for enhancing neuronal survival and regeneration as well as neuronal responses to cochlear implants.

Daniel Bodmer, Soledad Levano, Cristian Setz, Yves Brand, Vesna Radojevic

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Dissertationen

Seit dem 27. September 2012 darf sich **Zuzanna Makowska** von der Forschungsgruppe Hepatology (Departement Biomedizin Hebelstrasse Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Interferon signalling in the liver. Implications for the natural course and therapy of hepatitis C".

Mit der Doktorprüfung am 18. Oktober 2012 schloss **Annalisa Pianta** von der Forschungsgruppe Exp. Hematology (Departement Biomedizin Hebelstrasse) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "Genetic studies of hereditary thrombocythemia".

Am 19. November 2012 stellte sich **Manuele Muraro** von der Forschungsgruppe Oncology Surgery (ICFS/ Departement Biomedizin Hebelstrasse) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: «Functional validation of cancer stem cell markers in primary human colorectal cancer and established cell lines".

Am 21. November 2012 konnte **Clémentine Le Magnen** von der Forschungsgruppe Oncology Surgery (ICFS/Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema "Identification, properties, and clinical significance of putative stem-like cell populations in prostate cancer".

Mit der Doktorprüfung am 23. November 2012 beendete **Sonja Rothweiler** von der Forschungsgruppe Liver Biology (Departement Biomedizin Hebelstrasse) erfolgreich ihre Dissertationszeit. Das Thema ihrer Doktorarbeit lautete: "Notch1 signaling in the hepatic microcirculation and chronic liver disease)".

Venia docendi an Gabriela Kuster Pfister und Arnaud Scherberich

In ihrer Sitzung am 26. September 2012 hat die Regenz der Universität Basel **Gabriela Kuster Pfister** von der Forschungsgruppe Myocardial Research (Departement Biomedizin Hebelstrasse) die Venia docendi für Kardiologie erteilt. Am 7. November 2012 erhielt **Arnaud Scherberich** von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin Hebelstrasse) die Venia docendi für Experimentelle Medizin. Beide dürfen nun den Titel eines Privatdozenten führen.

Karl Heinimann und Dieter Kunz werden Titularprofessoren

Der Universitätsrat hat am 18. Oktober 2012 die von der Regenz beschlossene Ernennung von **Karl Heinimann** von der Forschungsgruppe Medical Genetics (Departement Biomedizin Mattenstrasse) zum Titularprofessor für Medizinische Genetik und von **Dieter Kunz** (Departement Biomedizin Klingelbergstrasse) zum Titularprofessor für Physiologie genehmigt.

Auszeichnungen

Michael Sinnreich erhält Robert-Bing-Preis 2012

Gemeinsam mit Prof. Andreas Papassotiropoulos ist **Michael Sinnreich** von der Forschungsgruppe Neuromuscular Research von der Schweizerischen Akademie der Medizinischen Wissenschaften (SAMW) mit dem Robert-Bing-Preis 2012 ausgezeichnet worden. Die Verleihung des mit 60'000 CHF dotierten Preises findet an der Jahrestagung der Swiss Society of Neurosciences am 2. Februar 2013 in Genf statt. Der Robert-Bing-Preis erinnert an den Neurologen Robert Bing (1878–1956), der 1932 zum Ordinarius an die Universität Basel berufen wurde, und geht alle zwei Jahre an jüngere Forschende für herausragende Leistungen auf dem Gebiet der Neurologie.

Herzliche Gratulation an alle!

Medizinische Träume

Im Traum passieren mir die merkwürdigsten Sachen. Noch mehr als im Personalwesen. Und das will etwas heissen. Mit dem alten deutschen Aussenminister Hans-Dietrich Genscher in die Semperoper zu gehen, daran bin ich gewöhnt. Verschlossene Kühltruhen durch das angrenzende Kabel zu verlassen, ist keine Sache für mich. Selbst Rainer Calmund im Traum zu begegnen, macht mir keine Angst. Doch Hippokrates?

Das ist schon ein starkes Stück. Hätte er mir nicht gesagt, wer er ist, ich hätte den Mann aus Kos nicht erkannt. «Was möchtest Du von mir?», hörte ich mich fragen, «ich bin doch keine Ärztin». «Eben drum», entgegnete er, «von Dir erhalte ich einen unabhängigen Bericht. Unabhängigkeit ist wichtig, das war schon zu meinen Zeiten so». Als ich noch Politik studierte, hätte ich gerne einmal Perikles getroffen, aber Hippokrates? Was mache ich nur mit ihm? Er: «Du könntest mir einen Wunsch erfüllen». Schon wieder ein Mediziner, schon wieder ein Wunsch, dachte ich mir. Mediziner habe ich doch den ganzen langen Tag über. Aber Hippo liess mir keine Chance. Ganz Mediziner. Da ich nun einmal in einem Spital arbeite, könne ich ihm doch behilflich sein.

«Also gut», murmelte ich. «Ich möchte gerne wissen, was aus dem Eid geworden ist, der nach mir benannt wurde. Halten sich die Menschen an die körperliche und geistige Hygiene, die persönliche Integrität und Empathie, die sie geschworen haben?», fuhr er fort. Ich: «Und wie soll ich das angehen?» Hippo: «Das überlasse ich ganz Dir. Vielleicht eine Liste?»

Schon wieder eine Liste. Nicht nur die immer neuen Kennzahlen für das interne Controlling, jetzt auch noch eine «Gesinnungsliste» für einen toten Medizinethiker ... «Ich melde mich morgen früh wieder». Sprach es und verschwand.

Illustration: Emmanuel Traunecker

An erholsames Schlafen war nicht mehr zu denken. Am Ende der Nacht hatte ich alles erledigt.

Fein säuberlich aufgelistet der Operationsplan vom vergangenen Tag (die Einnahmen liessen sich in der kurzen Zeit nicht feststellen):

OP 1 Brustvergrösserung, Dauer 8 Stunden
OP 2 Das Ganze nur umgekehrt, 8 Stunden
OP 3 Fettreduktion, 2 Stunden, anschliessend Schamlippenkorrektur
OP 4 Nasenbegradigung, 1.5 Stunden
OP 5 «Sixpack-Operation» (abdominale Silhouette-Veränderung), 4 Stunden
OP 6 Zeugungsfähigkeit wieder herstellen, 4 Stunden

Risiken bei allen: Narkose, Thrombose, Lungenembolie, Infektionen, Nachblutungen, Blutverluste, Fremdbluttransfusionen, Entwicklung chronischer Schmerzen.

Als Hippokrates zurückkehrt, gebe ich ihm die Liste. Er schüttelt den Kopf. «Die Fettzellen, die man abgesaugt hat, kann man im Cellsorter behandeln und dann zum Unterspritzen der Brust verwenden», versuche ich zu erklären. «Aber die Menschen sind dadurch nicht gesünder geworden», er klingt bitter.

«Was ist eigentlich aus der älteren Frau geworden, die ich gestern mit dem Oberschenkelhalsbruch bei der Einlieferung sah?», möchte er wissen. «Man hat ihr schon ein Hüftgelenk dritter Klasse reserviert. Sie muss aber noch warten, bis heute Vormittag die Penisverlängerung in OP 7 durch ist.»

Die Penisverlängerung hat mich wach gemacht. Hippokrates ist verschwunden.

Heidi Hoyermann

Selected publications by DBM members

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

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

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

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

Deadline for the next issue is January 31, 2013.

Gastroenterology Gastroenterology **2012;143:777–786** IF 11,675

Interferon-γ–Stimulated Genes, but Not USP18, Are Expressed in Livers of Patients With Acute Hepatitis C

Michael T. Dill[1,2], Zuzanna Makowska[1], Francois H. T. Duong[1], Franzisca Merkofer[1], Magdalena Filipowicz[1], Thomas F. Baumert[4], Luigi Tornillo[3], Luigi Terracciano[3], Markus H. Heim[1,2]

Background & Aims: Approximately 50% of patients with chronic hepatitis C (CHC) have a sustained virologic response to treatment with pegylated interferon (pegIFN)-α and ribavirin. Nonresponse to treatment is associated with constitutively increased expression of IFN-stimulated genes (ISGs) in the liver. Treatment of patients with acute hepatitis C (AHC) is more effective, with sustained virologic response rates greater than 90%. We investigated mechanisms of the different responses of patients with CHC and AHC to pegIFN-α therapy.

Methods: We analyzed IFN signaling and ISG expression in liver samples from patients with AHC, patients with CHC, and individuals without hepatitis C (controls) using microarray, immunohistochemical, and protein analyses. Findings were compared with those from primary human hepatocytes stimulated with IFN-α or IFN-γ, as reference sets.

Results: Expression levels of hundreds of genes, primarily those regulated by IFN-γ, were altered in liver samples from patients with AHC compared with controls. Expression of IFN-γ–stimulated genes was induced in liver samples from patients with AHC, whereas expression of IFN-α–stimulated genes was induced in samples from patients with CHC. In an expression analysis of negative regulators of IFN-α signaling, we did not observe differences in expression of suppresor of cytokine signaling 1 or SOCS3 between liver samples from patients with AHC and those with CHC. However, USP18 (another negative regulator of IFN-α signaling), was up-regulated in liver samples of patients with CHC that did not respond to therapy, but not in AHC.

Conclusions: Differences in expression of ISGs might account for the greater response of patients with AHC, compared with those with CHC, to treatment with pegIFN-α and ribavirin. Specifically, USP18 is up-regulated in liver samples of patients with CHC that did not respond to therapy, but not in patients with AHC.

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The Journal of Cell Biology JCB Vol. 198 No. 3 421–437 IF 10,264

Agrin regulates CLASP2-mediated capture of microtubules at the neuromuscular junction synaptic membrane

Nadine Schmidt[1], Sreya Basu[1], Stefan Sladecek[1], Sabrina Gatti[1], Jeffrey van Haren[2], Susan Treves[3,4], Jan Pielage[5], Niels Galjart[2], Hans Rudolf Brenner[1]

Agrin is the major factor mediating the neuronal regulation of postsynaptic structures at the vertebrate neuromuscular junction, but the details of how it orchestrates this unique three-dimensional structure remain unknown. Here, we show that agrin induces the formation of the dense network of microtubules in the subsynaptic cytoplasm and that this, in turn, regulates acetylcholine receptor insertion into the postsynaptic membrane. Agrin acted in part by locally activating phosphatidylinositol 3-kinase and inactivating GSK3β, which led to the local capturing of dynamic microtubules at agrin-induced acetylcholine receptor (AChR) clusters, mediated to a large extent by the microtubule plus-end tracking proteins CLASP2 and CLIP-170. Indeed, in the absence of CLASP2, microtubule plus ends at the subsynaptic muscle membrane, the density of synaptic AChRs, the size of AChR clusters, and the numbers of subsynaptic muscle nuclei with their selective gene expression programs were all reduced. Thus, the cascade linking agrin to CLASP2-mediated microtubule capturing at the synaptic membrane is essential for the maintenance of a normal neuromuscular phenotype.

Introduction

The function of the dynamic cytoskeleton in synapse formation and maintenance is poorly understood. At the neuromuscular junction (NMJ) the array of synaptic proteins such as the acetylcholine receptors (AChRs) is determined by the specific set of genes induced by the nerve selectively in the muscle nuclei underlying the synapse. However, although the nerve-induced synaptic gene expression program can explain the set of proteins expressed in the synaptic region, it does not account for their focal insertion into the postsynaptic muscle membrane where the density of, e.g., AChRs declines sharply from ~10,000/μm² to <5/μm² within a few micrometers of muscle fiber length. One possibility is a focal transport involving microtubules (MTs) oriented toward and captured at the subsynaptic muscle membrane.

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Cell Death and Disease Cell Death & Disease (2012) 3, e325; doi:10.1038/cddis.2012.65 IF 8,849

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

JS Tchorz[1], M Tome[1,*], D Cloëtta[1,*], B Sivasankaran[2], M Grzmil[3], RM Huber[2,3], F Rutz-Schatzmann[1], F Kirchhoff[4,5], N Schaeren-Wiemers[6], M Gassmann[1], BA Hemmings[3], A Merlo[2], B Bettler[1]

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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Development | Development dev.biologists.org | 139, 4250–4260 (2012) | IF 6,596

Smad4 is required to induce digit ray primordia and to initiate the aggregation and differentiation of chondrogenic progenitors in mouse limb buds

Jean-Denis Bénazet[1,*], Emanuele Pignatti[1,*], Ashleigh Nugent[1], Erkan Unal[1,2], Frédéric Laurent[1], Rolf Zeller[1]

Summary

SMAD4 is an essential mediator of canonical TGFβ/BMP signal transduction and we inactivated *Smad4* in mouse limb buds from early stages onward to study its functions in the mesenchyme. While this *Smad4* inactivation did not alter the early *Sox9* distribution, prefiguring the chondrogenic primordia of the stylopod and zeugopod, it disrupted formation of all *Sox9*-positive digit ray primordia. Specific inactivation of *Smad4* during handplate development pointed to its differential requirement for posterior and anterior digit ray primordia. At the cellular level, *Smad4* deficiency blocked the aggregation of *Sox9*-positive progenitors, thereby preventing chondrogenic differentiation as revealed by absence of collagen type II. The progressive loss of SOX9 due to disrupting digit ray primordia and chondrogenesis was paralleled by alterations in genes marking other lineages. This pointed to a general loss of tissue organization and diversion of mutant cells toward non-specific connective tissue. Conditional inactivation of *Bmp2* and *Bmp4* indicated that the loss of digit ray primordia and increase in connective tissue were predominantly a consequence of disrupting SMAD4-mediated BMP signal transduction. In summary, our analysis reveals that SMAD4 is required to initiate: (1) formation of the *Sox9*-positive digit ray primordia; and (2) aggregation and chondrogenic differentiation of all limb skeletal elements.

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Journal of Investigative Dermatology | Journal of Investigative Dermatology | (2012) 132, 2275–2285 | IF 6,314

T-Cadherin Is an Auxiliary Negative Regulator of EGFR Pathway Activity in Cutaneous Squamous Cell Carcinoma: Impact on Cell Motility

Emmanouil Kyriakakis[1,*], Kseniya Maslova[1,*], Maria Philippova[1], Dennis Pfaff[1], Manjunath B. Joshi[1], Stanislaw A. Buechner[2], Paul Erne[3], Thérèse J. Resink[1]

Genetic and epigenetic studies in different cancers, including cutaneous carcinomas, have implicated T-cadherin (T-cad) as a tumor suppressor. Immunohistochemical and *in vitro* studies have suggested that T-cad loss promotes incipient invasiveness in cutaneous squamous cell carcinoma (SCC). Molecular mechanisms are unknown. This study found that the main consequence of T-cad silencing in SCC is facilitation of liganddependent EGFR activation, whereas T-cad overexpression impedes EGFR activation. Gain-and loss-of-function studies in A431 SCC cells demonstrate T-cad-controlled responsiveness to EGF with respect to pharmacological inhibition of EGFR and to diverse signaling and functional events of the EGFR activation cascade (EGFR phosphorylation, internalization, nuclear translocation, cell retraction/de-adhesion, motility, invasion, integrin β1, and Rho small GTPases such as RhoA, Rac1, and Cdc42 activation). Further, T-cad modulates the EGFR pathway activity by influencing membrane compartmentalization of EGFR; T-cad upregulation promotes retention of EGFR in lipid rafts, whereas T-cad silencing releases EGFR from this compartment, rendering EGFR more accessible to ligand stimulation. This study reveals a mechanism for fine-tuning of EGFR activity in SCC, whereby T-cad represents an auxiliary "negative" regulator of the EGFR pathway, which impacts invasion-associated behavioral responses of SCC to EGF. This action of T-cad in SCC may serve as a paradigm explaining other malignancies displaying concomitant T-cad loss and enhanced EGFR activity.

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The Journal of Immunology | The Journal of Immunology | 2012, 189: 3751–3758 IF 5,788

Spleen Tyrosine Kinase Is Important in the Production of Proinflammatory Cytokines and Cell Proliferation in Human Mesangial Cells following Stimulation with IgA1 Isolated from IgA Nephropathy Patients

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IgA immune complexes are capable of inducing human mesangial cell (HMC) activation, resulting in release of proinflammatory and profibrogenic mediators. The subsequent inflammation, cellular proliferation, and synthesis of extracellular matrix lead to the progression of IgA nephropathy (IgAN). Spleen tyrosine kinase (SYK) is an intracellular protein tyrosine kinase involved in cell signaling downstream of immunoreceptors. In this study, we determined whether SYK is involved in the downstream signaling of IgA1 stimulation in HMC, leading to production of proinflammatory cytokines/chemokines and cell proliferation. Incubation of HMC with IgA1 purified from IgAN patients significantly increased the synthesis of MCP-1 in a dose-dependent manner. There was also significantly increased production of IL-6, IL-8, IFN-γ–inducible protein-10, RANTES, and platelet-derived growth factor-BB. Stimulation of HMC with heat-aggregated IgA1 purified from IgAN patients induced significantly increased HMC proliferation. Both pharmacological inhibition of SYK and knockdown of SYK by small interfering RNA significantly reduced the synthesis of these mediators and inhibited HMC proliferation. Moreover, positive immunostaining for total and phospho-SYK in glomeruli of kidney biopsies from IgAN patients strongly suggests the involvement of SYK in the pathogenesis of IgAN. To our knowledge, we demonstrate, for the first time, the involvement of SYK in the downstream signaling of IgA1 stimulation in HMC and in the pathogenesis of IgAN. Hence, SYK represents a potential therapeutic target for IgAN.

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The Journal of Immunology | The Journal of Immunology | 2012, 189: 000–000 IF 5,788

MicroRNAs Control the Maintenance of Thymic Epithelia and Their Competence for T Lineage Commitment and Thymocyte Selection

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Thymic epithelial cells provide unique cues for the lifelong selection and differentiation of a repertoire of functionally diverse T cells. Rendered microRNA (miRNA) deficient, these stromal cells in the mouse lose their capacity to instruct the commitment of hematopoietic precursors to a T cell fate, to effect thymocyte positive selection, and to achieve promiscuous gene expression required for central tolerance induction. Over time, the microenvironment created by miRNA-deficient thymic epithelia assumes the cellular composition and structure of peripheral lymphoid tissue, where thympoiesis fails to be supported. These findings emphasize a global role for miRNA in the maintenance and function of the thymic epithelial cell scaffold and establish a novel mechanism how these cells control peripheral tissue Ag expression to prompt central immunological tolerance.

The thymus provides a unique stromal microenvironment that instructs the differentiation of blood-borne precursors to functionally mature T lymphocytes proficient in effecting an immune response against microbial pathogens while unable to elicit an autoimmune reaction (1). The major structural components of the thymus are thymic epithelial cells (TEC) that can further be classified as cortical (cTEC) or medullary TEC (mTEC) subpopulations based on distinct structural, antigenic, and functional features (2, 3). The molecular programs that control TEC growth, differentiation, and maintenance are, however, only incompletely characterized.

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Neurobiology of Disease | Neurobiology of Disease | 49 (2013) 221–231 | IF 5,403

An essential role of MAG in mediating axon–myelin attachment in Charcot–Marie–Tooth 1A disease

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Abstract:
Charcot–Marie–Tooth disease type 1A (CMT1A) is a hereditary demyelinating peripheral neuropathy caused by the duplication of the PMP22 gene. Demyelination precedes the occurrence of clinical symptoms that correlate with axonal degeneration. It was postulated that a disturbed axon–glia interface contributes to altered myelination consequently leading to axonal degeneration. In this study, we examined the expression of MAG and Necl4, two critical adhesion molecules that are present at the axon–glia interface, in sural nerve biopsies of CMT1A patients and in peripheral nerves of mice overexpressing human PMP22, an animal model for CMT1A. We show an increase in the expression of MAG and a strong decrease of Necl4 in biopsies of CMT1A patients as well as in CMT1A mice. Expression analysis revealed that MAG is strongly upregulated during peripheral nerve maturation, whereas Necl4 expression remains very low. Ablating MAG in CMT1A mice results in separation of axons from their myelin sheath. Our data show that MAG is important for axon–glia contact in a model for CMT1A, and suggest that its increased expression in CMT1A disease has a compensatory role in the pathology of the disease. Thus, we demonstrate that MAG together with other adhesion molecules such as Necl4 is important in sustaining axonal integrity.

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The Journal Of Biological Chemistry | jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY | Vol. 287, No. 33, 2012 | IF 4,773

Modular Dispensability of Dysferlin C2 Domains Reveals Rational Design for Mini-dysferlin Molecules*

Bilal A. Azakir[1], Sabrina Di Fulvio[1], Steven Salomon[2], Marielle Brockhoff[2], Christian Therrien[2], Michael Sinnreich[1]

Dysferlin is a large transmembrane protein composed of a C-terminal transmembrane domain, two DysF domains, and seven C2 domains that mediate lipid-and protein-binding interactions. Recessive loss-of-function mutations in dysferlin lead to muscular dystrophies, for which no treatment is currentlyavailable. The large size of dysferlin precludes its encapsulation into an adeno-associated virus (AAV), the vector of choice for gene delivery to muscle. To design mini-dysferlin molecules suitable for AAV-mediated gene transfer, we tested internally truncated dysferlin constructs, each lacking one of the seven C2 domains, for their ability to localize to the plasma membrane and to repair laser-induced plasmalemmal wounds in dysferlin-deficient human myoblasts. We demonstrate that the dysferlin C2B, C2C, C2D, and C2E domains are dispensable for correct plasmalemmal localization. Furthermore, we show that the C2B, C2C, and C2E domains and, to a lesser extent, the C2D domain are dispensable for dysferlin membrane repair function.On the basis of these results, we designed small dysferlin molecules that can localize to the plasma membrane and reseal laserinduced plasmalemmal injuries and that are small enough to be incorporated into AAV. These results lay the groundwork for AAV-mediated gene therapy experiments in dysferlin-deficient mouse models.

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British Journal of Pharmacology BJP BRITISH JOURNAL OF PHARMACOLOGY (2012) 166 2277–2288 IF 4,409

Carvedilol inhibits the cardiostimulant and thermogenic effects of MDMA in humans

CM Hysek[1], Y Schmid[1], A Rickli[1], LD Simmler[1], M Donzelli[1], E Grouzmann[2], ME Liechti[1]

Background And Purpose
The use of ±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') is associated with cardiovascular complications and hyperthermia.

Experimental Approach
We assessed the effects of the α_1-and β-adrenoceptor antagonist carvedilol on the cardiostimulant, thermogenic and subjective responses to MDMA in 16 healthy subjects. Carvedilol (50 mg) or placebo was administered 1 h before MDMA (125 mg) or placebo using a randomized, double-blind, placebo-controlled, four-period crossover design.

Key Results
Carvedilol reduced MDMA-induced elevations in blood pressure, heart rate and body temperature. Carvedilol did not affect the subjective effects of MDMA including MDMA-induced good drug effects, drug high, drug liking, stimulation or adverse effects. Carvedilol did not alter the plasma exposure to MDMA.

Conclusions And Implications
α1-and β-Adrenoceptors contribute to the cardiostimulant and thermogenic effects of MDMA in humans but not to its psychotropic effects. Carvedilol could be useful in the treatment of cardiovascular and hyperthermic complications associated with ecstasy use.

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Plos One PLoS one May 2012 | Vol. 7 | Issue 5 | e36476 IF 4,092

Duloxetine Inhibits Effects of MDMA (''Ecstasy'') *In Vitro* and in Humans in a Randomized Placebo-Controlled Laboratory Study

Cédric M. Hysek[1,*], Linda D. Simmler[1,*], Valentina G. Nicola[1], Nerina Vischer[1], Massimiliano Donzelli[1], Stephan Krähenbühl[1], Eric Grouzmann[2], Jörg Huwyler[3], Marius C. Hoener[4], Matthias E. Liechti[1]

Abstract
This study assessed the effects of the serotonin (5-HT) and norepinephrine (NE) transporter inhibitor duloxetine on the effects of 3,4–methylenedioxy-methamphetamine (MDMA, ecstasy) *in vitro* and in 16 healthy subjects. The clinical study used a double-blind, randomized, placebo-controlled, four-session, crossover design. *In vitro,* duloxetine blocked the release of both 5-HT and NE by MDMA or by its metabolite 3,4-methylenedioxyamphetamine from transmitter-loaded human cells expressing the 5-HT or NE transporter. In humans, duloxetine inhibited the effects of MDMA including elevations in circulating NE, increases in blood pressure and heart rate, and the subjective drug effects. Duloxetine inhibited the pharmacodynamic response to MDMA despite an increase in duloxetine-associated elevations in plasma MDMA levels. The findings confirm the important role of MDMA-induced 5-HT and NE release in the psychotropic effects of MDMA. Duloxetine may be useful in the treatment of psychostimulant dependence.

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Psychopharmacology Springer DOI 10.1007/s00213-012-2761-6 IF 4,077

Effects of MDMA alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin on pupillary light reflex

Cédric M. Hysek and Matthias E. Liechti

Abstract
Rationale Pupillometry can be used to characterize autonomic drug effects.

Objective This study was conducted to determine the autonomic effects of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), administered alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin, on pupillary function.

Methods Infrared pupillometry was performed in five placebo-controlled randomized studies. Each study included 16 healthy subjects (eight men, eight women) who received placebo–MDMA (125 mg), placebo–placebo, pretreatment– placebo, or pretreatment–MDMA using a crossover design.

Results MDMA produced mydriasis, prolonged the latency, reduced the response to light, and shortened the recovery time. The impaired reflex response was associated with subjective, cardiostimulant, and hyperthermic drug effects and returned to normal within 6 h after MDMA administration when plasma MDMA levels were still high. Mydriasis was associated with changes in plasma MDMA concentration over time and longer-lasting. Both reboxetine and duloxetine interacted with the effects of MDMA on pupillary function. Clonidine did not significantly reduce the mydriatic effects of MDMA, although it produced miosis when administered alone. Carvedilol and doxazosin did not alter the effects of MDMA on pupillary function.

Conclusions The MDMA-induced prolongation of the latency to and reduction of light-induced miosis indicate indirect central parasympathetic inhibition, and the faster recovery time reflects an increased sympathomimetic action. Both norepinephrine and serotonin mediate the effects of MDMA on pupillary function. Although mydriasis is lasting and mirrors the plasma concentration–time curve of MDMA, the impairment in the reaction to light is associated with the subjective and other autonomic effects of MDMA and exhibits acute tolerance.

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Psychopharmacology Springer (2012) 222:293–302 IF 4,077

MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions

Cédric M. Hysek[1], Gregor Domes[2], Matthias E. Liechti[1]

Abstract
Rationale 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) increases sociability. The prosocial effects of MDMA may result from the release of the "social hormone" oxytocin and associated alterations in the processing of socioemotional stimuli.

Materials and methods We investigated the effects of MDMA (125 mg) on the ability to infer the mental states of others from social cues of the eye region in the Reading the Mind in the Eyes Test. The study included 48 healthy volunteers (24 men, 24 women) and used a double-blind, placebo-controlled, within-subjects design. A choice reaction time test was used to exclude impairments in psychomotor function. We also measured circulating oxytocin and cortisol levels and subjective drug effects.

Results MDMA differentially affected mind reading depending on the emotional valence of the stimuli. MDMA enhanced the accuracy of mental state decoding for positive stimuli (e.g., friendly), impaired mind reading for negative stimuli (e.g., hostile), and had no effect on mind reading for neutral stimuli (e.g., reflective). MDMA did not affect psychomotor performance, increased circulating oxytocin and cortisol levels, and produced subjective prosocial effects, including feelings of being more open, talkative, and closer to others.

Conclusions The shift in the ability to correctly read socioemotional information toward stimuli associated with positive emotional valence, together with the prosocial feelings elicited by MDMA, may enhance social approach behavior and sociability when MDMA is used recreationally and facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings.

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Clinical Immunology | Clinical IMMUNOLOGY | (2012) 144,70–79 IF 4,046

Altered microRNA expression in B lymphocytes in multiple sclerosis Towards a better understanding of treatment effects

Claudia Sievers[1], Maria Meira[1], Francine Hoffmann[1], Paulo Fontoura[2], Ludwig Kappos[1], Raija L.P. Lindberg[1]

Abstract
MicroRNAs (miRNAs) are posttranscriptional regulators of gene expression. We compared the expression of 1059 miRNAs in B lymphocytes from untreated and natalizumab treated relapsing–remitting multiple sclerosis (RRMS) patients and healthy volunteers (HV). Forty nine miRNAs were down-regulated in untreated MS patients compared with HV. A distinct pattern of 10 differentially expressed miRNAs was found in natalizumab treated patients compared with untreated patients. Two clusters, i.e. miR-106b-25 and miR-17-92, were particularly deregulated. MiRNA–mRNA interaction analysis revealed B cell receptor, phosphatidyl-inositol-3-kinase (PI3K) and phosphatase and tensin homology (PTEN) signaling being the key affected pathways. We discovered deregulated viral miRNAs in untreated patients as compared with HV and natalizumab treated patients, a novel finding that may be related to latency and activation of viruses in MS. Our findings provide first insights into miRNA dependent regulation of B cell function in MS and the impact of a therapy not primarily targeting B cells on this regulation.

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REVIEWS

Nature Reviews Neuroscience | nature REVIEWS NEUROSCIENCE | Volume 13/June 2012 IF 30,445

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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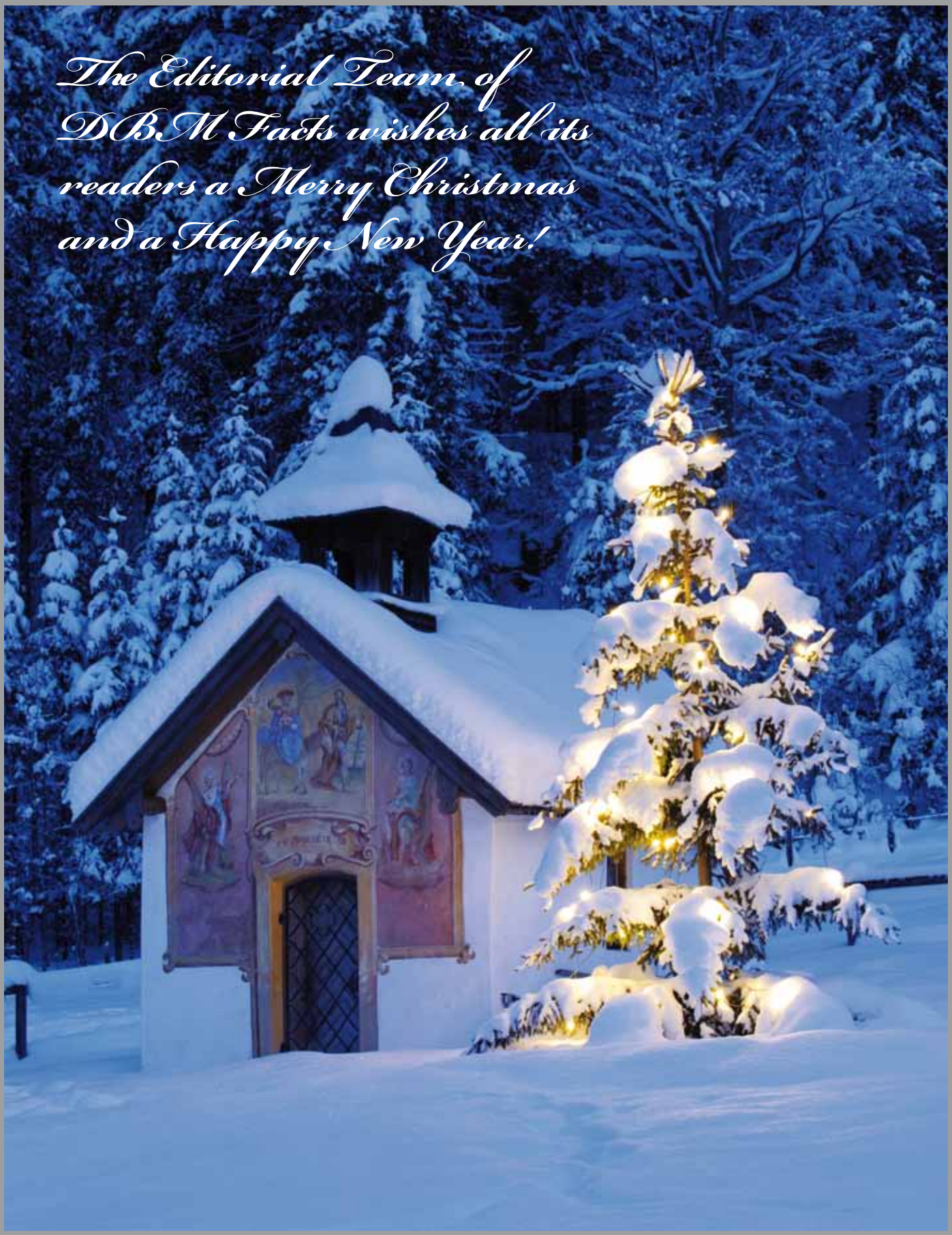

Christmas Chapel in Bavaria

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Adi Raveh
Synaptic Plasticity

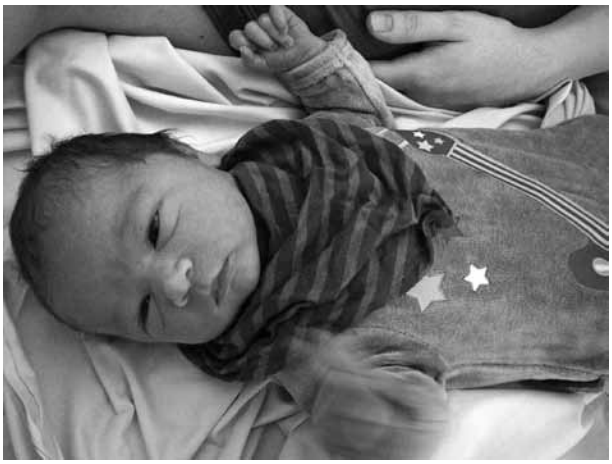
Congratulations

Manon Brecht Brüngger
Geboren am 09.07.2012

Amanda Spagnoli Iezzi
Geboren am 10.10.2012

Lucy Christine Kreuzaler
Geboren am 24.07.2012

Das DBM gratuliert ganz herzlich!



Vivien Rajalu
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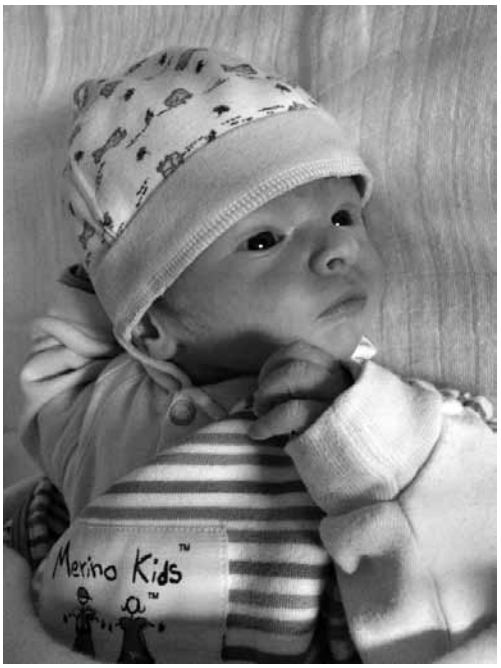


David Ivanek
Geboren am 30.09.2012

Lewis King Schreiner
Geboren am 06.09.2012

Lukas Tang Barz
Geboren am 05.11.2012

Herzlich willkommen, allerseits!

Second "First Year International" at DBM

First Year is a career specific series of courses the University Hospital Basel is running for new staff members, organised by Human Resources and Organizational Development in cooperation with the local Human Resources. In this case it was organized by Heidi Hoyermann.

Second "First Year International" at DBM

November 23rd, 2012, in seminar room 313, Department of Biomedicine
Programme :

09:00 Introduction, Heidi Hoyermann HR DBM
09:05 Welcome, Radek Skoda, Head DBM
09:15 "How I enjoy research in Basel", Ed Palmer, Groupleader Transplantation Immunology DBM
09:30 To be a PhD student at DBM, Nicole Schaeren-Wiemers, DBM PhD representative
09:45 Welcome to our PhD Club, Yvonne Fink
10:00 Welcome to our Postdoc Club, Jeroen Geurts
11:00 "Life Sciences in old Basel", guided tour through the city (two groups German/English)
13:00 Group lunch in the personnel restaurant Centro, USB

Fotos: Frank Neumann and Marc Bichsel

What Killed Professor De Laney

Picture this: Professor Edward De Laney is falling to his death. Don't feel bad, he was a really evil guy, and nobody loved him. I used to wonder if real love was required for real hate, but Professor De Laney proved otherwise.

He is falling from the top of the DBM and quickly accelerating towards the courtyard in the back, where kids are supposed to play and scientists smoke.

They say that when you are about to die, your whole life flashes in front of you. That's not true. In the case of Professor De Laney, the tissue-engineering lab on the 4th floor is the first thing to flash by. He can't see the tissue-engineering students, postdocs, and technicians because they are drinking coffee in the hallway. But what he does notice is this: large writing in red lipstick against the tissue-engineering lab window. He knows the writing is addressed to him. It says "1. Technical Expertise. Love, Andrea." And then his descent continues.

The day before his death Professor Edward De Laney found himself in a pickle, which is a British expression for a bad situation. Four students came to him with four figures for one paper. In Edward's mind, four first authors was out of the question. He thought to himself, 'How to choose the first author?"

In between the fourth and third floor, falling to his death, Edward recalls a memory from his grad school days. It was Canada, during the 1980's, the medieval times of modern science. His boss was supposedly a descendant of Transylvanian vampires. Not a drop of blood was ever spilt, but everyone in the lab felt they had lost something, something essential to their being.

One day in this lab, a young Edward was pipetting at his bench. His boss suddenly appeared behind him, pulled him to the floor, and threw him out of the lab. "Edward, there are four types of westerns" said the boss. "The good, the bad, the ugly, and then yours,

Edward". This was one of the first jokes Edward ever understood, and that was his last western.

Edward turned to microscopy. Where a western had shown nothing interesting, microscopy revealed a membrane to nucleus translocation. Edward published high tier, and left the life-sucking-lab thinking he had learned something about success and how to generate it.

Edwards's memory of his Canadian lab and the image of the DBM fly by. The third floor approaches.

Edward sat in his DBM office chair and gazed at his twiddling thumbs, which were perched on top of his circular belly, at the end of his long and otherwise flat body. How to solve the authorship problem? Amusing himself, he settled on a microscopy solution: whoever could demonstrate the greatest mastery of image acquisition would win the first authorship. He sent an email and summoned the students.

Falling to the third floor he saw this: "2. Sample Preparation. Love, Jamie". His nose began to itch from the cold air and the velocity. And he began to understand.

The four students were gathered at four o'clock to give four answers. Only three turned up.

The first student began, "Good microscopy requires technical expertise. It requires sound knowledge of numerical aperture, color correction, pixel size, saturation, deconvolution and more. A solid foundation in these technical basics allows you to be creative, exploit the system, and capture the perfect image."

The second student stepped forward and said, "Sample preparation, sample preparation, sample preparation. Sample preparation is everything. If you use paraformaldehyde when you should have used methanol, if you use a glass that is merely 0.01mm the wrong thickness, if you don't have good antibodies, and if your mounting medium doesn't match the refractive index of your immersion medium then you are not only wasting your time, you will never capture a good image. No technical expert, no matter how gifted they are, will ever acquire a good image if the sample is not well prepared."

Edward looked at the first student and imagined the student's whole future career and life crumble before his eyes. Edward smiled.

The second floor hides The Postdoc from Edward's lab. The Postdoc has been writing for two weeks, yet nothing that will be published has been written. The Postdoc thinks of its' family, and wonders if a career in science is really for The Postdoc in Edward's lab. In the window The Postdoc sees its' reflection. There are droplets of rain on the window, blurring the image of The Postdoc to itself. There is no red lipstick message for Edward on the second floor. The Postdoc and Edward see eye to eye as Edward flies by. The Postdoc smiles.

Edward enjoyed the second student's response because it crushed the first student. "That's the spirit you need to get ahead in science" he thought. Arrogance resonated in the second student's tone, but deep inside Edward detected a hint of sarcasm, which he promptly ignored after the shock of the third student's answer.

In the small period of time between the second and the first floor, just a few meters before his death, Edward remembers his family but cannot, no matter how hard he tries, bring the image of their faces to his mind.

"I concede." said the third student - he had wanted to say something about image analysis and quantification, but could not. Edward opened his mouth and silence filled the room.

The third student continued, "I will not, and find I cannot compete because I have heard the fourth students answer." While this put the third student in a pickle, it also made Edward curious about the fourth and final answer.

When the first floor came into view, there was just 3 meters to go, Edward saw the fourth student looking at him through the window. In his right hand was a camera, in the left hand was the red lipstick.

It was a short answer, five words long. Edward read the answer and at that very moment the student acquired an image with the camera in his right hand.

Edward said to the third student, "You cannot concede you little brat. You're fired. This is science, this is my lab, play by the rules or leave."

In response, the third student handed a letter to Edward. It was from the fourth student, an invitation to come to the roof of the building for a practical demonstration of his passionate beliefs in image acquisition.

Exactly when the fourth student took the picture, Edward understood the fourth and final answer: "image is nothing without story". Edward didn't have time to put it into his own words; he was trapped in a moment, lost in thought without words. In the photograph of Edward falling to his death, he smiles.

They say that just before you die, your life flashes in front of your eyes. That's not true. In his last moment, Edward remembers the first time he looked into a microscope. At first he thought it was like looking at stars, but after hours of taking images it felt like something else: the darkness, the small things revealed, the images and the thoughts without words, the discovery of a microscopic world, and the endless search for the big picture. *Michael Abanto*

Of elves and billy goats: Joulu in Finland

The Finnish word for Christmas, *joulu,* has its origin in the Viking word *hjul,* meaning "sun wheel" and goes back to pre-Christian Finland where the return of the sun was celebrated in December at the time of winter solstice. The Finnish *joulu,* as it is known and celebrated today, is an assimilation of traditions and habits of the old pagan feast called *kekri* (named after the ancient Finnish cattle protector and fertility god) with Christian Christmas celebration after Christianity reached Finland in the 12th century.

Christmas celebration at my home starts in the morning on Christmas Eve (December 24th) by decorating the Christmas tree. Typically Christmas decorations in Finland are minimalistic and inspired by nature – a very common object is "pukki", a goat made of straw. Lanterns made of ice or snow are prepared in the front yards, but you won't see multicoloured flying reindeers, exploding Santa Clauses or anything alike. After the stressful job of decorating the Christmas tree it is the perfect time for *joulupuuro:* a special Christmas rice porridge made of short grain rice and milk, which has been simmering for around one hour under almost constant stirring until a perfect consistency is achieved. Together with cold milk, sugar and cinnamon it is for me personally THE taste of Christmas. And to add to the fun, an almond is hidden in the porridge and whoever will receives it will be blessed by good fortune for the next year.

For many Finns the real Christmas celebrations start at noon, when, at a special ceremony broadcasted live on television or radio, "Christmas peace" is declared. In this speech citizens are prompted to celebrate Christmas time peacefully and to avoid "noisy and rowdy" behaviour. This declaration dates back to the 13th century and in fact criminal actions committed during this period of Christmas peace were sentenced harder, than at any other time during the year.

And then for most people it is time for the sauna. For centuries it used to be the center of life where the sick were treated, people died and the babies were born. So of course it is an important and holy element during this very special feast to clean and purify body and soul.

Before enjoying dinner in most houses the Christmas story from the Gospel of Luke is now read. Then a rich Christmas buffet is served which traditionally includes dishes such as oven-baked ham, different kinds of vegetable casseroles, graved salmon with

Picture "Joulupukki" from the book "Santa Claus" by Mauri Kunnas ©Otava Publishing

sweet mustard sauce, meat balls and beetroot salad. The food is left on the table at all times so that the elves *("tonttu")* can also have their share after everyone else has gone to bed. A *tonttu* is a good spirit who is believed to live and guard every house. If they are ignored or not treated in an appropriate manner, they might cause all sorts of trouble and mischief – and in a worst case scenario even abandon the house leaving it unprotected. Therefore we try to treat our *tonttuja* with respect at any time of the year, but of course especially at Christmas time to keep them in good humour and to ensure good fortune for our home, in other words: to prolong their contract of employment.

And then the highlight of Christmas gets close: a visit of Santa Claus, *joulupukki,* which literally means "Christmas billy goat". Again, our *joulupukki* has its origin in old pagan Nordic shaman traditions where it used to be a fertility god looking like a buck. Over the centuries this frightening creature wearing a mask and a pair of horns was transformed to a good-tempered old man who nowadays looks like that seen in the Coca-Cola commercials. At Christmas Eve *joulupukki* comes a long way with his sleigh drawn by reindeer from Lapland in northern Finland, where he lives together with his wife and many *tonttuja* in a place called *Korvatunturi.* On arrival he loudly knocks on the door and asks if there are good children around – although he of course knows everything, as his elves have been spying on you lately. Good children get their presents and often in return play or sing a song or recite a poem before *joulupukki* has to hurry off to the many houses and children still to visit all around the world. And sometimes he is so busy that he can't come personally, but sends one of his elves, who will place all the presents under the Christmas tree and disappear unsighted.

Although a Christian feast, the Finnish *joulu* celebration is still strongly connected to rural traditions of ancient times with spirits and elves still playing an important role, which for us is not a contradiction at all. In this spirit: keep your eyes open and you might spot a *tonttu.*

Merry Christmas! HYVÄÄ JOULUA!

Karoliina Pelttari

Picture "Tonttu" from the book "The Book of Finnish Elves" by Mauri Kunnas ©Otava Publishing

To tell you that Davos is the most beautiful place in the world wouldn't make a lot of sense, since most of you would disagree and, as we are talking about my home, I am heavily biased. But whatever you might think of the town, with its mixed architecture and its lack of a neat old town center, you can hardly deny the beauty of the mountains surrounding it.

Davos does not easily fall into a category. It is not really a village, but at the same time not yet a city. During Christmas season, the number of inhabitants triples and it can get very crowded, but as soon as the ski stations have closed, you almost have to actively look for people. You will probably find them in the "Kaffee Klatsch", our famous coffee house. This place is so successful that there's now a copy in Zürich and it has become a must for visitors. It is one of those places where you walk through the door and instantly feel at home. It is very easy to spend hours in here, but finding a table can be tough, especially during bad weather. Luckily, if it is not snowing, the weather is usually great; the word "fog" is only used to describe the weather elsewhere.

The most obvious thing to do on a sunny winter day is skiing. If you are looking for the ultimate skiing experience, catch the first cable car at 8.15. This might sound brutally early but I assure you, it's worth it. There is just something about skiing on an empty slope. It's addictive. I guess that's kind of what all those free-riders are looking for when they risk their lives by going off-piste. However, as noon approaches, the slopes get more crowded, a good time to have lunch in one of the ski huts. Afterwards, you can ski the rest of the afternoon, or you can relax on one of the sunbeds. Just be careful, the sun is very intense up here and you don't want to get the bright-red "tourist-glow".

Simplicity is the key – calm down and relax in Davos

Besides skiing, there are many other activities. In the last couple of years, cross-country skiing gained enormously on popularity. Partly, this new hype is certainly due to Dario Cologna, the so-called "Roger Federer of cross-country skiing", who lives in Davos. On the other hand, the widespread enthusiasm for endurance sports might also have contributed. Cross-country skiing is quite a complex sport, demanding good balance, technique and physical fitness. But don't let that stop you from trying; it's also fun without those skills (I should know). The usage of the total 75km cross-country tracks in Davos is free, and rent of equipment relatively inexpensive. Also, the tracks can be easily reached, as they go along the whole valley.

After all this exercise, it's time to relax. When I was a kid, we used to have a public indoor and an outdoor pool. For you, this might make perfect sense, as you probably live somewhere with an actual summer. For us, the outdoor area could only be used for maybe two to three weeks a year. So when the site was renovated in 2006, a heated outdoor pool was built and a spacious spa was added. Located in the middle of Davos, adjacent to the Kurpark, it's the perfect place to recover from a day on the slopes.

Despite all the possibilities, my favourite way to unwind is very simple: taking a walk. I highly recommend the "Hohe Promenade", which leads all along town, about hundred meters above it. Here, you can calm down in the quiet of the forest, breath some fresh air and enjoy the view over Davos. You will realize that the clocks are ticking slightly slower up here, so lean back and enjoy.

Yvonne Fink

Violoncello

It all started when I was still a young child. My parents both play instruments – only as a hobby, mind you – and so it was a natural decision to have both me and my brother learn an instrument too. We were first put into the "early musical education" program of the local music school at age four or something, which consisted of a horde of children learning to sing and playing the recorder (a kind of flute, Blockflöte in German). I probably learned my hate for that horrible instrument during that time.

Nonetheless, I survived and was soon presented with the luxury of choosing which instrument I actually wanted to learn. Somehow, I arrived at the Cello. I was five at the time, still in my first year of elementary school. My parents got me a cello teacher at the music school and rented my first 1/8-sized cello. Now, if you are a small child learning a string instrument there are basically two possibilities: one, you are born a genius. The children of a cello teacher I know are an example of this kind. Both started studying their respective instruments at an actual university under actual professors before they were ten years old and proceeded to give numerous solo performances with orchestras shortly after. I was of the other kind. Still, my parents endured, and I was thrilled on that first day. I immediately tried to get some sort of sound out of that instrument and eagerly awaited my first lesson.

Shortly after the harsh reality set in. Learning an instrument was difficult! It was work! And it turned out that my parents were far more committed to this whole experiment than I ever could be.

Cruel as they were, they actually made me practice each and every day. For ten whole minutes! You have no idea how long ten minutes can be. I got into the habit of putting a watch next to my sheet music, and as soon as those ten minutes had passed I would drop everything right then and there and already dread the next day.

My lessons were shared with another kid who added the insult of consistently playing better than I did. His name was Aurelio, which even sounded like some classical prodigy! Not that that motivated me in any way to practice harder. Anyway, it

continued like that for a while. I soon had my first public solo performance at a Christmas play in elementary school.

Looking back, the only things I really remember from that time are a few still images. My brain must have gone into survival mode and erased all traces of sound as soon as possible. Still, the enforced diligence somewhat worked. As I started to improve, my lessons were moved from being shared with Aurelio to solo lessons, and instead of having them in a classroom at some public school we went to the actual music school which was a gigantic, imposing building with lots of columns and high windows, situated on the only hill in the middle of the city just below an old castle.

I steadily got better at playing the cello, performed willingly in school during music classes and at public exhibitions of the music school. I even started to get praised for my progress by other teachers. But even so, after the first five years I got bored enough to start trying to figure out how to tell my parents that I wanted to quit. At that time, my music teacher decided that I was good enough to join the music schools orchestra, which I promptly refused. Playing in an orchestra with a bunch of other children who were all bound to be older than me was far too intimidating.

Now, more than fifteen years later I own a cello and still play, so something happened. Obviously it was a girl. She was a little older than me and had her cello lessons right after me, and being the shy boy I was I never so much as spoke to her. And then one day out of the blue she asked me if I didn't want to join the orchestra. The only possible answer, which greatly confused my poor teacher, was an enthusiastic yes. And so I ended up in my first orchestra. It was great. Playing together with children of my age under an amazing conductor is no doubt what saved me from quitting. After all, music is always better in a group. Concerts were always fun, as were the band camps leading up to those (catch the reference?). Orchestra practice became something I looked forward to every week. One of my nicknames at school was the "guy with the coffin", referencing of course my large cello case.

At some point I even was part of 3 different orchestras at the same time, that's how much of a cello nerd I was turned into. I made great friends, I played with fantastic musicians (even professional ones), I learned of the never ending viola jokes (those poor instruments at the very bottom of the food chain). So, if there is any message I am trying to bring across on these two pages, it is this: if you want your children to learn an instrument, have them start early and choose an instrument that enables them to play in a group. It may just turn out to be something great.

Charles Hemion

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

News from the DBM-IT

Windows XP
From the summer of 2014 Microsoft are ceasing to support Windows XP, which means there will be no further updates as of then. For security reasons we must therefore gradually replace all Windows XP installations with Windows 7 during 2013.
If you have a computer which is running Windows XP we would ask you to please get in contact with us so we can advise you about this eventual migration.

Apple
The new iMacs ("late 2012" models) as well as the new MacBooks Retina and MacBook Air can no longer be upgraded post purchase. With the exception of the 27" model it is no longer to upgrade the RAM in any of the models. As a result you must now plan for the long term when making a new purchase and ensure that the computer has enough memory and hard disk space. Due to the very thin size of the iMacs Apple have attached the glass back to the LCD screen with extremely strong glue!
In order to ensure you get the optional machine for your needs we recommend that you contact us before placing your order. We can be contacted via email at support-dbm@unibas.ch or you can contact your responsible IT personnel.

More from Apple
Effective immediately all Apple MacBook models, MacBook Air, iMac and Mac mini as well as MacPro Desktop models and Apple accessories such as Thunderbolt monitors etc. can be ordered directly from Apple with a 20% discount. All iPods, iPhones and iPads are excluded from this offer. This offer is not a sale but is effective immediately, with no time limit. Orders must be made via the DBM-IT.
You can make your choices on the Apple website http://store.apple.com/ch-de/.
If you require a tender please send us an email at support-dbm@unibas.ch. You may also order an offer directly from us by email. We will require the details of the product to be ordered such as model, design, disk size etc.

Neuigkeiten von der DBM-IT

Windows XP
Per Sommer 2014 wird Microsoft seinen Support für das Windows XP einstellen d.h. ab diesem Datum wird es keine Updates mehr geben. Wegen der Sicherheit werden wir im 2013 Schritt für Schritt alle Windows XP Installationen durch Windows7 ersetzen müssen.
Sollten Sie einen Rechner mit Windows XP haben, so setzen Sie sich bitte mit uns in Verbindung, damit wir Sie bei einer allfälligen Migration beraten können.

Apple
Die neuen iMacs (Modell "Late 2012") als auch die neuen MacBooks Retina und MacBook Air's lassen sich nachträglich nicht mehr aufrüsten. Ausser beim 27" kann bei keinem Modell mehr nachträglich das RAM aufgerüstet werden. Somit muss man bei der Beschaffung immer auch langfristig planen und allenfalls das Gerät mit genügend grossem Arbeitsspeicher und Harddisk bestellen. Bei den iMacs hat Apple aufgrund der extrem schmalen Bauweise die Glasscheibe mit dem LCD auf das Rückteil mit extrem haftendem Leim festgeklebt!
Damit Sie das optimale Gerät für Ihre Aufgabe beschaffen können, empfehlen wir Ihnen, uns vor der Beschaffung zu kontaktieren. Schreiben Sie uns ein Email an support-dbm@unibas.ch oder rufen Sie Ihre Vor-Ort Informatik an.

Apple zum 2.
Ab sofort können wir alle MacBook Modelle, MacBook Air, iMac und Mac mini als auch MacPro Desktop Modelle, aber auch Apple Zubehör wie Thunderbolt Monitore etc. mit bis zu 20% Rabatt direkt bei Apple bestellen. Ausgenommen von diesem Angebot sind alle iPod, iPad und iPhones. Dies ist keine Einkaufsaktion, sondern gilt ab sofort und ohne zeitliche Limitierung. Bestellungen laufen über die DBM-IT.
Informieren Sie sich auf der Apple Homepage unter http://store.apple.com/ch-de/. Wenn Sie eine Offerte benötigen, schreiben Sie uns ein Email an support-dbm@unibas.ch. Sie können uns auch direkt per Email einen Auftrag erteilen. Dazu benötigen wir die Angaben zu den zu bestellenden Produkten wie Modell, Ausbau, Speicherplatz etc.

Teresa Salvaggio, Lohnadministration

Meine Erinnerungen beginnen am 5. Dezember 1965, als wir nach Basel kamen. Die Lichter der Stadt, es war kalt, aber es lag kein Schnee. Ich war damals fünf Jahre alt, als meine Eltern mit meinem Bruder und mir von Neapel nach Basel zogen. Bis ich in die Primarschule kam, verbrachte ich die ganze Woche, von Sonntag- bis Freitagabend, im Kindergarten «Missione Cattolica» bei den italienischen Nonnen. Mädchen und Jungen waren streng getrennt, nur mein kleiner Bruder durfte mit seinen drei Jahren bei mir schlafen, dann konnte ich ihm die Hand halten. Unsere Eltern arbeiteten damals den ganzen Tag. Mit sieben kam ich in die Primarschule «Scuola Lucia Barbarigo», wieder von italienischen Nonnen geführt und unter italienischen Kindern. So konnte ich wenig Deutsch, als ich auf die

Realschule kam, dieses Mal war ich die einzige Italienerin in der Klasse. Ich nahm Privatstunden. Von den Lehrern erfuhr ich grosse Unterstützung, ich fühlte mich gut aufgehoben. Anschliessend machte ich eine kaufmännische Lehre, arbeitete in einem Baugeschäft und kam dann bald ans Unispital.

Heute bin ich in der Lohnadministration für das Departement Biomedizin, die Direktion, die Unterassistenten, die AZUBI und alle Drittmittelanstellungen verantwortlich. So kenne ich viele von Euch vom Namen her. Weiss, wer seine Doktorprüfung erfolgreich bestanden hat, einen Unfall hatte, gerade im Mutterschaftsurlaub ist oder gekündigt hat. Spätestens beim Austritt sehe ich dann alle auch von Angesicht zu Angesicht.

Gerne erinnere ich mich an die Weihnachtszeit, wenn die wenigen Verwandten, die in der Schweiz lebten, zusammen kamen. Die Frauen kochten und die Kinder genossen die Momente im Familienkreis. Ein Rezept, das ich selbst immer wieder gerne zu Weihnachten zubereite und typisch neapolitanisch ist, ist Struffoli. Es besteht aus vielen kleinen Teigkügelchen, die mit bunten Perlen und kandierten Früchten hübsch dekoriert

werden. In Neapel benutzt man zur Dekoration auch bunte Kugeln mit Anissamen, die dem Struffoli einen besonderen Geschmack geben. Der Struffoli wird schon einen Tag vor dem Verzehr zubereitet und mit einem Gläschen gut gekühltem Limoncello serviert. Man kann den Struffoli abgedeckt etwa eine Woche aufbewahren.

Lange war Italien für mich mehr Ferienland. Jedes Jahr ging es in den Urlaub nach Poggiomarino, einem kleinen Ort am Fusse des Vesuvs und später nach Marina di Camerota. Seit meine Eltern nach ihrer

Pensionierung zurückgegangen sind, zieht es mich jetzt öfter nach Italien. Es ist ein Hin und Her. Falls ich zurück müsste, würde ich mich wahrscheinlich schnell wieder einleben. Wenn ich nach Italien fahre, fasziniert mich das Kulturelle, im Gegensatz zur Politik. Die letzten Jahre war ich neben den Sommerferien, die wir weiterhin jedes Jahr in Italien verbringen, fünf Mal in Rom und häufig in Neapel, immer entdecke ich etwas Neues, etwas Faszinierendes.

Wenn Ihr nach Neapel fahrt, vor allem vor Weihnachten, müsst Ihr die Krippengasse besuchen. Die Via San Gregorio Armeno ist eine der antiksten Strassen in der Altstadt Neapels und in der ganzen Welt als die «Straße der Krippenbauer» bekannt. Die Weihnachtskrippe, «Il presepe», hat in Neapel eine sehr lange Tradition und spielt in der Weihnachtszeit eine wichtige Rolle. In den zahlreichen Geschäften der Kunsthandwerker könnt Ihr zauberhafte Krippenfiguren bewundern. Nicht die bekannten religiöse Krippenfiguren stehen im Mittelpunkt, sondern vor allen Dingen die Figuren des täglichen Lebens: Fisch- und Obsthändler, Kastanienverkäufer, Pizzabäcker mit flackernden Pizzaöfen, Metzger und Bäcker. Die Krippenfiguren gibt es in allen Größen und Preisklassen, von der kleinen Plastikfigur bis zur in Handarbeit liebevoll gefertigten Statue.

Buon Natale!

Rezept Struffoli

Zutaten (für ca. 12 Portionen):

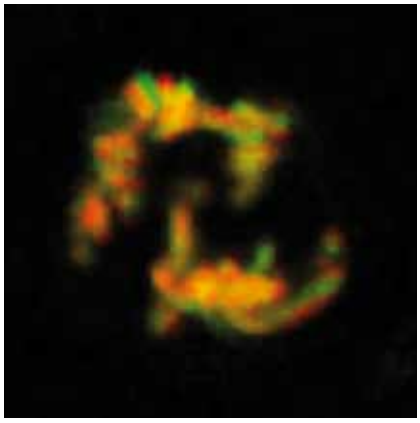
500 g Mehl, 5 Eier, 2 EL Anisschnaps (ersatzweise Brandy oder Rum), 100 g Butter, 1 Essl. Zucker, abgeriebene Schale von je 1/2 unbehandelten Orange und Zitrone, 1 Prise Salz, ca. 1 l Sonnenblumenöl zum Frittieren, 50 g Orangeat (gewürfelt), 50 g Zitronat (gewürfelt), 50 g buntes Früchtemix (kandiert und gewürfelt), 300 g feincremiger Honig , 150 g Zucker, 8 kandierte Kirschen, bunte Zuckerperlen

Zubereitung:

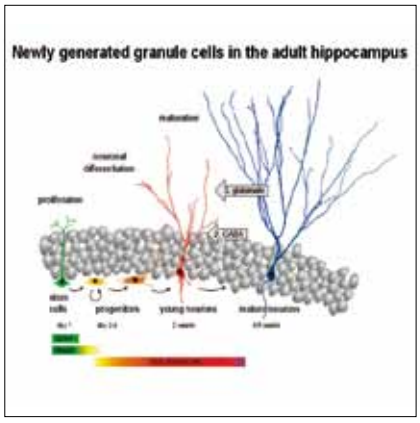
1. *Mehl, Eier, 1 Essl. Anisschnaps, Butter, 1 Essl. Zucker, die abgeriebene Zitronen- und Orangenschale und eine Prise Salz zu einem geschmeidigen Teig verarbeiten.*
2. *Den Teig zugedeckt einige Stunden gehen lassen.*
3. *Den Teig auf einer bemehlten Arbeitsfläche fingerdick ausrollen und in etwa 1 cm lange Stücke schneiden. Bei der Anordnung der Stückchen auf der Arbeitsfläche darauf achten, dass sie nicht aneinander kleben bleiben.*
4. *Die Teigkügelchen portionsweise im heissen Öl frittieren, bis sie goldbraun (nicht braun!) sind. Auf einem Teller mit Küchenpapier abtropfen lassen. Falls das Öl während des Frittierens schaumig werden sollte, muss es gegen frisches Öl ausgetauscht werden.*
5. *In einem grossen und hohen Topf den Zucker leicht karamellisieren. Danach den Honig, 1 Essl. Anisschnaps sowie ca. 5 Essl. Wasser dazugeben. Alles erhitzen, bis die Mischung gelb wird.*
6. *Bei leichter Hitze die Teigkügelchen und die Hälfte des Orangeats und Zitronats zur Mischung geben. Solange vorsichtig verrühren, bis der Honig sich gut verteilt hat.*
7. *Die Kugeln auf eine grosse runde Platte stürzen.*
8. *Mit feuchten Händen einen Kegel formen.*
9. *Die Kugeln mit bunten Perlen, kandierten Kirschen, kandiertem Früchtemix und dem Rest des Orangeats/Zitronates dekorieren.*
10. *Den Struffoli abkühlen lassen. Erst nach 5 – 6 Stunden oder besser einen Tag später verzehren.*

VORSCHAU PREVIEW

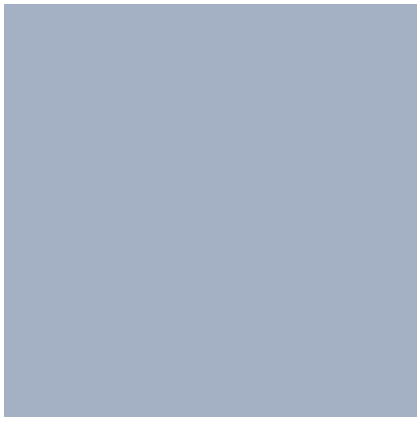
In der nächsten Ausgabe . . .



. . . entführt uns Christoph Hess in die Welt der Immunobiology



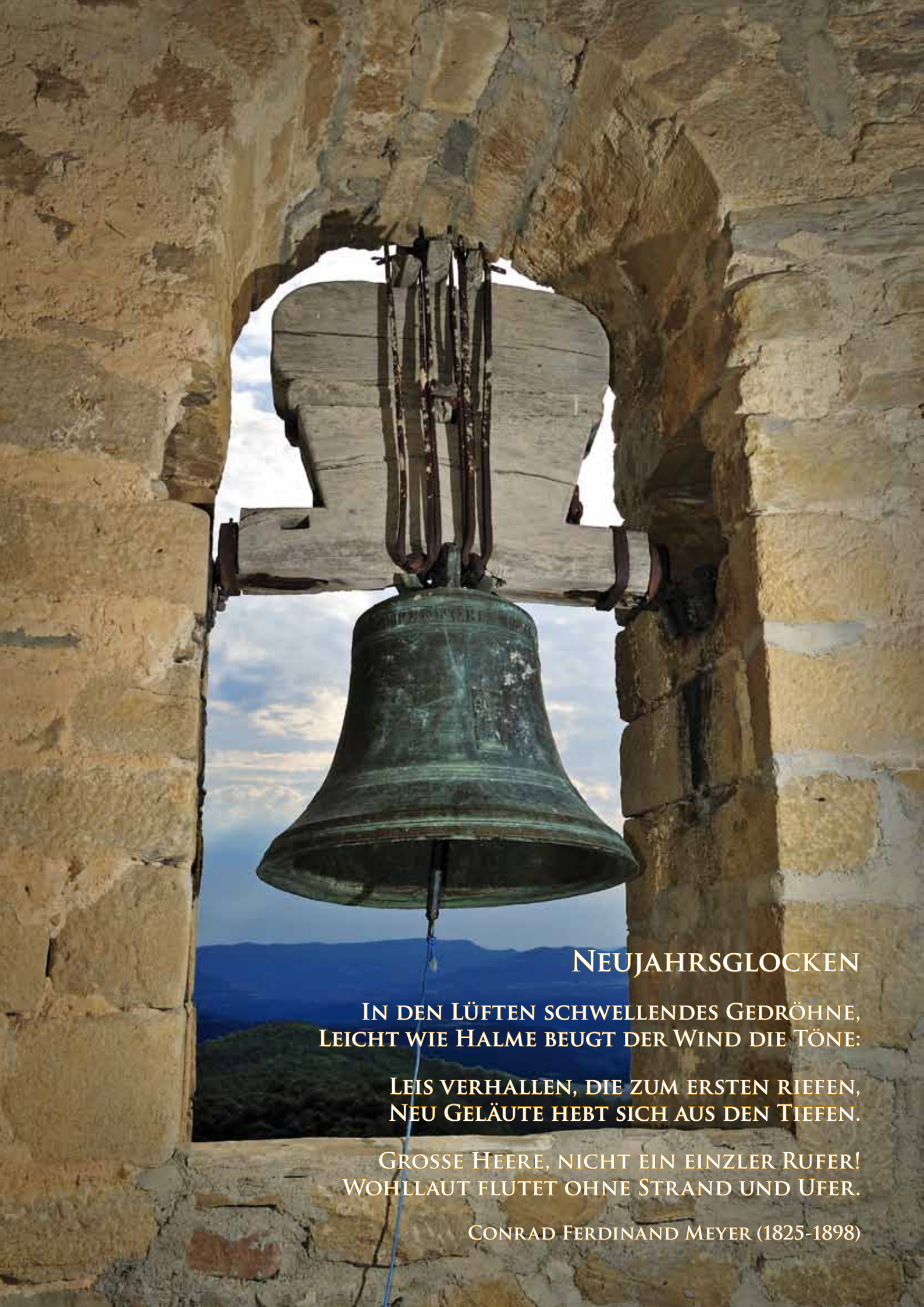
. . . erfahren wir von Josef Bischofberger mehr über Cellular Neurophysiology



. . . zeigt uns Elise Dalmas ihr Paris

. . . nehmen wir es mit dem ICFS sportlich

. . . gehen wir der Frage nach, was Heimat ist



Neujahrsglocken

In den Lüften schwellendes Gedröhne,
Leicht wie Halme beugt der Wind die Töne:

Leis verhallen, die zum ersten riefen,
Neu Geläute hebt sich aus den Tiefen.

Grosse Heere, nicht ein einzler Rufer!
Wohllaut flutet ohne Strand und Ufer.

Conrad Ferdinand Meyer (1825-1898)