DBM FACTS

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

Tumor Biology: from starving tumors to migrating cancer cells | Nanomedicine | Wie aus einer Ente 17 wurden

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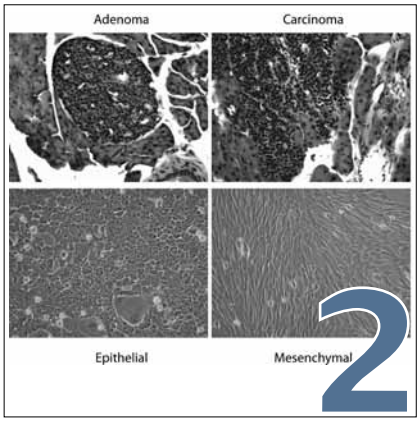
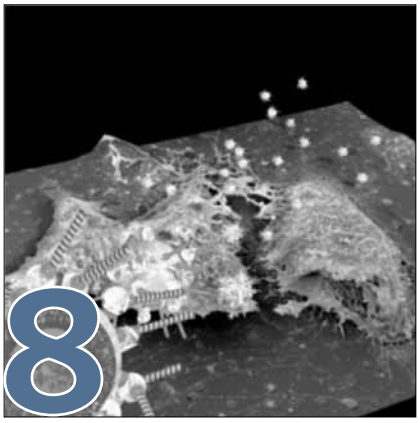
Departement Biomedizin Basel



Tumor Biology: from starving tumors to migrating cancer cells
from Gerhard Christofori



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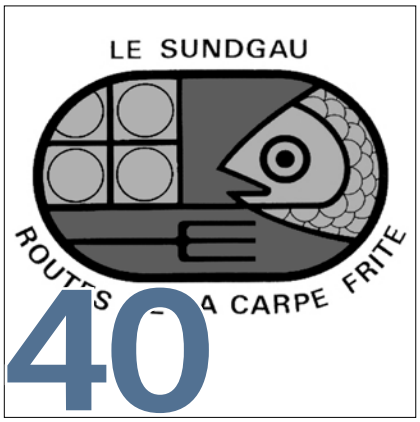

Strasse des gebackenen Karpfens
von Emmanuel Traunecker

IMPRESSUM

Redaktion
Heidi Hoyermann (Leitung)
Verena Jäggin

Übersetzungen
Paula Cullen

Layout:
Eric Spaety, Morf Bimo Print AG, Binningen

Fotos:
Thomas Aerni (privat)
Cardoro de Matos-Gatti (privat)
Thierry Girard (privat)
Verena Jäggin (13, 26, 28, 42)
Peter Mullen (privat)
Dieter Naeher (privat)
Nicole Schaeren-Wiemers (privat)
Jürg Schwaller (privat)

Titelfoto:
Agathe, Nicole Schaeren-Wiemers

Druck
Morf Bimo Print AG, Binningen

Anschrift
Redaktion DBM Facts
Departement Biomedizin
Hebelstrasse 20
4031 Basel
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UKBB Universitäts-Kinderspital beider Basel

Universitätsspital Basel

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Der Sommer steht vor der Tür. Was gibt es Neues zu berichten? Jakob Passweg tritt die Nachfolge von Alois Gratwohl an. Wohlbekannt, von seinem früheren Aufenthalt in Basel, wird er ab 1. Januar 2011 die Leitung der Abteilung für Hämatologie übernehmen. Marc Donath wird ab dem 1. Juli 2010 neuer Leiter der Endokrinologie am USB und wird am DBM seine Forschungsgruppe aufbauen. Sein Schwerpunkt liegt in der Erforschung entzündlicher Mechanismen in der Entstehung des Diabetes mellitus. Beiden ein herzliches Willkommen am Departement Biomedizin!

Gerhard Christofori nimmt uns heute mit auf die Reise in die Welt der «Tumor Biology». Patrick Hunziker gibt uns einen Einblick in das Tätigkeitsfeld der «Nanomedicine». Die neuesten Publikationen aus dem DBM finden Sie auf Seite 14.

In die Wissenschaft vom Wein führt uns Jürg Schwaller ein (ab Seite 30). Ebenfalls eine ganz andere Art von Forschung betreibt Nicole Schaeren-Wiemers in ihrer Freizeit, mehr dazu ab Seite 36. Das und vieles mehr bietet die neueste Ausgabe der DBM Facts.

Schöne Ferien und gute Erholung wünscht Ihnen
Radek Skoda

Dear Readers

The summer is almost upon us. What news do we have? Jakob Passweg is to take over as the successor of Alois Gratwohl. Well-known from his previous sojourn in Basel, he will take over the Department for Haematology from the 1 January 2011. Marc Donath will be the new head of Endocrinology at the USB from the 1 July 2010, and will build his research group at the DBM. His focus is on research into inflammatory mechanisms in the origin of Diabetes mellitus. We send them both a hearty welcome to the Department of Biomedicine.

Gerhard Christofori brings us on a journey through the world of "Tumor Biology". Patrick Hunziker gives us insight into the "Nanomedicine" field of activity. The latest publications from the DBM can be found on page 14.

The science of wine is brought to us by Jürg Schwaller (page 32). In addition, a completely different type of research is undertaken by Nicole Schaeren-Wiemers in her free time, more about this can be found on page 36. All this and more can be found in this latest issue of DBM Facts.

Wishing you all happy and relaxing holidays
Radek Skoda

Tumor Biology: from starving tumors to migrating cancer cells

Tumor Biology Group 2009/2010
from left to right, front row: Vanessa Baeriswyl (PhD student), Neha Tiwari (PhD student), Akiko Kunita (postdoc), Mahmut Yilmaz (PhD student)
middle row: Annette Orleth (joint postdoc with Clinical Oncology), Dorothea Maaß (PhD student), Helena Antoniadis (technician), Petra Schmidt (technician), Ernesta Fagiani (postdoc),
back row: Imke Albrecht (postdoc), Natalie Schlegel (postdoc), Chantal Heck (PhD student), Gerhard Christofori (group leader), Lukas Mannhart (bioinformatician), Lorenz Waldmeier (PhD student).
Missing on the picture are Raphael Bieri (Master student), Maren Diepenbruck (Master student), Anna Fantozzi (postdoc), Michael Flori (Master student), Ulrike Hopfer (postdoc), Ursula Schmieder (technician), Adrian Zumsteg (PhD student).

Introduction

The metastatic dissemination of cancer cells is the primary cause of death in cancer patients. Hence, understanding the molecular mechanisms underlying malignant tumor progression, most importantly the local invasion and systemic dissemination of tumor cells and their metastatic outgrowth in distant organs, represents one of the great challenges in exploratory cancer research. During the progression to tumor malignancy, primary tumor cells as well as the tumor microenvironment undergo characteristic cellular and molecular changes, which are essential for the metastatic dissemination of tumor cells. Tumor cell-intrinsic alterations include the loss of cell polarity and alterations in cell-cell and cell-matrix adhesion as well as deregulated growth factor and cytokine signaling, which together support detachment, migration and invasion of tumor cells. On the other hand, the tumor stroma, consisting of endothelial cells, fibroblasts and infiltrating cells of the immune system, is engaged in an active molecular crosstalk within the tumor microenvironment. The concomitant formation of new blood vessels (tumor angiogenesis) and lymphatic vessels (tumor lymphangiogenesis) together with inflammatory and immune-suppressive responses further promote cancer cell migration and invasion and the initiation of the metastatic process.

The major objective of our research group is the identification and characterization of the molecular events underlying malignant tumor progression and metastasis formation, potential targets for innovative cancer therapies. In particular, we focus on the contribution of tumor angiogenesis and lymphangiogenesis to tumor progression and on the molecular mechanisms underlying the transition from benign neoplasia to malignant cancers and the metastatic dissemination of tumor cells. In addition to tumor cell lines *in vitro,* we employ transgenic mouse models of tumorigenesis to determine causal connections between the expression of particular genes and tumor progression *in vivo.*

Tumor angiogenesis and lymphangiogenesis

The early stages of tumor formation are based on a combination of genetic and epigenetic alterations that activate oncogenes and/or inhibit tumor suppressor genes. Consequently, the rate of cell proliferation is increased while apoptosis is diminished, concomitant processes resulting in early hyperplastic growth. However, once the tumor mass has reached a critical size, tumor cells located in a distance to the next blood vessel lack an appropriate supply of oxygen and nutrients, they undergo apoptosis, and further tumor growth is impaired. Unfortunately, tumor cells can overcome this growth inhibition by inducing the formation of new blood vessels from pre-existing blood vessels, a process known as tumor angiogenesis. This well-characterized multistep process contributes to tumor progression, not only by providing oxygen and nutrients for tumor outgrowth but also by offering a route for tumor cells to disseminate via the blood stream to distant organs and to form metastases.

The transition from pre-vascular hyperplasia to highly vascularized and progressively outgrowing tumors is referred to as the "angiogenic switch" (Figure 1). The angiogenic switch is controlled by changes in the fine-tuned balance between pro- and anti-angiogenic factors secreted either by tumor cells or by cells of the tumor microenvironment. In our laboratory, we investigate the molecular regulation of tumor blood vessel angiogenesis and tumor lymphangiogenesis and their contribution to cancer metastasis. We have generated a number of transgenic mouse models that offer the unique opportunity to study the pathological, physiological and molecular consequences of different qualities and quantities of angiogenesis and lymphangiogenesis for tumor progression and metastasis. For example, we manipulate the regulation of angiogenesis during tumor development, either by transgenic expression of various angiogenic factors, such as Vascular Endothelial Growth Factor-A (VEGF-A), or by interfering with the function of angiogenic factors by pharmacological inhibitors or by the expression of soluble versions of their cognate receptors (so-called trap constructs). Altogether, these experiments demonstrate that the onset of angiogenesis plays a critical role in tumor outgrowth, yet does not necessarily contribute to tumor metastasis. It appears that, in addition to increased blood vessel densities, tumor cells themselves need to change their identity from a benign, adhesive epithelial character to

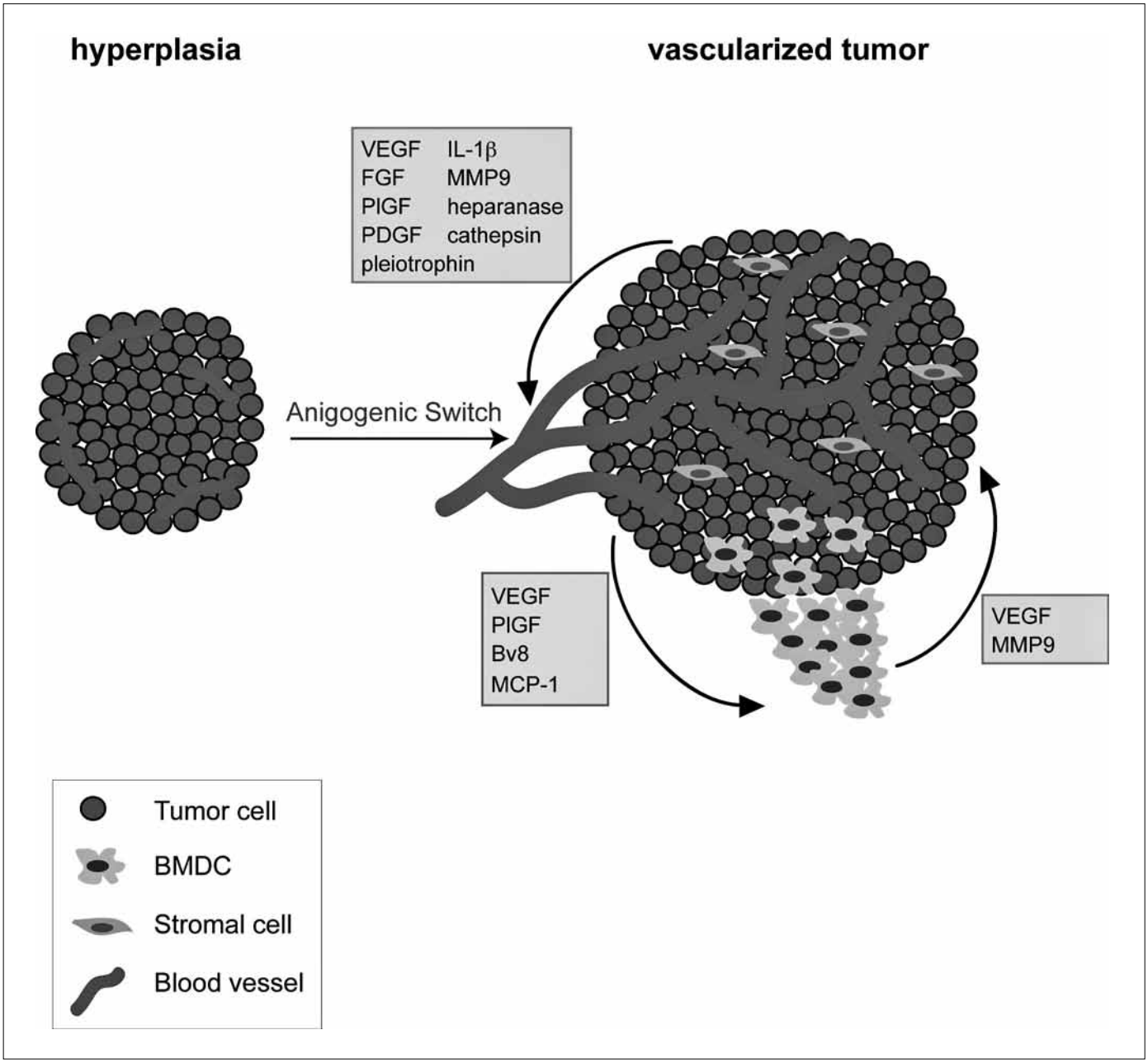

Figure 1:
Schematic representation of the molecular and cellular players underlying the angiogenic switch. The angiogenic switch takes place when the balance between pro- and anti-angiogenic factors tilts in favor of the pro-angiogenic factors, resulting in the transition from dormant hyperplasia to growing hypervascularized tumors. Specifically depicted are the pro-angiogenic factors and proteases secreted by the tumor cells themselves, by the cells of the immune system recruited to the tumor site, and the factors secreted by the tumor cells to recruit inflammatory cells.

a migratory, malignant phenotype in order to invade into the surrounding tumor stroma and to intravasate into blood vessels. Conversely, the forced expression of the lymphangiogenic factors VEGF-C and VEGF-D leads to the increased formation of lymphatic vessels (lymphangiogenesis) and subsequently to the formation of lymph node metastasis. These results indicate that an increased lymphatic vessel density in the tumor environment is sufficient to support a first metastatic dissemination of tumor cells to regional lymph nodes. The correlation between the expression of VEGF-C and D, upregulated lymphangiogenesis, and lymph node metastasis has been subsequently confirmed in cancer patients by many laboratories.

In a separate project, we have also investigated the contribution of bone marrow-derived cells to tumor angiogenesis and lymphangiogenesis. Using a combination of adoptive cell transfer and genetic lineage tracing experiments we have not detected any bone marrow-derived cell integrating into tumor blood vessels, yet we have found that cells of the myeloid lineage transdifferentiate into lymphatic endothelial cells and, by integrating into lymphatic vessels, contribute to tumor lymphangiogenesis. We have been able to recapitulate the transdifferentiation of macrophages into lymphatic endothelial cells in culture systems *in vitro* which offers the opportunity to dissect the critical players of this process on a molecular level. First gene expression profiling and functional validation experiments have revealed that fibroblast growth factor receptor signaling and the chemokine CXCL12/CXCR4 signaling axis play critical roles in the transdifferentiation process.

Finally, we employ our various transgenic mouse models for the design and testing of innovative cancer therapies. In collaboration with pharmaceutical partners we are investigating the efficacies and biological consequences of treatments with pharmacological inhibitors that specifically target pro-angiogenic signal transduction pathways. These experiments have revealed that contrary to the expectations, tumors develop resistance against anti-angiogenic therapies by switching from one angiogenic growth factor system to another. Moreover, depending on the type of anti-angiogenic treatment, increased hypoxia in treated tumors may result in increased tumor invasiveness and metastasis formation, an undesired outcome. Hence, in collaboration with Dr. Andreas Wicki, PD Dr. Christoph Mamot, and Prof. Christoph Rochlitz, DBM, Clinical Oncology, we have designed and tested immunoliposomes that directly target the tumor vasculature. This approach has been highly successful in the preclinical setting and is hopefully soon translated into clinical use.

Despite the arising problems with current anti-angiogenic therapies, in the next few years most cancer patients with solid tumors will be treated with one or the other form of anti-angiogenic therapy. However, currently no surrogate markers are available for clinicians to select the suitable anti-angiogenic regimen and to monitor treatment efficacy within the first days of therapy. To this end, we are currently employing our transgenic mouse models of cancer to identify novel cellular and molecular markers for tumor angiogenesis and lymphangiogenesis present in the peripheral blood, markers that are urgently needed for the diagnosis, prognosis and clinical monitoring of cancer patients being treated with anti-angiogenic therapies.

Metastasis

Despite major efforts in metastasis research, we still lack detailed insights into how cancer cells actually migrate out of primary tumors and invade into neighboring tissue, how they enter (intravasate) into the blood or the lymphatic circulation, how they survive 'homelessness' and immune surveillance in the blood stream, and how they target certain organs to leave (extravasate) the blood circulation and to initiate metastatic outgrowth in specific target organs. Obviously, the migratory and invasive capabilities of a cancer cell present critical parameters in the metastatic cascade. Plenty of molecular pathways define distinct types of migration and invasion in a cancer cell-autonomous manner, including single cell amoeboid and mesenchymal migration and collective cell migration. In many instances, stromal cells, such as blood vessel and lymphatic endothelial cells, cancer-associated fibroblasts or bone marrow-derived inflammatory cells, act as modulators of cancer cell migration and invasion and as pathfinders in the extracellular matrix. Moreover, chemokine gradients within the tumor microenvironment or in the blood and lymphatic system, as well as the establishment of an appropriate 'metastatic niche' in future metastatic organs, contribute to the targeted colonization of distant organs.

The development of malignant tumors is in part characterized by a tumor cell's capability to overcome cell-cell adhesion and to invade surrounding tissue. A hallmark of malignant tumor progression is the loss of the expression of the adherens junction molecule E-cadherin by tumor cells. We have previously demonstrated that the loss of E-cadherin function plays a critical role in the transition from epithelial, benign tumors to invasive, malignant tumors, a process referred to as

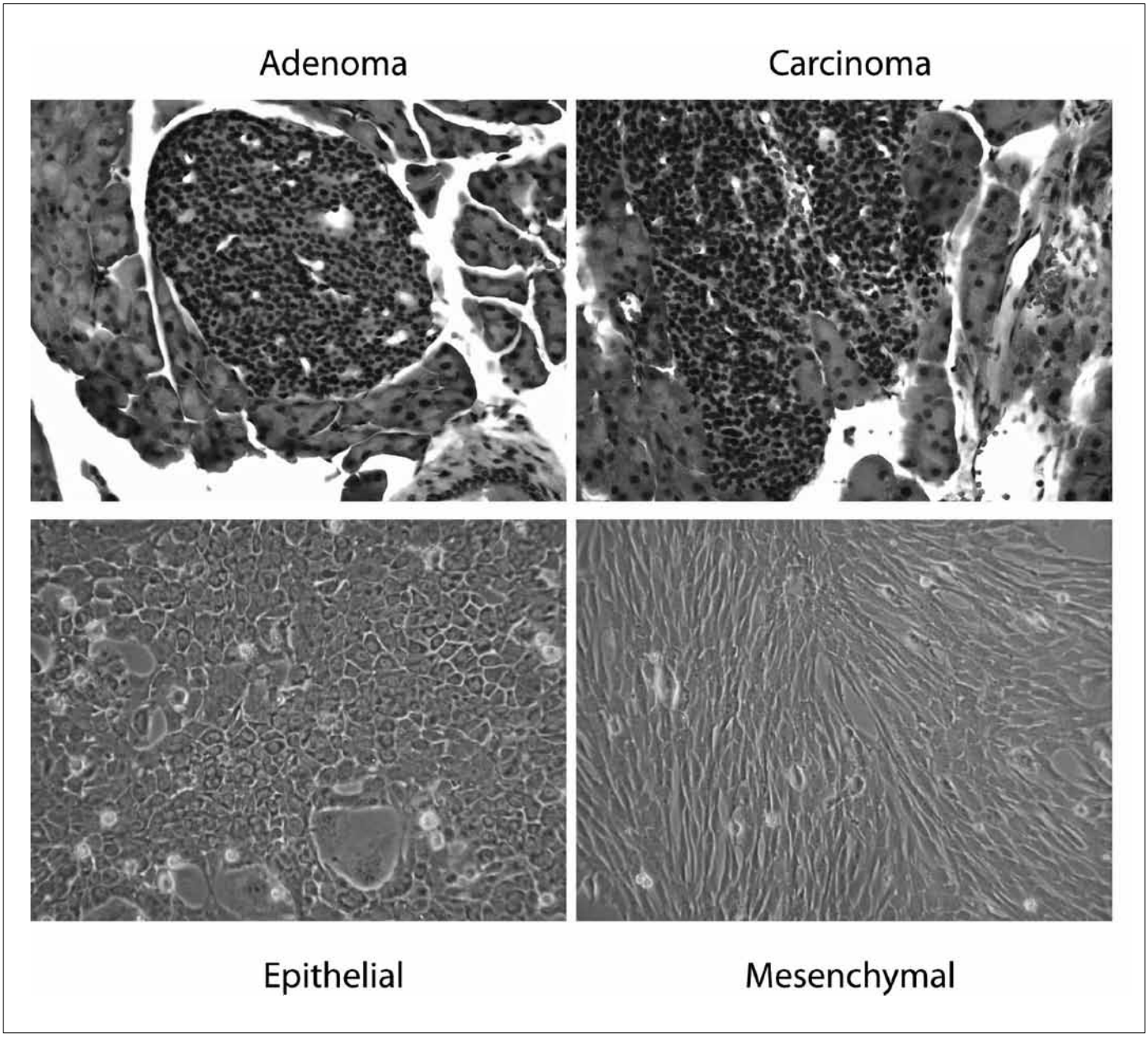

Figure 2:
Tumor cell invasion in vivo and in vitro. The transition from an epithelial adenoma to invasive carcinoma is exemplified by histological sections of tumors arising during multistage carcinogenesis in the Rip1Tag2 transgenic mouse model of pancreatic β-cell carcinogenesis (upper panels). Epithelial-Mesenchymal Transition (EMT) of cancer cells is observed in cultured epithelial breast cancer cells (bottom left panel) that upon genetic inactivation of the E-cadherin gene lose their epithelial morphology and gain migratory and invasive capabilities (bottom right panel)

epithelial-mesenchymal transition (EMT; Figure 2). In the past years, we have learned that EMT occurs in multiple stages and is regulated by sophisticated molecular networks regulating the expression of a large number of protein- and miRNA-encoding genes. Notably, we have identified a number of signaling pathways and transcription factors that appear critical not only in the initiation and execution of the morphogenic process of EMT but also in providing survival signals to cancer cells. We currently investigate the direct target genes of such transcription factors and their functional contribution to tumor metastasis. These EMT-pathways may also define "cancer-initiating cells" which are able to seed metastasis, and we study them also in the context of the epigenetic regulation of gene expression, such as activated and repressive histone modifications and DNA

methylation. Finally, we assess the role of miRNAs and their target genes in the regulation of EMT and metastatic dissemination. With these experimental approaches we aim at the identification of the master regulators of EMT and metastasis and we plan to scrutinize their potential as therapeutic targets for preventing metastatic disease.

We have recently also identified a process of collective cell invasion that does not involve EMT. We have found that podoplanin, a highly glycosylated cell surface molecule, is expressed in the outer cell layer of the invading front of most human squamous cell carcinomas and a few breast cancers, notably in the absence of any loss of E-cadherin expression. In order to study the functional contribution of podoplanin to tumor invasion, we have expressed podoplanin in tumor cells of transgenic mice and in breast cancer cells in culture. Indeed, podoplanin induced migration and invasion of tumor cells in the absence of any loss of E-cadherin expression by inducing the formation of filopodia and the loss of actin stress fibers. These results raise the intriguing possibility that tumor cells not only invade as single cells, as exemplified by losing their epithelial identity during EMT, but also in a collective manner in the absence of EMT, for example by gaining podoplanin expression. How podoplanin induces filopodia formation and cell migration in cancer cells is a focus of our current research.

Cancer cell migration and invasion are certainly critical processes in the metastatic cascade. As described above, they can be induced and executed by various signaling pathways and regulatory networks. Many of these pathways seem to overlap with developmental processes and are being abused by cancer cells and also by the tumor microenvironment. Yet, while we have made substantial progress in the understanding of the molecular mechanisms underlying cancer cell migration and invasion in experimental systems, we still lack sufficient insights into the actual processes at work in cancer patients. This divergence between clinico-pathological and experimental observations is mainly based on the lack of appropriate surrogate markers and the lack of complex *in vivo* models that appropriately recapitulate human stochastic carcinogenesis. However, it is likely that the ongoing cell biological research on cell migration and EMT will provide the tools for the development of improved diagnosis and prognosis and eventually for the design of innovative therapies.

Gerhard Christofori

Nanomedicine & the Nanomedicine Research Group

What is Nanomedicine ?
Nanomedicine is the application of the nanosciences and nanotechnologies to the benefit of human health. In technology, the nanosciences are often defined by pure dimensions, i.e. classifying imaging and in particular manufacturing and manipulation of individual objects with a size significantly below a micrometer as part of the nanosciences, while methods that analyse or manipulate small matter just as a statistical entity of molecules, as is typically done in chemistry and pharmacology, are not considered a part of the nanosciences.

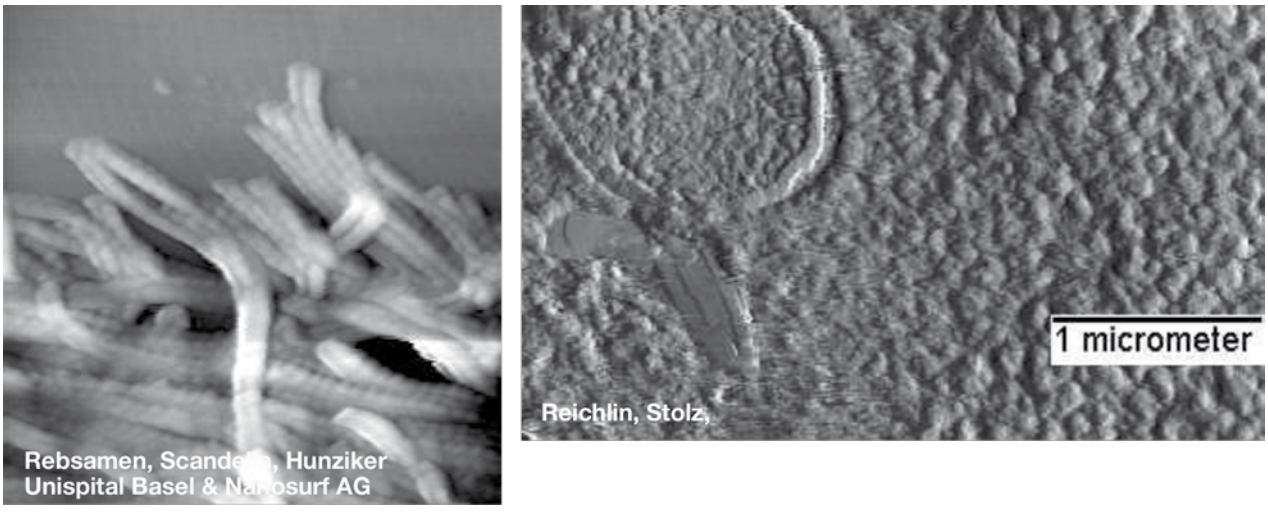

Figure 1:
Imaging biological structures by atomic force microscopy in physiological medium:
Left: vascular wall with 67nm band structure as molecular "fingerprint" of collagen type 1.
Right: High resolution surface imaging of living endothelial cell within living artery.

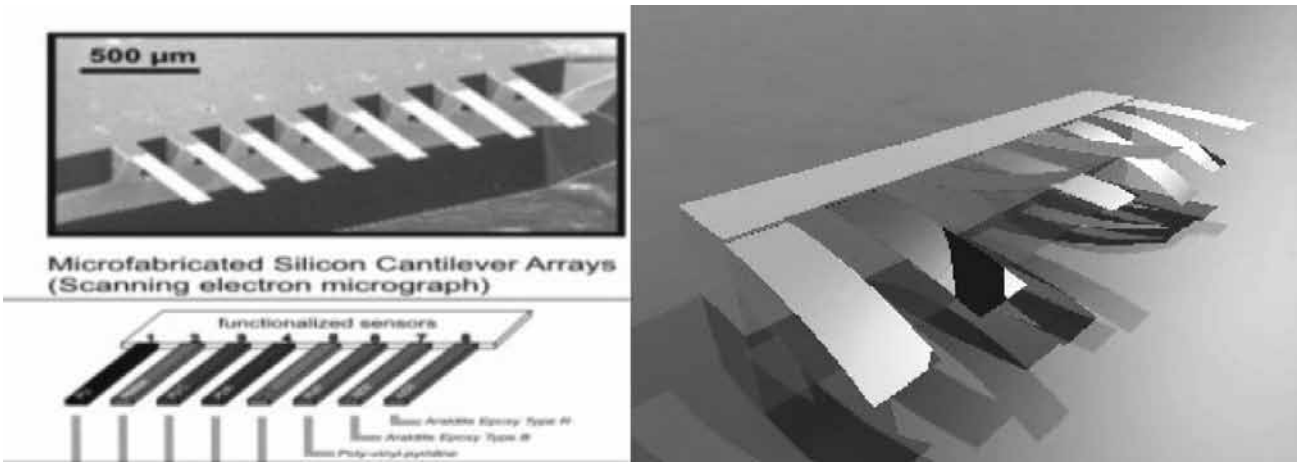

Figure 2:
Nanomechanical sensor for exhaled air and liquid samples: silicone cantilevers coated on one side with a capture layer will bend by a few nanometers upon exposure to a sample. Optical readout to an artificial neural network yields a device for rapid bedside diagnosis, as validated in our intensive care unit (Schmid,Lang,Gerber,Hunziker)

The invention of microscopes with nanometer resolution, in particular the scanning probe microscopes (Nobel price 1981 to Rohrer & Binnig) together with the electron microscope have shown that life itself is fundamentally nanostructured, but disease likewise has its origins frequently at the nanoscale: atherosclerosis development is driven by LDL-nanoparticles, viruses are infectious nanoparticles, and environmental dangers, e.g. diesel exhaust and cigarette smoke are dangerous nanoparticles too.

Another way of delineating the field of nanoscience is by its tools, methods, and materials:
The atomic force microscope – 'nanomechanically'

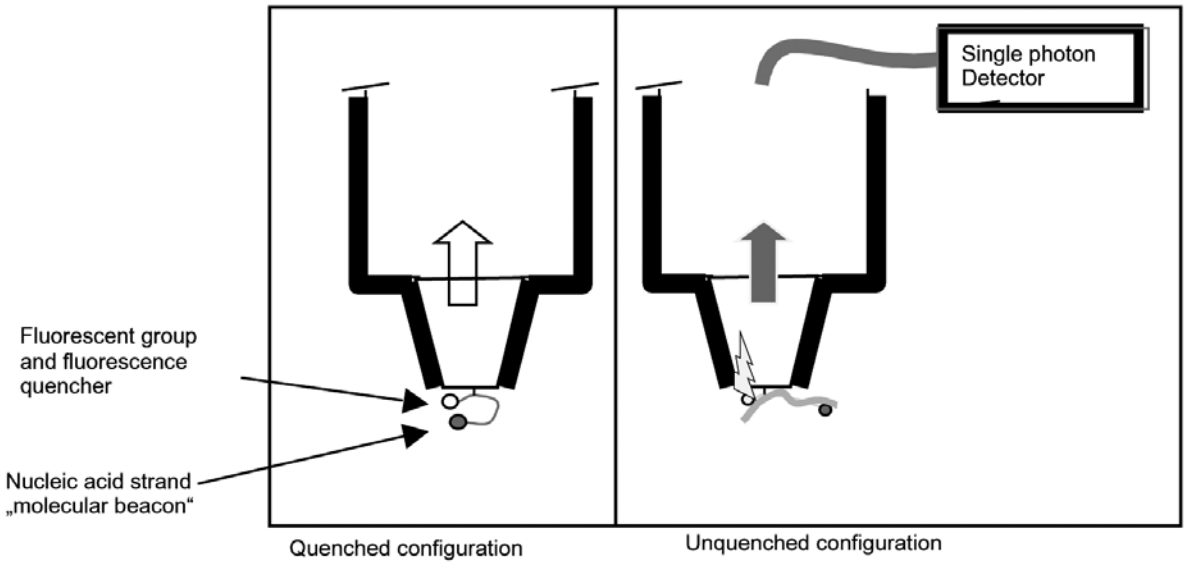

Figure 3:
Nanooptical sensor to detect single molecule nucleic acid hybridization based on mechanical 'switch fluorescence on' function using molecular beacon containing a fluorescence group and a quencher group. Nucleic acid hybridization leads to spatial separation of fluorescence group and quencher group, and thus to light emission by the fluorescence group, an event that can be measured with sensitive photodetectors. Thus, specific detection of single nucleic acids strands is feasible.

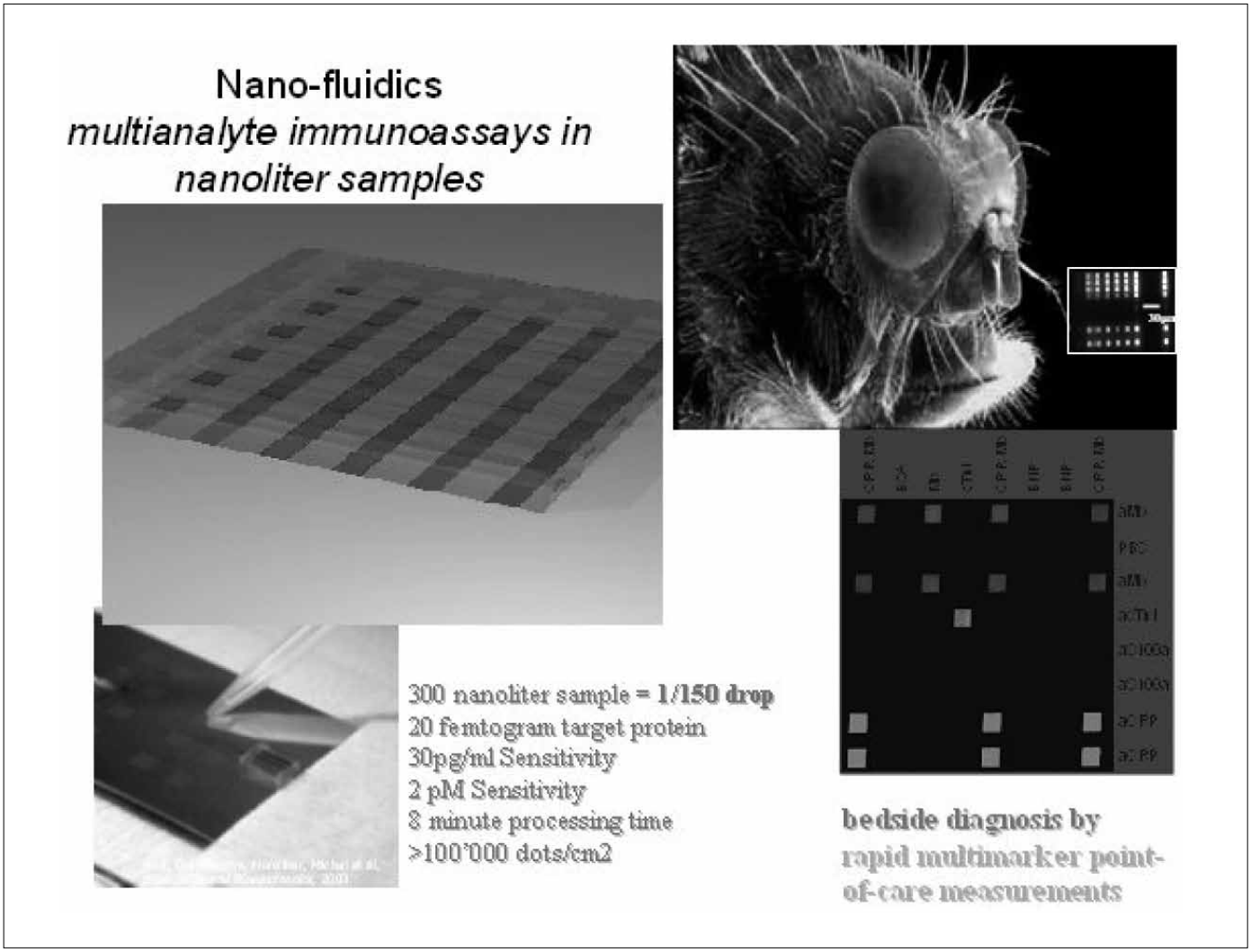

Figure 4:
Ultraminiaturization of diagnostic tests, here a sandwich immunoassay, by micro/nanofluidics technology.
Wolf, Delamarche, Hunziker, Michel, et al.

probing surfaces from nanometer – to sub-angstrom resolution allows imaging of atoms, molecules, and living cells (Figure 1) in physiological environment. Nanomechanical sensors can also be used as highly sensitive detectors of biomolecules from exhaled air or body fluids (Figure 2).

The scanning near field optical microscope: optical imaging of individual molecules with resolution far below the diffraction limit of lambda/2. An optical sensor built on the principles of single molecule detection of nucleic acids is shown in Figure 3.

The technology of micro-/nano-fluidics: handling tiny amount of fluids, e.g. for testing of biomarkers (Figure 4).

Nanomaterials comprise an important field of study: The term nanomaterials is usually used to describe man-made molecular and supramolecular structures made of inorganic and organic materials, often in combination with biomaterials. Nanomaterials include carbon structures like carbon nanotubes and fullerenes (although these have not found broad acceptance for nanomedical purposes) as well as metallic, polymeric, and hybrid materials with novel properties. Nanomaterials are sometimes used to improve properties of bulk materials (e.g. more stability at lower weight), but are particularly important to convey specific properties to surfaces and particles. Examples are super-hydrophobic, super-hydrophilic, or self-cleaning surfaces. A particularly important field is nanomaterials as targeted carriers for

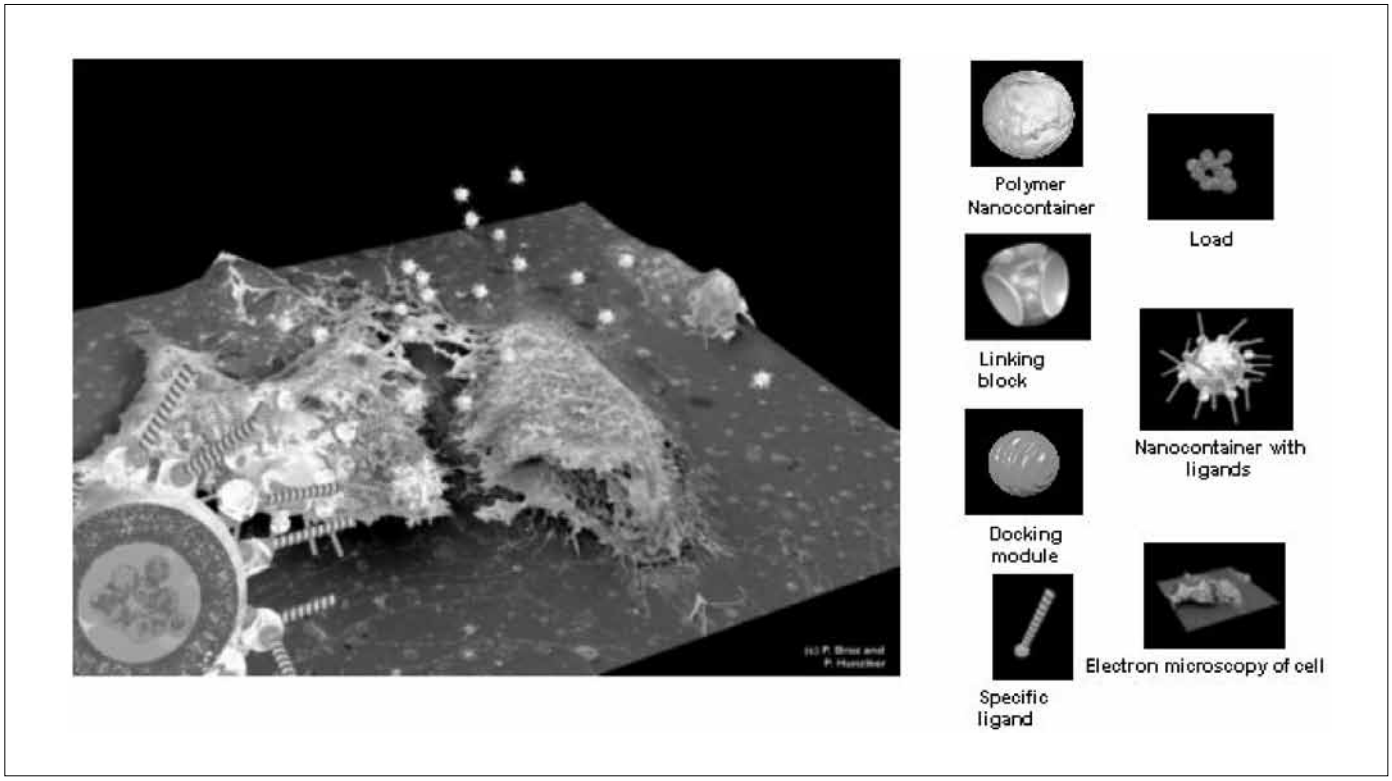

Figure 5:
Composite delivery system composed of polymeric shell filled with drug molecules and equipped with target-cell specific ligand. Targeted therapy leads to increase in drug efficacy, while avoidance of bystander cells leads to reduction of side effects.

diagnostic or therapeutic agents or a combination of both ('theragnostics'). To better understand the behaviour of matter at the nanoscale, computational nanoscience is becoming more and more important.

Last but not least, a fascinating new field is the domain of complex, man-made, nanoscale composite systems for various purposes, e.g. intelligent, responsive bioinspired materials for conditional therapeutic activity.

The Nanomedicine Research Group

The Nanomedicine Research Group is translating nanoscience technologies, tools and materials towards clinical application, in particular to those patients which present unsolved clinical problems in the Intensive Care Unit of the University Hospital Basel, the home of the group. Its group members at current are Prof. Patrick Hunziker; Xueya Wang MD, PhD (biomed); Philippe Polleux, PhD (Chemist); Alexey Morozov (Engineer); Marc Wolf, MD; Kai Tisljar, MD; Kei Mikami (Nanoscientist); Damian Clamer; PD Dr. Lukas Hunziker, MD; Evelyn Frischknecht, MD. (see also homepage: http://www.swissnano.org)

An important part of our activities is to understand, how nano-objects of increasing complexity like carriers, synthetic/biologic hybrid objects and complex nanosystems can be designed, synthesized, and utilized. There are many important questions: How do nanomaterials act on biological systems? How do biological systems handle nanomaterials? How do such supramolecular constructs differ from small drug molecules and biomolecules in terms of uptake, biodistribution, metabolism, and elimination? How about pharmacodynamics and toxicity? What are the advantages of nanocarriers compared to conventional drug therapy?

Because many nanomaterials are not commercially available in sufficiently good quality, we synthesize them in our group, collaborating with the Department of Chemistry of our university. Starting from complex poly-

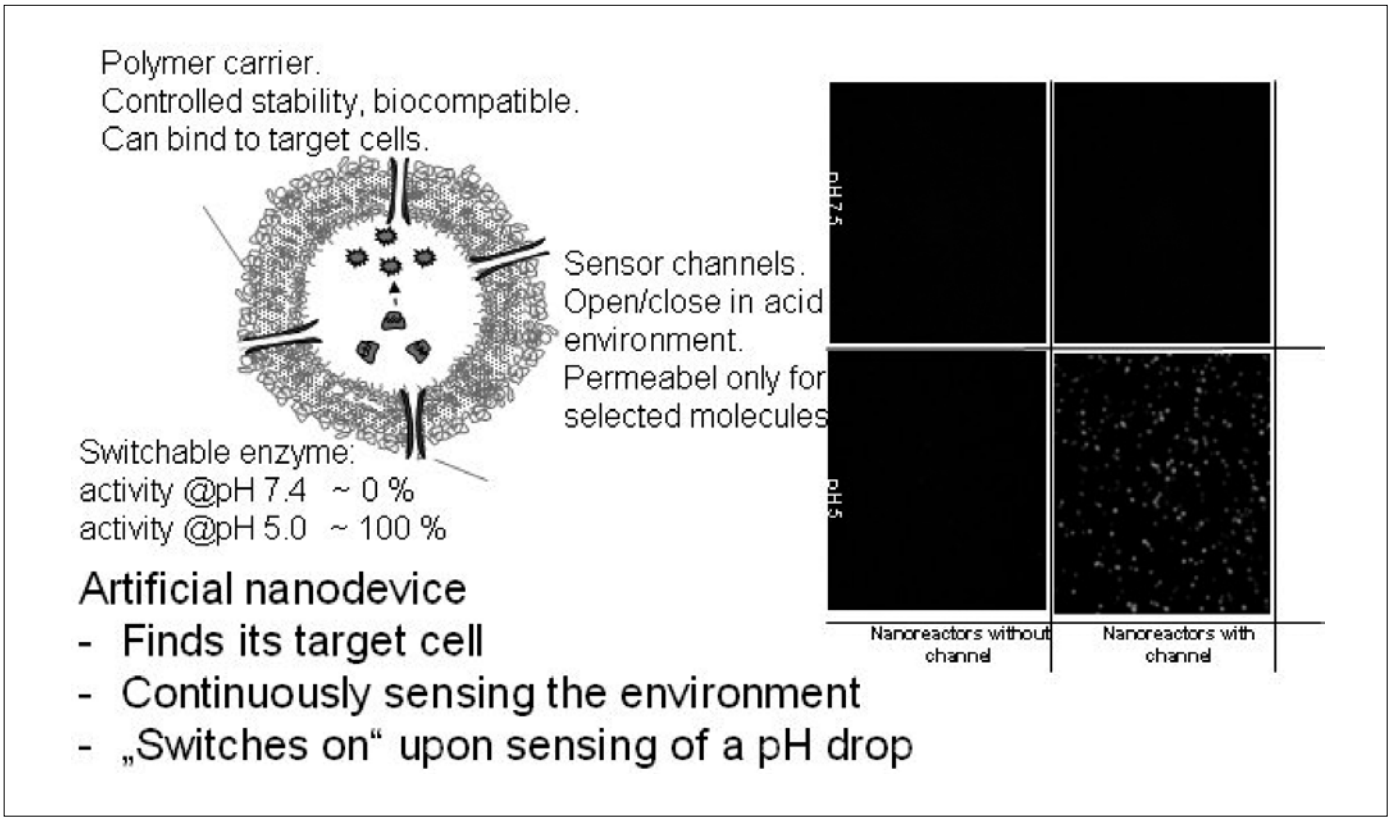

Figure 6:
Bioinspired Nanodevices: sense and respond to the environment

mers, we build polymeric vesicles of about 30–200nm diameter, which we then modify for specific purposes.

A scheme of a polymeric targeted delivery vehicle is shown in figure 5. Compared to conventional drug therapy, effects on the targeted cell are much stronger, while side effects on bystander can be suppressed. Compared to monoclonal antibodies, such systems can have a much larger payload. Compared to liposomes, better stability and excellent "stealth functionality" lead to better drug delivery.

A more complex nanosystem developed in our group is shown in figure 6: here, we have added to such a stable polymeric vesicle the complex function '*switch-on upon arrival in the target cell*', allowing target-selective biochemical activity.

Going a step further, we have developed the concept of *artificial nanoscale* organelles built as hybrid systems incorporating polymeric and biomolecules. As biological organelles typically have a specific metabolic task, incorporate an own biochemical compartment, and have a specific enzymatic equipment, we have done the same using synthetic chemistry/biology: We have built a stable polymeric shell which contains an own physicochemical 'nanoenvironment', can be equipped with desired enzymatic functionality, and can be transported (e.g. using the endocytotic pathway as 'Trojan horse') into a specific cell, where these organelles remain intact and are able to perform the desired metabolic task, either 'replacing' lost metabolic functionality or 'adding' novel functionality to this cell. Because gene transfer is not needed in certain cases (although gene transfer can be done with such systems), we believe that this approach might circumvent some concerns of gene therapy like tumour induction; because lost function could be replaced in some cases without the need for stem cell transplantation, it may offer an interesting third option to stem cell therapies in certain cases, although

a combination with the latter might be a highly interesting approach, too.

An important next step is the thorough analysis of the behaviour of nanomaterials and complex nanosystems in living cells and organisms from animals ultimately towards patients, and ongoing work in our group focuses on tailoring such complex nanosystems to a range of deadly diseases important in our intensive care unit. To this end, we apply various imaging methods from fluorescence microscopy to *in-vivo* fluorescence imaging, chemical tissue mapping using time-of-flight secondary ion mass spectroscopy (TOF-SIMS) and computer-vision-enhanced image analysis. Computational modelling of various aspects of our research on our group-owned small supercomputer (2 Teraflops) permits a deepened understanding of various events.

The European Conference for Clinical Nanomedicine
Together with the European Foundation for Clinical Nanomedicine and on behalf of the European Society for Nanomedicine, we organize the European Conference for Clinical Nanomedicine, an annual event that has attracted participants from 32 countries in 2010 and is considered a key European event in the field by the EU.

Patrick Hunziker

From left to right: Damian Clamer, Marc Wolf, Xueya Wang, Patrick Hunziker, Kei Mikami, Philippe Polleux, Kai Tisljar, Alexey Morozov.

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 July 31, 2010.

Nature nature 465, 231–235, 2010 IF 31,4

Native $GABA_B$ receptors are heteromultimers with a family of auxiliary subunits

J. Schwenk[1], M. Metz[2], G. Zolles[1], R.Turecek[2,6], T. Fritzius[2], W. Bildl[1], E. Tarusawa[4], A. Kulik[4], A. Unger[4], K. Ivankova[2], R. Seddik[2], J. Y. Tiao[2], M. Rajalu[2], J. Trojanova[6], V. Rohde[3], M. Gassmann[2], U. Schulte[1,3], B. Fakler[1,5] and B. Bettler[2]

Abstract:
$GABA_B$ receptors are the G-protein-coupled receptors for γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain. They are expressed in almost all neurons of the brain, where they regulate synaptic transmission and signal propagation by controlling the activity of voltage-gated calcium (Ca_v) and inward-rectifier potassium (K_{ir}) channels[1]. Molecular cloning revealed that functional $GABA_B$ receptors are formed by the heteromeric assembly of $GABA_{B1}$ with $GABA_{B2}$ subunits[2-5]. However, cloned $GABA_{B(1,2)}$ receptors failed to reproduce the functional diversity observed with native $GABA_B$ receptors[6-8]. Here we show by functional proteomics that $GABA_B$ receptors in the brain are high-molecular-mass complexes of $GABA_{B1}$, $GABA_{B2}$ and members of a subfamily of the KCTD (potassium channel tetramerization domain-containing) proteins. KCTD proteins 8, 12, 12b and 16 show distinct expression profiles in the brain and associate tightly with the carboxy terminus of $GABA_{B2}$ as tetramers. This co-assembly changes the properties of the $GABA_{B(1,2)}$ core receptor: the KCTD proteins increase agonist potency and markedly alter the G-protein signalling of the receptors by accelerating onset and promoting desensitization in a KCTD-subtype-specific manner. Taken together, our results establish the KCTD proteins as auxiliary subunits of $GABA_B$ receptors that determine the pharmacology and kinetics of the receptor response.

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Hepatology *Hepatology* 51, 1127–1136, 2010 IF 11.4

Cleavage of mitochondrial antiviral signaling protein in the liver of patients with chronic hepatitis C correlates with a reduced activation of the endogenous interferon system

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Abstract:
Hepatitis C virus (HCV) infection induces the endogenous interferon (IFN) system in the liver in some but not all patients with chronic hepatitis C (CHC). Patients with a pre-activated IFN system are less likely to respond to the current standard therapy with pegylated IFN-α. Mitochondrial antiviral signaling protein (MAVS) is an important adaptor molecule in a signal transduction pathway that senses viral infections and transcriptionally activates IFN-β. The HCV NS3-4A protease can cleave and thereby inactivate MAVS ***in vitro***, and, therefore, might be crucial in determining the activation status of the IFN system in the liver of infected patients. We analyzed liver biopsies from 129 patients with CHC to investigate whether MAVS is cleaved *in vivo* and whether cleavage prevents the induction of the endogenous IFN system. Cleavage of MAVS was detected in 62 of the 129 samples (48%) and was more extensive in patients with a high HCV viral load. MAVS was cleaved by all HCV genotypes (GTs), but more efficiently by GTs 2 and 3 than by GTs 1 and 4. The IFN-induced Janus kinase (Jak)-signal transducer and activator of transcription protein (STAT) pathway was less frequently activated in patients with cleaved MAVS, and there was a significant inverse correlation between cleavage of MAVS and the expression level of the IFN-stimulated genes *IFI44L*, Viperin, *IFI27*, *USP18*, and *STAT1*. We conclude that the pre-activation status of the endogenous IFN system in the liver of patients with CHC is in part regulated by cleavage of MAVS.

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Hepatology *Hepatology* 51, 741–751, 2010 IF 11,4

Hepatitis C virus-induced up-regulation of protein phosphatase 2A inhibits histone modification and DNA damage repair

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Abstract:
The molecular mechanisms underlying hepatocarcinogenesis in chronic viral hepatitis are poorly understood. A potential tumorigenic pathway could involve protein phosphatase 2A (PP2A) and protein arginine methyltransferase 1 (PRMT1), because both enzymes are dysregulated in chronic hepatitis C, and both enzymes have been involved in chromatin remodeling and DNA damage repair. We used cell lines that allow the inducible expression of hepatitis C virus proteins (UHCV57.3) and of the catalytic subunit of PP2A (UPP2A-C8) as well as Huh7.5 cells infected with recombinant cell culture-derived hepatitis C virus (HCVcc) to study epigenetic histone modifications and DNA damage repair. The induction of viral proteins, the overexpression of PP2Ac, or the infection of Huh7.5 cells with HCVcc resulted in an inhibition of histone H4 methylation/acetylation and histone H2AX phosphorylation, in a significantly changed expression of genes important for hepatocarcinogenesis, and inhibited DNA damage repair. Overexpression of PP2Ac in NIH-3T3 cells increased anchorage-independent growth. These changes were partially reversed by the treatment of cells with the methyl-group donor S-adenosyl-L-methionine (SAMe). Conclusion: Hepatitis C virus-induced overexpression of PP2Ac contributes to hepatocarcinogenesis through dysregulation of epigenetic histone modifications. The correction of defective histone modifications by S-adenosyl-L-methionine makes this drug a candidate for chemopreventive therapies in patients with chronic hepatitis C who are at risk for developing hepatocellular carcinoma.

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PNAS PNAS 107, 7251–7256, 2010 IF 9,4

Recapitulation of endochondral bone formation using human adult mesenchymal stem cells as a paradigm for developmental engineering

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Abstract:
Mesenchymal stem/stromal cells (MSC) are typically used to generate bone tissue by a process resembling intramembranous ossification, i.e., by direct osteoblastic differentiation. However, most bones develop by endochondral ossification, i.e., via remodeling of hypertrophic cartilaginous templates. To date, endochondral bone formation has not been reproduced using human, clinically compliant cell sources. Here, we aimed at engineering tissues from bone marrow-derived, adult human MSC with an intrinsic capacity to undergo endochondral ossification. By analogy to embryonic limb development, we hypothesized that successful execution of the endochondral program depends on the initial formation of hypertrophic cartilaginous templates. Human MSC, subcutaneously implanted into nude mice at various stages of chondrogenic differentiation, formed bone trabeculae only when they had developed in vitro hypertrophic tissue structures. Advanced maturation in vitro resulted in accelerated formation of larger bony tissues. The underlying morphogenetic process was structurally and molecularly similar to the temporal and spatial progression of limb bone development in embryos. In particular, Indian hedgehog signaling was activated at early stages and required for the in vitro formation of hypertrophic cartilage. Subsequent development of a bony collar in vivo was followed by vascularization, osteoclastic resorption of the cartilage template, and appearance of hematopoietic foci. This study reveals the capacity of human MSC to generate bone tissue via an endochondral program and provides a valid model to study mechanisms governing bone development. Most importantly, this process could generate advanced grafts for bone regeneration by invoking a "developmental engineering" paradigm.

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Leukemia Leukemia 24, 601–612, 2010 IF 8,6

Functional characterization of high levels of meningioma 1 as collaborating oncogene in acute leukemia

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Abstract:
Retroviral expression of leukemogenic oncogenes in the murine hematopoietic system is essential but not sufficient to induce acute leukemia. Proviral integration-mediated elevated expression of the meningioma 1 (MN1) oncogene suggested MN1 acting as cooperating event in mixed-lineage leukemia 1 (MLL) and eleven nineteen leukemia (ENL)-induced murine leukemia. Indeed, co-expression of MN1 with MLL-ENL enhanced transformation *in vivo*, and resulted in a significantly reduced latency for induction of an aggressive acute leukemia when compared with MN1 or MLL-ENL alone. In addition, co-expression of MN1 increased the granulocyte macrophage progenitor cell population with leukemia-initiating properties as shown in secondary transplantation experiments. Gene expression profiling experiments identified putative downstream MN1 targets, of which FMS-like tyrosine kinase 3 (FLT3) and CD34 were upregulated in both MN1-overexpressing murine leukemias and in pediatric acute leukemias with high MN1 levels. Interestingly, small interfering RNA (siRNA)-mediated MN1 knockdown resulted in cell cycle arrest and impaired clonogenic growth of human leukemia cell lines with high MN1 levels. Our work shows for the first time that high MN1 levels are important for the growth of leukemic cells, and that increased MN1 expression can synergize with MLL-ENL and probably other transforming fusion genes in leukemia induction through a distinct gene expression program that is able to expand the leukemia-initiating cell population.

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STEM CELLS STEM CELLS 28, 611–619, 2010 IF 7.7

High-Throughput Flow Cytometry Purification of Transduced Progenitors Expressing Defined Levels of Vascular Endothelial Growth Factor Induces Controlled Angiogenesis In Vivo

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Abstract:
Delivery of therapeutic genes by genetically modified progenitors is a powerful tool for regenerative medicine. However, many proteins remain localized within or around the expressing cell, and heterogeneous expression levels can lead to reduced efficacy or increased toxicity. For example, the matrix-binding vascular endothelial growth factor (VEGF) can induce normal, stable, and functional angiogenesis or aberrant angioma growth depending on its level of expression in the microenvironment around each producing cell, and not on its total dose. To overcome this limitation, we developed a flow cytometry-based method to rapidly purify transduced cells expressing desired levels of a therapeutic transgene. Primary mouse myoblasts were transduced with a bicistronic retrovirus expressing VEGF linked to a nonfunctional, truncated form of the syngenic molecule CD8a. By using a clonal population uniformly expressing a known VEGF level as a reference, cells producing similar VEGF amounts were rapidly sorted from the primary population on the basis of their CD8a fluorescence intensity. A single round of sorting with a suitably designed gate yielded a purified population that induced robust, normal, and stable angiogenesis, and completely avoided angioma growth, which was instead always caused by the heterogeneous parent population. This clinically applicable high-throughput technique allowed the delivery of highly controlled VEGF levels in vivo, leading to significantly improved safety without compromising efficacy. Furthermore, when applied to other suitable progenitor populations, this technique could help overcome a significant obstacle in the development of safe and efficacious vascularization strategies in the fields of regenerative medicine and tissue engineering

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American Journal of Transplantation American Journal of Transplantation 9, 2624–2630, 2009 IF 6,6

Regulatory Allospecific NK Cell Function Is Differentially Associated with HLA C Allotypes

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Abstract:
Major histocompatibility complex I (MHC I) molecules 'silence' natural killer (NK) cell activity. Conversely, NK cell activity is triggered through cells lacking expression of autologous MHC I. Unexpectedly we found that a subset of NK cells is activated rather than silenced when interacting with cells expressing normal levels of autologous MHC I. Instead of inducing an inflammatory phenotype, however, activation led to the secretion of the regulatory cytokines TGF-β and IL-10. Importantly, in vitro models of allogeneic interactions showed that targets co-expressing HLA C1 and C2 epitopes best supported, or even enhanced, this cell-contact-mediated regulatory NK cell function. Together, these data ascribe a novel pattern of reactivity to NK cells, with potential implications both in autologous and allogeneic systems.

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The Journal of Immunology | The Journal of Immunology | 184, 1235–1241, 2010 IF 6,0

Early Recycling Compartment Trafficking of CD1a Is Essential for Its Intersection and Presentation of Lipid Antigens

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Abstract:
A major step in understanding differences in the nature of Ag presentation was the realization that MHC class I samples peptides transported to the endoplasmic reticulum from the cytosol, whereas MHC class II samples peptides from lysosomes. In contrast to MHC class I and II molecules that present protein Ags, CD1 molecules present lipid Ags for recognition by specific T cells. Each of the five members of the CD1 family (CD1a–e) localizes to a distinct subcompartment of endosomes. Accordingly, it has been widely assumed that the distinct trafficking of CD1 isoforms must also have evolved to enable them to sample lipid Ags that traffic via different routes. Among the CD1 isoforms, CD1a is unusual because it does not have a tyrosine-based cytoplasmic sorting motif and uniquely localizes to the early endocytic recycling compartment. This led us to predict that CD1a might have evolved to focus on lipids that localize to early endocytic/recycling compartments. Strikingly, we found that the glycolipid Ag sulfatide also localized almost exclusively to early endocytic and recycling compartments. Consistent with colocalization of CD1a and sulfatide, wild-type CD1a molecules efficiently presented sulfatide to CD1a-restricted, sulfatide-specific T cells. In contrast, CD1a:CD1b tail chimeras, that retain the same Ag-binding capacity as CD1a but traffic based on the cytoplasmic tail of CD1b to lysosomes, failed to present sulfatide efficiently. Thus, the intracellular trafficking route of CD1a is essential for efficient presentation of lipid Ags that traffic through the early endocytic and recycling pathways.

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Molecular Therapy | Molecular Therapy | 18, 651–659, 2010 IF 5,9

Intranodal Immunization With a Vaccinia Virus Encoding Multiple Antigenic Epitopes and Costimulatory Molecules in Metastatic Melanoma

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Abstract:
Recombinant vaccinia virus (rVV) encoding tumor-associated antigens (TAAs) and adhesion or costimulatory molecules may represent important immunogenic reagents for cancer immunotherapy. Recently, intranodal (IN) antigen administration was suggested to be more immunogenic than intradermal (ID) vaccination. However, IN rVV administration has not been attempted so far. We used a rVV encoding $gp100_{280–288}$, Melan-A/$MART\text{-}1_{27–35}$ and $tyrosinase_{1–9}$ HLA-A0201 restricted epitopes and CD80 and CD86 costimulatory molecules in stage III and IV melanoma patients in a phase 1/2 trial. Of 15 patients initiating treatment, including two cycles of IN immunization, each comprising one rVV administration and three recall injections of the corresponding peptides, accompanied by subcutaneous granulocyte macrophage–colony stimulating factor supplementation, five withdrew due to progressing disease. Of 10 remaining patients seven showed evidence of induction of cytotoxic T lymphocytes (CTLs) directed against at least one epitope under investigation, as detectable by limiting dilution analysis (LDA) of specific precursors and multimer staining. Adverse reactions were mild (National Cancer Institute (NCI) grade 1–2) and mainly represented by fever, skin rashes, and pruritus. These data indicate that IN administration of rVV encoding melanoma-associated epitopes and costimulatory molecules is safe and immunogenic.

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Free Radical Biology & Medicine | FREE RADICAL BIOLOGY & MEDICINE | 48, 1182–1187, 2010 IF 5,4

Redox-mediated reciprocal regulation of SERCA and Na^+–Ca^{2+} exchanger contributes to sarcoplasmic reticulum Ca^{2+} depletion in cardiac myocytes

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Abstract:
Myocardial failure is associated with increased oxidative stress and abnormal excitation-contraction coupling characterized by depletion of sarcoplasmic reticulum (SR) Ca^{2+} stores and a reduction in Ca^{2+}-transient amplitude. Little is known about the mechanisms whereby oxidative stress affects Ca^{2+} handling and contractile function; however, reactive thiols may be involved. We used an in vitro cardiomyocyte system to test the hypothesis that short-term oxidative stress induces SR Ca^{2+} depletion via redox-mediated regulation of sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) and the sodium-Ca^{2+} exchanger (NCX) and that this is associated with thiol oxidation. Adult rat ventricular myocytes paced at 5 Hz were superfused with H_2O_2 (100 μM, 15 min). H_2O_2 caused a progressive decrease in cell shortening followed by diastolic arrest, which was associated with decreases in SR Ca^{2+} content, systolic $[Ca^{2+}](i)$, and Ca^{2+}-transient amplitude, but no change in diastolic $[Ca^{2+}]_i$. H_2O_2 caused reciprocal effects on the activities of SERCA (decreased) and NCX (increased). Pretreatment with the NCX inhibitor KB-R7943 before H_2O_2 increased diastolic $[Ca^{2+}]_i$ and mimicked the effect of SERCA inhibition with thapsigargin. These functional effects were associated with oxidative modification of thiols on both SERCA and NCX. In conclusion, redox-mediated SR Ca^{2+} depletion involves reciprocal regulation of SERCA and NCX, possibly via direct oxidative modification of both proteins. (c) 2010 Elsevier Inc. All rights reserved.

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European Journal of Immunology | European Journal of Immunology | 40, 888–898, 2010 IF 4,9

Altered expression of miR-17-5p in $CD4^+$ lymphocytes of relapsing-remitting multiple sclerosis patients

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Abstract:
MicroRNA (miRNA) are a class of post-transcriptional regulators of gene expression targeting mRNA for translational repression and/or degradation. We analyzed the expression of 365 miRNA in lymphocytes in relapsing-remitting MS patients, and show the first evidence for distinct miRNA expression profiles in $CD4^+$, $CD8^+$ and B cells in MS when compared with those in healthy volunteers. MiR-17-5p, which is involved in autoimmunity, was up-regulated in $CD4^+$ cells from MS patients. This was correlated with alterations in the expression of potential target genes of miR-17-5p, i.e. phosphatase and tensin homology and phosphatidyl-inositol-3-kinase regulatory subunit 1, which were down-regulated upon stimulation of $CD4^+$ cells with anti-CD3/CD28 in vitro. Functional experiments with a synthetic inhibitor of miR-17 supported the link between miRNA expression and the altered target gene expression. Moreover, we found distinct responses of deregulated miRNA to stimulation, i.e. miR-17-5p and miR-193a were strongly up-regulated, in contrast to the down-regulation of miR-497, miR-1 and miR-126. Other deregulated miRNA did not respond to the stimulation probably due to other, non-T-cell activation related, mechanisms in their mode of action. Our findings support the role of miRNA-dependent regulatory mechanisms in the immunopathogenesis of MS.

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Pharmacogenetics and genomics DOI: 10.1097/FPC.0b013e3283339c08, 2009 IF 4,4

A mathematical model to improve on phenotyping for molecular genetic research in malignant hyperthermia

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Abstract:

Background: The in-vitro contracture test is the standard test to diagnose malignant hyperthermia (MH) susceptibility. Maximum sensitivity is important for patient safety. For scientific purposes, the reduced specificity of contracture testing is a major drawback, and precise phenotyping is of utmost importance. Our study aimed to improve phenotyping for MH susceptibility to more accurately select patients for molecular genetic research in MH, thus, improving the probability to detect novel MH associated variants.

Methods: Patients who underwent contracture and molecular genetic testing were selected from the database of two MH investigation centres (Basel and Leipzig). The area under the curve of halothane and caffeine contracture tests was calculated and a logistic regression model was applied to determine the odds of carrying a MH associated genetic variant. This model was subsequently applied to patients without familial MH related genetic variant.

Results: Validation of the logistic regression model showed 98% concordance with molecular genetic results. Among patients with unclear in-vitro contracture test diagnosis (MH equivocal), half of the mutation carriers were classified as positive by the model, whereas 86% of those without familial mutation were classified as negative. Excluding the MH equivocal group, the model showed sensitivity of 0.99 (95% confidence interval: 0.95-0.99) and specificity 0.98 (95% confidence interval: 0.94-0.99), respectively, to identify genetically positive MH individuals.

Conclusion: Our model is a valuable tool to select patients from MH families for further molecular genetic research. This preselection increases the probability of successful molecular genetic research and is important when available resources are limited.

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European cells & materials 19, 127–135, 2010 IF 4,3

Towards an intraoperative engineering of osteogenic and vasculogenic grafts from the stromal vascular fraction of human adipose tissue

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Abstract:

Grafts generated by cultivation of progenitor cells from the stromal vascular fraction of human adipose tissue have been proven to have osteogenic and vasculogenic properties ***in vivo***. However, *in vitro* manufacture of such implants is challenged by complex, impractical and expensive processes, and requires implantation in a separate surgery. This study investigates the feasibility of an intraoperative approach to engineer cell-based bone grafts with tissue harvest, cell isolation, cell seeding onto a scaffold and subsequent implantation within a few hours. Freshly isolated adipose tissue cells from a total of 11 donors, containing variable fractions of mesenchymal and endothelial progenitors, were embedded at different densities in a fibrin hydrogel, which was wrapped around bone substitute materials based on beta-tricalcium phosphate (ChronOS®), hydroxyapatite (Engipore®), or acellular xenograft (Bio-Oss®). The resulting constructs, generated within 3 hours from biopsy harvest, were immediately implanted ectopically in nude mice and analysed after eight weeks. All explants contained blood vessels formed by human endothelial cells, functionally connected to the recipient's vasculature. Human origin cells were also found within osteoid structures, positively immunostained for bone sialoprotein and osteocalcin. However, even with the highest loaded cell densities, no frank bone tissue was detected, independently of the material used. These results provide a proof-of-principle that an intraoperative engineering of autologous cell-based vasculogenic bone substitutes is feasible, but highlight that – in the absence of *in vitro* commitment – additional cues (e.g., low dose of osteogenic factors or orthotopic environmental conditions) are likely needed to support complete osteoblastic cell differentiation and bone tissue generation.

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Clinical Immunology | Clinical IMMUNOLOGY | 136, 123–129, 2010 | IF 3,6

The production of mannan-binding lectin is dependent upon thyroid hormones regardless of the genotype: A cohort study of 95 patients with autoimmune thyroid disorders

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Abstract:
Complement mannan-binding lectin (MBL) deficiency is associated with increased susceptibility to infections and autoimmune diseases. Previous studies suggested that the production of MBL is stimulated by thyroid hormones. The aim of our study was to investigate this association in patients with autoimmune thyroid diseases (AITD). Serum levels of MBL and parameters of the thyroid function were determined in 62 patients with Hashimoto's thyroiditis, 33 with Graves' disease and 47 blood donors. Follow-up measurements were performed after 6 to 24 months. *MBL2* genotypes were determined using multiplex PCR and compared to 359 healthy Czech individuals. Serum levels of MBL tightly correlated with thyroid hormones, leading to strongly increased MBL levels in hyperthyroidism and decreased levels in hypothyroidism. With normalization of the thyroid function during follow-up, MBL levels decreased or increased respectively. The observed correlations were not due to MBL polymorphisms since the frequency of *MBL2* polymorphisms in AITD patients was not different from the general population. We conclude that AITD are not associated with MBL polymorphisms. However, the MBL production is strongly dependent on thyroid function, regardless of the genotype.

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Virology | VIROLOGY | 399, 322–331, 2010 | IF 3,5

The polyomavirus BK agnoprotein co-localizes with lipid droplets

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Abstract:
Agnoprotein encoded by human polyomavirus BK (BKV) is a late cytoplasmic protein of 66 amino acids (aa) of unknown function. Immunofluorescence microscopy revealed a fine granular and a vesicular distribution in donut-like structures. Using BKV(Dunlop)-infected or agnoprotein-transfected cells, we investigated agnoprotein co-localization with subcellular structures. We found that agnoprotein co-localizes with lipid droplets (LD) in primary human renal tubular epithelial cells as well as in other cells supporting BKV replication in vitro (UTA, Vero cells). Using agnoprotein-enhanced green fluorescent protein (EGFP) fusion constructs, we demonstrate that agnoprotein aa 20–42 are required for targeting LD, whereas aa 1–20 or aa 42–66 were not. Agnoprotein aa 22–40 are predicted to form an amphipathic helix, and mutations A25D and F39E, disrupting its hydrophobic domain, prevented LD targeting. However, changing the phosphorylation site serine-11 to alanine or aspartic acid did not alter LD co-localization. Our findings provide new clues to unravel agnoprotein function.

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European Journal of Heart Failure doi: 10.1093/eurjhf/hfq054, 2010 IF 3,4

Acute effects of urocortin 2 on cardiac function and propensity for arrhythmias in an animal model of hypertension-induced left ventricular hypertrophy and heart failure

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Abstract:

Aims:

To test acute effects of the corticotropin-releasing factor-related peptide urocortin 2 (Ucn2) on left ventricular (LV) function and the propensity for ventricular arrhythmias in the isolated heart of an animal model of hypertension-induced heart failure.

Methods and results:

Hearts from Dahl salt-sensitive rats with severe LV dysfunction were perfused according to Langendorff. Left ventricular developed pressure and the positive and negative derivatives of LV pressure were analysed before and after perfusion with Ucn2 (n = 15) or normal perfusion solution (control, n = 9). Intracellular calcium cycling parameters were assessed by surface fluorometry. Furthermore, monophasic action potential duration (MAPD) and ventricular fibrillation threshold (VFT) were determined, the latter by a train-of-pulses method at increasing voltage to scan the vulnerable period of repolarization. Urocortin 2 significantly affected intracellular calcium cycling and improved LV contractile function and relaxation. Compared with baseline values, Ucn2 significantly decreased MAPD at 30, 50, and 90% repolarization and significantly increased VFT compared with baseline values. No changes were observed in control experiments.

Conclusion:

Administration of Ucn2 rapidly improves LV function and increases VF threshold in failing, isolated rat hearts with increased propensity for ventricular arrhythmias. These observations suggest a potential use of Ucn2 as a safe and novel agent for the treatment of acute heart failure.

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Journal of Neuroimmunology Neuroimmunology 220, 114–119, 2010 IF 3,2

A highly sensitive electrochemiluminescence immunoassay for the neurofilament heavy chain protein

J. Kuhle[1], A. Regeniter[2], D. Leppert[1], M. Mehling[1], L. Kappos[1], R. L. P. Lindberg[1] and A. Petzold[3]

Abstract:

Background: The loss of neurological function is closely related to axonal damage. Neurofilament subunits are concentrated in neurons and axons and have emerged as promising biomarkers for neurodegeneration. Electrochemiluminescence (ECL) based assays are known to be of superior sensitivity and require less sample volume than conventional ELISAs.

Method: We developed an ECL based solid-phase sandwich immunoassay to measure the neurofilament heavy chain protein (NfH^{SMI35}) in CSF. We employed commercially available antibodies as previously used in a conventional ELISA (Petzold et al., 2003; Petzold and Shaw, 2007). The optimised and validated assay was applied in a reference cohort and defined patient groups.

Result: Analytical sensitivity (background plus three SD) of our assay was 2.4 pg/ml. The mean intra-assay coefficient of variation (CV) was 4.8% and the inter-assay CV 8.4%. All measured control and patient samples produced signals well above background. Patients with multiple sclerosis (MS) (median 46.2 pg/ml, n = 95), amyotrophic lateral sclerosis (ALS) (160.1 pg/ml, n = 50), mild cognitive impairment/Alzheimer's disease (MCI/AD) (65.6 pg/ml, n = 20), Guillain–Barre syndrome (GBS) (91.0 pg/ml, n = 20) or subarachnoid hemorrhage (SAH) (345.0 pg/ml, n = 20) had higher CSF NfH^{SMI35} values than the reference cohort (27.1 pg/ml, n = 73, $p < 0.0001$ for each comparison).

Conclusions: The new ECL based assay for NfH^{SMI35} in CSF is superior in terms of sensitivity, precision and accuracy to previously published methods (Petzold et al., 2003; Shaw et al., 2005; Teunissen et al., 2009). The improved performance and small sample volume requirement qualify this method in experimental settings and clinical trials designed to perform a number of tests on limited amounts of material.

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Obesity Surgery OBESITY SURGERY 20, 84–92, 2010 IF 2,9

Mitochondrial DNA Content in Human Omental Adipose Tissue

A. Lindinger[1], R. Peterli[1], T. Peters[2], B. Kern[1], M. von Flüe[1], M. Calame[3], M. Hoch[3], A. N. Eberle[3] and P. W. Lindinger[3]

Abstract:
Background: Impairment of mitochondrial function plays an important role in obesity and the development of insulin resistance. The aim of this project was to investigate the mitochondrial DNA copy number in human omental adipose tissue with respect to obesity.

Methods: The mitochondrial DNA (mtDNA) content per single adipocyte derived from abdominal omental adipose tissue was determined by quantitative RT-PCR in a group of 75 patients, consisting of obese and morbidly obese subjects, as well as non-obese controls. Additionally, basal metabolic rate and fat oxidation rate were recorded and expressed as total values or per kilogram fat mass.

Results: MtDNA content is associated with obesity. Higher body mass index (BMI) resulted in a significantly elevated mtDNA count (ratio = 1.56; $p = 0.0331$) comparing non-obese (BMI < 30) to obese volunteers (BMI ≥ 30). The mtDNA count per cell was not correlated with age or gender. Diabetic patients showed a trend toward reduced mtDNA content. A seasonal change in mtDNA copy number could not be identified. In addition, a substudy investigating the basal metabolic rate and the fasting fat oxidation did not reveal any associations to the mtDNA count.

Conclusions: The mtDNA content per cell of omental adipose tissue did not correlate with various clinical parameters but tended to be reduced in patients with diabetes, which may partly explain the impairment of mitochondrial function observed in insulin resistance. Furthermore, the mtDNA content was significantly increased in patients suffering from obesity (BMI above 30). This might reflect a compensatory response to the development of obesity, which is associated with impairment of mitochondrial function.

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Journal of Biomedical Materials Research Part A 92A, 1461–1467, 2009 IF 2,7

Effect of bone sialoprotein coating of ceramic and synthetic polymer materials on *in vitro* osteogenic cell differentiation and *in vivo* bone formation

S. Schaeren, C. Jaquiéry, F. Wolf, A. Papadimitropoulos, A. Barbero, E. Schultz-Thater, M. Heberer and I. Martin

Abstract:
In this study, we addressed whether Bone Sialoprotein (BSP) coating of various substrates could enhance the *in vitro* osteogenic differentiation and *in vivo* bone formation capacity of human Bone Marrow Stromal Cells (BMSC). Moreover, we tested whether synthetic polymer-based porous scaffolds, despite the absence of a mineral component, could support ectopic bone formation by human BMSC if coated with BSP. Adsorption of recombinant human BSP on tissue culture-treated polystyrene (TCTP), β-tricalcium phosphate (Osteologic™) or synthetic polymer (Polyactive™) substrates was dose dependent, but did not consistently accelerate or enhance *in vitro* BMSC osteogenic differentiation, as assessed by the mRNA expression of osteoblast-related genes. Similarly, BSP coating of porous β-tricalcium phosphate scaffolds (Skelite™) did not improve the efficiency of bone tissue formation following loading with BMSC and ectopic implantation in nude mice. Finally, Polyactive™ foams seeded with BMSC did not form bone tissue in the same ectopic assay, even if coated with BSP. We conclude that BSP coating of a variety of substrates is not directly associated with an enhancement of osteoprogenitor cell differentiation *in vitro* or *in vivo*, and that presentation of BSP on polymeric materials is not sufficient to prime BMSC functional osteoblastic differentiation in vivo

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Genesis genesis The Journal of Genetics and Development 47, 595–602, 2009 IF 2,2

A mouse model for visualization of $GABA_B$ receptors

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Abstract:

$GABA_B$ receptors are the G-protein-coupled receptors for the neurotransmitter γ-aminobutyric acid (GABA). Receptor subtypes are based on the subunit isoforms $GABA_{B1a}$ and $GABA_{B1b}$, which combine with $GABA_{B2}$ subunits to form heteromeric receptors. Here, we used a modified bacterial artificial chromosome (BAC) containing the *$GABA_{B1}$* gene to generate transgenic mice expressing $GABA_{B1a}$ and $GABA_{B1b}$ subunits fused to the enhanced green fluorescence protein (eGFP). We demonstrate that the $GABA_{B1}$-eGFP fusion proteins reproduce the cellular expression patterns of endogenous $GABA_{B1}$ proteins in the brain and in peripheral tissue. Crossing the *$GABA_{B1}$-eGFP* BAC transgene into the *$GABA_{B1}^{-/-}$* background restores pre and postsynaptic $GABA_B$ functions, showing that the $GABA_{B1}$-eGFP fusion proteins substitute for the lack of endogenous $GABA_{B1}$ proteins. Finally, we demonstrate that the $GABA_{B1}$-eGFP fusion proteins replicate the temporal expression patterns of native GABAB receptors in cultured neurons. These transgenic mice therefore provide a validated tool for direct visualization of native $GABA_B$ receptors.

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Fundamental & Clinical Pharmacology Fundamental & Clinical Pharmacology 23, 567–572, 2009 IF 2,1

Human internal thoracic arteries from diabetic patients are resistant to endothelial dysfunction

M. T. R. Grapow[1,2], D. C. Reineke[3], T. Kern[4], E. Müller-Schweinitzer[1,2], T. Carrel[3], and F. S. Eckstein[1,2]

Abstract:

The aim of this analysis was to compare vasoreactive properties of internal thoracic arteries (ITA) grafts from diabetic (DM) to those of non-diabetic (ND) patients. Ring segments of ITA, taken from patients undergoing coronary artery bypass grafting, were suspended in organ bath chambers filled with modified Krebs-Henseleit solution and contractile responses to potassium chloride (KCl), noradrenaline (NA), endothelin-1 (ET-l), and endothelium-dependent relaxant responses to acetylcholine (ACH) were recorded isometrically. The receptor-mediated agonists NA and ET-1 stimulated ITA from both groups within similar concentration ranges while ITA from DM patients proved to be significantly more sensitive to KCl than ITA from ND. Furthermore, maximal contractile responses indicated that KCl (3.79 ± 0.30 g, $n = 7$ in DM and 2.50 ± 0.23 g, $n = 29$ in ND, $P < 0.05$) evoked significantly higher responses in ITA from DM as compared to the ND control group while both NA and ET-l stimulated ITA from both groups with similar efficacies. Endothelium-dependent relaxant responses to ACH proved to be similar in both groups when expressed as percentages of the pre-existing tone. The present data support the contention that in comparison to ND controls arteries from DM patients are more sensitive to depolarization but endothelial dysfunction is less frequent in human ITA than expected from observations in systemic vascular beds.

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European Journal of Dermatology EJD EUROPEAN JOURNAL OF DERMATOLOGY 20, 246–247, 2010 IF 2,0

Precalcaneal congenital fibrolipomatous hamartomas: is there a pathogenetic relationship with Gardner Syndrome?

P. H. Itin[1], K. Heinimann[2], M. Attenhofer[2], N. Boesch[2], R. De Lorenzo[1], S. Trüb[1], and B. Burger[3]

Abstract:

Precalcaneal congenital fibrolipomatous hamartoma (PCFH) was first described in 1977 by Elsahy and Lorimer, who termed them congenital fibrolipomata [1]. In 1990, the same condition was described in a series of 4 cases [2]. PCFH are clinically characterized by the presence of unilateral or bilateral, symmetric papulous lesions in the medial precalcaneal plantar region of the heel. Because of their distinctive shape and location, diagnosis is usually made clinically. In most cases the lesions appear within the first few months of life but they can be present at birth. The aetiology of PCFH is unknown. Histological examination of lesions shows mature adipose tissue enveloped in predominantly collagenous fibrous sheaths. The differential diagnosis of PCFH, recently discussed in detail [3], includes numerous entities, e.g. juvenile plantar fibromatosis and calcified nodules. However, all of these differ markedly from PCFH, with respect to clinical features.

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PLOS one PLoS one 5, e10122, 1–10, 2010 IF N,A

Dysferlin Interacts with Tubulin and Microtubules in Mouse Skeletal Muscle

B. A. Azakir[1], S. Di Fulvio[1], C. Therrien[1] and M. Sinnreich[1,2]

Abstract:
Dysferlin is a type II transmembrane protein implicated in surface membrane repair in muscle. Mutations in dysferlin lead to limb girdle muscular dystrophy 2B, Miyoshi Myopathy and distal anterior compartment myopathy. Dysferlin's mode of action is not well understood and only a few protein binding partners have thus far been identified. Using affinity purification followed by liquid chromatography/mass spectrometry, we identified alpha-tubulin as a novel binding partner for dysferlin. The association between dysferlin and alpha-tubulin, as well as between dysferlin and microtubules, was confirmed in vitro by glutathione S-transferase pulldown and microtubule binding assays. These interactions were confirmed in vivo by co-immunoprecipitation. Confocal microscopy revealed that dysferlin and alpha-tubulin co-localized in the perinuclear region and in vesicular structures in myoblasts, and along thin longitudinal structures reminiscent of microtubules in myotubes. We mapped dysferlin's alpha-tubulin-binding region to its C2A and C2B domains. Modulation of calcium levels did not affect dysferlin binding to alpha-tubulin, suggesting that this interaction is calcium-independent. Our studies identified a new binding partner for dysferlin and suggest a role for microtubules in dysferlin trafficking to the sarcolemma.

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[2] Neuromuscular Center, Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland

Schwebende von Hans Geissberger

Hans Geissberger, 1921–1999, Bronzeplastik von 1964

Standort:

St. Alban Anlage, im Park beim St. Alban-Tor

Dissertationen

Seit Anfang März 2010 darf sich Alexandre Goncalves von der Forschungsgruppe Developmental Genetics (Institut für Anatomie) Herr Dr. nennen. Er befasste sich in seiner Dissertation mit dem Thema: „Epithelial-mesenchymal feedback signalling during vertebrate organogenesis: Genetic analysis of BMP-Gremlin1 Antagonistic Interactions".

Am 3. März 2010 hat Nermin Raafat von der Forschungsgruppe Oncology Surgery (Departement Biomedizin USB) ihre Dissertation erfolgreich abgeschlossen. Der Titel ihrer Doktorarbeit hiess: „VACCINIA VIRUS EXPRESSING ICP47: A NOVEL PLATFORM FOR CANCER VACCINES HIGHLIGHTING TUMOR EPITOPES AND HIDING VIRAL ANTIGENS ".

Mit der Doktorprüfung am 11. März 2010 schloss Marco Cavallari von der Forschungsgruppe Exp. Immunology (Departement Biomedizin USB) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: „Antigen-presentation of non-peptidic antigens lipid trafficking and loading".

Im März 2010 war es auch für Jan Tchorz von der Forschungsgruppe Synaptic Plasticity (Institut für Physiologie) soweit, er beendete mit Erfolg seine Doktorandenzeit, in der er sich mit „Notch2 signalling in development and cancer" auseinandergesetzt hatte.

Am 7. Mai 2010 stellte sich Daniel Vonwil von der Forschungsgruppe Tissue Engineering (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Doktorarbeit lautete: „Chondro Progenitor Cell Response to Specifically Modified Substrate Interfaces".

Auszeichnungen

Neue Argovia-Professur der Universität Basel am Kantonsspital Aarau
Beat Müller, Bereichsleiter Medizin, Chefarzt für innere Medizin und Endokrinologie am Kantonsspital Aarau, wurde im April 2010 vom Universitätsrat zum Ordinarius an der Universität Basel gewählt. Beat Müller wird weiterhin am Kantonsspital Aarau tätig sein.

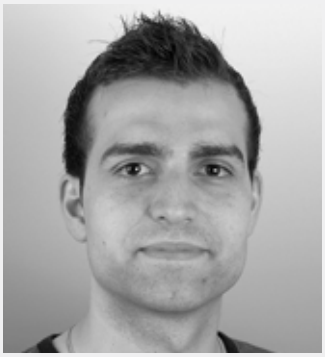
Venia docendi an Beat Kaufmann
Beat Kaufmann von der Forschungsgruppe Cardiovascular Molecular Imaging (Departement Biomedizin USB) hat von der Regenz in ihrer Sitzung am 26. Mai 2010 die Venia docendi für Kardiologie erhalten und darf damit den Titel eines Privatdozenten führen.

Amtszeit von Alex N. Eberle verlängert
Der Universitätsrat hat im März 2010 die von der Regenz beschlossene Verlängerung des Vizerektorats von Alex N. Eberle um zwei Jahre (von 2011 bis 2013) genehmigt. Alex N. Eberle ist seit 2009 Vizerektor Entwicklung mit den Kernaufgaben Qualitätsentwicklung und Evaluation.

Herzliche Gratulation!

DEPARTEMENT BIOMEDIZIN USB

Sabrina Di Fulvio
Neuromuscular Research



Philippe Megel
Hepatology

Hedwig Niederer
Clinical Immunology

Iris Spörri
Dermatology

Nina Khanna
Infection Biology

Patrizia Hägler
Clinical Pharmacology

Niklaus Vogt
Informatics

INSTITUT FÜR PHYSIOLOGIE

M. M. Tome Montesinos
Synaptic Plasticity

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Christel Widia-Lübcke
Molecular Diagnostics

Zeliha Özkan
Molecular Diagnostics

Interne Wechsel:

DEPARTEMENT BIOMEDIZIN USB

Anne-Sophie Benischke,
Ocular Pharmacology and Physiology
Mathias Schmaler,
Immunoregulation

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN USB

Andrea Kaiser,
Ocular Pharmacology and Physiology
Fabronia Murad,
Ocular Pharmacology and Physiology
Daniele Riva, Immunoregulation

Marc Schneider, Animal Facility
Sucharita Geiger, Metabolism

INSTITUT FÜR BIOCHEMIE UND GENETIK

Claudia Krawczyk, Molecular Genetics
Alain Weber, Molecular Genetics

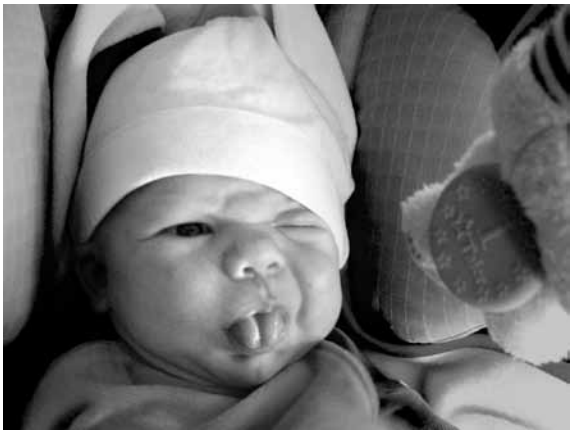
INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Thi Thu Ha Pharm Blume,
Molecular Diagnostics

Congratulations

Das DBM gratuliert ganz herzlich!

Léa Cardoso de Matos-Gatti
Geboren am 31.3.2010



Santiago Harfst (Naeher)
Geboren am 23.3.2010

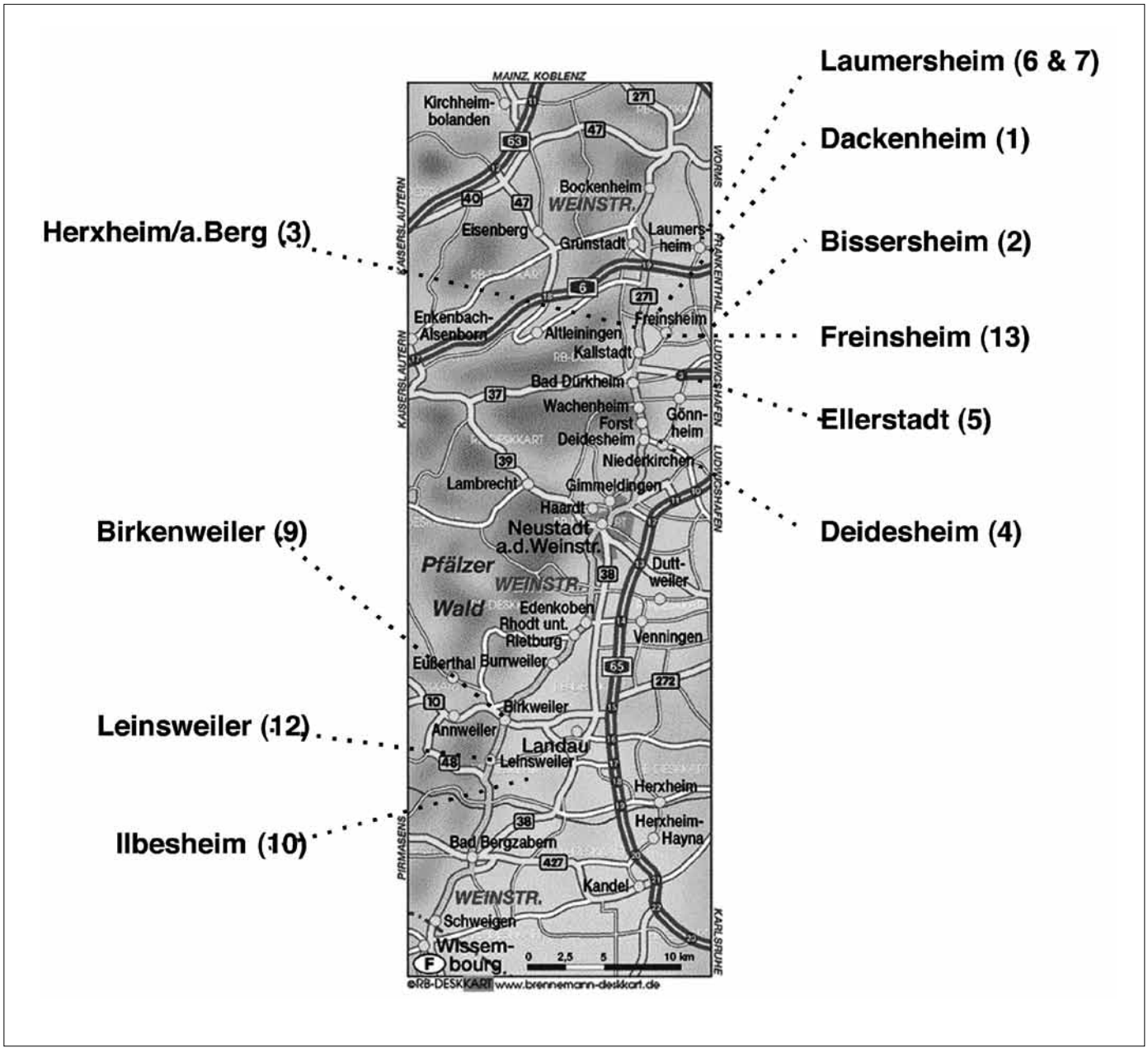
Sophie Girard-Rossi
Geboren am 4.5.2010

Herzlich willkommen, allerseits!

A wine trip to the Pfalz!

Yes, I like wine! Wine is my (second) passion. Actually, I think that wine is more than drinking; similar to science, wine has a lot to do with being curious and willing to discover new things. And most importantly my interest in wine turned out to be a key to meeting interesting people that share one important thing: to enjoy life. It all started over two decades ago when Marcus and I explored the wine-growing region around Alba in Piemont in Northern Italy to learn more about famous wines like Barolo or Barbaresco. Actually at that time, we spent most of our vacations in the vineyards and cellars, and since then I was infected with a virus called "wine". From then on, wherever we were living or traveling, visiting the local wine makers became a must. But as there were no wine makers around Boston, I regularly met in a little circle of interested people to taste wines from all around the world. It was actually at that time when I first came in contact with German wine. George, our "teacher" (actually a manager from one of the biggest wine stores in the Boston area), was a big fan of German Riesling that is most probably the most famous white wine grown in many German regions from the Rhine, Mosel, Ahr to the Pfalz.

Although living close to the border for years, it took over 20 years for my first wine trip to Germany. My



friends Marcus and Peter proposed to visit the "Pfalz", a region that they have visited several times before. The Pfalz is a region in southwest Germany; it is, if you like, the northern continuation from the Alsace in France, so somewhat north of Strasbourg and west of Heidelberg and Mannheim. People say that this is one of the warmest regions in Germany with over 1800 hours of sunshine a year where people can grow fruits like peaches, almonds or even lemons but most of all they grow wine on over 20'000 hectares, which makes the Pfalz the second largest wine region of Germany. Topography (relatively flat in the north, and hillsides in the south) and the endless variety of the soil compositions allows the winemakers to grow not only Riesling but a large number of different grapes for white (Pinot Blanc, Chardonnay, Gewürztraminer, Muskateller, Rieslaner, Scheurebe) and red wine (Pinot Noir, Dornfelder, Portugieser, St. Laurent, Syrah, Tempranillo, Merlot, Cabernet, and many more) which makes the Pfalz an Eldorado for any curious wine freak.

It seemed that the weather god did not agree with our going on a wine trip as it was raining cats and dogs and not even 10°C when we headed North on Thursday May 6. From Basel we followed the A5 highway to Baden-Baden then crossing the Rhine to France and following

the highway (A35) to Wissenbourg (which is located at the Southern tip of the Pfalz), then following the A65 north. After about 4 hours we reached the small village of Dackenheim about 10 miles south of Grünstadt in the northern part of the Pfalz. Marcus made some reservation for a vacation home that turned out to be the perfect base for our visits to the winemakers for the upcoming two days. We actually stayed at the "LANDHAUS TAEFFNER" a townhouse built in 1587 and carefully renovated by the Taeffner family. In this three-floor building located on a side street in the center of the village, we found 3 nicely furnished bedrooms, 2 bathrooms and a well-equipped kitchen **(1)**. Being late, we were looking for an easy going spot to have dinner and Mr. Taeffner suggested to visit the "Vinothek" of the MUSSLER winery located in Bissersheim about 5 miles from Dackenheim. The "Vinothek" turned out to be more a modern Tuscan-style farmhouse with a restaurant that serves simple but tasty dishes that join their own wines **(2)**. We enjoyed a bottle of fresh and crisp Riesling and made some plans for the upcoming day that should start rather early.

Indeed by close to 10am we were standing in front of the WEINGUT PETRI located in Herxheim am Berg only a short ride away from Dackenheim **(3)**. The owner Mr. Petri knew my friends from former visits and he immediately suggested tasting his wines, especially comparing the Rieslings from 2008 and the most recent 2009 vintage. It was indeed interesting to learn how different these years were. Actually, all 2008 wines that we tasted during our trip were fresh, crisp with a fragile mostly lemony fruit and mineral flavors with an impressive acidity; in contrast the wines from 2009 were richer, very fruity reminiscent to yellow fruits peaches, pears or even banana still with a good but lower acidity. It was actually not easy to choose from the vast list comprising over 40 different wines, but I found that the Riesling "Herxheimer Honigsack" Spätlese 2009 would be a rather good choice. Actually, the Weingut Petri offers generally rather good quality wine for a good price. After chatting and tasting (which here clearly means spitting not swallowing) with Mr. Petri about two hours we were heading south to the REICHSRAT VON BUHL estate located in Deidesheim, a village that is famous for its Riesling vineyards **(4)**. The Von Buhl estate has been a family-owned business for over 150 years and has ranked among the most prestigious estates in Germany ever since well known for their Riesling wines. Since the 2008 vintage, the estate has been involved in an official procedure to obtain certification for organic cultivation. Guided by brilliant comments by Mr. Küsters we tasted almost the entire selection of Riesling wine the estate currently offers. On top of their quality pyramid are a few grand crus (here called "Grosses Gewächs") from single low-yield (around 20hl/ha) vineyards located in Deidesheim ("Paradiesgarten"), Ruppertsberg ("Reiterpfad") or Forst ("Pechstein", "Ungeheuer", "Kirchenstück"). The "Riesling Reiterpfad Ruppertsberg 2008" characterized by deep fruit aromas blended with a balanced mineral character and a good acidity especially pleased my palate. Wines with the label "Grosse Gewächse" (we called them "GGs") are rather expensive wines but you get something special that will keep for years. After this highlight we headed back North to visit the estate of MARKUS SCHNEIDER **(5)**. In no time this winery became famous for its red wines made from old low-yield Portugieser vineyards bottled with modern labels as "Rotwein Alte Reben" or "Einzel-

stueck" or blended with Cabernet, Merlot or St. Laurent sold under names like "Tohuwabohu", "Einzelstueck" or "Black Print". The commercial success of Markus Schneider is reflected by the brand-new estate (it looks like a grey rock) located outside Ellerstadt. Although we had some very good wine from Schneider in the past, we were rather disappointed by the current selection. Surprisingly, all three of us thought that all red wines seemed to have some "green" flavors reminiscent of branches and leaves. Or was our palate tired from tasting all these Rieslings? We were not sure when we headed north to visit the PHILLIP KUHN winery in Laumersheim **(6)**. The winery produces wine from 20ha vineyards (50% white/50% reds) and is headed by Phillip Kuhn who produced his first wine in 1992. I selectively tasted only Pinot Noir (here called "Spätburgunder") and I was deeply impressed by the perfect vinification resulting in wines with complexity, deep fruit, mineral tones and well-integrated wood flavors and silky tannins. It seemed that our palates were still working very well and we were able to distinguish excellence from mediocracy. I immediately fell in love with the "Spätburgunder Steinbuckel 2007" (also a "GG"). I was deeply convinced that this wine would be a challenge for any high-rated Burgundies when presented in any blind tasting! As Pinot Noir is my favorite red grape, I am pretty sure I will visit this winery again in the (near) future. The small village of Laumersheim actually also hosts a second well-known winemaker the estate from Volker and Werner KNIPSER **(7)**. We were not the only guests that aimed to taste the Knipser wines, and the small tasting room became more and more crowded while tasting almost the entire selection of red wines. Knipser wines are of excellent quality throughout. They seem to need time to develop, as we tasted an excellent "Spätburgunder Grosskarlbacher Burgweg" from 2004. We also tasted three "GG" Pinot Noirs remembering the "Kirschgarten Spätburgunder, 2006". Surprisingly, I was not so impressed by the elsewhere highly acclaimed "Cuvee X" a blend from Cabernet and Merlot that seems the Pfälzer equivalent to a St. Emillion from Bordeaux. After this "tasting marathon" we drove back to Herxheim am Berg to wrap up this rather busy day in the restaurant of the Petri family (here called "Gutsausschank") where we enjoyed regional typical dishes from the Pfalz.

We decided to spend the second day in the Southern part of the Pfalz to visit a group of five young winemakers that present themselves as the "Südpfalz ConneX-

ion" **(8)**. While driving south the weather was constantly improving and we even enjoyed the first hours of sunshine that nicely illuminated this area characterized by small villages surrounded by hills hosting the vineyards. We first stopped in Birkweiler at the WEINGUT SIENER **(9)**. While tasting the Rieslings (served by the mother of Peter Siener) it became rapidly clear that this young winemaker tries to produce wine that are clearly characterized by the soil were the grapes are grown (some people call this also "terroir"). The wines are labeled as "Vom Rotliegenden","Vom Kalkmergel" or "Vom Buntstandstein" indicating the different types of soil the grapes were cultivate. And believe it or not, but you can taste the difference in the glass! Generally the wines are dominated by mineral tones (that I like) and also characterized by a rather high acidity. Siener also produces red wine of which I remember two of them: "Spätburgunder NO. 1, 2008"; an easy drinking Pinot Noir characterized by a wonderful charming fruit; and the "Spätburgunder Birkenweiler Kastanienbusch Buntsandstein, 2007" a wine of more complexity and deepness that will need still some time to fully develop. We then followed the "Südpfälzer Weinstrasse" to reach the village of Ilbesheim where we headed to the winery of the KRANZ family **(10)**. Here we had the opportunity to taste a large selection of white and red wines commented by Kerstin Kranz the wife of the winemaker Boris Kranz in newly installed tasting room. Mrs. Kranz told us that although not yet commercialized, she wanted to serve us each wine from the 2008 and the 2009 (whenever possible) in comparison. From this interesting rally, I remember well the "Riesling Kalmit 2008" as well as the "Spätburgunder Kalmit 2007". The first was presenting with a wonderful nose of yellow fruits and mineral notes carried with good acidity, the latter was a luscious Pinot Noir with wonderful fruit and well-integrated wood flavors. From the top floor of the Kranz winery you can actually see the "Kleine Kalmit" the highest hill in the Rhine valley and well known for his southwestern exposed vineyards (where Kranz has his finest vineyards). After this extensive tasting we needed to "recover" enjoying a dish of "Pfälzer Spargel" (asparagus) sitting on a terrace of a restaurant in Ilbesheim. As our transport capacity for more wine began to reach critical limits, we decided to visit only one additional winery on this trip. The choice

was not easy as the region of the Southern Pfalz is the home of some well-known estates producing high-quality wines like Friedrich Becker in Schweigen, Weingut Dr. Wehrmann in Birkenweiler or Weingut Oekonomierat Rebholz in Siebeldingen **(11)**. On our way back we passed the village of Leinsweiler where the Weingut SIEGRIST is located **(12)**. Entering the village we followed the little arrow signs that brought us to a narrow one-way street with a black Labrador dog sitting in the middle of the road in front of the winery buildings. As the dog seemed not to be disturbed by the car we curved the car around him to the parking lot. The winemaker of the estate Bruno Schimpf welcomed us. On our way to the tasting room he explained that, by sitting in the middle of the road, his black Labrador (named Arthur) tries to keep the street a quiet and safe playground for his children. The Siegrist estate produces wine from about 15 hectares of (as usual in the Pfalz) a large variety of grapes including Riesling, Pinot Noir, Pinot Blanc, Chardonnay, and others. We tasted a nice selection covering almost all his Rieslings starting from the Kabinett Trocken to the Riesling from the Sonnenberg also a so-called "Grosses Gewächs". We had again the chance to compare the 2008 and 2009 vintages for most of the wines. I remember very well the Riesling "Eigensinn" being very complex with deep fruit and mineral notes covered by a good acidity. The 2009 that was not yet commercialized will be a fantastic wine for its price. To convince us how his wines are able to mature over time, Mr. Schimpf also opened a bottle of the Riesling Sonnenberg 2004 (GG): this wine developed wonderful notes of

exotic fruits with a rather smooth tip of acidity. Of course we could not resist to also tasting some reds. I especially remember the "Frühburgunder Trocken 2007" as well as the Pinot Noir** and Pinot Noir***. All these wines are very clean, with a bright fruit, some minerality and perfectly balanced touches of the oak barrels used. Mr. Schimpf explained to us that the Frühburgunder grapes (which is kind of an earlier maturing grape developed from a mutation of the Spätburgunder) are especially beloved by the wild boars that pass his vineyards from the forest located just behind the winery. We passed a wonderful afternoon at the Siegrist estate full of passion for wine. We spent our last evening in the Pfalz by visiting Freinsheim a nice village with some very old buildings close to our "Landhaus" with some very old buildings **(13)**. We enjoyed some typical Pfälzer dishes at the "Weinstube an der Bach" drinking a good bottle from a local winery called RINGS.... to maybe be visited next year. During these two days we visited 8 wineries and had the opportunity to taste many good and even some outstanding wines. Nice and friendly people always welcomed us. As there are close to 1600 different winemakers listed in that region it is highly likely that we will go back to the Pfalz for new discoveries **(14)**.

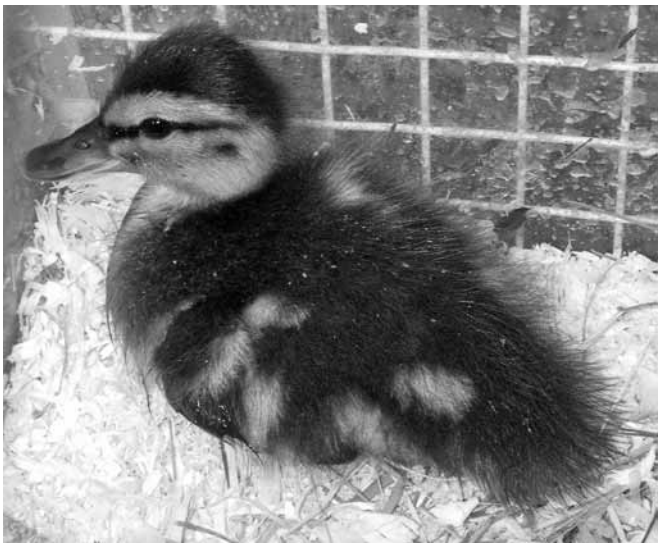
Jürg Schwaller

Useful links for a wine trip to the Pfalz:

1. **www.landhaus-taeffner.de**
2. **www.weingut-mussler.de/vinothek-mussler.html**
3. **www.weingut-petri.de/**
4. **http://reichsrat-von-buhl.de/english**
5. **www.black-print.net/**
6. **www.weingut-philipp-kuhn.de/**
7. **www.weingut-knipser.de/**
8. **www.suedpfalz-connexion.de/**
9. **www.weingutsiener.de/**
10. **www.weingut-kranz.de/**
11. **www.fuenf-winzer.de**
12. **www.weingut-siegrist.de/**
13. **www.freinsheim.de/**
14. **www.pfalz.de/de/winzersuche**

Auf den Spuren von Konrad Lorenz oder wie aus einer Ente 17 wurden

Es war ein Tag im April 2009, als Frances Kern mir erzählte, dass eine Ente im Lichthof zwischen Pharmazentrum und Kragenbau Junge zur Welt brachte. Natürlich mussten wir die alle sehen und gingen Gianni Morson besuchen, der nach der Familie schaut. Zwischen den Farnen schienen die Kleinen gut geschützt zu sein, aber da hatten wir uns getäuscht. Krähen hatten dieses potentielle Futter entdeckt und gingen im Sturzflug auf die Jungen los. Auf dieser Flucht hatte sich eines der Kücken verletzt und konnte nicht mehr schnell laufen. Da es nun nicht mehr wegrennen konnte, fragte Gianni uns, was wir da machen könnten. Da meine Tochter, eine angehende Tierärztin, auch gerade im Labor auf Besuch war, schlugen wir vor, dieses Kücken nach Hause zu nehmen und es aufzuziehen. Gianni fing es ein und wir sahen, dass das rechte Bein schlaff war. Ob nun das Bein gebrochen oder der Muskel gequetscht war, konnten wir nicht bestimmen, aber wir nahmen es zu mir nach Hause.



Agathes neues Zuhause (19.4.09)

Dort angekommen, wurde ein Katzentransportkäfig in ein erstes Zuhause für Agathe, wie wir die kleine Ente tauften, umfunktioniert. Wir legten eine Plastikkiste mit Hobelspänen aus, stellten ein Schälchen mit Wasser hinein, platzieren Futter und installierten eine Wärmelampe. So hatte das Kleine warm und war vor meinen Katzen sicher.

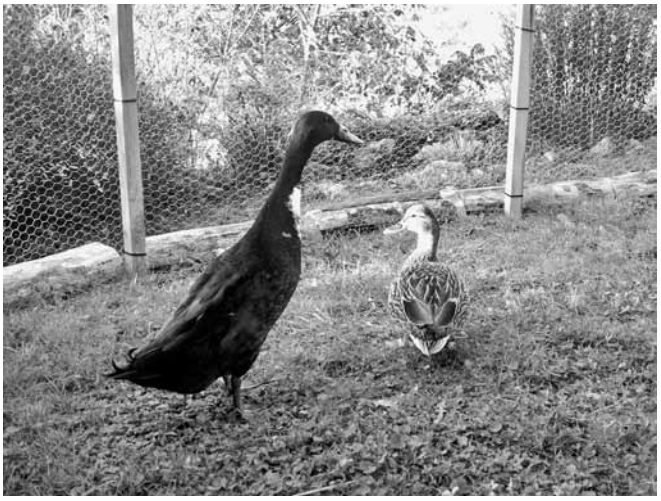
Nun, dann ab in die Landi Futter kaufen und sich schlau machen, was so ein Entenkücken alles braucht. Zum Glück sind ja die Entenjungen schon fast für alles im Leben vorbereitet; sie essen von alleine und ich musste einfach schauen, dass es genügend Wasser und Wärme hatte. Schon nach einer Woche war es schon so gross, dass ich es in den Kaninchenkäfig umsiedeln konnte. Dazu bekam es sein erstes Plantschbecken. Das war für zwei Wochen in Ordnung, aber bald musste etwas Grösseres, vor allem mit mehr Wasser, her. Es war erst Anfang Mai, und es noch zu klein, um es nach draussen in den Garten auszuquartieren.

Schwimmen in meiner Badewanne (9.5.09)

Der einzige Ort, wo ich in meinem Hause viel Wasser haben kann, ist meine Badewanne. Also wurde die Badewanne in einen Ententeich verwandelt, inklusive Insel. Da hatte Agathe ihren Spass. Das war für die nächsten vier Wochen ihr zu Hause, und ich musste auf mein Wellnessbad verzichten. Enten können eigentlich von Anfang an schwimmen, aber Agathe hatte nie wirklich Wasser in grösserer Menge erlebt. So musste ich am Anfang den Wasserspiegel so halten, dass sie noch stehen konnte. Langsam habe ich immer mehr Wasser eingefüllt und Agathe musste lernen, ihr Gleichgewicht zu halten. Nach einem Tag war auch das kein Problem mehr. Der Tag kam, da war auch die Badewanne zu klein, und ich baute ihr ein Gehege um den Regenwasserauffangtrog in meinem Garten, schön von meinem Wohnzimmer aus zu sehen. Das war ihr erstes Paradies – richtige Blumen und ein Teich zum Tauchen.

Agathes kleines Reich (7.6.09)

Sie war nun ca. 7 Wochen alt und eine stattliche Stockente geworden. Das Gefieder ausgebildet und aus dem Piepsen wurde ein lautes Quacken, welches mich jeden Morgen und Abend empfing. Wir zwei hatten ein schönes Verhältnis – irgendwie vertraut, was aber zur Folge hatte, dass ich sie nicht aussetzen konnte; sie wäre sofort ein Abendessen vom Fuchs oder meinem über den Baumkronen segelnden Milan geworden. Alleine wollte ich sie aber auch nicht lassen. Nach einem Telefongespräch mit dem Zolli war klar, dass ein Männchen her muss, da Enten gerne als Pärchen zusammen leben. Laufenten seien ideal, meinte der aus dem Zolli. Nun, wo bekomme ich eine Laufente her? Internet sei Dank, und der Zufall wollte es, dass eine Frau im Nachbardorf Nunningen junge indische Laufenten zu verschenken hatte.



Agathes neuer Freund Radjiv (26.10.09)

Agathe und Radjiv, das war – man hatte den Eindruck – Liebe auf den ersten Blick. Die Zwei turtelten und machten alles zusammen. Agathe, zwar dreimal kleiner, aber älter, war die bestimmende.

Es wurde Winter, und dieser Winter hatte es in sich. Viel Schnee und minus 16 Grad! Alles war zeitweise mit bis zu 30cm Schnee zugedeckt und zugefroren. Aber nicht der Teich von Agathe und Radjiv! Die beiden waren clever; sie waren meistens im Teich, vor allem in der Nacht, was ein Zufrieren verhinderte! Auch der hohe Schnee machte ihnen kein Problem; wichtig war immer, frisches Wasser zu haben, damit sie ihr Gefieder pflegen können, was dazu führte, dass Wasser nicht nur abperlte, sondern auch solche Minusgrade gut zu bewältigen waren.

30 cm Schnee und -16 Grad Kälte (8.1.10)

Bei dieser Kälte hatten die beiden auch ihre Hochzeitsnacht bzw. -nächte. Mitten im Februar, bei immer noch frostigen Temperaturen und Schnee, fand ich das erste Ei am Boden. Tja, was sollte das? Ich nahm mal wieder meinen Entenratgeber zur Hand und fand heraus, dass Enten die ersten Eier als Attrappe legen, um zu schauen, ob der ausgesuchte Nistplatz sicher ist. Nun, ich nahm es weg. Darauf folgten 12 Eier, die an verschiedenen Orten platziert wurden. Sie schienen auch nicht befruchtet zu sein, und Agathe sass auch nicht auf ihnen. Dann Mitte März fand ich die ersten Eier in der Hütte. Ich dachte: «Ok, lassen wir ihr den Spass.» Sie verbrachte nun die meiste Zeit mit Brüten und kam nur noch ab und zu zum Fressen und Baden heraus. Ich dachte, es seien so eine Handvoll. Da habe ich mich aber getäuscht! Am Mittwoch, den 21. April 2010, quakte sie völlig aufgeregt, als ich ihr Futter brachte. Da musste ich doch wissen, was da vor sich ging. Ein Blick genügte, die ganze Hütte war voller Küken...

Die ersten Bilder (21.4.10)

Was für eine Aufregung und ich war ziemlich gefordert. Schon nach einer Stunde war die ganze Familie draussen auf ihrem ersten Spaziergang. Radjiv musste von der Familie getrennt werden; laut Ratgeber könnten Väter in den ersten 6 Wochen die Kücken töten. Dann merkte ich, dass die Maschen vom Zaun zu gross waren, und dass ein paar Kücken ausserhalb des Geheges waren. Meine Katzen waren schon ganz neugierig. Also Kücken zurück scheuchen, Maschendrahtzaun installieren, Radjiv in die Isolation.

Das erste Mal draussen - eine stolze Agathe

Ich war ja in der Annahme, dass es nur im Höchstfall eine Handvoll Eier wären; tja, ich brauchte dieses Bild um heraus zu finden, dass 16 Junge geboren wurden! Eines ist zwar zwei Tage später verstorben, aber alle anderen waren quick lebendig.

Was wir uns alle schon lange fragten: Was gibt es aus dieser Paarung? Laufende Stockenten oder fliegende Laufenten? Also, es ist eine F1 Generation von Mischlingen, haben wir mal alle gelernt. Der erste Eindruck: Die Hälfte schaut aus wie ihre Mutter, die andere Hälfte wie ihr Vater. Die waren schwarz mit einem orangefarbenen Brustfleck. Zuerst musste mal wieder das Gehege vergrössert werden, weil die Jungen mindestens zwei Monate bei der Mutter bleiben müssen. Die entwickelten sind rasant und täglich waren sie grösser. Das Daunen-

2 Wochen später (3.5.10)

gefieder verloren zuerst diejenigen, die wie Stockenten aussahen. Die ersten Brustfedern kamen schon nach drei Wochen und mit einem Monat hatten sie nur noch Daunen auf dem Rücken. Heute sind sie sechs Wochen alt und haben schon die Hälfte der Länge der Flugfedern und sind so gross wie ihre Mutter.

Diejenigen, die nach ihrem Vater schlagen, haben Reste des schwarzen Daunengefieders noch heute. Der Brustfleck wurde weiss und die ersten schwarzen Federn sind am Bauch zu sehen. Eines ist auffällig; alle laufen mit durch gestreckten Beinen und rennen Roadrunnermässig durchs Gehege. Kein einziges der Jungen watschelt wie die Mutter.

Die Flugfedern sind noch nicht ganz ausgebildet und das Geschlecht ist noch nicht zu erkennen. Das geht noch eine Weile laut www.stockenten.ch. Am Morgen empfängt mich nicht mehr ein Piepsen, nein, jetzt ist es durchmischt mit lautem Quacken. Radjiv kann nicht quacken, der piepst nur. Ist das auch ein Unterschied zwischen Stockenten und Laufenten? Fragt mich nicht, ich bin noch keine Expertin, was Enten anbetrifft, aber Enten sind unterhaltsamer als jedes Fernsehprogramm.

3 Wochen später (8.5.10)

Die Jungen fangen an, die Mutter nachzuahmen. Zum Beispiel versucht mal mit dem Kopf nach hinten unter dem Flügel zu schlafen! Enten können das, und zwar einbeinig stehend, wie ein Flamingo. Ohne ausgewachsenen Flügel geht das noch nicht so einfach, aber Übung macht den Meister. Einbeinig stehen können sie auch noch nicht, mal schauen, wann das kommt.

4 Wochen später (16.5.10)

Ein paar nachträgliche Bemerkungen

Agathes rechtes Bein hat sich gut erholt, aber ist ein wenig krumm. Sie steht oft mit ihrem rechten Fuss auf ihrem linken (siehe Titelbild). Das beste Entenfutter gibt es in Belgien, das Land der Wasservögel, aber ich habe zum Glück einen Vertreiber in Hornussen gefunden; die Adresse gebe ich gerne weiter. Fazit: So mancher mag einen Vogel haben, ich habe eine Ente und das macht Spass – hätte ich nie gedacht.

Nicole Schaeren-Wiemers

Gute Plätze gesucht

Der Kreis hat sich nun geschlossen, aber was mache ich mit so vielen Enten? Wer Freude an einem Pärchen hätte, möge es mich wissen lassen. Ich verschenke sie gerne an ein Plätzchen, aber nicht für den Grill. Es braucht einen Garten, sie fressen liebend gern Schnecken, und mindestens einen Brunnen, in dem sie plantschen können. Die Haltung ist einfach, und wenn ihr die Eier zum Frühstück esst, dann wird sich die Anzahl auch nicht vergrössern.

Strasse des gebackenen Karpfens

Weltweit bekannt ist die oberelsässische Weinstrasse (La Route du Vin). Die Umgebung ist zwar wunderbar, die schmucken Riegelhäuser bemerkenswert, der Wein schmeckt hervorragend, die Winzer und Weinhändler sind von Stolz erfüllt. Das einzige Problem: Die Region wird in den Sommer- und Herbstmonaten hoffnungslos von Touristen überlaufen.

Deswegen werde ich Euch eine andere, fast unbekannte vorstellen: Anstatt eine Reise von Basel bis in die Region von Colmar zu unternehmen, kann man innerhalb von ein paar Minuten, sei es mit dem Tram, Auto oder Fahrrad, diese Route im Sundgau erreichen: Die Strassen des gebackenen Karpfens.

Die Route des gebackenen Karpfens
(Routes de la carpe frite)
Bei diesen Strassen handelt es sich um verschiedene Strecken, die einander nur wenig überschneiden und nach Belieben kombiniert werden können.

Ausgehend vom Wunsch, die örtlichen Traditionen bekannt zu machen, haben sich etwa vierzig Gastwirte im Verein des Gebratenen Karpfens zusammengeschlossen. Der Sundgau bietet nicht nur Erholung, er ist auch ein Schlemmerparadies. Wenn man eine Wanderung auf einer dieser Routen unternimmt, wird man begeistert sein von den anheimelnd kleinen Dörfern (Grentzingen), den blühenden Strassen (Hirtzbach), den mittelalterlichen Schlössern, Kirchen und Abteien (Ferrette, Lucelle, Feldbach) und den historischen Denkmälern (Altkirch, Sentier des Casemates). Oder man geht ganz einfach auf einem Wanderweg und betrachtet die Natur (Remel, Manlefelsen Grotte). Anschliessend kann man sich gemütlich in einer der Wirtschaften verwöhnen lassen.

Diese Gastwirte haben sich verpflichtet, das Nationalgericht des Sundgaus und des Juras auf den Tisch zu bringen: Den Karpfen. Frisch «g´metzgt», also gerade geschlachtet, entgrätet, in dicke Scheiben geschnitten, wird die Delikatesse anschliessend in Bierteig gewendet. Beidseitig wird der Fisch nun in siedendem Fett gebadet. Man serviert ihn noch brutzelnd, knusprig und mit einer hausgemachten Mayonnaise. Als Beilagen zum gebackenen Karpfen kommen traditionell höchstens gekochte Kartoffeln, eine Zitronenscheibe und ein grüner Salat in Frage. Bon Appetit!

Das Logo der Routes de la carpe frite ist, wie könnte es anders sein, ein Fischkopf, dem sich eine Gabel nähert.

Die Sage der Goldkarpfen
Zu jener Zeit ging der Sohn des Grafen von Ferrette gern in der Gegend von Liebsdorf spazieren. Eines Tages traf er eine junge Schäferin, deren Schönheit ihn blendete. Über beide Ohren in sie verliebt und nicht wagend, ihr seine Gefühle zu zeigen, drückte er seine Liebe in einem Gedicht aus, das er auf den Stein ritzte, an dem sie sich gern anlehnte.

Die durch diese zarte Nachricht verführte Schäferin willigte sofort ein, den Ritter zu heiraten. Leider musste man noch den Grafen von Ferrette überzeugen, der zu dieser Hochzeit nicht sein Einverständnis gab. Der Graf forderte von der Schäferin, dass sie ausserordentliche Taten erfülle, um dieser Heirat würdig zu sein.

Das junge Mädchen schlug ihm vor, seine geheimnisvollen «Goldfische» zu probieren. Neugierig nahm der Graf an. Es ging dann Karpfen fischen, die es nach seiner Art zubereitete und in Öl braun werden liess. Der Graf war begeistert und nahm die Verbindung der beiden an. Er liess ihnen sogar ein Schloss auf dem Stein, dem Zeugen ihrer Idylle, unter dem Namen von Liebenstein bauen. Somit wurde der gebratene Karpfen ein im Sundgau so geschätztes Gericht.

Tradition

Die Tradition der Karpfenzucht im Sundgau ist uralt. Am Anfang standen die tonhaltigen Böden, auf denen sich ideal Zuchtteiche anlegen ließen. Das Wasser ist so sauber, dass man gleichzeitig Forellen darin halten kann. Dank optimalen Zuchtbedingungen können die Karpfen bis zu 10 kg schwer und einen Meter lang werden. Die Idee, diese Fische zu züchten, geht auf Zisterzienser-Mönche in Lucelle (Lützel) zurück, die wahrscheinlich vermeiden wollten, dass die Elsässer verhungerten. Es war ihnen bewusst, wie es auch der Basler Geograf Sebastian Münster in 1548 schrieb: «Das fleissige Volk, was dort lebt, gebt in der Regel sein ganzes Haben um zu trinken und essen aus, macht kein Vorrat für die Zukunft, und wenn durch Zufall, als Folge von Frost, ein Kälteeinbruch oder ein Krieg, gibt es einen Mangel an Wein oder Weizen, leiden die Menschen unter der Knappheit und hohen Lebenshaltungskosten.»

Ein persönlicher Tipp

Das Schöne an diesen Karpfenteichen ist: Sie sind unbewacht und liegen öfters in der Wildnis. Da kann man heimlich angeln gehen, besonders unauffällig ist man nachts, wenn alles so still und ruhig ist. Aber mein Rat ist: Geht mit Pfeil und Bogen! Dies geht zwar nur am Tag, weil man, um einen Treffer zu machen, sehen muss, wo sich der Karpfen befindet. Nämlich dort, wo das Schilf sich bewegt. Für diesen Zweck braucht man aber leider ein Boot oder Floss. Und nicht zu vergessen: Eine junge Schäferin, die den Karpfen auch zubereiten kann.

Weitere Informationen (Karte, Wirtschaften, etc.) unter: http://www.sundgau-sudalsace.com/de/gastronomie/route-carpe-frite.htm

Emmanuel Traunecker

Zur Pensionierung von Thomas Aerni

Thomas Aerni begann vor 40 Jahren seine Tätigkeit im Reinigungsdienst (Putz-Equipe) als Fensterputzer im damaligen Bürgerspital. Nach etwa drei Jahren hatte er genug von Fenster-, Hallen-, Treppen- und Zimmerreinigungen und wechselte in die Tierstation. Die Tierstation war im Klinikum 1 untergebracht und wurde von Robert Käsermann geleitet. Er betreute mit anderen Tierpflegern alle bei uns gehaltenen Versuchstiere und war für die Zucht der Kaninchen und Ratten zuständig. Die Käfige und Boxen mussten alle von Hand geputzt werden und er sagte oft, dass das kein Job für Weicheier sei. Das Sägemehl, welches als Einstreu in die Boxen der Nager gegeben wurde, holten wir in grossen Stoffsäcken bei der Schreinerei des Technischen Dienstes. Dass das eine sehr staubige Angelegenheit war, sei nebenher erwähnt, dafür schmeckte danach ein feines Bier umso besser.

In seiner Freizeit spielte er sehr gerne Handball, später wechselte er zu Squash und fuhr täglich mit dem Velo zur Arbeit. So hielt er sich über all die Jahre körperlich fit und hatte dabei praktisch keine Absenzen wegen Krankheit (Bravo Thomas!). Nach langer Planungs- und Bauzeit konnte endlich die neue Station im ZLF im Jahr 1979 in Betrieb genommen werden. Um diese Station im Vollbetrieb zu betreiben, brauchte man auch mehr Personal. Leider blieben nur wenige über längere Zeit und so war die Personalfluktuation über die Jahre relativ hoch, was das Arbeiten und den Alltag nicht vereinfacht haben.

Thomas Aerni war mehr und mehr für die Waschküche zuständig, um all das Material zu reinigen und autoklavieren. Er führte die Waschküche mit grossem Engagement und versorgte uns immer mit genügend sauberem Material. Nebenbei war er auch zuständig für die Ver- und Entsorgung der Station. Thomas ist ein Fussball- und Eishockey-Fan, vor allem vom FCB. Er besitzt eine Jahreskarte vom FCB und besucht jedes Heimspiel.

Heinz Künzi und Ulrich Schneider

Niklaus Vogt,

neuer Bereichsinformatiker am Departement Biomedizin USB

Seit dem 1. Juni 2010 hat Niklaus Vogt die Verantwortung für die Informatik am Departement Biomedizin USB übernommen. Nach seiner Tätigkeit als Geschäftsführer der A&F Computer AG in Bern war Niklaus als Systemadministrator an der Hochschule für Gestaltung und Kunst an der Fachhochschule Nordwestschweiz tätig, bevor er an das DBM wechselte. An der FHNW hat er den 2nd Level Support sichergestellt, die OSX Serversysteme aufgebaut und betreut. In den letzten Jahren war er vor allem für die Erstellung von Betriebs-, Unterhalts-, Integrations- und Sicherheitskonzepten zuständig. Niklaus ist verheiratet und hat drei Jungs, die ihn ebenso wie Haus und Garten in seiner Freizeit ziemlich auf Trab halten. Zeit für sein Piccolo muss aber sein: So spielt Niggi in der Fasnachtsclique «Die Zaichnete», und wenn der Winter ausgetrieben ist, «american 10 hole fife» beim «Wildbunch Drum and Fife Corps». Wer will, kann ihn im Sommer beim «Basel Tattoo» oder auch anderen «Musters» und «Tattoo's» wie z. B. in Brunnen, Interlaken, Hausgauen bewundern. Ausserdem liegt Niggi die E. E. Zunft zu Rebleuten am Herzen, in deren Vorstand er sich engagiert. Was er sonst noch so macht, soll er Euch selbst erzählen. Und manchmal macht er auch gar nichts, sondern geniesst einfach nur das Leben. Herzlich willkommen, Niggi. Und herzlichen Dank an Ismerai, die so tapfer allein die letzten Monate die Informatik am DBM am Laufen gehalten hat!

Peter Mullen, Clinical Pharmacology

Every day millions of people around the world take drugs called statins. Their doctors have prescribed them to lower the production of cholesterol, a risk factor for cardiovascular diseases. They are highly effective drugs that have been credited with saving countless lives. However, for some patients statins have a nasty and life-threatening side effect: they make their muscles waste away.

For the past three years I have been working in the laboratory of Prof Stephan Krähenbühl trying to figure out what is going on at the molecular level to cause this side effect. So far we have shown that statins have a huge range of actions in the cell, turning up in all sorts of different places and influencing such diverse processes as mitochondrial integrity and protein function. We published a paper on this last year and have two more in the pipeline. We are now looking in detail at the IGF-1 signalling cascade, which looks like being crucial to the muscle-wasting side effect.

In December I will come to the end of my PhD in Basel and my time in Switzerland. In my three years here I have learnt so much, not just about cell biology but also about life in a different country. For me, skiing and Swiss German have been particularly exciting to grapple with. As I'm from Manchester, I'd come across neither until coming to Switzerland, but I tackled them both the same way – things started ok, went downhill quickly, and finished in an undignified crash at the end. I've been on safer ground when munching through my own body weight of chocolate or spending half my monthly salary at the Manor cheese counter, though I doubt my experiments with novel and unexpected fondue combinations can be called an unqualified success (see Pete & Swarna's Fusion Fondue).

Once I've wrapped up my PhD work in Basel, I'm hoping to do my post-doc in Canada. All being well, this time next year I will be in Toronto, where I am hoping to work in oncology.

Pete and Swarna's Fusion Fondue

Boil some dark beer with lots of thyme, rosemary, garlic, chilli powder and sugar.

Add a soft, a hard and a blue cheese (brie, roquefort and cheddar work well).
Thicken with cornflour mixed with schnaps.
Stand back and watch the Fribourgeois look on with horror!

The music of Manchester

To the casual observer, my lab technique could look like a form of expressive dance, or music day at the local kindergarten. I like to roam the labs, pipette in hand, singing and dancing along to my iPod. You see, for us folk from Manchester music is in our blood and must be integrated into every moment of the day. Manchester is one of England's greatest musical cities. Nearby Liverpool may be famous for giving the world the Beetles, but that's just a one-hit-wonder in comparison with the generations of innovative music churned out by Manchester's countless local bands. At turns subversive, irreverent, melancholy and euphoric, Manchester's music has had an impact far beyond the limits of this northern industrial city. Since I'm duty-bound to spread the gospel according to Manchester, here's some of our best bands and singers, and a song from each. Look them up if you don't already know them, they're the tip of the iceberg.

The Smiths (and Morrissey): Manchester's most influential group – There is a Light that Never Goes Out.

The Bee Gees: squeaky-voiced disco – Tragedy.

The Fall: abstract music and lyrics, and John Peel's favourite group – The Classical.

Joy Division/New Order: two different styles, the second formed after the suicide of Ian Curtis – Love Will Tear us Apart/Blue Monday.

Oasis: arrogant, repetitive, but huge – Live Forever.

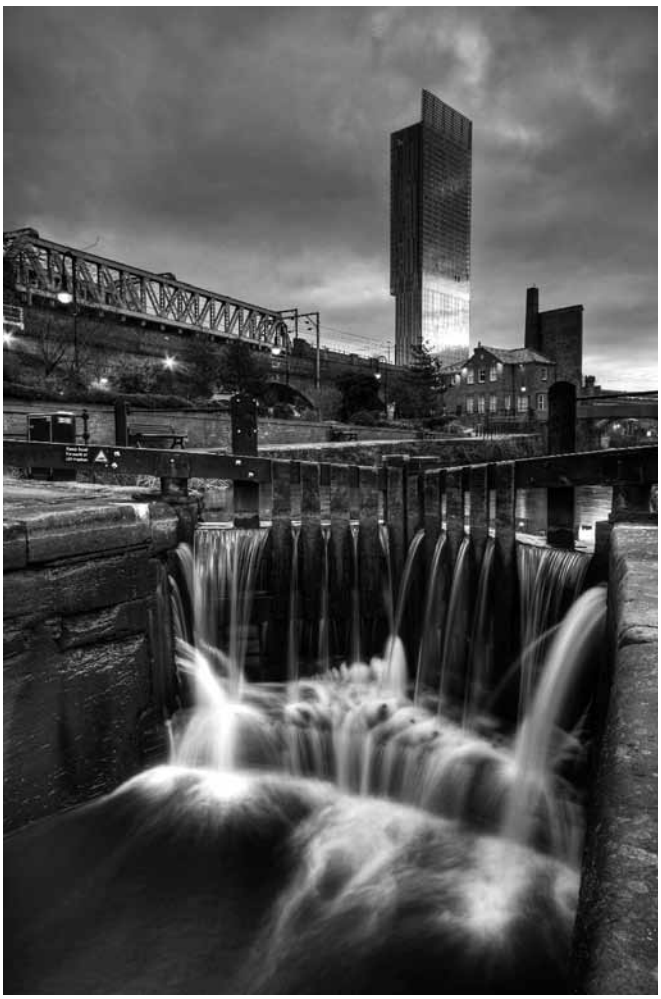
Mr Scruff: eclectic DJ and animator – Get a Move on.

Happy Mondays: Haçienda-fuelled Madchester-era dance – Step on.

Take That: the definitive boyband – Never Forget.

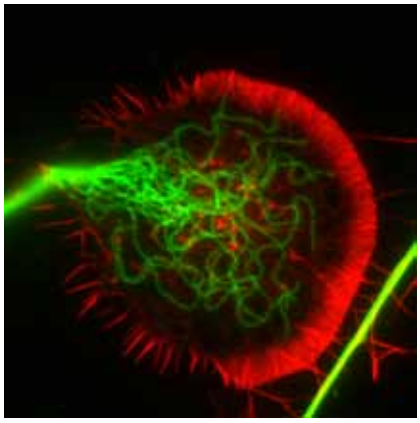
The Stone Roses: Guitars and dance, a better Oasis – Fool's Gold.

The Ting Tings: Catchy pop with funny lyrics – That's Not my Name.

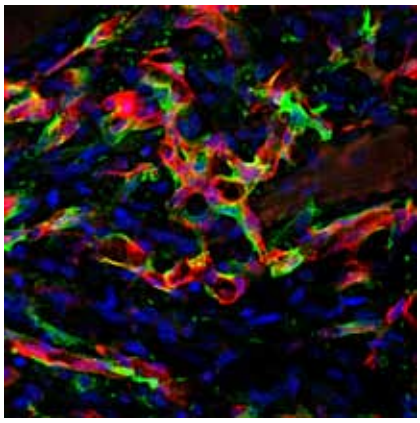


VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



... entführt uns Olivier Pertz in die Welt der Cell Migration and Neuritogenesis

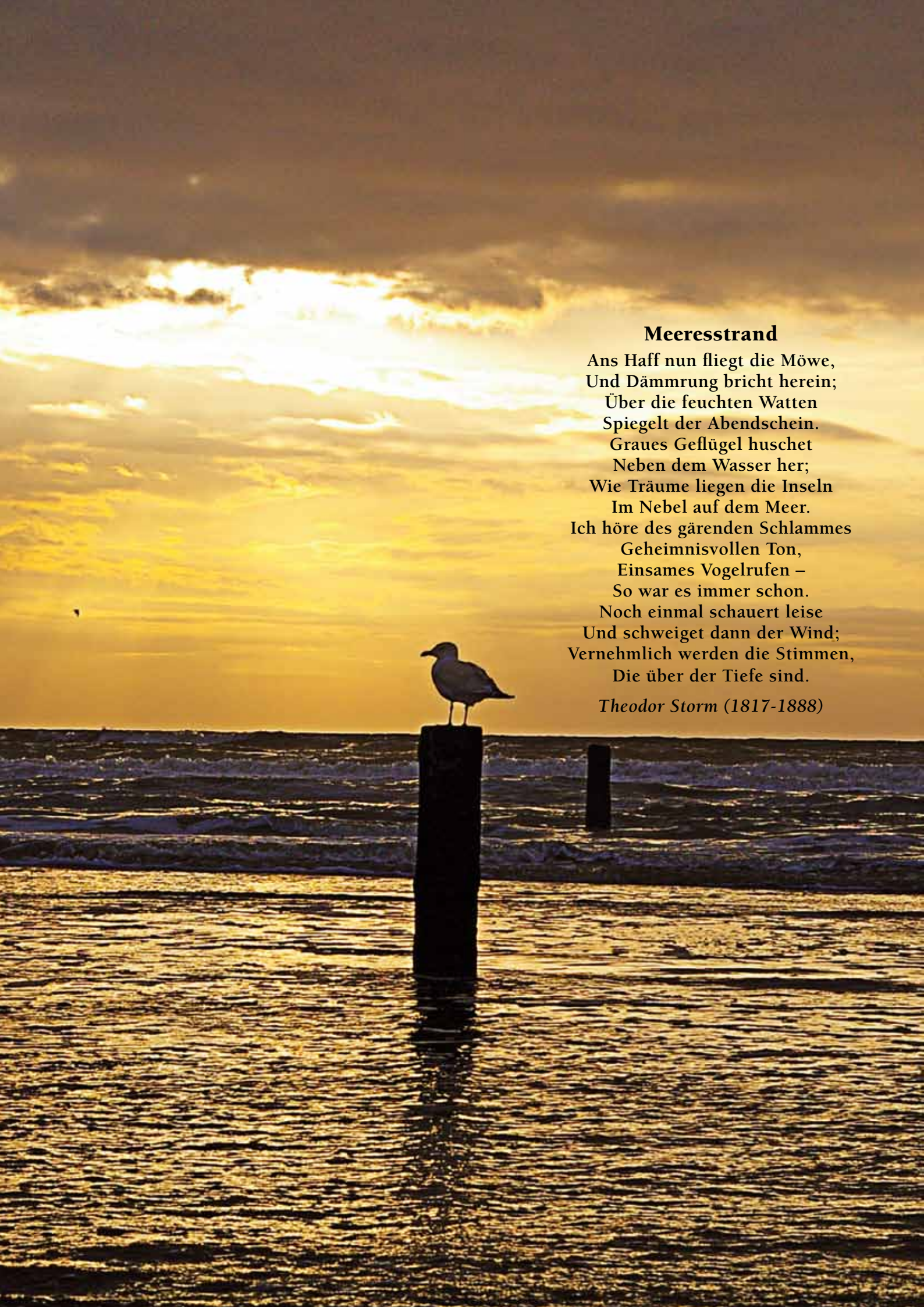


... bringt uns Andrea Banfi die Arbeit der Forschungsgruppe Cell and Gene Therapy näher

... wildern wir mit Stefanie Fritz in Thailand Affen aus

... erzählen wir die Geschichte vom Pferd

... machen wir einen nicht alltäglichen Stadtrundgang durch Basel



Meeresstrand

Ans Haff nun fliegt die Möwe,
Und Dämmrung bricht herein;
Über die feuchten Watten
Spiegelt der Abendschein.
Graues Geflügel huschet
Neben dem Wasser her;
Wie Träume liegen die Inseln
Im Nebel auf dem Meer.
Ich höre des gärenden Schlammes
Geheimnisvollen Ton,
Einsames Vogelrufen –
So war es immer schon.
Noch einmal schauert leise
Und schweiget dann der Wind;
Vernehmlich werden die Stimmen,
Die über der Tiefe sind.

Theodor Storm (1817-1888)