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Universität Basel, Universitätsspital Basel und
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Translating the biology of glioblastoma towards clinics |
Adaptation: a key factor for living in New York City! |
Gedanken zu Advent und Weihnachten

2 | 09

INHALT CONTENTS

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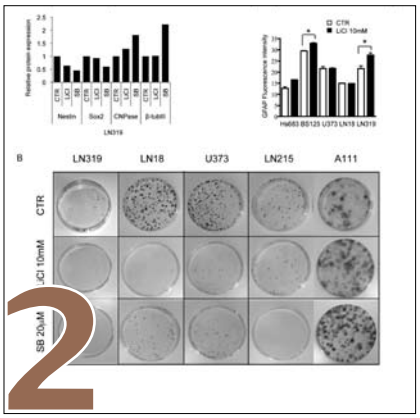
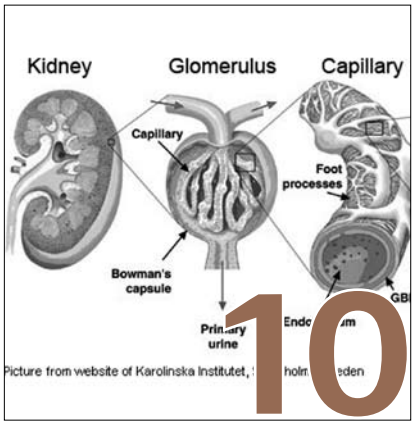


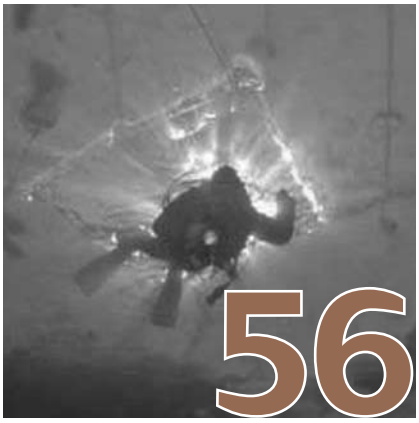
2

Translating the biology of glioblastoma towards clinics
from Adrian Merlo



10

Diabetes mellitus: Why and how does the kidney fail?
from Jonas Sieber and Andreas Jehle



56

Eistauchen
von Armin Bieri

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16

Adaptation: a key factor for living in New York City!
from Anna Marsano

58

Gedanken zu Advent und Weihnachten
von Jürg Merz

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

2009 neigt sich dem Ende zu. Ein positives Jahr für das DBM, das sich weiter entwickeln konnte. Am 1. September 2009 hat Michael Sinnreich seine Tätigkeit als Forschungsgruppenleiter des Labors «Neurobiology» aufgenommen. Zusätzlich wurde Matthias Liechti ein SCORE Beitrag des Schweizerischen Nationalfonds zugesprochen, seit 1. Oktober 2009 leitet er die Forschungsgruppe «Psychopharmacology Research». Beiden einen guten Start am DBM und viel Erfolg!

Das Labor «Endocrinology» von Alex Eberle hat am 30. November 2009 seine Tore nach 30 Jahren geschlossen. Alex Eberle wird an der Veröffentlichung verschiedener Projekte noch weiterarbeiten und übernimmt als Vizerektor Planung eine verantwortungsvolle Funktion für die Universität Basel. Mit Regine Landmann verlässt uns ein weiteres Gründungsmitglied und Vorsteherin des ehemaligen Departements Forschung. Auch Regine Landmann übernimmt als Vizedekanin Nachwuchs wichtige Aufgaben und bleibt in unserer Fakultät tätig. Beiden danke ich herzlich für ihre vielen Beiträge zum Departement und wünsche viel Erfolg und Erfüllung in ihren neuen Tätigkeitsbereichen.

In der nun vorliegenden Ausgabe nehmen uns Adrian Merlo und sein Team mit auf die Reise in die Forschungsaktivitäten der «Neurooncology» und Andreas Jehle führt uns in die Welt der «Molecular Nephrology» ein. Eine Auswahl der neuesten Publikationen finden Sie ab Seite 20.

Einmal aus ganz anderer Perspektive erleben wir die Adventszeit am USB mit Spitalpfarrer Jürg Merz (ab Seite 58).

Allen Leserinnen und Lesern wünsche ich eine interessante Lektüre, Frohe Weihnachten und ein gutes 2010!
Radek Skoda

Dear readers,

2009 is drawing to a close. It was a positive year for the DBM, which was able to develop further. On 1st September 2009 Michael Sinnreich took up his position as research group leader of the Neurobiology Lab. In addition, Matthias Liechti received a SCORE award from the Swiss National Science Foundation and since 1st October 2009 he has been leading the Psychopharmacology Research group. We wish them both a good start at the DBM and much success.

The Endocrinology Lab of Alex Eberle shut its doors on 30th November 2009, after 30 years in operation. Alex Eberle will continue to work on various projects for publication and takes on a responsible position for the University of Basel as vice-rector. The departure of Regine Landmann sees another founding member and manager of the former Department of Research. She is also taking on important duties and responsibilities as she takes up a position as vice-dean, and will still remain active in our faculty. We thank them both for their many contributions to the department and wish them much success and fulfilment in their new positions.

In the current issue Adrian Merlo and his team take us on a journey through the research activities of Neurooncology, and Andreas Jehle introduces us to the world of Molecular Nephrology. A selection of the latest publications can be found on page 20.

We experience advent at the USB from a very different perspective with hospital minister Jürg Merz (on page 58).

I wish all of our readers an interesting read, Happy Christmas and a good 2010!
Radek Skoda

Translating the biology of glioblastoma towards clinics

From left to right (back row): Balasubramanian Sivasankaran, Brian Hemmings, Adrian Merlo, Serdar Korur, Béatrice Dolder Schlienger, Marie-Christine Müller, Jacqueline Rauch. From left to right (front row): Maria Maddalena Lino, Roland Huber, Elisabeth Taylor Iten

Glioblastoma multiforme (GBM), the most common and malignant primary tumor of the central nervous system (CNS) in adults [1], with an incidence of about 5/100'000 represents an orphan disease [1]. GBM is characterized by exponential growth and diffuse invasiveness with a median survival of less than one year [2,3]. Although the diverse causative genotypes giving rise to a consistent pleomorphic phenotype are well defined, effective therapy inducing tumor cell apoptosis has not been established so far. Following surgery, billions of invasive tumor cells remain to be targeted by systemic and local therapies. Different physiological and physical factors render GBM a daunting challenge [4] . The blood-brain barrier (BBB) restricts the passage of most chemical substances into the neural tissue. In GBM, the BBB gets leaky because tumors can actively degrade tight junctions by secreting soluble factors [5]. Nevertheless, drug uptake is very limited reaching about 1:1000th of systemically injected compounds [6]. Drug uptake can be enhanced by designing lipophilic compounds or by directly injecting drugs into the interstitial space of the tumor. In addition, progressive GBM cells stimulate the formation of new blood vessels by secreting vascular endothelial growth factor (VEGF). However, the resulting vessels are structurally abnormal and leaky, giving rise to edema, high interstitial fluid pressure and, consecutively, low oxygen tension. This hostile microenvironment selects for a more malignant phenotype by clonal outgrowth of hypoxia-resistant tumor cells representing an additional obstacle for GBM treatment [7].

Molecular genetics of human gliomas

Over the past twenty years, considerable progress has been made in the knowledge of genetic alterations in gliomas and subsequently, on mechanisms of gliomagenesis. Unique combinations of major pathways controlling growth and nutrition, cell cycle, apoptosis, genomic integrity and energy demand have been detected and confirmed in two recent studies by sequencing the entire genome of GBM [4]. The most frequent genetic alterations are amplification of the *EGFR* gene and subsequent deletion that generates the constitutively active variant vIII; the homozygous deletion of the *CDKN2A* locus encoding both p14^{ARF} and p16^{INK4A} tumor suppressors; microdeletions in the gene for NF1, a negative regulator of Ras signaling; allelic losses that uncover missense mutations of the *PTEN* and *TP53* tumor suppressor genes [8]. More specific to oligodendroglioma (OG) – a less malignant glioma subtype - the combined allelic loss of chromosomes 1p and 19q, resulting from uneven translocation, is associated with better patient outcome [9,10]. The gene that is targeted by 1p/19q translocation has not been identified so far. Recent genome-wide surveys of genetic alterations and mutations in glioma have further identified dominant mutations at the Krebs cycle gene *IDH1* and low frequencies of missense mutations in the *NF1* and *RB1* gene [11,12]. 1p/19q loss associated with *IDH* mutation is largely prevalent in OG (~80%) while *TP53* mutation together with *IDH* mutation is dominant in astrocytic glioma (~80%) [13]. *IDH* status may therefore become a biomarker for the distinction between GBM vs astrocytoma or OG [14].

Brain tumor models in the mouse and in *Drosophila*

Among the various glioma models, two murine models have been generated that give rise to glioblastomas with high penetrance [15]. In both models, co-operation of two distinct pathways is required: either activation of both *AKT* and *RAS*, both operating downstream of growth factor and PTEN signaling, or simultaneous CNS-specific inactivation of *TP53* and *PTEN*, leading to Myc activation. In the second model, the malignant glioma originated from a neural stem cell population with high self-renewal capacity [16,17]. Interestingly, a brain tumor model also exists in *Drosophila* that harbor a mutant *brain tumor (brat)* gene. The *brat* mutation prevents terminal differerentiation and promotes self-renewal of neural progenitor cells inducing brain tumors at larval stage [18]. Whether there is a brat-homologous pathway in human gliomas has not been clarified so far.

Identification of *GPR26* and *TRIM3* as candidate glioma suppressor genes

In addition to *PTEN* on 10q23, somatic deletion mapping pointed to a second suppressor locus on 10q25-26 [19]. We found that the corresponding minimal area of loss contains the gene encoding the G protein-coupled receptor GPR26. Overexpression of *GPR26* in HEK and in U87 glioma cells increased intracellular cAMP concentration which is considered to induce astrocytic

differentiation. Interestingly, *GPR26* is concomitantly silenced with *MGMT* which also lies in the same region. GPR26 and MGMT could be epigenetically co-regulated [20]. The 10q25-26 region may therefore contain an important epigenetic pathway in brain tumorigenesis. Malignant gliomas harboring *TP53* mutations are associated with 11p15 allelic loss [21]. By performing somatic deletion mapping, we identified that a subgroup of patients with younger age had a 11p15 minimally lost region with putative homozygous deletions that target the *TRIM3* gene. *TRIM3* is the human orthologue of the *Drosophila* brain tumor suppressor gene *brat* [20]. This pathway controlling the precursor cell pool may therefore be conserved throughout evolution.

Interaction between Notch and tenascin in gliomas

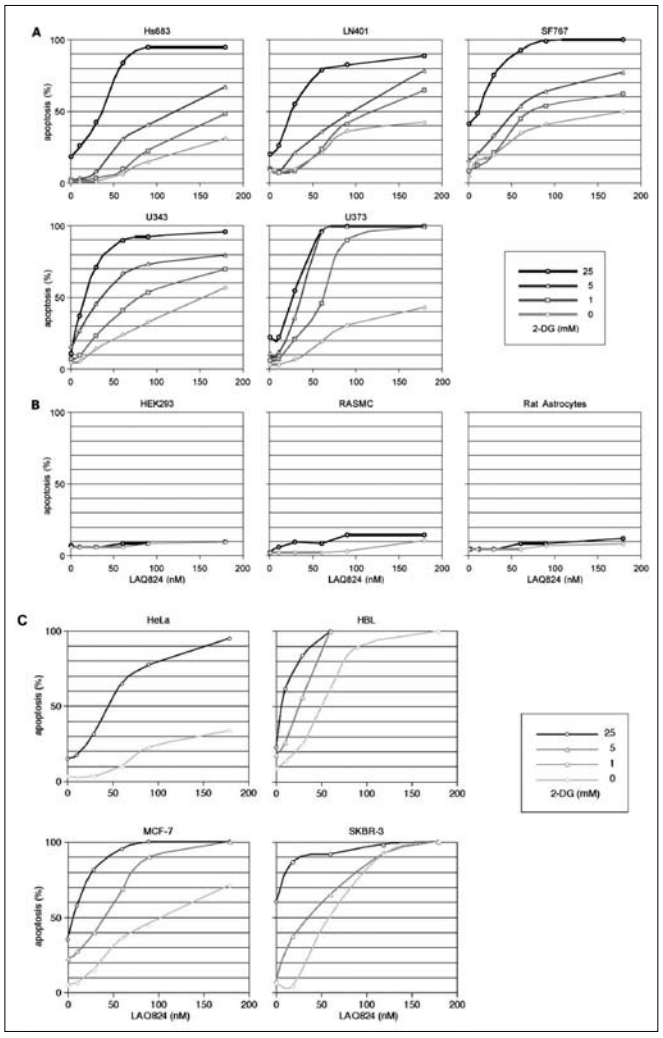
The developmental genes Notch1 and Notch2 are part of an emerging pathway in cancer including malignant gliomas [22]. We identified the Notch2 gene by tumor suppressor gene mapping on chromosome 1p11, comparing glioblastomas with oligodendrogliomas [23]. This study was initiated by the counter-intuitive claim in the medical community that 1p loss may be predictive for chemoresponse. Our hypothesis was that 1p loss points to a prognostically better glioma pathway and that, therefore, chromosome 1p harbors a developmentally critical gene. Interestingly, the Notch2 status appears to correlate with the degree of malignancy: the Notch2 protein was not expressed in oligodendrogliomas that deleted the Notch2 gene locus. In contrast, Notch2 protein was highly expressed in most GBM which show retention at the Notch2 locus. The association of the 1p/19q deletion with a more benign prognosis may therefore not be due to a more favorable response to medical intervention, but may simply reflect the involvement of a glioma pathway linked with better outcome. This conception appears to be confirmed in a recent clinical study on anaplastic oligodendroglioma where there was no correlation between chemoresponse and genetic status [24]. Continuous expression of Notch2 may force tumor precursor cells into an undifferentiated state, while deleting this pathway appears to allow a higher degree of differentiation during gliomagenesis, e.g. the generation of oligodendroglioma .

Tenascin-C (TNC) expression is known to correlate with malignancy in GBM [25]. It is one of the factors – beside others [26] – that regulate tumor cell invasion and migration. In GBM cell lines, we found Notch2 and the related transcription co-factor RBPJk to be strongly co-expressed with TNC. The *TNC* gene was found to be trans-activated by Notch2 in an RBPJk-dependent manner by an RBPJk binding element in the *TNC* promoter. TNC-stimulated glioma cell migration represents a mechanism for the invasive properties of glioma cells controlled by Notch signaling and defines a novel glioma pathway that may be targeted for therapeutic intervention in GBM patients [27].

Attacking biological resistance, the net effect of selection and mutation

To identify the genetic alterations in GBMs, 20,661 protein coding genes were sequenced in a recent study to determine the presence of amplifications and deletions and to define gene expression profiles [11]. This comprehensive analysis confirmed the involvement of major cancer pathways as discussed above [28]. A variety of genes that were not known to be altered in GBMs were discovered, however, at low frequency. The high mutational load in GBM was dramatically increased after radio- and chemotherapy using alkylating agents as previously observed [29]. Intensive chemotherapy should therefore be cautiously indicated in low-grade gliomas.

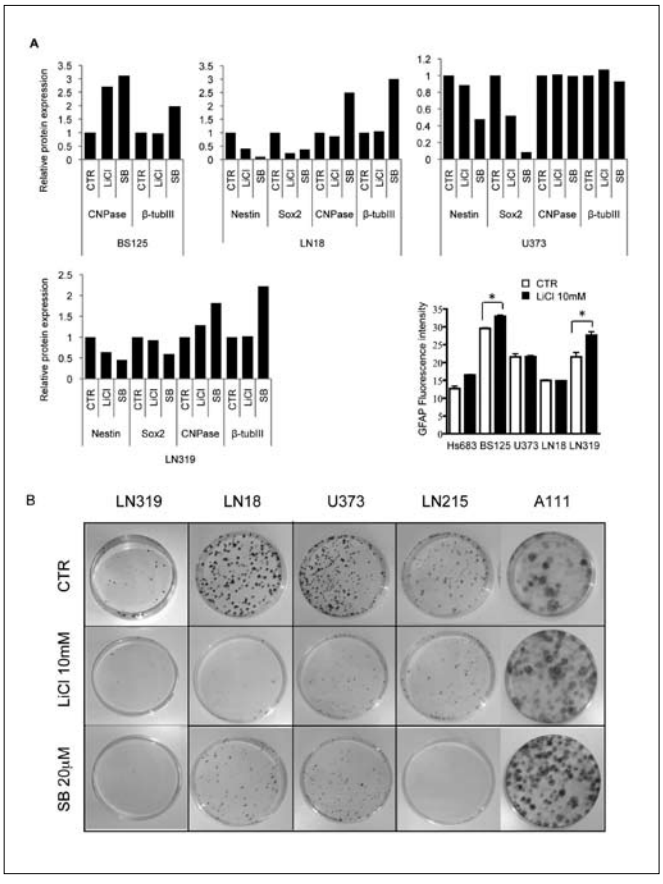
The epidermal growth factor receptor (EGFR) pathway triggers downstream phosphatidylinositol 3- kinase (PI3K)/RAS-mediated signaling cascades. However, complete blockade of EGFR activation does not result in apoptosis in human glioblastoma cells, suggesting additional cross-talk between downstream pathways. Based on these observations, we investigated combination therapies using protein kinase inhibitors against EGFR (AEE788), platelet-derived growth factor receptor (Gleevec), and mammalian target of rapamycin (RAD001), assessing glioblastoma cell survival. Clinically relevant doses of AEE788, Gleevec (imatinib), and RAD001 (everolimus) as single agent or in combination were not capable to induce glioblastoma cell apoptosis. In contrast, simultaneous inactivation of the EGFR downstream targets mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase and PI3K triggered rapid tumor cell death (Figure 1). Blocking EGFR in combina-



tion with sublethal concentrations of the microtubule stabilizer patupilone also induced apoptosis and reduced cell proliferation in glioblastoma cells, accompanied by downregulation of activity of AKT and ERK (Figure 1) [30]. These data underline the critical role of the PI3K/AKT/mTOR and the MAPKinase signaling cascades in the cell-intrinsic survival program of glioblastoma.

Targeting the epigenome in GBM

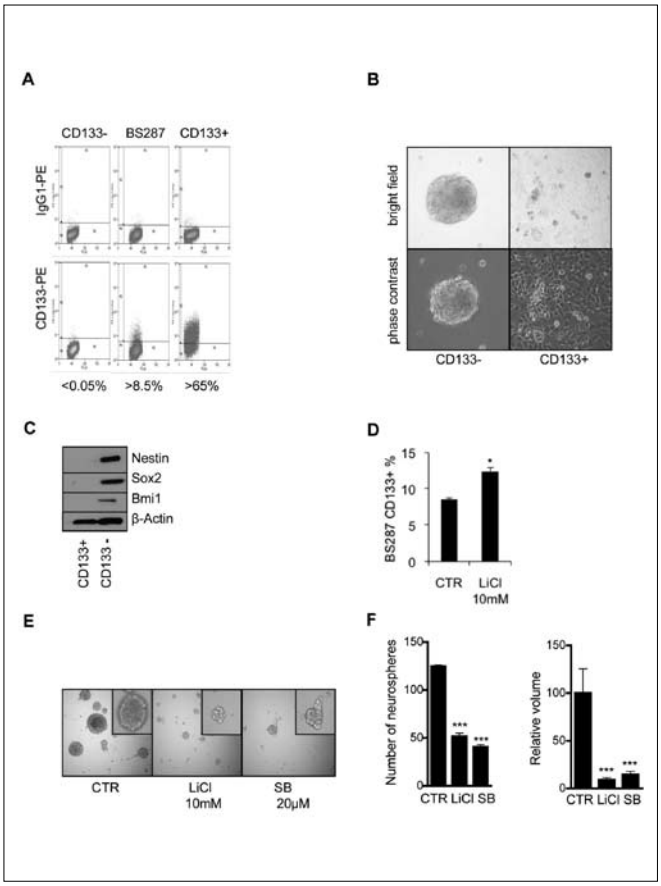
Epigenetic modulation of gene expression is essential for normal cellular development and is highly abnormal in cancers [31]. An epigenetic hallmark of cancer cells is promoter CpG island hypermethylation and transcriptional silencing of tumor suppressor genes and pro-differentiation factors. Repressive chromatin patterns mediated by lysine methylation of histone 3 are typically associated with DNA hypermethylation in adult cancers and have also been detected in embryonic cancer cells [31]. This chromatin pattern in stem or progenitor cells may leave critical genes vulnerable to aberrant DNA hypermethylation and heritable gene silencing during tumor initiation and progression. Drugs that revert cancer-prone chromatin patterns may therefore be promising to treat glioblastomas, e.g. histone deacetylase inhibitors (HDI). We have shown that the HDI trichostatin A, sodium butyrate, and low nanomolar doses of LAQ824 (Novartis) combined with the glycolysis inhibitor 2-deoxy-D-glucose strongly induced apoptosis in cancer cell lines of brain, breast, and cervix tumors in a p53-independent manner (Figure 2). HDIs upregulate p21 which was found to be blocked by concomitant administration of 2 deoxy-D-glucose [32]. A straightforward explanation of these observations would be that the glioma cell's resistance to epigenetic remodeling is an energy-sensitive process.



Differentiation of glioblastoma stem cells by blocking GSK3β induces apoptosis

The cancer stem cell (CSC) hypothesis proposes that cancers are derived from a small fraction of cancer cells which constitute a self-sustaining cell reservoir. The stem cell phenotype may be acquired by a series of se-

lected mutations, or precursor cells acquire tumorigenic mutations. GBM cancer stem cells (GCSC) share gene expression signatures with progenitor cells of the developing forebrain [33]. A subpopulation of cells which carry the marker CD133 has been identified in many tumors including GBM. In another study on aggressive cancers, histologically poorly differentiated tumors showed preferential overexpression of genes normally enriched in embryonic stem (ES) cells, combined with repression of Polycomb-regulated genes. The stem cell hypothesis may only represent one side of the coin, since it had been convincingly shown in a glioma animal model expressing EGFR in an *ink4a/arf*-deficient background that glioblastoma-like tumors can evolve both from precursor cells and from differentiated astrocytes [34]. Neural stem cells and differentiated astrocytes have been equally permissive for tumorigenesis upon lowering the apoptotic treshold (*arf:* p53 pathway), deblocking cell cycle regulation (*ink4a:* Rb-pathway) and activation of EGFR (Ras-pathway). We found that Bmi1 is consistently and highly expressed in GBM. Down-regulation of Bmi1 by shRNAs induced a phenotype of differentiation and reduced the expression of the stem cell markers Sox2 and Nestin, and, interestingly, also of glycogen synthase kinase 3-beta (GSK3β) which we found to be consistently expressed in primary GBM. This suggested a functional link between Bmi1 and GSK3β. Interference with GSK3β activity either with siRNA or with the specific inhibitor SB216763 or with Lithium chloride induced tumor cell differentiation and, in addition, enhanced tumor cell apoptosis, impaired formation of neurospheres in size and number, and reduced clonogenicity in a dose-dependent manner (Figure 3). GBM cell lines mostly consist of CD133-negative cells. Interestingly we found that *ex vivo* cells from primary tumor biopsies allowed identification of a CD133-negative subpopulation of cells that express stem cell markers and can be depleted by inactivation of GSK3β. Drugs that inhibit GSK3β including Lithium chloride - an established psychiatric drug - may deplete the GBM stem cell reservoir independently of the CD133-status [35].



How to treat GBM

For therapeutic exploitation, the challenge now is to detect crossroads within the aberrant and complex individual signaling network that are common in most GBM. Given the extreme adaptability of GBM cells, a therapeutic intervention has to lead to tumor cell death to prevent sublethal hits of tumor cells with subsequent outgrowth of even more malignant clonal cell populations. This critical requirement explains the inherent limitations of purely antiproliferative and anti-angiogenetic approaches as a main therapeutic pillar. Historically, treatment of GBM has relied on debulking surgery for the nodular component of the disease and unspecific cytotoxic stress for the invasive component of the disease. Usually, a combination of fractionated external beam radiotherapy and cytotoxic, mainly alkylating agents is being used leading mostly to a Pyrrhic victory. Within 2 years following diagnosis, most patients will have died because of tumor progression or recurrence [36]. Interestingly, intense chemotherapy, e.g. using temozolomide, increased the mutational load within the cancer genome 17-fold in comparison to untreated GBM cells [11].

Targeting non-overlapping pathways, rather than a single agent approach, is more likely to be effective.

Blocking different pathways can inactivate the compensatory crosstalk between them. Such a mechanism may be operative when two key cellular pathways are simultaneously targeted, e.g. PI3K from the PKB/mTOR-pathway and MEK from the MAPK pathway [30,37]. This approach is realized by reversing epigenetic modifications using pharmacological inhibitors such as histone deacetylase inhibitors (HDI). HDI act selectively, altering the expression of only 2-10% of genes [38]. This new class of drugs targeting the epigenome was found to markedly synergize with 2-deoxyglucose [32], inducing high levels of apoptosis in most GBM cells. ATP deprivation may be the critical step in this combination, since energy supply is essential for the re-induction of multifold gene-expression. Important regulatory genes in stem or progenitor cells may be vulnerable to aberrant DNA hypermethylation and heritable gene silencing and can potentially be re-induced by HDI [31]. Progress in systemic therapy introducing modern new drugs will be crucial to fundamentally improve long term prognosis of GBM patients in order to control the invasive component of the disease. Following successful local control by surgery, billions of invasive tumor cells are left behind within the perifocal edematous area that can also be detected in the contralateral brain hemisphere. The potential of local drug application has not been fully explored yet. Injecting targeted drugs directly into the enlarged extracellular space of a tumor or into the resection cavity holds relevant promise of an additional therapeutic effects that does not rely on the passage through the BBB [6,39]. Indeed, small targeted radiolabeled peptidic vectors rapidly diffuse along axonal pathways and perivascular clefts within a few minutes, following the ususal routes of tumor cell infiltration. Beta-emitting radionuclides are useful to treat the nodular tumor component. However, to target small infiltrating cell clusters, highly energetic short range alpha-emitters should be used, e.g. Bismuth-213 [40] or Astatine-211 that have been successfully tested in clinical pilot studies [41]. Such protocols with low toxicity are especially promising for younger patients affected by low-grade gliomas given the limited toxicity due to tumor cell specific targeting of the alpha-emitting radionuclides hooked up to a carrier peptide.

Conclusions

It is unlikely that one day a single magic bullet will cure GBM. Two major genotypes lead to the very similar GBM phenotype which may require distinct drug approaches. The main goal of any drug approach has to be induction of apoptosis of tumor cells given the hypermutability of GBM as a reaction to a therapeutic challenge. Antiangiogenetic, antiproliferative and anti-invasive strategies represent adjuvant strategies. Systemically, novel drug combinations have to be developed that not only target key molecules at the signaling crossroads, but also exploit energy demand and the epigenetic cancer program of GBM. Considering the many obstacles of drug distribution in the target area, advances in molecular disease imaging are needed to get direct answers on the therapeutic effect and the degree of drug penetration within the tumor. Besides systemic applications, local strategies also bear a great potential especially for attacking the invasive component of the disease, because drug distribution follows the same avenues that are used by infiltrating tumor cells, perivascular clefts and axonal pathways.

Maria Maddalena Lino, Jean-Louis Boulay, Serdar Korur, Roland Huber, Balasubramanian Sivasankaran, Béatrice Dolder, Elisabeth Taylor, Jacqueline Rauch, Marie-Christine Müller, Adrian Merlo.

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Diabetes mellitus: Why and how does the kidney fail?

A new research group started their work in the Laboratory for "Molecular Nephrology" of Prof. Reto Krapf at the Department of Biomedicine in July 2008. The new team is investigating the pathogenesis of diabetic kidney disease. One main focus of the research group lies in the identification and molecular characterization of pro-apoptotic and anti-apoptotic factors determining podocyte survival. Together with the group of PD Dr. Barbara Biedermann, the new team, led by Dr. Andreas Jehle, forms the second group in the Laboratory of "Molecular Nephrology".

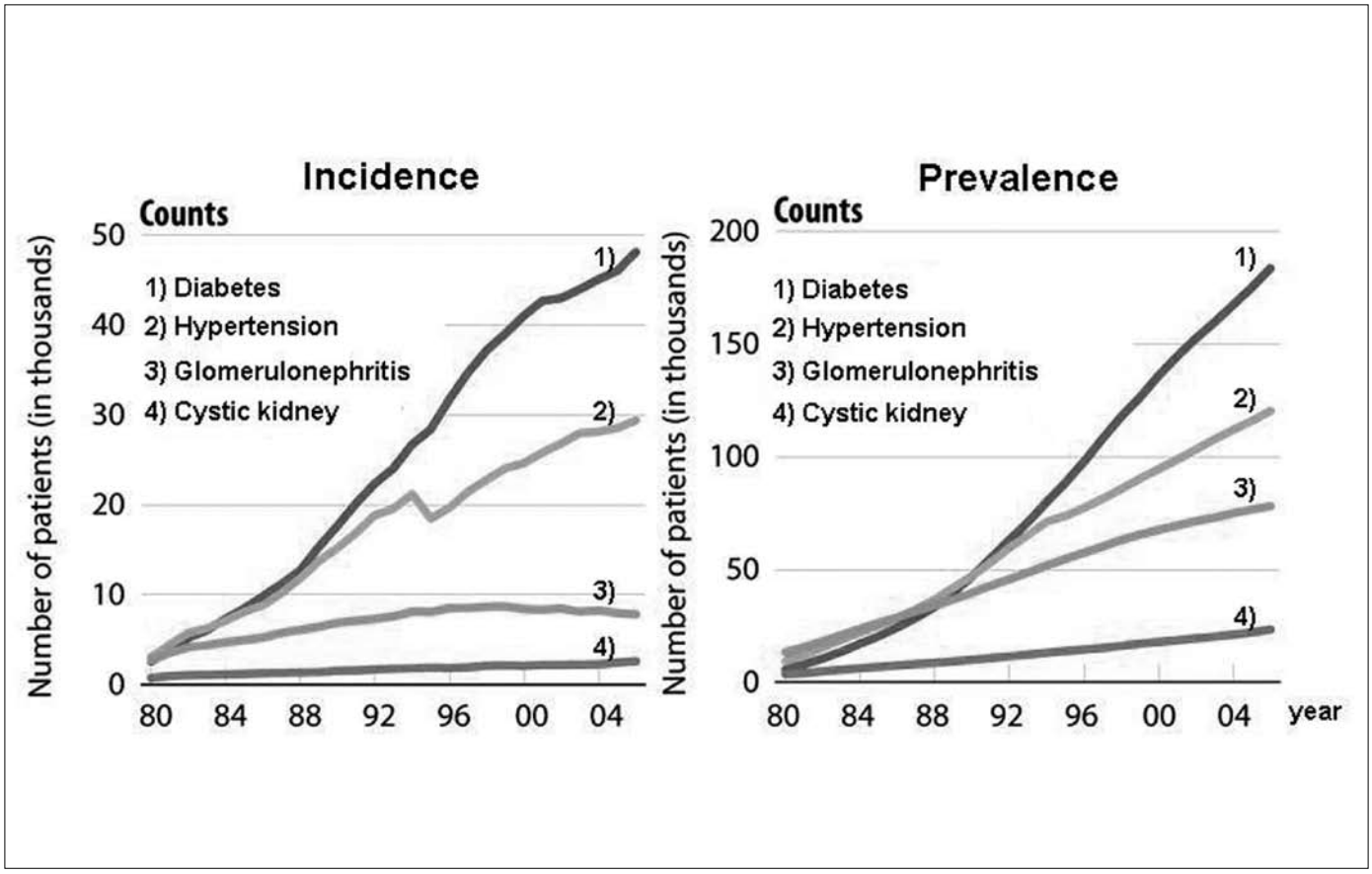

Figure 1: Incidence and prevalence of end-stage renal disease in the U.S.
Incidence and prevalence of end-stage renal disease in the U.S. according to underlying disease. Source: United States Renal Data System.

Why to do research on diabetic kidney disease?

A combination of the following: The urgent need to make progress in this research area, personal interest and expertise, and the recent availability of novel cell culture models.

Diabetes mellitus has become the most common cause of end-stage renal disease requiring renal replacement therapy in the U.S. (Figure 1) and Europe. This is due to the fact that diabetes mellitus is increasing in prevalence and diabetes patients live longer. Only 20-40% of patients with diabetes ultimately develop nephropathy, and the natural history of diabetic kidney disease is highly variable. Progression to end-stage renal disease is less likely in patients with type 2, than with type 1, diabetes. Nonetheless, the prevalence of type 2 diabetes is much greater, and most diabetic patients starting renal replacement therapy today have type 2 diabetes. It has become clear that hyperglycemia alone is neither the only contributing factor, nor sufficient to cause diabetic kidney disease. An increasing number of hemodynamic, metabolic, inflammatory, structural, and genetic factors have been identified in the disease process [1]. However, further advances are urgently needed to give halt to the steep increase in its incidence and prevalence.

Although new to the field of diabetic nephropathy, our group's expertise is based on a longstanding interest for the aging and failing kidney [2], which combined with a molecular background in renal physiology [3-5] as well as cell biology [6] should enable us to investigate diabetic kidney disease.

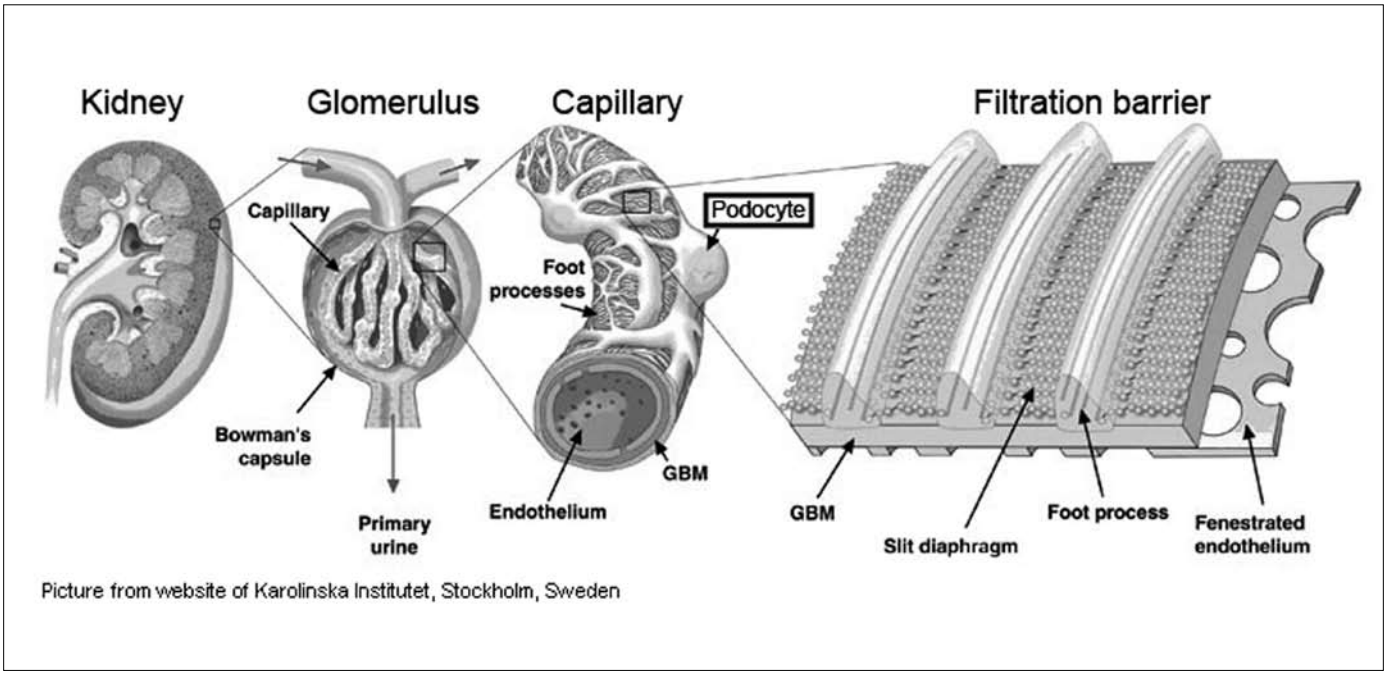

Figure 2: Structure of the glomerular filtration barrier
The human kidney contains about one million filtration units called glomeruli. A glomerulus consists of a bag-like Bowman's capsule containing several capillary loops. The filtration barrier consists of the fenestrated endothelium of the capillary wall, the glomerular basement membrane (GBM), and the podocytes with their interdigitating foot processes. Picture: Karolinska Institute, Stockholm, Sweden.

From bench to bedside and back

Most would agree that studying humans is ideal and represents "the gold standard" for medical research. However, experimental models in animals and cell culture models have proved to be important complimentary tools in many research fields where studies in humans are limited. Specifically, cell culture models are indispensable to study and understand a disease process at the molecular level. This is particularly difficult for solid organs made up of terminally differentiated cells such as the kidney. Fortunately, different renal cells are available today, including the highly differentiated podocytes, which in conjunction with the glomerular endothelium and the glomerular basement membrane (GBM) constitute the filtration barrier (Figure 2).

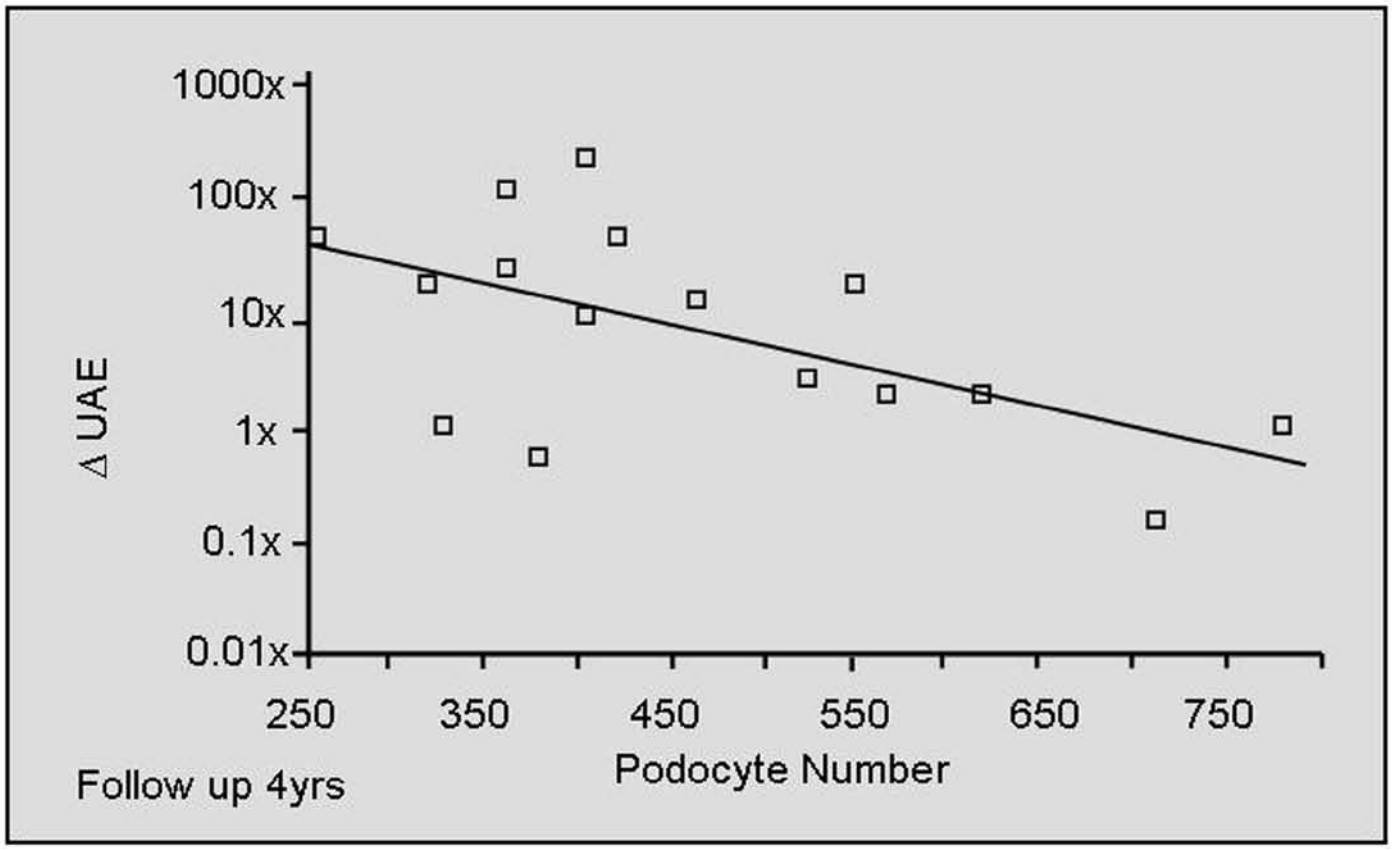

Figure 3: Podocyte number predicts change in urinary albumin excretion
Podocyte number at basline in 16 Pima Indiens with type 2 diabetes mellitus and change in urinary albumine excretion (Δ UAE) 4 years later [7].

Loss and apoptosis of podocytes at the onset of diabetic kidney disease

Urinary loss of albumin and other proteins (= proteinuria) is an early characteristic of diabetic kidney disease. Proteinuria is presumed to result from increased passage of proteins through the glomerular filtration barrier as a consequence of raised intraglomerular/transcapillary pressure as well as structural alterations of the glomerular filtration barrier. Importantly, studies in patients with type 1 and type 2 diabetes have shown an inverse relationship between urinary albumin excretion and the number and/or density of podocytes. Also, podocyte number predicted changes of urinary albumin excretion over time in type 2 diabetic patients with albuminuria [7] (Figure 3).

As podocytes have no, or only very limited, ability to replicate, apoptosis is likely a main mechanism for podocyte loss in diabetes. Of note, in a recent study in mice, apoptosis of podocytes occurred at the onset of diabetes, coincided with the onset of urinary albumin excretion, and preceded significant losses of podocytes as well as glomerular extracellular matrix accumulation [8]. Therefore, efforts to understand and potentially prevent mechanisms leading to damage, apoptosis and finally loss of podocytes in patients with diabetic kidney disease are needed.

A fine balance for life and death decisions

The "right" balance between pro-apoptotic and anti-apoptotic (survival) factors will determine whether a podocyte will undergo apoptosis or not. In particular, owing to advances in the field of cancer research, the complexity of the apoptotic program which is characterized by considerable crosstalk between different apoptotic and survival pathways is already known in quite some detail. However, data about pro-apoptotic factors co-determining the faith of podocytes in diabetic kidney disease is limited and even less is known about anti-

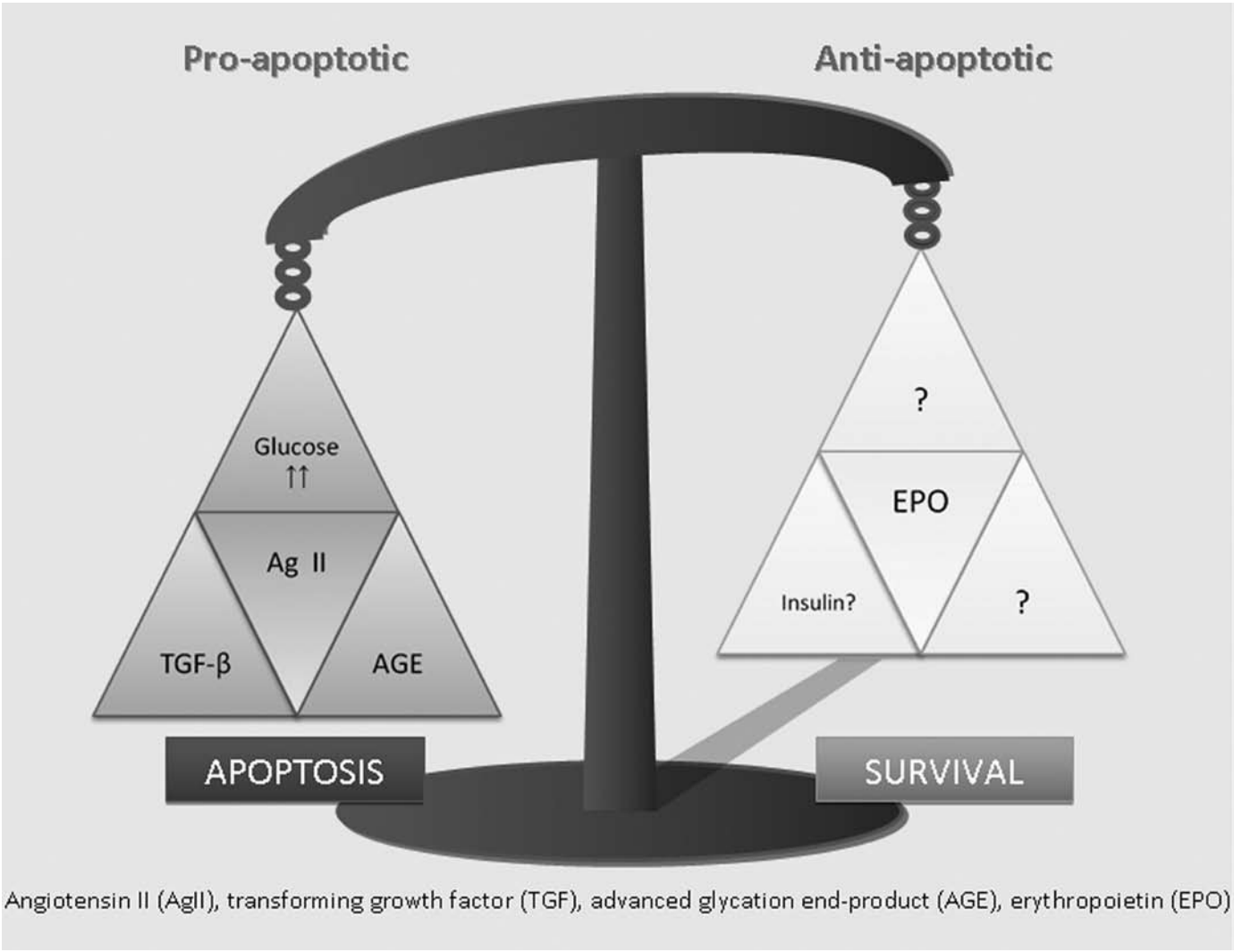

Figure 4: The delicate balance between life and death
The balance between pro-apoptotic and anti-apoptotic (survival) factors will determine whether a podocyte will undergo apoptosis or not. Apart from high glucose levels an increasing number of additional pro-apoptotic factors are known. Data about anti-apoptotic factors are still very limited.

apoptotic signals counterbalancing apoptotic stimuli. Important players in the life and death decisions of podocytes with specific evidence to be involved in diabetic kidney disease are summarized in Figure 4.

The trick to grow and study podocytes

Cell culture experiments allow direct study of mechanistic events and control of the environment such that a specific hypothesis can be tested. For podocytes, as for many other cell types, rapid dedifferentiation in vitro is a major problem. In the late 1990s Dr. Peter Mundel and co-workers achieved to culture differentiated podocytes outgrown from glomeruli [9]. However, in vitro studies with these primary podocytes were limited as differentiated podocytes do not proliferate. A major breakthrough was achieved by the generation of conditionally immortalized podocyte cell lines derived from the Immortomouse. In brief, this approach allows growing of highly proliferative podocytes in the presence of γ-interferon at 33°C which leads to the expression of a temperature sensitive SV40 large T antigen. After withdrawal of γ-interferon and a temperature shift to 37°C the cells stop proliferating, they turn to a quiescent state, and express the vast majority of podocyte-specific proteins described in vivo [10]. We are fortunate to be able to work with this cell culture model

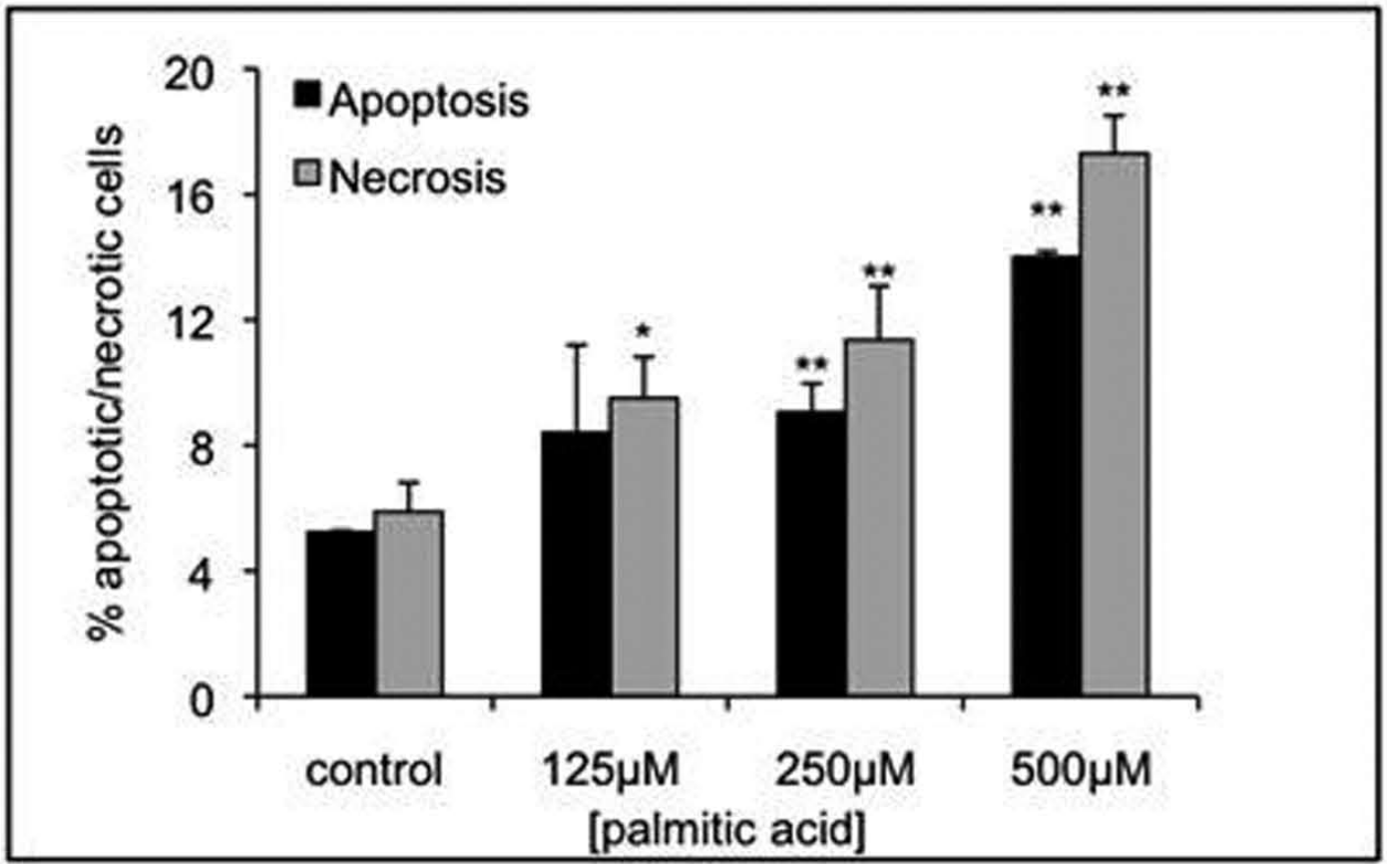

Figure 5: Palmitic acid induces apoptosis and necrosis of podocytes in a dose-dependent manner.
Podocytes were incubate in medium containing fatty acid free BSA (control) or BSA complexed with variable concentrations of palmitic acid (125 – 500 µM) for 38 h. Apoptosis of podocytes was determined by annexin V/PI staining followed by flow cytometry. Bar graph represents the mean percentages +/–SD of annexin V-positive/PI-negative (early apoptotic) and annexin V-positive/PI-positive (late apoptotic/necrotic) podocytes ($n = 3$; $^{*}p < 0.05$, $^{**}p < 0.01$). Unpublished data Sieber, and Jehle.

developed by Dr. Peter Mundel (currently in Miami) and in collaboration with him we have been able to generate our own conditionally immoratized podocyte cell lines from knockout mice. This should enable us to characterize the molecular pathways determining the fine balance for life and death of podocytes in more detail.

Ongoing research

The important role of free fatty acids is well known for the pathogenesis of diabetes mellitus. Based on our own preliminary data free fatty acids seem also to be critically involved in the balancing act between life and death of podocytes (Figure 5). Currently we are exploring the molecular pathways involved herein and in collaboration with Dr. Clemens Cohen from Zurich we are able to compare our in vitro findings with gene expression analysis on glomerular and non-glomerular fractions of kidney biopsies from patients with diabetic kidney disease. We hope to present and publish these data in detail in the near future.

Phagocytosis of apoptotic cells is the final step of the apoptotic program leading to an orderly disposal of damaged cells and preventing release of toxic, pro-inflammatory substances from the dying cell. Our preliminary data indicate that podocytes are able to phagocytose apoptotic podocytes themselves. Ongoing experiments aim at characterizing this in detail as well as the inflammatory or anti-inflammatory response elicited by this process.

Conclusion

Diabetic kidney disease is the most common cause of end-stage renal disease in developed countries and achieving a better understanding of its pathogenesis is needed to avoid this serious condition. There is now ample evidence that damage, apoptosis and loss of podocytes contributes to the pathogenesis of diabetic nephropathy. Results of in vitro experiments in conjunction with molecular analysis of kidney biopsies from patients with diabetic kidney disease harbor a great potential to identify new targets for the prevention and treatment of renal complication of diabetes mellitus. We hope that we will be able to contribute to this progress with the ultimate aim to improve overall morbidity and mortality of affected patients.

Jonas Sieber and Andreas Jehle

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Adaptation: a key factor for living in New York City!

How many books, movies and songs talk about living in New York City (NYC)?? So many… and you think that you know it all and you are fully prepared for it, even if the NY life turns out to be like the one represented in the ironic comedies by Woody Allen. Well, I have to say that the life there did surprise me almost everyday, and not always in the most positive way. The change for me had actually been quite big - from the quiet, organized and neat Basel to NYC. After my PhD, I decided to work in the US since I was told that US research was really advanced and conducted at a completely different 'pace' and level to that in Europe. So I joined the laboratory of Stem Cell and Tissue Engineering, directed by Professor Vunjak Novakovic at Columbia University.

Needless to say, there were many difficulties and they occurred from the very beginning! I did not know anybody in the city and the fact that I had to move there, alone for the first time in my life, did not help. Despite the great prestige and fame of Columbia University, they did not provide me with any accommodation

Fig 1. View of the diner which became famous in the Woody Allen movie.

or help, so at the beginning I had to find a bedroom in an apartment in the Dominican neighbourhood through internet. After two months of intense and problematic searching, I found a small studio of 18 square meters, with a kitchen at one wall and a tiny, tiny bathroom. The size of the studio was not what bothered me most, but the traffic lights just in front of my window, the great

Fig 2. View of Times Square, where the crowd of tourists is dazzled by the countless bewitched advertisements 24 hours a day.

noise coming from the street and the bus station, the associated tradditional noise and pollution, and last BUT believe me not least, were my *roommates*! Yes, I soon discovered that I was not alone in the tiny studio… several huge cockroaches were already living there. It seemed quite normal for a studio in Manhattan. But anyway. I had learnt that they are the most evolved creatures in this world, and reportedly can survive a nuclear bomb, but the real talent of these creatures was not in these facts, but that they could make a human being so miserable! They were very comfortable walking around even with the lights on, they can be very fast, and they can resist the most poisonous spray. Well, for the first months I didn't sleep much, because I was scared and city was noisy. I soon learned also that nobody would help me in case of danger, since the first evening I screamed quite loud for a long time as I fought against a big cockroach. Suddenly, in a moment of cold reality, I realized that I shouldn't scream so loud because my neighbours could also call the police. Well, nobody called anybody. Obviously it took me a while to adjust to my *roommates*, but after few months my screaming was considerably lowered and I started to consider the cockroaches as the pets that I would have always liked to foster. Indeed when I came back home, I expected my 'pets' to run to welcome me…

Fortunately, after 8 months I found another studio which was very comfortable and big (50 square meters!) and I could rest much better and start to enjoy all the amusements that NYC offers! The greatest thing of NYC is that there is an opportunity for any pocket; even if you were without money you could enjoy free concerts,

Fig 3. Picture of Manhattan from Long Island City during the Manhattanhenge, which is a semi-annual occurrence in which the setting sun aligns with the east-west streets of Manhattan's main street grid. The term is derived from Stonehenge, at which the sun aligns with the stones on the solstices.

opera in the parks and concerts at the Lincoln Center and even of Broadway shows of very high quality at a very affordable price!

Making friends was also not easy, most of the time I felt really lonely even in such a big, crowded, cosmopolitan city, such as NYC. NYC has indeed always welcomed people from the entire world, providing typical cooks and space for continuing their cultural habits. The multi-culture environment of NYC should be kept as an example for every city; there people from so different countries and cultures can live together in a respectful

Fig 4. The Jacqueline Kennedy Onassis Reservoir in Central Park, where I spent most of my time and where I ran away most of my sorrows. This is the part of NYC that will remain in my heart forever.

and peaceful way, willing to share their habits and in particular their typical food! However, the real New Yorkers seemed pretty doubtful if they met a friendly person, they possibly assign ulterior motives to friendliness. Consequently, it takes time for them to trust somebody. It took me almost one year before I would have a few close friends.

I really missed biking, hiking in nature and every breath I took made me think 'have I already compromised my health or am I still ok?' The noise of the city was unending. I always tried to close my ears in the subway at the passage of the trains, at the continuous sirens of police or fireman trucks and ambulances. Most of the people, even though they are not in a hurry, kept running fast heedless that they were banging into others on the way.

Central Park looked to me to be a bizarre refuge for green lovers, but with a still vivid memory of the beautiful Alps and green wide lawns, I felt so sad looking at all the people trying to enjoy the fake wild nature, walking, jogging, biking, doing Tai Chi among the trees, skating, even snowshoeing, cross-country and mountain skiing with either real or artificial snow!!!

Two very good friends told me their secret 'mantra' to survive NYC's stress and craziness: yoga and running. Well, I started to do both and I managed to increase my sleep and reduce the stress at work.

The first time I went to a *Yoga* studio, I was really late, very stressed since I had to cross Manhattan to get there. When I finally got there, I had the impression that all the people who were getting out of class were so relaxed and peaceful, and this cheerfulness somehow got on my nerves!! But as soon as I entered the little cosy studio, with warm colours and candles my mood changed. The teacher's voice was amazingly sweet and guided me into each step of the Asanas. I enjoyed the time in class, without realizing I focused so much on the details of the instructions that my mind cleared, and at the end I was like one of those peaceful persons myself and I wondered if the class had worked its magic. Yoga changed my life so drastically, that after two years of learning, I was ready to undertake the 'teacher training' to get certified for sharing the benefits of practicing yoga with others.

'Going running' was something therapeutic for me and opened my relief valve to immediately release the pressure accumulated during a bad day. Soon I joined the NYC Road-Runner Club and started to participate in small races in the city. It was really beautiful and I beca-

me a part of the crazy crowd that went running at 5 am, in sun, rain, ice or snow. At that point, amazingly, Central Park seemed to be the most beautiful place in the world, and the surrounding sky-scrapers were my Alps. Later in spring 2008, along with some new friends I participated in the annual lottery that allowed few people to participate in the NYC marathon. Much to my amazement, I happened to get the lucky number! Before I got time to digest this fact, I was already running late in terms of training myself. My friends convinced me not to miss this occasion, and soon I found myself gearing-up for the longest run ever in my life! The 2nd of November is currently recorded in my diary as the first major joyous fitness event of my life and now when I look back I see only exhilaration, overwhelming emotion and pride. I had friends in all the 5 neighbourhoods waiting to cheer me on as I crossed one lap after another!

It was suddenly so beautiful to see the entire city stopping for the runners and getting into the streets to cheer, give food, water, paper towels, a smile or a hug… Every neighbourhood was different: different people, different music bands, different rhythms. I enjoyed every second of this long, long journey when every unknown face smiled and encouraged me to run. Suddenly, life takes a peculiar turn and you are running this race with 43,000 people, yet the spotlight senses only you and you feel as if you are carried over by a storm of humanity! To burst my bubble of cheerfulness, my knee started to hurt in the last 5 miles, so instead of running, I slowed down to a walk, yet the adrenalin failed to leave me, people were supporting me from everywhere, even more than earlier, and finally I completed the 26.2 miles and I had tears streaming down my face.

Fig 5. NYC Marathon: the great joy after finishing the first half of the 26.2 miles… later on the smile faded away!

I don't know what this marathon did to me, but somehow I began to look on the brighter side of my stay there. Away from my closest family and friends, my experience in NYC was beneficial as I had time to realise many things about myself. I probably would not have known the joy of yoga and the once-in-a-lifetime experience of running a marathon, had I not crossed the ocean and flown to NYC. Also at work, I had began to utilise every opportunity to learn and gradually I was able to handle the most critical and stressful situations. I felt myself growing more confident in my scientific abilities as I continued to work on cardiac tissue engineering. I was chiefly investigating the capability of mesenchymal stem cells to differentiate into cardiac lineage. In the end, we optimized conditions for generating in vitro functional cardiac patches by using neonatal rat cardiomyocytes. I found myself patting myself on the back one evening, and somehow I felt, I had made it in NYC.

On one fine afternoon, at the metro station I happened to see some tourists who looked horrified at the cockroaches and rats proudly walking around; and then I saw them close their ears at the passage of the train. I found myself smiling at their predicament and thought that they too would get to know and love this city just as I had done…. it would be just a matter of time.

'And if I can make it there, I'm gonna make it anywhere, it's up to you, New York New York', croons Frank Sinatra and frankly, I think it is quite true!

Anna Marsano

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

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

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The Journal of Experimental Medicine 323, 1957–1970, 2009 IF15,4

Dissection of PIM serine/threonine kinases in FLT3-ITD–induced leukemogenesis reveals PIM1 as regulator of CXCL12–CXCR4-mediated homing and migration

R. Grundler[1], L. Brault[2], C. Gasser[2], A. N. Bullock[3], T. Dechow[1], S. Woetzel[1], V. Pogacic[2], A. Villa[4], S. Ehret[2], G. Berridge[3], A. Spoo[5], C. Dierks[5], A. Biondi[4], S. Knapp[3], J. Duyster[1] and J. Schwaller[2]

Abstract:
FLT3-ITD–mediated leukemogenesis is associated with increased expression of oncogenic PIM serine/threonine kinases. To dissect their role in FLT3-ITD–mediated transformation, we performed bone marrow reconstitution assays. Unexpectedly, FLT3-ITD cells deficient for PIM1 failed to reconstitute lethally irradiated recipients, whereas lack of PIM2 induction did not interfere with FLT3-ITD–induced disease. PIM1-deficient bone marrow showed defects in homing and migration and displayed decreased surface CXCR4 expression and impaired CXCL12–CXCR4 signaling. Through small interfering RNA–mediated knockdown, chemical inhibition, expression of a dominant-negative mutant, and/or reexpression in knockout cells, we found PIM1 activity to be essential for proper CXCR4 surface expression and migration of cells toward a CXCL12 gradient. Purified PIM1 led to the phosphorylation of serine 339 in the CXCR4 intracellular domain in vitro, a site known to be essential for normal receptor recycling. In primary leukemic blasts, high levels of surface CXCR4 were associated with increased PIM1 expression, and this could be significantly reduced by a small molecule PIM inhibitor in some patients. Our data suggest that PIM1 activity is important for homing and migration of hematopoietic cells through modification of CXCR4. Because CXCR4 also regulates homing and maintenance of cancer stem cells, PIM1 inhibitors may exert their antitumor effects in part by interfering with interactions with the microenvironment.

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Plos Biology 7, e10000093, 2009 IF14,1

Base Excision by Thymine DNA Glycosylase Mediates DNA-Directed Cytotoxicity of 5-Fluorouracil

C. Kunz[1], F. Focke[1], Y. Saito[1], D. Schuermann[1], T. Lettieri[2], J. Selfridge[3] and P. Schär[1]

Abstract:
5-Fluorouracil (5-FU), a chemotherapeutic drug commonly used in cancer treatment, imbalances nucleotide pools, thereby favoring misincorporation of uracil and 5-FU into genomic DNA. The processing of these bases by DNA repair activities was proposed to cause DNA-directed cytotoxicity, but the underlying mechanisms have not been resolved. In this study, we investigated a possible role of thymine DNA glycosylase (TDG), one of four mammalian uracil DNA glycosylases (UDGs), in the cellular response to 5-FU. Using genetic and biochemical tools, we found that inactivation of TDG significantly increases resistance of both mouse and human cancer cells towards 5-FU. We show that excision of DNA-incorporated 5-FU by TDG generates persistent DNA strand breaks, delays S-phase progression, and activates DNA damage signaling, and that the repair of 5-FU–induced DNA strand breaks is more efficient in the absence of TDG. Hence, excision of 5-FU by TDG, but not by other UDGs (UNG2 and SMUG1), prevents efficient downstream processing of the repair intermediate, thereby mediating DNA-directed cytotoxicity. The status of TDG expression in a cancer is therefore likely to determine its response to 5-FU–based chemotherapy.

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Hepatology *Hepatology* 50, 871–879, 2009 IF11,3

Notch2 signaling promotes biliary epithelial cell fate specification and tubulogenesis during bile duct development in mice

J. S. Tchorz[1], J. Kinter[2], M. Müller[3], L. Tornillo[4], M. H. Heim[5] and B. Bettler[1]

Abstract:
Intrahepatic bile duct (IHBD) development begins with the differentiation of hepatoblasts into a single continuous biliary epithelial cell (BEC) layer, called the ductal plate. During ductal plate remodeling, tubular structures arise at distinct sites of the ductal plate, forming bile ducts that dilate into the biliary tree. Alagille syndrome patients, who suffer from bile duct paucity, carry *Jagged1* and *Notch2* mutations, indicating that Notch2 signaling is important for IHBD development. To clarify the role of Notch2 in BEC differentiation, tubulogenesis, and BEC survival, we developed a mouse model for conditional expression of activated Notch2 in the liver. We show that expression of the intracellular domain of Notch2 (Notch2ICD) differentiates hepatoblasts into BECs, which form additional bile ducts in periportal regions and ectopic ducts in lobular regions. Additional ducts in periportal regions are maintained into adulthood and connect to the biliary tight junction network, resulting in an increased number of bile ducts per portal tract. Remarkably, Notch2ICD-expressing ductal plate remnants were not eliminated during postnatal development, implicating Notch2 signaling in BEC survival. Ectopic ducts in lobular regions did not persist into adulthood, indicating that local signals in the portal environment are important for maintaining bile ducts.
Conclusion: Notch2 signaling regulates BEC differentiation, the induction of tubulogenesis during IHBD development, and BEC survival

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Cancer Research **Cancer Research** 69, 458–465, 2009 IF7,6

Tenascin-C Is a Novel RBP Jκ-Induced Target Gene for Notch Signaling in Gliomas

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Abstract:
Tenascin-C (TNC) expression is known to correlate with malignancy in glioblastoma (GBM), a highly invasive and aggressive brain tumor that shows limited response to conventional therapies. In these malignant gliomas as well as in GBM cell lines, we found Notch2 protein to be strongly expressed. In a GBM tumor tissue microarray, RBPJk protein, a Notch2 cofactor for transcription, was found to be significantly coexpressed with TNC. We show that the *TNC* gene is transactivated by Notch2 in an RBPJk-dependent manner mediated by an RBPJk binding element in the TNC promoter. The transactivation is abrogated by a Notch2 mutation, which we detected in the glioma cell line Hs683 that does not express TNC. This *L1711M* mutation resides in the RAM domain, the site of interaction between Notch2 and RBPJk. In addition, transfection of constructs encoding activated Notch2 or Notch1 increased endogenous TNC expression identifying *TNC* as a novel Notch target gene. Overexpression of a dominant negative form of the transcriptional coactivator MAML1 or knocking down RBPJk in LN319 cells led to a dramatic decrease in TNC protein levels accompanied by a significant reduction of cell migration. Because addition of purified TNC stimulated glioma cell migration, this represents a mechanism for the invasive properties of glioma cells controlled by Notch signaling and defines a novel oncogenic pathway in gliomagenesis that may be targeted for therapeutic intervention in GBM patients.

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Human bone marrow mesenchymal stem cells and chondrocytes promote and/or suppress the in vitro proliferation of lymphocytes stimulated by interleukins 2, 7 and 15

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Abstract:
Objectives: To investigate whether human bone marrow-derived mesenchymal stem cells (BM-MSCs) and articular chondrocytes (ACs) affect the in vitro proliferation of T lymphocytes and peripheral blood mononuclear cells (PBMCs) driven by the homeostatic interleukin (IL)2, IL7 and IL15 cytokines binding to the common cytokine receptor -chain (c) in the absence of T cell receptor (TCR) triggering.

Methods: PBMCs, total T cells and T cell subsets (CD4+ and CD8+) were stimulated with IL2, IL7 or IL15 and exposed to cultured BM-MSCs and ACs at varying cell:cell ratio either in contact or in transwell conditions. Lymphocyte proliferation was measured by 3H-thymidine uptake or by flow cytometry of carboxyfluorescein succinimidyl ester (CFSE)-labelled lymphocytes.

Results: MSCs and ACs enhanced and inhibited lymphocyte proliferation depending on the extent of lymphocyte baseline proliferation and on the MSC/AC to lymphocyte ratio. Enhancement was significant on poorly proliferating lymphocytes and mostly at lower MSC/AC to lymphocyte ratio. Suppression occurred only on actively proliferating lymphocytes and at high MSC/AC to lymphocyte ratio. Neither enhancement nor inhibition required cell–cell contact.

Conclusions: There is a dichotomous effect of MSCs/ACs on lymphocytes proliferating in response to the homeostatic IL2, IL7 and IL15 cytokines likely to be encountered in homeostatic and autoimmune inflammatory conditions. The effect is determined by baseline lymphocyte proliferation, cell:cell ratio and is dependent on soluble factor(s). This should be taken into account when planning cellular therapy for autoimmune disease (AD) using stromal-derived cells such as MSCs.

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Oncogene Oncogene 28, 2969–2978, 2009 IF 7,2

Methylation profiles of 22 candidate genes in breast cancer using high-throughput MALDI-TOF mass array

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Abstract:
Alterations of DNA methylation patterns have been suggested as biomarkers for diagnostics and therapy of cancers. Every novel discovery in the epigenetic landscape and every development of an improved approach for accurate analysis of the events may offer new opportunity for the management of patients. Using a novel high-throughput mass spectrometry on matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) silico-chips, we determined semiquantitative methylation changes of 22 candidate genes in breast cancer tissues. For the first time we analysed the methylation status of a total of 42 528 CpG dinucleotides on 22 genes in 96 different paraffin-embedded tissues (48 breast cancerous tissues and 48 paired normal tissues). A two-way hierarchical cluster analysis was used to classify methylation profiles. In this study, 10 hypermethylated genes (*APC*, *BIN1*, *BMP6*, *BRCA1*, *CST6*, *ESRb*, *GSTP1*, *P16*, *P21* and *TIMP3*) were identified to distinguish between cancerous and normal tissues according to the extent of methylation. Individual assessment of the methylation status for each CpG dinucleotide indicated that cytosine hypermethylation in the cancerous tissue samples was mostly located near the consensus sequences of the transcription factor binding sites. These hypermethylated genes may serve as biomarkers for clinical molecular diagnosis and targeted treatments of patients with breast cancer.

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Oncogene Oncogene 28, 899–909, 2009 IF 7,2

Normal colorectal mucosa exhibits sex- and segment-specific susceptibility to DNA methylation at the hMLH1 and MGMT promoters

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Abstract:
Silencing of gene expression by aberrant cytosine methylation is a prominent feature of human tumors, including colorectal cancers. Epigenetic changes of this type play undisputed roles in cell transformation when they involve genes that safeguard genome stability, and they can also be detected in precancerous lesions and seemingly normal peritumoral tissues. We explored physiological conditions associated with aberrant promoter methylation involving two DNA-repair genes in normal colorectal mucosa. Samples of cecal, transverse colon, sigmoid and rectal mucosa collected from 100 healthy individuals undergoing screening colonoscopy were analysed for *hMLH1* and *MGMT* promoter methylation with a quantitative PCR assay. Positivity in at least one colon segment was common in both sexes, with methylation involving 0.1–18.8% of the alleles (median=0.49%). Samples from males showed no consistent patterns for either promoter, but there were striking age- and colon segment-specific differences in the female subgroup. Here, the prevalence of *hMLH1* and *MGMT* methylation increased significantly with age, particularly in the right colon, where there was also an age-related increase in the percentage of alleles showing hMLH1 methylation. Concomitant methylation of both promoters was also significantly more common in the right colon of women. These findings paralleled immunohistochemical patterns of *hMLH1* and *MGMT* protein loss in an independent series of 231 colorectal cancers and were consistent with current epigenetic profiles of colorectal cancer subsets. They suggest the intriguing possibility that the epigenetic signatures of cancers may have early-stage, normal-tissue counterparts that reflect potentially important aspects of the initial carcinogenetic process.

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The Faseb Journal 23, 4011–4021, 2009 IF7,0

Extracellular cadherin repeat domains EC1 and EC5 of T-cadherin are essential for its ability to stimulate angiogenic behavior of endothelial cells

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Abstract:
T-cadherin (T-cad) promotes survival, proliferation, and migration of endothelial cells and induces angiogenesis. We aimed to identify domains of T-cad functionally relevant to its effects on endothelial cell behavior. To specifically target the functional properties of the 5 cadherin repeat domains (EC1–EC5) of T-cad, endothelial cells were transduced with lentivectors containing specific T-cad-domain-deletion mutant constructs (I, II, III, IV, V). Empty (E) lentivector-transduced cells served as control. Similarly to overexpression of native T-cad, cells expressing II, III, or IV displayed elevated levels of p-Akt and p-GSK3β and increased proliferation rates (for II, III) vs. E. I- and V-transduced cells exhibited reduced levels of p-Akt and p-GSK3β and retarded growth rates vs. E. Stimulatory effects of native T-cad overexpression on Akt and GSK3β phosphorylation were dose dependently inhibited by coexpression of I or V. Subsequent functional analyses compared only I-, II-, and V-mutant constructs with E as a negative control. Unlike II cells, I and V cells failed to exhibit homophilic ligation and deadhesion responses on a substratum of T-cad protein. In the wound assay, migration was increased for II cells but impaired for I and V cells. In endothelial cell-spheroid assay, angiogenic sprouting was augmented for II cells but inhibited for I and V cells. We conclude that EC1 and EC5 domains of T-cad are essential for its proangiogenic effects. I and V constructs may serve as dominant-negative mutants and as potential tools targeting excessive angiogenesis.—Joshi, M. B., Kyriakakis, E., Pfaff, D., Rupp, K., Philippova, M., Erne, P., Resink, T. J. Extracellular cadherin repeat domains EC1 and EC5 of T-cadherin are essential for its ability to stimulate angiogenic behavior of endothelial cells.

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Cutting Edge: IL-7 Regulates the Peripheral Pool of Adult RORγ$^+$ Lymphoid Tissue Inducer Cells

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Abstract:
During fetal life, CD4$^+$CD3$^-$ lymphoid tissue inducer (LTi) cells are required for lymph node and Peyer's patch development in mice. In adult animals, CD4$^+$CD3$^-$ cells are found in low numbers in lymphoid organs. Whether adult CD4$^+$CD3$^-$ cells are LTi cells and are generated and maintained through cytokine signals has not been directly addressed. In this study we show that adult CD4$^+$CD3$^-$ cells adoptively transferred into neonatal CXCR5$^{-/-}$ mice induced the formation of intestinal lymphoid tissues, demonstrating for the first time their bona fide LTi function. Increasing IL-7 availability in wild-type mice either by IL-7 transgene expression or treatment with IL-7/anti-IL-7 complexes increased adult LTi cell numbers through de novo generation from bone marrow cells and increased the survival and proliferation of LTi cells. Our observations demonstrate that adult CD4$^+$lineage– cells are LTi cells and that the availability of IL-7 determines the size of the adult LTi cell pool.

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The Journal of Immunology | The Journal of Immunology | 182, 7110–7118, 2009 IF 6,0

Lipoproteins in Staphylococcus aureus Mediate Inflammation by TLR2 and Iron-Dependent Growth In Vivo

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Abstract:
Lipoproteins (Lpp) are ligands of TLR2 and signal by the adaptor MyD88. As part of the bacterial cell envelope, Lpp are mainly involved in nutrient acquisition for *Staphylococcus aureus*. The impact of Lpp on TLR2-MyD88 activation for *S. aureus* in systemic infection is unknown. *S. aureus* strain SA113 deficient in the enzyme encoded by the prolipoprotein diacylglyceryl transferase gene (Δlgt), which attaches the lipid anchor to pro-Lpp, was used to study benefits and costs of Lpp maturation. Lpp in *S. aureus* induced early and strong cytokines by TLR2-MyD88 signaling in murine peritoneal macrophages. Lpp contributed via TLR2 to pathogenesis of sepsis in C57BL/6 mice with IL-1β, chemokine-mediated inflammation, and high bacterial numbers. In the absence of MyD88-mediated inflammation, Lpp allowed bacterial clearing from liver devoid of infiltrating cells, but still conferred a strong growth advantage in mice, which was shown to rely on iron uptake and storage in vitro and in vivo. With iron-restricted bacteria, the Lpp-related growth advantage was evident in infection of MyD88$^{-/-}$, but not of C57BL/6, mice. On the other hand, iron overload of the host restored the growth deficit of Δlgt in MyD88$^{-/-}$, but not in immunocompetent C57BL/6 mice. These results indicate that iron acquisition is improved by Lpp of *S. aureus* but is counteracted by inflammation. Thus, lipid anchoring is an evolutionary advantage for *S. aureus* to retain essential proteins for better survival in infection.

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Molecular and Cellular Biology | 29, 4841–4851 IF 5,9

Alpha Interferon Induces Long-Lasting Refractoriness of JAK-STAT Signaling in the Mouse Liver through Induction of USP18/UBP43

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Abstract:
Recombinant alpha interferon (IFN-α) is used for the treatment of viral hepatitis and some forms of cancer. During these therapies IFN-α is injected once daily or every second day for several months. Recently, the long-acting pegylated IFN-α (pegIFN-α) has replaced standard IFN-α in therapies of chronic hepatitis C because it is more effective, supposedly by inducing a long-lasting activation of IFN signaling pathways. IFN signaling in cultured cells, however, becomes refractory within hours, and little is known about the pharmacodynamic effects of continuously high IFN-α serum concentrations. To investigate the behavior of the IFN system in vivo, we repeatedly injected mice with IFN-α and analyzed its effects in the liver. Within hours after the first injection, IFN-α signaling became refractory to further stimulation. The negative regulator SOCS1 was rapidly upregulated and likely responsible for early termination of IFN-α signaling. For long-lasting refractoriness, neither SOCS1 nor SOCS3 were instrumental. Instead, we identified the inhibitor USP18/UBP43 as the key mediator. Our results indicate that the current therapeutic practice using long-lasting pegIFN-α is not well adapted to the intrinsic properties of the IFN system. Targeting USP18 expression may allow to exploit the full therapeutic potential of recombinant IFN-α.

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Brain Pathology 19, 459–466, 2009 IF 5,5

Molecular Changes in White Matter Adjacent to an Active Demyelinating Lesion in Early Multiple Sclerosis

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Abstract:
A stereotactic biopsy of a 17-year-old woman revealed an active inflammatory demyelinating lesion compatible with pattern III multiple sclerosis (MS) according to Lucchinetti et al. The biopsy included a white matter region distant from the active inflammatory demyelinating lesion with abnormal MRI signal, lacking histopathological signs of demyelination and/or oligodendrocyte apoptosis. Expression analysis of this area revealed a strong up-regulation of neuronal nitric oxide synthase (nNOS). Furthermore, detection of nitrotyrosine provided evidence for reactive nitrogen species (RNS)-mediated damage to oligodendrocytes. Concomitantly, genes involved in neuroprotection against oxidative stress such as heme oxygenase 1 were up-regulated. Even though a single case report, this study shows earliest molecular changes in white matter surrounding an actively demyelinating lesion during the first manifestation of MS, pointing toward a more widespread pathological process. Therapeutic targeting of the identified mechanisms of tissue injury might be crucial to prevent further lesion formation or secondary tissue damage.

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Tissue Engineering **Tissue Engineering** 15, 869–875, 2009 IF 5,4

Platelet Lysate as a Serum Substitute for 2D Static and 3D Perfusion Culture of Stromal Vascular Fraction Cells from Human Adipose Tissue

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Abstract:
Fetal bovine serum (FBS) and fibroblast growth factor (FGF)-2 are key supplements for the culture of stromal vascular fraction (SVF) cells from adipose tissue, both for typical monolayer (2D) expansion and for streamlined generation of osteogenic–vasculogenic grafts in 3D perfusion culture. The present study investigates whether factors present in human platelet lysate (PL) could substitute for FBS and FGF-2 in 2D and 3D culture models of SVF cells from human lipoaspirates. SVF cells were grown in medium supplemented with 10% FBS+FGF-2 or with 5% PL. In 2D cultures, PL initially supported SVF cell proliferation, but resulted in growth arrest shortly after the first passage. Freshly isolated SVF cells cultured with both media under perfusion for 5 days within 3D ceramic scaffolds induced bone formation after subcutaneous implantation in nude mice. However, blood vessels of donor origin were generated only using FBS+FGF-2–cultured cells. This was unexpected, because the proportion of $CD34^+/CD31^+$ endothelial lineage cells was significantly higher with PL than that of FBS+FGF-2 (33% vs. 3%, respectively). These results support the use of PL as a substitute of FBS+FGF-2 for short-term culture of human SVF cells, and indicate that more specific serum-free formulations are required to maintain a functionally vasculogenic fraction of SVF cells expanded under 3D perfusion.

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European Respiratory Journal 34, 616–628, 2009 IF5,3

Decreased hyaluronan in airway smooth muscle cells from patients with asthma and COPD

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Abstract:
Glycosaminoglycans (GAG) are essential extracellular matrix molecules which regulate tissue flexibility, a parameter that is reduced in airways of patients with asthma and chronic obstructive pulmonary disease (COPD). We investigated the expression of GAG and their metabolising enzymes in primary human airway smooth muscle cells (ASMC) obtained from healthy donors (controls) and patients with asthma or COPD.
Total GAG synthesis was assessed by [3H]-glucosamine incorporation. GAG were isolated, purified, fractionated by electrophoresis and characterised using specific GAG-degrading enzymes. Secretion of hyaluronic acid (HA) by ASMC from patients with asthma or COPD was significantly decreased compared with controls. RT-PCR analysis and western blotting revealed that this decrease was associated with a significant reduction in the expression of HA synthase-1 and -2 and a significant increase of hyaluronidase-1. Furthermore, the expression of the HA receptor CD44 was significantly decreased, whereas the receptor for HA-mediated motility was not expressed in asthma or COPD.
Our results indicate that there is a decreased expression of HA in asthma and COPD associated with a synergistic regulation of HA metabolising enzymes that may regulate the pathological airway remodelling in these lung diseases.

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Neoplasia 11, 987–1002, 2009 IF5,2

Tumor-Endothelial Interaction Links the CD44$^+$/CD24$^-$ Phenotype with Poor Prognosis in Early-Stage Breast Cancer

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Abstract:
Materials and Methods:
The genomic effects of tumor-endothelial interactions in cancer are not yet well characterized. To study this interaction in breast cancer, we set up an ex vivo coculture model with human benign and malignant breast epithelial cells with endothelial cells to determine the associated gene expression changes using DNA microarrays.
Results:
The most prominent response to coculture was the induction of the M-phase cell cycle genes in a subset of breast cancer cocultures that were absent in cocultures with normal breast epithelial cells. In monoculture, tumor cells that contained the stem cell-like CD44$^+$/CD24$^-$ signature had a lower expression of the M-phase cell cycle genes than the CD44$^-$/CD24$^+$ cells, and in the CD44$^+$/CD24$^-$ cocultures, these genes were induced. Pretreatment gene expression profiles of early-stage breast cancers allowed evaluating in vitro effects in vivo. The expression of the gene set derived from the coculture provided a basis for the segregation of the tumors into two groups. In a univariate analysis, early-stage tumors with high expression levels (n = 137) of the M-phase cell cycle genes had a significantly lower metastasis-free survival rate (P = 1.8e - 5, 50% at 10 years) and overall survival rate (P = 5e - 9, 52% at 10 years) than tumors with low expression (n = 158; metastasis-free survival, 73%; overall survival, 84%).
Conclusions:
Our results suggest that the interaction of endothelial cells with tumor cells that express the CD44$^+$/CD24$^-$ signature, which indicates a low proliferative potential, might explain the unexpected and paradoxical association of the CD44$^+$/CD24$^-$ signature with highly proliferative tumors that have an unfavorable prognosis.

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Differential Responsiveness to IL-2, IL-7, and IL-15 Common Receptor γ Chain Cytokines by Antigen-specific Peripheral Blood Naive or Memory Cytotoxic CD8+ T Cells From Healthy Donors and Melanoma Patients

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Abstract:
Common receptor γ chain (c-γ) cytokines (CKs) support proliferation of CD8+ T cells in presence or absence of antigen triggering and help maintaining the immunologic memory. We addressed the effects of low (<=5 ng/mL)-dose interleukin (IL)-2, IL-7, or IL-15 on human naive and memory antigen-specific CD8+ T cells. Peripheral blood CD8+ lymphocytes proliferated with decreasing efficiency in response to IL-15, IL-7, and IL-2. Of note, IL-15 preferentially promoted expansion of CD45RA-/CD8+ T-cell memory subset. Accordingly, cytotoxic T lymphocytes specific for cytomegalovirus-derived antigens from seropositive donors proliferated in response to IL-15 and, to lesser extent to IL-7, but poorly to IL-2. CD8+ T cells were then pretreated with CK before antigen stimulation using, as read out, specific cytotoxic activity. After the pretreatment with IL-15, but not IL-2, previously experienced viral antigens induced vigorous cytotoxic responses. Minor effects of IL-7 were also detectable. In contrast, IL-2 best supported the cytotoxic T lymphocyte generation from prevailingly naive CD8+ T cells from HLA-A*0201+ healthy donors, specific for L27Melan-A/MART-126-35 melanoma-associated antigen. Cells from melanoma patients were tested before and after Melan-A/MART-1–targeted antigen-specific immunotherapy. Untreated patients showed heterogeneous patterns of responsiveness to c-γ CK. However, when naive patients whose CD8+ T cells best responded to IL-2 were vaccinated, a modified responsiveness pattern was detectable. After immunization, cells displayed a significantly higher response to IL-15 than to IL-2 pretreatment. Thus, responsiveness to c-γ CK is critically influenced by naive or memory status of peripheral blood CD8+ T cells.

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Furanone at Subinhibitory Concentrations Enhances Staphylococcal Biofilm Formation by luxS Repression

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Abstract:
Brominated furanones from marine algae inhibit multicellular behaviors of gram-negative bacteria such as biofilm formation and quorum sensing (QS) without affecting their growth. The interaction of furanone with QS in gram-positive bacteria is unknown. Staphylococci have two QS systems, agr and luxS, which lower biofilm formation by two different pathways, RNAIII upregulation and bacterial detachment, and polysaccharide intercellular adhesin (PIA) reduction, respectively. We synthesized natural furanone compound 2 [(5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone] from *Delisea pulchra* and three analogues to investigate their effect on biofilm formation in gram-positive bacteria. Compound 2, but not the analogues, enhanced the biofilms of *Staphylococcus epidermidis* 1457 and 047 and of *S. aureus* Newman at concentrations between 1.25 and 20 μM. We show the growth inhibition of *S. epidermidis* and *S. aureus* by free furanone and demonstrate bactericidal activity. An induction of biofilm occurred at concentrations of 10 to 20% of the MIC and correlated with an increase in PIA. The biofilm effect was *agr* independent. It was due to interference with *luxS*, as shown by reduced *luxS* expression in the presence of compound 2 and independence of the strong biofilm formation in a *luxS* mutant upon furanone addition. Poly(L-lysine)-grafted/poly(ethylene glycol)-grafted furanone was ineffective on biofilm and not bactericidal, indicating the necessity for free furanone. Free furanone was similarly toxic for murine fibroblasts as for staphylococci, excluding a therapeutic application of this compound. In summary, we observed a biofilm enhancement by furanone in staphylococci at subinhibitory concentrations, which was manifested by an increase in PIA and dependent on *luxS*.

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Efficacy of Daptomycin in Implant-Associated Infection Due to Methicillin-Resistant *Staphylococcus aureus*: Importance of Combination with Rifampin

A. K. John[1], D. Baldoni[1], M. Haschke[2], K. Rentsch[3], P. Schaerli[4], W. Zimmerli[5] and A. Trampuz[1,6]

Abstract:
Limited treatment options are available for implant-associated infections caused by methicillin (meticillin)-resistant *Staphylococcus aureus* (MRSA). We compared the activity of daptomycin (alone and with rifampin [rifampicin]) with the activities of other antimicrobial regimens against MRSA ATCC 43300 in the guinea pig foreign-body infection model. The daptomycin MIC and the minimum bactericidal concentration in logarithmic phase and stationary growth phase of MRSA were 0.625, 0.625, and 20 µg/ml, respectively. In time-kill studies, daptomycin showed rapid and concentration-dependent killing of MRSA in stationary growth phase. At concentrations above 20 µg/ml, daptomycin reduced the counts by >3 log10 CFU/ml in 2 to 4 h. In sterile cage fluid, daptomycin peak concentrations of 23.1, 46.3, and 53.7 µg/ml were reached 4 to 6 h after the administration of single intraperitoneal doses of 20, 30, and 40 mg/kg of body weight, respectively. In treatment studies, daptomycin alone reduced the planktonic MRSA counts by 0.3 log10 CFU/ml, whereas in combination with rifampin, a reduction in the counts of >6 log10 CFU/ml was observed. Vancomycin and daptomycin (at both doses) were unable to cure any cage-associated infection when they were given as monotherapy, whereas rifampin alone cured the infections in 33% of the cages. In combination with rifampin, daptomycin showed cure rates of 25% (at 20 mg/kg) and 67% (at 30 mg/kg), vancomycin showed a cure rate of 8%, linezolid showed a cure rate of 0%, and levofloxacin showed a cure rate of 58%. In addition, daptomycin at a high dose (30 mg/kg) completely prevented the emergence of rifampin resistance in planktonic and adherent MRSA cells. Daptomycin at a high dose, corresponding to 6 mg/kg in humans, in combination with rifampin showed the highest activity against planktonic and adherent MRSA. Daptomycin plus rifampin is a promising treatment option for implant-associated MRSA infections.

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Molecular Cancer Research Molecular Cancer Research 6, 1702–1709, 2008 IF 4,5

High-Throughput Hacking of the Methylation Patterns in Breast Cancer by In vitro Transcription and Thymidine-Specific Cleavage Mass Array on MALDI-TOF Silico-Chip

R. Radpour[1], M. M. Haghighi[2], A. Xiu-Cheng Fan[1], P. M. Torbati[3], S. Hahn[1], W. Holzgreve[1] and X. Y. Zhong[1]

Abstract:
Over the last decade, the rapidly expanding interest in the involvement of DNA methylation in developmental mechanisms, human diseases, and malignancies has highlighted the need for an accurate, quantitative, and high-throughput assay. Existing methods are limited and are often too laborious for high-throughput analysis or inadequate for quantitative analysis of methylation. Recently, a MassCLEAVE assay has been developed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry to analyze base-specific methylation patterns after bisulfite conversion. To find an efficient and more cost-effective high-throughput method for analyzing the methylation profile in breast cancer, we developed a method that allows for the simultaneous detection of multiple target CpG residues by using thymidine-specific cleavage mass array on matrix-assisted laser desorption/ionization time-of-flight silicon chips. We used this novel quantitative approach for the analysis of DNA methylation patterns of four tumor suppressor genes in 96 breast tissue samples from 48 patients with breast cancer. Each individual contributed a breast cancer specimen and corresponding adjacent normal tissue. We evaluated the accuracy of the approach and implemented critical improvements in experimental design.

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Molecular Cancer Research | Molecular Cancer Research | 7, 601–613, 2009 IF 4,5

Targeting Melanoma with Dual Phosphoinositide 3-Kinase/Mammalian Target of Rapamycin Inhibitors

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Abstract:
GPhosphoinositide 3-kinase (PI3K)/protein kinase B/Akt and Ras/mitogen-activated protein kinase pathways are often constitutively activated in melanoma and have thus been considered as promising drug targets. Exposure of melanoma cells to NVP-BAG956, NVP-BBD130, and NVP-BEZ235, a series of novel, potent, and stable dual PI3K/mammalian target of rapamycin (mTOR) inhibitors, resulted in complete G1 growth arrest, reduction of cyclin D1, and increased levels of p27KIP1, but negligible apoptosis. In contrast, treatment of melanoma with the pan-class I PI3K inhibitor ZSTK474 or the mTORC1 inhibitor rapamycin resulted only in minor reduction of cell proliferation. In a syngeneic B16 mouse melanoma tumor model, orally administered NVP-BBD130 and NVP-BEZ235 efficiently attenuated tumor growth at primary and lymph node metastatic sites with no obvious toxicity. Metastatic melanoma in inhibitor-treated mice displayed reduced numbers of proliferating and significantly smaller tumor cells. In addition, neovascularization was blocked and tumoral necrosis increased when compared with vehicle-treated mice. In conclusion, compounds targeting PI3K and mTOR simultaneously were advantageous to attenuate melanoma growth and they develop their potential by targeting tumor growth directly, and indirectly via their interference with angiogenesis. Based on the above results, NVP-BEZ235, which has entered phase I/II clinical trials in patients with advanced solid tumors, has a potential in metastatic melanoma therapy.

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Bioconjugate Chemistry | 20, 984–993, 2008 IF4,3

Glycosylated DOTA–α-Melanocyte-Stimulating Hormone Analogues for Melanoma Targeting: Influence of the Site of Glycosylation on in Vivo Biodistribution

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Abstract:
Dα-Melanocyte-stimulating hormone (α-MSH) is known to bind to the melanocortin receptor 1 (MC1R) which is overexpressed on melanotic and amelanotic melanoma cells. α-MSH analogues are potential candidates for specific targeting of melanoma metastases. Several linear and cyclic radiolabeled MSH peptides have been designed and tested in the past, showing both high affinity for the MC1R in vitro and good incorporation in tumor xenografts in vivo. However, considerable kidney reabsorption of the radiopeptides could not be avoided. With the aim to increase the tumor-to-kidney ratio, we synthesized six glycosylated derivatives of NAPamide, an α-MSH octapeptide analogue with high tumor selectivity and coupled them to the chelator DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). The peptides were evaluated in vitro for MC1R binding and bioactivity and, after labeling with 111In, for in vitro cellular uptake and in vivo tissue distribution in mice carrying B16F1 melanoma tumors. The glycopeptides showed excellent binding affinities in the low nanomolar to subnanomolar range using both murine and human melanoma cell lines. However, five glycopeptides displayed lower selectivity in vivo than the parent DOTA–NAPamide, because of either a lower tumor uptake or a higher kidney uptake. In particular C-terminal extension of the amide group by a galactosyl moiety increased the kidney retention dramatically. By contrast, an N-terminally positioned galactose residue in DOTA–Gal-NAPamide improved the tumor-to-kidney ratio (4–48 h AUC of 1.34) by a factor of about 1.2 as compared to the parent DOTA–NAPamide (4–48 h AUC of 1.11), thus serving as new lead compound for MC1R-targeting molecules.

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Linezolid Alone or Combined with Rifampin against Methicillin-Resistant *Staphylococcus aureus* in Experimental Foreign-Body Infection

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Abstract:
We investigated the activity of linezolid, alone and in combination with rifampin (rifampicin), against a methicillin-resistant *Staphylococcus aureus* (MRSA) strain in vitro and in a guinea pig model of foreign-body infection. The MIC, minimal bactericidal concentration (MBC) in logarithmic phase, and MBC in stationary growth phase were 2.5, >20, and >20 µg/ml, respectively, for linezolid; 0.01, 0.08, and 2.5 µg/ml, respectively, for rifampin; and 0.16, 0.63, >20 µg/ml, respectively, for levofloxacin. In time-kill studies, bacterial regrowth and the development of rifampin resistance were observed after 24 h with rifampin alone at 1x or 4x the MIC and were prevented by the addition of linezolid. After the administration of single intraperitoneal doses of 25, 50, and 75 mg/kg of body weight, linezolid peak concentrations of 6.8, 12.7, and 18.1 µg/ml, respectively, were achieved in sterile cage fluid at 3 h. The linezolid concentration remained above the MIC of the test organism for 12 h with all doses. Antimicrobial treatments of animals with cage implant infections were given twice daily for 4 days. Linezolid alone at 25, 50, and 75 mg/kg reduced the planktonic bacteria in cage fluid during treatment by 1.2 to 1.7 log10 CFU/ml; only linezolid at 75 mg/kg prevented bacterial regrowth 5 days after the end of treatment. Linezolid used in combination with rifampin (12.5 mg/kg) was more effective than linezolid used as monotherapy, reducing the planktonic bacteria by 3 log10 CFU ($P < 0.05$). Efficacy in the eradication of cage-associated infection was achieved only when linezolid was combined with rifampin, with cure rates being between 50% and 60%, whereas the levofloxacin-rifampin combination demonstrated the highest cure rate (91%) against the strain tested. The linezolid-rifampin combination is a treatment option for implant-associated infections caused by quinolone-resistant MRSA.

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Cell Calcium cell calcium 45, 192–197, 2009 IF4,3

A recessive ryanodine receptor 1 mutation in a CCD patient increases channel activity

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Abstract:
Ryanodine receptors plays a crucial role in skeletal muscle excitation–contraction coupling by releasing calcium ions required for muscle contraction from the sarcoplasmic reticulum. At least three phenotypes associated with more than 100 *RYR1* mutations have been identified; in order to elucidate possible pathophysiological mechanisms of *RYR1* mutations linked to neuromuscular disorders, it is essential to define the mutation class by studying the functional properties of channels harbouring clinically relevant amino acid substitutions. In the present report we investigated the functional effects of the c.7304G > T *RYR1* substitution (p.Arg2435Leu) found in a patient affected by central core disease. Both parents were heterozygous for the substitution while the proband was homozygous. We characterized $Ca2^+$ homeostasis in myoD transduced myotubes from controls, the heterozygous parents and the homozygous proband expressing the endogenous mutation. We also expressed the recombinant mutant channels in heterologous cells and characterized their [^{3}H]ryanodine binding and single channel properties. Our results show that the p.Arg2435Leu substitution affects neither the resting [$Ca2^+$], nor the sensitivity of the ryanodine receptor to pharmacological activators, but rather reduces the release of $Ca2^+$ from intracellular stores induced by pharmacological activators as well as by KCl via the voltage sensing dihydropyridine receptor.

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Biochemical Journal 416, 271-280, 2008 IF4,3

A requirement for thioredoxin in redox-sensitive modulation of T-cadherin expression in endothelial cells

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Abstract:
T-cad (T-cadherin), a glycosylphosphatidylinositol-anchored cadherin superfamily member, is expressed widely in the brain and cardiovascular system, and absent, decreased, or even increased, in cancers. Mechanisms controlling T-cad expression are poorly understood. The present study investigated transcriptional regulation of T-cad in ECs (endothelial cells). Conditions of oxidative stress (serum-deprivation or presence of H2O2) elevate T-cad mRNA and protein levels in ECs. Reporter gene analysis, using serially deleted T-cad promoter stretches ranging from –99 to –2304 bp, located the minimal promoter region of T-cad within –285 bp from the translation start site. Reporter activity in ECs transfected with the –285 bp construct increased under conditions of oxidative stress, and this was normalized by antioxidant N-acetylcysteine. An electrophoretic-mobility-shift assay revealed a specific nucleoprotein complex unique to –156 to –203 bp, which increased when nuclear extracts from oxidatively stressed ECs were used, suggesting the presence of redox-sensitive binding element(s). MS analysis of the nucleoprotein complex unique to –156 to –203 bp after streptavidin–agarose pull-down detected the presence of the redox-active protein thioredoxin. The presence of thioredoxin-1 in a nuclear extract from oxidatively stressed ECs was demonstrated after immunoprecipitation and immunoblotting. Transfection of ECs with thioredoxin-1 small interfering RNA abrogated oxidative-stress-induced up-regulation of T-cad transcripts and protein. We conclude that thioredoxin-1 is an important determinant of redox-sensitive transcriptional up-regulation of T-cad in ECs.

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Cartilage tissue engineering using pre-aggregated human articular chondrocytes

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Abstract:
In this study, we first aimed at determining whether human articular chondrocytes (HAC) proliferate in aggregates in the presence of strong chondrocyte mitogens. We then investigated if the aggregated cells have an enhanced chondrogenic capacity as compared to cells cultured in monolayer. HAC from four donors were cultured in tissue culture dishes either untreated or coated with 1% agarose in the presence of TGFb-1, FGF-2 and PDGF-BB. Proliferation and stage of differentiation were assessed by measuring respectively DNA contents and type II collagen mRNA. Expanded cells were induced to differentiate in pellets or in Hyaff®-11 meshes and the formed tissues were analysed biochemically for glycosaminoglycans (GAG) and DNA, and histologically by Safranin O staining. The amount of DNA in aggregate cultures increased significantly from day 2 to day 6 (by 3.2-fold), but did not further increase with additional culture time. Expression of type II collagen mRNA was about two orders of magnitude higher in aggregated HAC as compared to monolayer expanded cells. Pellets generated by aggregated HAC were generally more intensely stained for GAG than those generated by monolayer-expanded cells. Scaffolds seeded with aggregates accumulated more GAG (1.3-fold) than scaffolds seeded with monolayer expanded HAC. In conclusion, this study showed that HAC culture in aggregates does not support a relevant degree of expansion. However, aggregation of expanded HAC prior to loading into a porous scaffold enhances the quality of the resulting tissues and could thus be introduced as an intermediate culture phase in the manufacture of engineered cartilage grafts.

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A JP - Lung Cellular and Molecular Physiology 297, 326–339, 2009 IF 3,9

Dimethylfumarate inhibits NF-κB function at multiple levels to limit airway smooth muscle cell cytokine secretion

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Abstract:
The antipsoriatic dimethylfumarate (DMF) has been anecdotically reported to reduce asthma symptoms and to improve quality of life of asthma patients. DMF decreases the expression of proinflammatory mediators by inhibiting the transcription factor NF-B and might therefore be of interest for the therapy of inflammatory lung diseases. In this study, we determined the effect of DMF on platelet-derived growth factor (PDGF)-BB- and TNF-induced asthma-relevant cytokines and NF-κB activation by primary human asthmatic and nonasthmatic airway smooth muscle cells (ASMC). Confluent nonasthmatic and asthmatic ASMC were incubated with DMF (0.1–100 μM) and/or dexamethasone (0.0001–0.1 μM), NF-κB p65 siRNA (100 nM), the NF-B inhibitor helenalin (1 μM) before stimulation with PDGF-BB or TNF (10 ng/ml). Cytokine release was measured by ELISA. NF-B, mitogen and stress-activated kinase (MSK-1), and CREB activation was determined by immunoblotting and EMSA. TNF-induced eotaxin, RANTES, and IL-6 as well as PDGF-BB-induced IL-6 expression was inhibited by DMF and by dexamethasone from asthmatic and nonasthmatic ASMC, but the combination of both drugs showed no glucocorticoid sparing effect in either of the two groups. NF-B p65 siRNA and/or the NF-κB inhibitor helenalin reduced PDGF-BB- and TNF-induced cytokine expression, suggesting the involvement of NF-κB signaling. DMF inhibited TNF-induced NF-κB p65 phosphorylation, NF-κB nuclear entry, and NF-B-DNA complex formation, whereas PDGF-BB appeared not to activate NF-κB within 60 min. Both stimuli induced the phosphorylation of MSK-1, NF-κB p65 at Ser276, and CREB, and all were inhibited by DMF. These data suggest that DMF downregulates cytokine secretion not only by inhibiting NF-κB but a wider range of NF-κB-linked signaling proteins, which may explain its potential beneficial effect in asthma.

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Osteoarthritis and Cartilage Osteoarthritis and Cartilage 17, 489–496, 2009 IF3,7

Intra-individual comparison of human ankle and knee chondrocytes in vitro: relevance for talar cartilage repair

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Abstract:
Objective: As compared to knee chondrocytes (KC), talar chondrocytes (TC) have superior synthetic activity and increased resistance to catabolic stimuli. We investigated whether these properties are maintained after TC are isolated and expanded in vitro.

Methods: Human TC and KC from 10 cadavers were expanded in monolayer and then cultured in pellets for 3 and 14 days or in hyaluronan meshes (Hyaff®-11) for 14 and 28 days. Resulting tissues were assessed biochemically, histologically, biomechanically and by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The proteoglycan and collagen synthesis rates in the pellets were also measured following exposure to Interleukin-1 beta (IL-1β).

Results: After 14 days of pellet culture, TC and KC expressed similar levels of type I collagen (CI) and type II collagen (CII) mRNA and the resulting tissues contained comparable amounts of glycosaminoglycans (GAG) and displayed similar staining intensities for CII. Also proteoglycan and collagen synthesis were similar in TC and KC pellets, and dropped to a comparable extent in response to IL-1β. Following 14 days of culture in Hyaff®-11, TC and KC generated tissues with similar amounts of GAG and CI and CII. After 28 days, KC deposited significantly larger fractions of GAG and CII than TC, although the trend was not reflected in the measured biomechanical properties.

Conclusion: After isolation from their original matrices and culture expansion, TC and KC displayed similar biosynthetic activities, even in the presence of catabolic stimuli. These in vitro data suggest a possible equivalence of TC and KC as autologous cell sources for the repair of talar cartilage lesions.

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Journal of Clinical Microbiology | Journal of Clinical Microbiology | 47, 774–776, 2009 | IF 3,7

Performance of Microcalorimetry for Early Detection of Methicillin Resistance in Clinical Isolates of *Staphylococcus aureus*

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Abstract:
We describe a calorimetric assay for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA) within 5 h. Microbial heat was calculated in culture with and without cefoxitin. Among 30 genetically distinct clinical isolates, 19/20 MRSA (95%) and 10/10 methicillin-susceptible *Staphylococcus aureus* (100%) were correctly identified. Microcalorimetry may be useful for rapid MRSA screening.

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Neuropsychologia | 47, 625–633, 2009 | IF 3,6

The age of second language acquisition determines the variability in activation elicited by narration in three languages in Broca's and Wernicke's area

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Abstract:
It is generally accepted that the presence of a second language (L2) has an impact on the neuronal substrates build up and used for language processing; the influence of the age of L2 exposure, however, is not established. We tested the hypothesis that the age of L2 acquisition has an effect on the cortical representation of a multilingual repertoire in 44 multilinguals with different age of exposure to a L2 (simultaneous or covert simultaneous exposure to L1 and L2, sequential acquisition of L1 and L2 between 1 and 5 years, late learning of L2 after 9 years of age) and all fluent in a late learned L3. Regional activation in a language production task showed a high in-between-subject variability, which was higher than within-subject variability between L1, L2, and L3. We, therefore, performed a single subject analysis and calculated the within-subject variance in the numbers of activated voxels in Broca's and Wernicke's area. Subjects with early exposure to L2 showed low variability in brain activation in all three languages, in the two early as well as the late learned language. In contrast, late multilinguals exhibited higher variability. Thus, cerebral representation of languages is linked to the age of L2 acquisition: early exposure to more than one language gives rise to a language processing network that is activated homogeneously by early and late learned languages, while the inhomogeneous activation in late multilinguals indicates more independent access to the multilingual repertoire. Early passive exposure to L2 results in the same low variance as active bilingual upbringing. Variability in local brain activity increases progressively from the simultaneous to late L2 exposure, indicating a gradual transition from the mode of early bilingual language representation to that of late ones.

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British Journal Dermatology 161, 199–202, 2009 IF 3,4

High T-cadherin expression is a feature of basal cell carcinoma

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Abstract:
SIR, Cadherins play important roles in controlling keratinocyte growth, differentiation and survival.1 Inappropriate expression or function of cadherins underlies many diseases of the epidermis. 2 Inverse associations between expression of atypical glycosylphosphatidylinositol-anchored T-cadherin (T-cad) and benign and malignant skin diseases [psoriasis vulgaris,3 invasive squamous cell carcinoma4 and basal cell carcinoma (BCC)5] have been reported but not yet confirmed. We examined T-cad protein expression in normal skin specimens and skin biopsies from 40 patients with BCC using goat antirecombinant human T-cad (aa 23–692) antibodies (R&D Systems, Abingdon, U.K.) and a universal immunoperoxidase polymer detection system (N-Histofine_ Simple Stain MAX PO; Nichirei Biosciences, Tokyo, Japan). BCCs were subclassified as superficial (n = 12), nodular (n = 18) or infiltrative (n = 10) in terms of their histological morphology.6
We found T-cad expression in all BCC specimens, irrespective of their histological classification (Fig. 1). Generally T-cad staining was stronger in BCC than in the basal cell layer of the epidermis and was very prominent at intercellular borders at tumour expansile edges, which appear to be the leading, invasive fronts of the tumours. In superficial BCC (Fig. 1a /a+,b /b+) and nodular BCC (Fig. 1c /c+,d /d+) there was a strong preferential membranous expression of T-cad on the palisading peripheral BCC cells and within the peripheral cleft at the junction between lesion and stroma (see Fig. 1a /a+,b /b+). The stromal cells within the nodules were also positive for T-cad, although the expression intensity of the palisading peripheral cells was stronger. In addition, staining patterns on the central stromal cells of some tumours were irregular and scattered, with varying intensity of expression. No differences in T-cad expression between the peritumoral epidermis and the epidermis in nontumoral skin biopsies were detectable.

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European Journal of Neuroscience 29, 2276–2290, 2009 IF3,3

The myelin protein MAL affects peripheral nerve myelination: a new player influencing p75 neurotrophin receptor expression

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Abstract:
The myelin and lymphocyte protein (MAL) is a raft-associated membrane protein predominantly expressed by oligodendrocytes and Schwann cells. Here we show that MAL regulates myelination in the peripheral nervous system. In mice overexpressing MAL, myelination was retarded and fibers were hypomyelinated, whereas myelination in MAL knockout mice was accelerated. This was not due to impaired Schwann cell proliferation, differentiation or axonal sorting. We found that the expression level of p75 neurotrophin receptor mRNA and protein was strongly reduced in developing sciatic nerves in MAL-overexpressing mice. This reduction is well correlated with the observed alterations in myelination initiation, speed of myelination and alterations in Remak bundle development. Our results suggest a functional role for MAL in peripheral myelination by influencing the expression of membrane components that mediate axon-glia interaction during ensheathment and myelin wrapping.

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Reproductive BioMedicine Online 18, 407–411, 2008 IF3,0

Circulating cell-free DNA as a potential biomarker for minimal and mild endometriosis

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Abstract:
It has recently been reported that high concentrations of circulating cell-free (ccf) nucleic acids in plasma and serum could be used as biomarkers for non-invasive monitoring a wide variety of malignant and benign proliferations and inflammatory conditions. Endometriosis is one of the most common benign gynaecological proliferations with inflammatory activation in premenopausal women. Real-time multiplex polymerase chain reaction was used for synchronized quantification of the glyceraldehyde-3-phosphate dehydrogenase gene sequence in nuclear DNA (nDNA) and the ATP synthase-8 gene sequence in mitochondrial DNA (mtDNA). DNA was extracted from 500 microl serum and plasma of 19 cases with endometriosis to measure the total amount of ccf nDNA and ccf mtDNA. The concentration of ccf nDNA in plasma was significantly higher in the endometriosis group than in the control group (P = 0.046). The cut-off value selected by a receiver operating characteristic curve could provide a sensitivity of 70% and a specificity of 87% to discriminate between the minimal or mild cases and normal controls. The finding of significantly increased concentrations of ccf nDNA in plasma of patients with endometriosis suggests that ccf nDNA might be a potential biomarker for developing non-invasive diagnostic test in endometriosis.

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Chemico-Biological Interactions 180, 472–477, 2009 IF3,0

Interaction between pivaloylcarnitine and l-carnitine transport into L6 cells overexpressing hOCTN2

L. Todesco[1], M. Bodmer[1], K. Vonwil[1], D. Häussinger[2] and S. Krähenbühl[1]

Abstract:
Patients ingesting pivalic acid containing prodrugs develop hypocarnitinemia. Pivalic acid is cleaved from such drugs and excreted renally as pivaloylcarnitine. Plasma concentrations (reflecting the concentration in the glomerular filtrate entering the proxinmal tubule) in patients treated with cefditoren pivoxil are approximately 5 μM for pivaloylcarnitine and 10 μM for carnitine. Kinetic studies were performed using L6 cells overexpressing the human kidney carnitine transporter (hOCTN2) to assess the mechanisms leading to hypocarnitinemia in such patients. l-carnitine transport showed saturation kinetics (Km 6.3 μM) and could be inhibited competitively by pivaloylcarnitine (Ki 70 μM). Pivaloylcarnitine was also transported by OCTN2 (Km 212 μM) and its transport could be inhibited competitively by l-carnitine (Ki 7.8 μM). Haldane and Eadie-Hofstee plots were linear for both carnitine and pivaloylcarnitine. Our data indicate that both carnitine and pivaloylcarnitine bind to OCTN2 at a single, identical site. Considering the low plasma and tubular pivaloylcarnitine concentration, the high Km of pivaloylcarnitine regarding OCTN2 and the inhibition of pivaloylcarnitine transport by carnitine, pivaloylcarnitine is unlikely to be reabsorbed under these conditions. On the other hand, our data indicate that the renal reabsorption of carnitine is not impaired in patients treated with pivalic acid containing prodrugs. Hypocarnitinemia in such patients therefore develops due to massive renal losses of pivaloylcarnitine and not due to inhibition of carnitine reabsorption by pivaloylcarnitine.

[1] Division of Clinical Pharmacology & Toxicology and Department of Research, University Hospital, CH-4031 Basel, Switzerland
[2] Department of Chemistry, University of Basel, Basel, Switzerland

European Journal of Neurology 16, 771–774, 2009 IF 2,5

Increased levels of inflammatory chemokines in amyotrophic lateral sclerosis

J. Kuhle[1,2], R. L. P. Lindberg[2], A. Regeniter[3], M. Mehling[1,2], A. J. Steck[1,2], L. Kappos[1,2] and A. Czaplinski[1]

Abstract:

Background and purpose: Amyotrophic lateral sclerosis (ALS) is classically assumed to be a neurodegenerative disorder. Inflammation has been observed in CNS tissue in ALS patients. We investigated the expression and prognostic relevance of proinflammatory chemokines in ALS.

Methods: We analyzed nine chemokines, eotaxin, eotaxin-3, IL-8, IP-10, MCP-1, MCP-4, macrophage derived chemokine (MDC), macrophage inflammatory protein-1β (MIP-1β), and serum thymus and activation- regulated chemokine (TARC) in serum and cerebrospinal fluid (CSF) of 20 ALS- and 20 non-inflammatory neurological disease (NIND)-patients.

Results: MCP-1 and IL-8 levels in CSF in ALS were significantly higher than in NIND (1304 pg/ml vs. 1055 pg/ml, P = 0.013 and 22.7 pg/ml vs. 18.6 pg/ml, P = 0.035). The expression of MCP-1 and IL-8 were higher in CSF than in serum (P < 0.001). There was a trend towards higher MCP-1 CSF levels in ALS patients with shorter time between first symptoms and diagnosis (r = –0.407; P = 0.075).

Conclusions: We confirmed previous findings of increased MCP-1 levels in CSF of ALS patients. Furthermore, increased levels of IL-8 in CSF suggest a stimulation of a proinflammatory cytokine cascade after microglia activation. We found a tendency for higher MCP-1 values in patients with a shorter diagnostic delay, who are known to have also a shorter survival. This may suggest an association of higher MCP-1 levels with rapidly progressing disease.

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[2] Therapeutic Area Neurodegeneration, Serono Laboratories, 9 Chemin de Mines, 1202 Geneva, Switzerland

Journal of Cancer Research and Clinical Oncology 135, 983–989, 2009 IF 2,3

Mitochondrial DNA content in paired normal and cancerous breast tissue samples from patients with breast cancer

A. Xiu-Cheng Fan[1], R. Radpour[1], M. Montazer Haghighi[2], C. Kohler[1], P. Xia[1], S. Hahn[1], W. Holzgreve[1,3] and X. Y. Zhong[1]

Abstract:

Introduction: We develop a multiplex quantitative real-time PCR for synchronized analysis of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) to investigate relative mtDNA abundance in paired normal and cancerous breast tissues.

Materials and methods: The amounts of nDNA and mtDNA in 102 tissue samples were quantified for both glyceraldehype-3-phosphodehydrogenase (GAPDH) gene and mtDNA encoded ATPase (MTATP) 8 gene. The average threshold cycle (Ct) number values of the nDNA and mtDNA were used to calculate relative mtDNA content in breast tissues.

Results: The median delta Ct (ΔCt) and the median mtDNA content for normal and cancerous breast tissues were 6.73 and 2.54, as well as 106.50 and 5.80 (P = 0.000, respectively). The mtDNA content was decreased in 82% of cancerous breast tissues compared with the normal ones. The changes were associated with hormone receptor status.

Conclusion Our finding suggests that decreased mtDNA content in breast cancer may have diagnostic and prognostic value for the disease.

[1] Laboratory for Prenatal Medicine and Gynecologic Oncology, Department of Biomedicine, Women's Hospital, University of Basel, Hebelstrasse 20, Room Nr. 416, 4031 Basel, Switzerland
[2] Azad University, East of Tehran Branch, Tehran, Iran
[3] University Medical Center, University of Freiburg, Hugstetter Str. 49, 79106 Freiburg, Germany

European Journal of Pharmacology | european journal of pharmacology | 612, 35–40, 2009 IF2,3

Modulators of signal transduction pathways can promote axonal regeneration in entorhino-hippocampal slice cultures

B. Bonnici and J. P. Kapfhammer

Abstract:
Axonal regeneration after lesions is usually not possible in the adult central nervous system but can occur in the embryonic and young postnatal nervous system. In this study we used the model system of mouse entorhino-hippocampal slice cultures to assess the potential of pharmacological treatments with compounds targeting signal transduction pathways to promote growth of entorhinal fibers after mechanical lesions across the lesion site to their target region in the dentate gyrus. Compounds acting on the cyclic AMP-system, protein kinase C and G-proteins have been shown before to be able to promote regeneration. In this study we have confirmed the potential of drugs affecting these systems to promote axonal regeneration in the central nervous system. In addition we have found that inhibition of the phosphoinositide 3-kinase pathway and of the inositol triphosphate receptor also promoted axonal growth across the lesion site and are thus potential novel drug targets for promoting axonal regeneration after central nervous system lesions. Our findings demonstrate that slice culture models can be used to evaluate compounds for their potential to promote axonal regeneration and that the pharmacological modulation of signal transduction pathways is a promising approach for promoting axonal repair.

Anatomical Institute, Department of Biomedicine Basel, University of Basel, 4056 Basel, Switzerland

International Journal of Oncology 34, 1135–1138, 2009 IF2,2

A natural antisense transcript, BOKAS, regulates the pro-apoptotic activity of human Bok

H. Zhang, S. Gao and C. De Geyter

Abstract:
Bok is a proapoptotic member in the Bcl-2 family and the expression of Bok is regulated by cellular stresses. In the present study, we have isolated and characterized a natural antisense transcript of Bok, BOKAS. The BOKAS gene consists of 2 exons, that expresses as a non-protein coding transcript. Both BOKAS and Bok are transcribed from the same locus but in opposite orientations. The mRNA expression of BOKAS was only detected in testis and certain cancer tissues but not in other normal adult tissues examined. Overexpression of BOKAS alone exhibited no significant anti- or pro-apoptotic activity but it was able to inhibit Bok-induced apoptosis in HeLa cells. Our results suggest that BOKAS may function specifically in the human testis, where it serves as an antisense molecule to regulate Bok-induced apoptosis. In addition, natural antisense transcripts were identified for BAD and BCL2L12.

University Women's Hospital Basel and Research Department of University Hospital, CH-4031 Basel, Switzerland.

Sciences Signaling 2, 74–, 2009 IF N.A

PI3Kgamma adaptor subunits define coupling to degranulation and cell motility by distinct PtdIns(3,4,5)P3 pools in mast cells

T. Bohnacker, R. Marone, E. Collmann, R. Calvez, E. Hirsch and M. P. Wymann

Abstract:
Phosphoinositide 3-kinase gamma (PI3Kgamma) plays a major role in chronic inflammation and allergy. It is a heterodimer of a catalytic p110gamma subunit and an adaptor protein, either p101 or the p101 homolog p84 (p87(PIKAP)). It is unclear whether both PI3Kgamma complexes specifically modulate responses such as chemotaxis and degranulation. In mast cells, the p84:p110gamma complex synergizes with immunoglobulin E (IgE)- and antigen-clustered FcepsilonRI receptor signaling and is required to achieve maximal degranulation. During this process, PI3Kgamma is activated by ligands of heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptors (GPCRs), in particular adenosine receptors, through autocrine and paracrine pathways. Here, we show that p110gamma needs p84 to relay signals from GPCRs to formation of phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3,4,5)P(3)], phosphorylation of Akt, migration of cells, and synergistic adenosine-enforced degranulation. Furthermore, the absence of adaptor subunits could not be compensated for by increased p110gamma abundance. Differentiated, p110gamma null cells also lost adaptor proteins. Complementation of p110gamma null mast cells with p101 and p110gamma restored the activation of Akt and cell migration, but failed to support degranulation. Lack of degranulation was attributed to a change in the spatiotemporal localization of PI3Kgamma-derived PtdIns(3,4,5)P(3); although both p84:p110gamma and p101:p110gamma complexes initially deposited PtdIns(3,4,5)P(3) at the plasma membrane, p101:p110gamma-derived PtdIns(3,4,5)P(3) was rapidly endocytosed to motile, microtubule-associated vesicles. In addition, p84:p110gamma, but not p101:p110gamma signaling was sensitive to disruption of lipid rafts. Our results demonstrate a nonredundant function for the p101 and p84 PI3Kgamma adaptor proteins and show that distinct pools of PtdIns(3,4,5)P(3) at the plasma membrane can elicit specific cell responses.

Institute of Biochemistry and Genetics, Department of Biomedicine, University of Basel, Mattenstrasse 28, Basel, Switzerland.

The Open Critical Care Medicine Journal 2, 28–37, 2009 IF N.A

Dissecting the Dualistic Effects of Transforming Growth Factor (TGF)-β on Fibroproliferation and Extracellular Matrix Production in Primary Human Lung Fibroblasts – The Role of p38δ MAP Kinase

K. E. Hostettler[1,2,3], S. Goulet[1], M. Roth[1,3], J. Zhong[2,3], J. K. Burgess[2,3], J. L. Black[2,3], M. Tamm[1], P. Borger[1,3]

Abstract:
Rationale: Inflammation, increased fibroblast proliferation, and increased deposition of extracellular matrix (ECM) are hallmarks of early lung fibrosis and asthma. Transforming growth factor-β (TGF-β) has been suggested as a key regulator of lung tissue homeostasis with several and often opposite effects on fibroblast proliferation and ECM production. In human and animal model systems, it has been shown that TGF-β induced several signaling cascades including Smads, p38 mitogen-activated protein (MAP) kinases, and extracellular signal-regulated kinases 1/2 (ERK). Information on how TGF-β regulates and controls normal primary lung fibroproliferation and ECM production is not present.
Objectives: We sought to dissect the effects of TGF-β on fibroproliferation and ECM production of primary adult human lung fibroblasts and elucidate the involved signaling pathways.
Results: Depending on the presence of fetal bovine serum (FBS; 10%), TGF-β exerted opposite effects on fibroproliferation. In the absence of FBS, low TGF-β concentrations (0.01 and 0.001 ng/ml) significantly induced fibroproliferation. In the presence of FBS, TGF-β (1 ng/ml, 10 ng/ml) significantly reduced fibroproliferation. TGF-β dose-dependently increased ECM deposition, which was independent of the presence of FBS. The anti-proliferative effect of TGF-β was associated with increased prostaglandin E2 (PGE2) production, that was induced via p38δ and ERK 1/2 MAP kinases. Indomethacin (2.5 μM) and a small interfering RNA specific for p38 MAP kinase completely reversed the TGF-β-dependent inhibition of fibroblast proliferation.
Conclusions: Both pro- and anti-proliferative cascades can be activated by TGF-β. In a mitogenic or inflammatory environment TGF-β induces PGE2 synthesis via activation of p38δ MAP kinase, which then exerts a strong antiproliferative effect. This dualistic nature of TGF-β may exist in order to maintain lung tissue integrity.

[1] Pulmonary Cell Research, Department of Biomedicine, University Hospital Basel, 4031 Basel, Switzerland
[2] Respiratory Research Group, Department of Pharmacology, University of Sydney, Sydney, 2006 New South Wales, Australia
[3] Woolcock Institute of Medical Research, University of Sydney, Sydney, 2006 New South Wales, Australia

Arbeitsrappen-Brunnen

Andreas Heusler-Strasse / vor dem Gebäude der Wirtschaftsmittelschule

In der Wirtschaftskrise der dreissiger Jahre wurde der Arbeitsrappen eingeführt. Von jedem Franken Lohn wurde ein Rappen abgezweigt, um die Wirtschaft - vornehmlich bauliche Objekte - wieder anzukurbeln. Innerhalb von zehn Jahren kamen mehr als 40 Millionen Franken zusammen. In den 1950er Jahren wurden mit dem übriggebliebenen Kapital des Arbeitsrappens Altwohnungen renoviert. Die Figur aus Bronze (Fischmännlein) steht in der Mitte der Bronzeschale und zeigt in der offenen rechten Hand ein Geldstück (eben den Arbeitsrappen). Die heutige Wirtschaftsmittelschule wurde 1943 mit Hilfe des Arbeitsrappens gebaut. Der Brunnen wurde deshalb als Erinnerung an diese Massnahme vor dieser Schule erstellt.

Dissertationen

Seit dem 31. März 2009 darf sich **Naja Jann** von der Forschungsgruppe Infection Biology (Departement Biomedizin USB) Frau Dr. nennen. Sie befasste sich in ihrer Dissertation mit dem Thema: „Neutrophil antimicrobial defense against Staphylococcus aureus – Contribution of Cathelicidin and the NADPH oxidase".

Im August 2009 stellte sich **Nicole Guetg** von der Forschungsgruppe Synaptic Plasticity (Institut für Physiology) erfolgreich den Fragen des Dissertationskomitees. Sie beschäftigte sich in ihrer Doktorarbeit mit dem Thema „$GABA_B$ Receptor Localization and Regulation".

Am 4. September 2009 hat **Xiucheng Fan** von der Forschungsgruppe Prenatal Medicine and Gyn. Oncology (Departement Biomedizin USB) seine Dissertation erfolgreich abgeschlossen. Der Titel seiner Doktorarbeit hiess: „Investigation of Quantitative and Qualitative MtDNA Alteration in Breast Cancer".

Mit der Doktorprüfung am 9. Oktober 2009 schloss **Nicola Miglino** von der Forschungsgruppe Pneumology (Departement Biomedizin USB) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: „Novel molecular pathologies in asthma and COPD".

Am 27. Oktober 2009 war es für **Daniela Baldoni** von der Forschungsgruppe Infectious Diseases (Departement Biomedizin USB) soweit, sie beendete erfolgreich ihre Doktorandenzeit, in der sie sich mit „Innovative Methods for the Diagnosis and Treatment of Implant-associated Infections" auseinandergesetzt hatte.

Am 29. Oktober 2009 stellte sich **Serdar Korur** von der Forschungsgruppe Neurooncology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Doktorarbeit lautete: „The role of the Bmi1-GSK3β pathway in glioblastoma".

Mathias Schmaler von der Forschungsgruppe Infection Biology (Departement Biomedizin USB) ging dem Thema „Staphylococcus aureus lipoproteins – TLR2-mediated activation of innate and adaptive immunity" nach und darf seit dem 16. November 2009 den Doktortitel tragen.

Herzlichen Glückwunsch an alle!

Auszeichnungen

Prof. Markus Heim von der Forschungsgruppe Hepatology (Departement Biomedizin USB) ist zum 1. Oktober 2009 zum neuen Mitglied des Nationalen Forschungsrats, Abteilung III (Biologie und Medizin), berufen worden.

Preise

Junior Hepatology Prize an Jan Tchorz

Jan Tchorz von der Forschungsgruppe Synaptic Plasticity (Institut für Physiologie) hat für seine Arbeit „Notch2 signaling promotes biliary epithelial cell fate specification and tubulogenesis during bile duct development in mice" (Hepatology 2009 Sep;50(3):871-3) den Junior Hepatology Prize erhalten.

BioValley Poster Awards vergeben

Am BioValley Science Day am 23. Oktober 2009 durften **Jason Gill** von der Forschungsgruppe Pediatric Immunology (Departement Biomedizin Mattenstrasse 28) und **Romy Walser** von der Forschungsgruppe Cancer- and Immunobiology (Departement Biomedizin Mattenstrasse 28) den Preis in der Kategorie Gold im Wert von 2'000.- CHF entgegennehmen. In der Kategorie Silber, die mit 1'500.- CHF dotiert ist, erhielten **Katrin Benakovitsch** von der Forschungsgruppe Cell Migration and Neuritogenesis (Departement Biomedizin Mattenstrasse 28) und **Neha Pandey** von der Forschungsgruppe Tumorbiology (Departement Biomedizin Mattenstrasse 28) den Preis. In der Kategorie Bronze (500.- CHF) gehörte **Alexandre Goncalves** von der Forschungsgruppe Developmental Genetics (Departement Biomedizin Mattenstrasse 28) zu den glücklichen Preisträgern.

Herzliche Gratulation!

DEPARTEMENT BIOMEDIZIN USB

Corinna Baumgartner
Cardiovasc. Mol. Imaging

Petra Bernegger
Tissue Engineering

Luigi Costa
Pneumology

Hatice Genc
Adm. ICFS

Anne Christin Gerspach
Gastroenterology

Chiara Giovenzana
Tissue Engineering

Fabienne Harrisberger
Neurobiology

Simon Hostettler
Exp. Immunology

Simone Keck
Transplantation Immunology

Laura Keglowich
Pneumology

Gino Lee
Molecular Nephrology

Zuzanna Makowska
Hepatology

Melissa Manser
Exp. Immunology

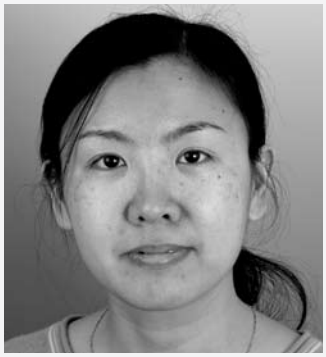
Benjamin Pippenger
Tissue Engineering

Sarah Thommen
Childhood Leukemia

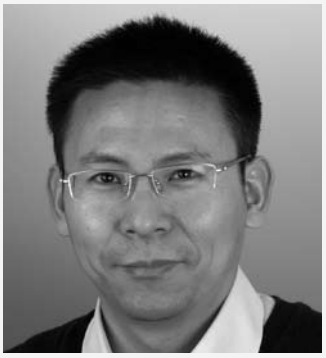
Emanuele Trella
Oncology Surgery

Sabina Tresch
Exp. Hematology

Stefano Vavassori
Exp. Immunology



Bin Fan
Ocul. Pharmac. & Physiology



Junyi Han
Oncology Surgery

Friederike Kesten
Immunobiology

Alexandra Gerber
Brain Tumor Biology

Matthias Liechti
Psychopharmacology Res.

Gregor Hutter
Brain Tumor Biology

Yves Hartmann
Technical Support

INSTITUT FÜR BIOCHEMIE UND GENETIK

Nicole von Burg
Develop. & Mol. Immunology

Anja Nusser
Develop. & Mol. Immunology

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Suzanne Edwards
Molecular Research

Elisabeth Hohmann
Molecular Diagnostics

Pascal Scheidegger
Molecular Research

INSTITUT FÜR PHYSIOLOGIE

Valérie Jacquier
Synaptic Plasticity

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN USB

Bilal Azakir, Neurobiology
Michael Sinnreich, Neurobiology
Donatina Kunz,
Cardiothoratic Surgical Research
Felicitas Müller, Dermatology
Teo Soon Siong, Exp. Hematology
Kawa Yousef, Oncology Surgerys
Matthias Mehling, Immunobiology

INSTITUT FÜR BIOCHEMIE UND GENETIK

Matthias Kreuzaler, Developmental and Molecular Immunology
Nadine Gehre, Developmental and Molecular Immunology

INSTITUT FÜR PHYSIOLOGIE

Josef Bischofberger,
Cellular Neurophysiology

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Juan Caceres Morales,
Technical Support
Melanie Hug, Molecular Diagnostics
Nesrin Saridas, Technical Support

Interne Wechsel:

DEPARTEMENT BIOMEDIZIN USB

Dietlinde John,
Cardiothoratic Surgical Research
Heidi Bodmer, Pneumology

Austritte:

DEPARTEMENT BIOMEDIZIN USB

Isabelle De Bie, Prenatal Medicine
Xiucheng Fan, Prenatal Medicine
Andrea Steinhuber,
Infectious Diseases
Linda Kenins, Exp. Hematology
Isabelle Plaisance, Cardiobiology
Marianne Messerli, Prenatal Medicine
Karin Probst, Infectious Diseases
Michaël Facompré, Exp. Immunology
Michel Mallaun,
Transplantation Immunology
Dragana Jankovic,
Childhood Leukemia

INSTITUT FÜR PHYSIOLOGIE

Mohammed Akaaboune,
Synapse Formation

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Maria Clemente, Technical Support

Yves Hartmann,

neuer Betriebsassistent am Departement Biomedizin USB

Seit dem 1. Oktober 2009 hat Yves Hartmann seine Tätigkeit am Departement Biomedizin USB aufgenommen. Gemeinsam mit Armin Bieri sorgt er dafür, dass an unserem Institut die Betriebsabläufe möglichst reibungslos vonstatten gehen. Yves ist Jahrgang 1971, gelernter Biologielaborant Richtung Pharma, hat seine Ausbildung von 1987 bis 1990 bei Sandoz-Wander in Bern absolviert. Nach 22 Jahren bei Sandoz/Novartis, wo er zum Schluss als Teamleiter für Labor und Office Support amtete, kam er nun zu uns ans Unispital, um die Nachfolge von Monika Hermle anzutreten und alles bei Novartis Gelernte nun auch bei uns in die Tat umzusetzen. So werden es einige schon gemerkt haben, die Anwendung von Gesundheits- und Sicherheitsvorschriften ist Yves gewohnt und auch Ver- und Entsorgungsfragen bereiten ihm kein Kopfzerbrechen. Wer Fragen hat oder Hilfe braucht, kann sich jederzeit an ihn wenden. Denn auch hier hat er durchaus die gleiche Auffassung wie Monika. Yves ist in Allschwil aufgewachsen, verheiratet und Hundepapa von zwei Cairn Terriern, er mag gerne englischen Humor und den 300m Schiessverein, dessen Präsident er seit 15 Jahren ist.

Yves, wir heissen Dich herzlich willkommen!
Heidi Hoyermann

Congratulations

Das DBM gratuliert ganz herzlich!

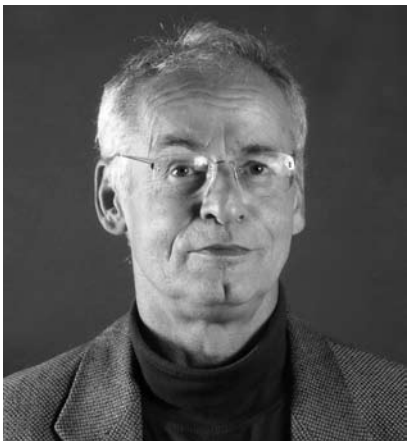
Klaara Göritz (Pelttari)
Geboren am 19.9 2009

Oliver Finley Hess
Geboren am 14.7.2009

Manuel Philipp Lindinger
Geboren am 24.4.2009

Giulia Banfi (Di Maggio)
Geboren am 21.7.2009

Zur Emeritierung von Lukas Landmann



Ende Juni 2008 ist Lukas Landmann, Extraordinarius für Anatomie und Embyologie, in den Ruhestand getreten. Lukas Landmann begann seine wissenschaftliche Laufbahn als Zoologe in Basel in der ausklingenden Aera Adolf Portmann. Den damaligen Ansätzen des Zoologischen Instituts folgend, basierte seine Forschung auf der präzisen Beobachtung von Form und Gestalt im Tierreich, welche zur Aufklärung heute noch gültiger, entwicklungsgeschichtlicher Zusammenhänge in den verschiedenen Tierstämmen führte. Die Beobachtungen wurden damals, d.h. vor dem digitalen Zeitalter, als Zeichnungen und Photographien dokumentiert.

Heute würde man in Neu-Deutsch auch eine Zeichnung oder eine Photographie von damals als 'Image' bezeichnen, bedeutet doch Image nichts anderes als ein wie auch immer erzeugtes Abbild eines physischen Objektes. Für Lukas Landmann ist Imaging eine lebenslange Leidenschaft geblieben. Sie begann im Jahre 1970 mit einer frühen Publikation (zusammen mit A. Portmann) über 'Schneckenhäuser', erschienen in der Zeitschrift 'Du'. Imaging hat seit damals eine stürmische Entwicklung erfahren, welche durch verbesserte Färbemethoden, neue mikroskopische Verfahren und durch den Einsatz von Rechnern die Dynamik und die Beziehung subzellulärer Strukturen zueinander auch mit lichtmikroskopischen Methoden sichtbar zu machen erlaubte. Imaging ist damit in der zell- und molekularbiologischen Forschung unverzichtbar geworden, und seine Bedeutung ist 2008 mit der Verleihung des Chemie-Nobelpreises für die Entwicklung von gezielter Fluoreszenzmarkierung von einzelnen Proteinen in lebenden Zellen unterstrichen worden.

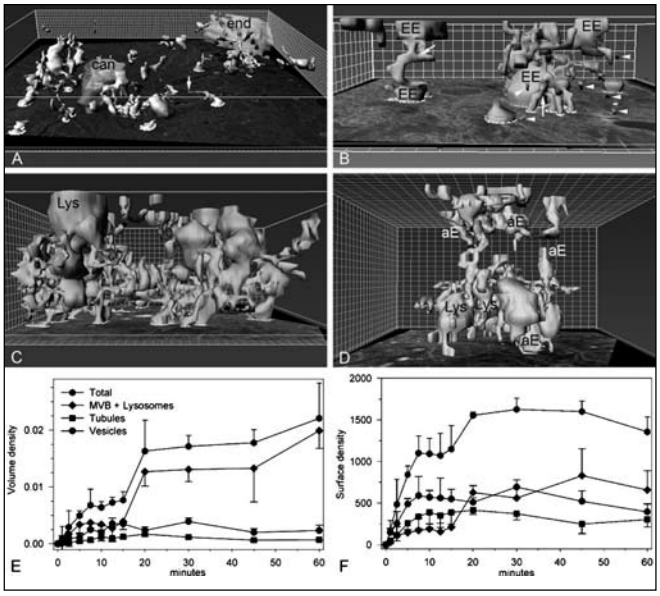


Fig. 1. Structure of endocytic compartments in rat livers infused with peroxidase for 10 min as shown by reconstruction of serial EM sections. (A) Two hepatocytes partially imaged between the basolateral cell pole (indicated by endothelium, end) and the apical canaliculus (can). Endocytic compartments are present in all regions. Note the multitude of tubules, only part of which is shown in this low power reconstruction, linking different compartments and extending over long distances (arrows). (B) Early endosomes (EE) in the basolateral cytoplasm are connected by mostly branched (arrows) tubules. Only part of the many small (60 nm) vesicles is shown (arrowheads). (C) Endocytic vesicles in the perinuclear region are interconnected by a closely knit tubular network. All large vesicles are MVB except for one lysosome (Lys). (D) Endocytic vesicles in the apical cytoplasm include apical endosomes (aE), lysosomes (Lys), and MVB (not labeled) and are linked by tubules. Mesh width = section thickness = 80-120 nm. Volume (E) and surface (F) densities of endocytic compartments after continuous peroxidase infusion (n = 3). Micr Res Techn 69 (2006): 693-707

Lukas Landmann war mit seinem methodischen Ansatz in der ehemaligen Vorklinik unserer Fakultät ein einsamer Pionier, und die Bedeutung seines Engagements und seiner ausserordentlichen Kompetenz wurde nicht immer von allen verstanden. Er hat die neuen Entwicklungen des Imaging und dessen Anwendungspotential früh erkannt und trotz bescheidener Unterstützung zäh und weitgehend auf sich allein gestellt verfolgt und eingesetzt. Dabei suchte er stets seine morphologischen Resultate mit physiologischen oder molekularbiologischen Ergeb-

nissen zu kombinieren. Dies zeigt exemplarisch eine Studie über die canaliculären Tight Junctions von Leberzellen bei mehreren Cholestasemodellen (1). Die Flexibilität und Aussagekraft quantitativer mikroskopischer Methoden nutzte er geschickt zum Nachweis und der Charakterisierung eines apikalen Endozytosewegs in Leberzellen (2). Stets bewusst war er sich der Gefahr der Ueberinterpretation von digital verarbeiteten Bildern. Er beschäftigte sich daher längere Zeit mit dem Problem der 3D Kolokalisation und mit dem Vermeiden von falsch positiven Resultaten, was ihn zu einem Verfechter des Image Processing durch Dekonvolution machte (3,4).

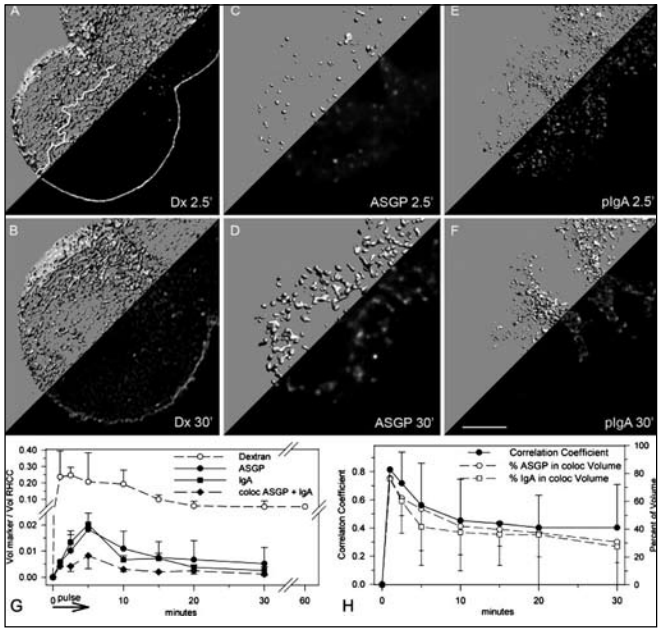
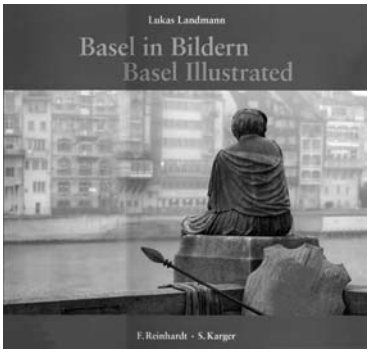


Fig. 2. Fig. 3. Surface renderings (upper left) and singular optical sections (lower right) show the subcellular distribution of the bulk phase endocytosis marker dextran (A, B), and of the pathway-specific marker proteins asialoglycoprotein (C, D) and pIgA (E, F) after 2.5 (A, C, E) and 30 min (B, D, F). Dextran applied in a 5 min pulse labeled a tubulovesicular compartment consisting of interconnected 200-nm tubules and 300-nm vesicles and extending in all cellular regions. The line in (A) traces a continuous series of vesicles and tubules connecting the basolateral and the apical cell pole. Initially (A), extran labels the network homogenously with a concentration in the basolateral cytoplasm. Later (B), dextran is concentrated in apical vesicles. Asialoglycoprotein concentrates in vesicles right after start of uptake (C) their number and size increasing by 30 min (D). In contrast, pIgA signal forms finer elements including tubules (E). Positive vesicles are distributed in all regions and concentrate in the apical cytoplasm after longer time intervals (F). Contrast has been adjusted in singular sections to show low intensity tubules and high intensity vesicles simultaneously. Bar = 5 μm. Volume of endocytic markers applied in a 5 min pulse (G) increases rapidly, peaks at 2.5 (dextran, n = 3) and 5 (ligands, n = 4) min and decreases thereafter. Colocalization of ligands displays similar, but less pronounced kinetics. Correlation coefficient and percentage of ligand present in colocalizing volume (H), which peak at 1 min, indicate rapid sorting of asialoglycoprotein and pIgA.

Lukas war aber nicht nur weitsichtiger Pionier, sondern auch ein 'good citizen' des DBM. In den Prozess der Studienreform hat er sich aktiv eingebracht. Noch heute schimmert im Curriculum der ersten beiden Studienjahre das Konzept durch, das er mit zwei Kollegen spontan erarbeitet hat. In kritischer Zeit hat er mit der interimistischen Uebernahme der Leitung des Anatomischen Instituts die damalige Departementsleitung des DKBW unterstützt. Zahlreiche Kollegen in Basel und auswärts hat er an seiner hevorragenden technischen Expertise teilhaben lassen und damit auch vielen Arbeiten, die primär nicht in seinem Labor entstanden sind, zum Durchbruch verholfen. Um so bedauerlicher ist es, dass sein Bemühen, für das DBM eine technische Plattform für modernste lichtmikroskopische Verfahren aufzubauen und seinen Mitgiedern mit Rat und Tat zur Seite zu stehen, von der Universität nicht honoriert worden ist. Dass dies nicht geschah, hat ihn tief getroffen. Denn als Team Player erwartete er, dass Versprechungen eingehalten oder bei veränderten Umständen neu ausgehandelt werden sollten. Deshalb hat er das DBM enttäuscht und im Unfrieden verlassen.



Auch nach seiner Pensionierung ist Lukas Landmann dem Imaging treu geblieben. Er hat soeben einen Bildband über die zahlreichen Facetten unserer Stadt Basel kreiert, der in diesen Wochen in einem bekannten Basler Verlag erschienen ist. Unsere besten Wünsche begleiten ihn in seinen neuen Lebensabschnitt, der leider durch den kürzlichen Tod seiner Frau überschattet wird.

Hans-Rudolf Brenner

1) C. Rahner, B. Stieger, and L. Landmann, Structure-function correlation of tight junctional impairment after intrahepatic and extrahepatic cholestasis in rat liver. Gastroenterology, 1996. 110: p. 1564-1578 (s. auch Kommentar dazu von: Anderson, J.M. Leaky junctions and cholestasis, Gastroeneterology 110 (1996):1662-1665).

2) Marbet, P., et al., Quantitative Microscopy Reveals 3D Organization and Kinetics of Endocytosis in Rat Hepatocytes Micr. Res. Techn., 2006. 69: p. 693-707.

3) Landmann, L., Deconvolution improves colocalization analysis of multiple fluorochromes in 3D confocal data sets more than filtering techniques. J. Micr., 2002. 208(2): p. 134-147.

4.) Landmann, L. and P. Marbet, Colocalization analysis yields superior results after image restoration. Micr. Res. Techn., 2004. 64: p. 103-112.

Regine Landmann-Suter

Regine Landmann-Suter hat selbstredend unzählige Facetten. Im Versuch sie zu charakterisieren mag einem die Symbolik des Leuchtturms in den Sinn kommen; diszipliniert, ruhig und ohne einem zu nahe zu treten, vermittelt und vermittelte Regine immer Halt und Orientierung. Nur ist ein Leuchtturm natürlich viel zu statisch um die Dynamik und den unermüdlichen Einsatz von Regine Landmann in vielen ganz unterschiedlichen Gebieten zu fassen. Auch passend zum Leuchtturm hat Regine aber viele Wellen anbrausen und Stürme kommen und gehen gesehen, kennt sie doch das Haus seit 1977 als sie im Labor von Professor Fritz Bühler begonnen hatte. Und an Ausstrahlung und Leuchtkraft hat sie in den mehr als 30 Jahren nie auch nur ein Lux verloren.

Ihre berufliche Tätigkeit hatte sie nach dem Medizinstudium 1972 in Genf aufgenommen, wo sie auch einen Teil ihres Studiums absolvierte. Regine war eine der ersten Frauen, die in der Inneren Medizin bei Professor Alex Müller gearbeitet hat. Nach 4 Jahren klinischer Arbeit in Genf und Utrecht kam sie nach Basel zurück. Sie nahm bei der Ciba-Geigy ihre Forschung auf und wechselte dann ans Departement Forschung. Über die Jahre entwickelte sich ihre Forschung zunächst in Richtung Onkologie (Prof. J. P. Obrecht und F. Gudat), bevor es in Richtung Immunologie/Infektiologie (Prof. Werner Zimmerli) mit Aufenthalten in London (1984) und La Jolla (1995) weiterging. Seitdem leitete sie ihre unabhängige Forschungsgruppe am Departement Forschung (jetzt im Departement Biomedizin integriert).

Ihre 4 Töchter sind zwischen 1973 und 1984 auf die Welt gekommen. Sie haben Regine Landmanns Tätigkeit als Forscherin im Sinne von «take your time» beeinflusst; interessante Forschung ist nicht immer mit sofortigen Resultaten verbunden. Regine zeigte mit ihrem unbrechbaren Optimismus, wie auch ein komplexes Leben gut gestaltet werden kann: Familie UND die Forschung waren und sind wichtig und möglich, wenn die nötige Ausgewogenheit zwischen den beiden Lebens-

bereichen gewährleistet ist. Regine kann heute stolz auf ihre Töchter UND auf ihre Forschung zurückblicken. Gerade deshalb ist sie ein Vorbild und exzellentes Beispiel für alle jungen Frauen, die Familie UND akademische Entwicklung in Einklang bringen möchten.

In der Tat hat Regine ihre wohl besten akademischen Jahre in den letzten 15 Jahren erlebt – Exzellenz in der Forschung mit besten wissenschaftlichen Publikationen – inklusive 2008 und 2009 – Verantwortungen in der Aus- und Weiterbildung junger Dissertanden der Medizinischen und Naturwissenschaftlichen Fakultäten, Verantwortung für das DF – welches sie interimistisch 2000-2001 geleitet hat – und für die Universität als Präsidentin der Gleichstellungskommission. Regine hat das «mentoring» für junge Akademikerinnen erfolgreich eingeführt. Das Programm läuft bestens und sollte auch weiter in Anspruch genommen werden.

Dabei ist Regine eine echte Baslerin: Bescheidenheit verknüpft mit herausragender Expertise, selbstloser Unterstützung der Forschung und ein großes Interesse allgemein an Wissenschaft und Kunst. Im DF ist sie immer bereit mitzuhelfen, zu erklären und an Zusammenarbeiten mitzuwirken (aber nur bei guten Projekten!).

Man sieht ihrem Gesicht sofort an, ob es ihr gut geht oder nicht. Es ist so schön, ihr zu begegnen, wenn sie einem mit ihrem strahlenden Lächeln entgegen kommt! Manchmal bedrücken sie aber auch Probleme, und dann ist ihr Ausdruck entsprechend; aber Probleme sind da, um gelöst zu werden, wie sie sagt. Die typische Basler Mundart ist ihr eigen, und sie wird euch daher erklären können, wie man sprachlich Burkart von Burckardt (ckdt!) unterscheidet. Und dazu spricht sie natürlich perfektes Französisch, die Sprache der Diplomaten …

Warum gehen die Jahre so schnell vorbei? Man möchte zum Augenblicke sagen «verweile doch, du bist so schön». Zum Glück wird Regine weiter aktiv sein. Sie hat Pläne bezüglich der Entwicklung eines Bakteriologie-Labors in Vietnam – wo sie zum Teil auch weilen wird – und sie hat zudem für die nächsten Jahre eine wichtige Arbeit unserer Fakultät übernommen, die Nachwuchsförderung. Schon wenige Wochen nach Aufnahme ihrer neuen fakultären Funktion hat sie Vorschläge unterbreitet. Unser Nachwuchs kann sich freuen, denn er wird unterstützt – nicht nur als Gruppe, sondern auch auf individueller Ebene. Bitte, Regine, mach weiter so. Den Ruhestand kann es für Dich ja ohnehin nicht geben, wird doch die «Nachwuchsförderung» im allerdirektesten Sinn – Deiner 4 Töchter also – Dir wohl viele stolze und freudige Momente, aber wenig Ruhe bescheren.

Liebe Regine, von Deiner Lebenserfahrung und Expertise möchten noch viele junge Menschen profitieren!

Jürg Schifferli

Verantwortlich ist man nicht nur für das, was man tut, sondern auch für das, was man nicht tut.
Laotse

Farewell to Ola Filipowicz

At the end of the year, Prof. Aleksandra Wodnar-Filipowicz, or Ola, as she is called by her friends and collaborators, retires from her position as research group leader and deputy head of the Laboratory for Hematology in the Department of Biomedicine, and as professor in Experimental Hematology at the medical faculty. The track of an outstanding scientific career will not come to an end but will just shift gears and change focus slightly.

Aleksandra Wodnar-Filipowicz was born in Warsaw where she graduated in biochemistry. A rapid and fascinating scientific career developed: A PhD programme at the Institute for Molecular Biology in Nutley, research adjunct at the Institute of Biochemistry and Biophysics in Warsaw, back as postdoc to Nutley and, in 1985 as a research fellow to the Friedrich Miescher Institute in Basel, together with her husband, Witold.

In 1990, she was asked by Prof. Catherine Nissen and Prof. Bruno Speck to join the hematology team and to lead the research programme on aplastic anemia. She rapidly pushed the field forward and her seminal papers on the role of FLT-3 ligand and stem cell factor in aplastic anemia remain reference works. They formed the basis for her habilitation on the topic "Control of blood cell development and function by hematopoietic growth factors".

This work on the control and regulation of normal hematopoietic was extended during the last decade to the control of leukemic stem cells by their niche-environ-

ment and by natural killer cells. Results from this research form the basis for the clinical translational stem cell transplantation programme on the use of these NK cells in the context of haploidentical donor transplants, one of the key leading experimental transplant programmes of the University Hospital Basel. The excellence of her research is probably best reflected in her award from the medical faculty for the highest ranking in publications last year.

Ola's life goes beyond pure science, it is devoted to science and family. Her attention to family life is not only reflected in her two children but also in the care she gives the collaborators in her team and her students. Few research group leaders at the department have such a track record of so many students winning the best medical thesis and other awards.

Her lectures are rated amongst the best and for many years she has been continuously invited as a teacher by the European School of Hematology. I myself have had the privilege to collaborate with Ola for many years on several local, national, and international projects related to scientific, educational, and administrative projects. I was always impressed by her rare gift of being able to concentrate on the essentials while also seeking consensus amongst partners.

For all those who know Prof. Aleksandra Wodnar-Filipowicz, it is no surprise that she will not "retire". Her devotion to science and education will continue within new fields, some of them already ongoing. She is, and will continue as, coordinator of the recently established Competence Centre of the University of Basel, the Basel Stem Cell Network BSCN. She holds a temporary mandate as advisor on stem cells by WHO. She will maintain an advisory function on many editorial and scientific boards and, last but not least, as mentor in the "Frauenförderung" program of the university. We will look forward to her achievements in the future.

Thank you, Ola, for all of your work and all the best.

Alois Gratwohl

Ein Winterabend

Wenn der Schnee ans Fenster fällt,
lang die Abendglocke läutet,
vielen ist der Tisch bereitet
und das Haus ist wohlbestellt.

Mancher auf der Wanderschaft
kommt ans Tor auf dunklen Pfaden.
Golden blüht der Baum der Gnaden
aus der Erde kühlem Saft.

Wanderer, tritt still herein;
Schmerz versteinerte die Schwelle.
Da erglänzt in reiner Helle
auf dem Tische Brot und Wein.

Georg Trakl, (1887 - 1914), österreichischer frühexpressionistischer Dichter und Lyriker

Monika Hermle

Monika kann man nicht beschreiben, Monika muss man erleben. Oder vielleicht doch? Machen wir den Versuch einer Annäherung. An Monika zu denken, gleicht für viele erst einmal dem Gefühl, beschwingt auf der Strasse zu fahren und einen Streifenwagen im Rückspiegel zu sehen. Der erste Gedanke: Könnte ich etwas falsch gemacht haben? Zweiter Gedanke: Wie ist die Laune des Polizeibeamten? Dritter Gedanke: Ja nichts Falsches sagen. Wer einmal mit kurzen Hosen im B2 Labor erwischt wurde oder Rettungstüren mit Utensilien verstellt hat, weiss, wovon ich rede. Aber: Monika ist auch die erste, die selbst Hand anlegt, um die Tür frei zu räumen und mit einem freundschaftlichen Klaps auf die Schulter dem Hosensünder signalisiert, dass alles wieder gut ist.

Wer es noch nicht ahnt, Monika ist unsere Betriebsorganisatorin und Sicherheitsbeauftragte. Durch sie habe ich gelernt, wie man einen Feuerlöscher bedient, dass man nicht von jedem geliebt werden kann (und darf) und sich nicht unter kriegen zu lassen. Sie ist eine Frau mit Zivilcourage! Und nicht nur das: Sie ist eine sehr versierte Laborantin mit viel Erfahrung und grossem Hintergrundwissen.

Das wusste auch Gilbert Thiel, der damalige Leiter des Nephrologie- und Typisierungslabors, als er sie im Frühjahr 1980 von München ans damalige Departement Biomedizin nach Basel holte, da sie eine Spezialtechnik beherrschte, die es an unserem Institut damals noch nicht gab, die «Mikropunktion an Rattennieren». Drei Jahre später wurde Monika Cheflaborantin. Ihr Spezialgebiet blieben Mikrooperationen technischer Art und an Tieren.

Ende der Neunziger Jahre wurde Monika von den technischen Mitarbeitenden als ihre Vertreterin in die Bereichsleitung gewählt, in der sie die Interessen der Laborantinnen und Laboranten vertrat. Sie organisierte Ausbildungen in diesem Bereich und war Ansprechpart-

nerin für so manches Problem. In dieser Zeit wechselte sie auch zu 50% in den Stab des Departements und behielt 50% ihrer Tätigkeit im Labor bei, weiterhin der Nephrologie verpflichtet, die jetzt von Jürg Steiger geleitet wurde.

Der Aufgabenbereich im Stab legte eine Erhöhung auf 100% nahe, was dann im Jahr 2002 auch geschah. Monika übernahm aufgrund ihrer grossen tierexperimentellen Kenntnisse unter anderen auch weitere Aufgaben in der Tierversuchsstation.

Im Laufe der Jahre hat sie in ihrem Tätigkeitsfeld das DBM, oder sagen wir in alter Tradition, das DF, auf Vorderfrau gebracht. Vieles hat sie inzwischen wohl geordnet an ihren Nachfolger Yves Hartmann übergeben, manches wird noch folgen.

Mit Monika geht eine Ära zu Ende. Viele werden ihren rauhen, aber herzlichen Ton genauso vermissen, wie ihre Kompetenz und die interessanten, vielfältigen Gespräche mit ihr.

Monika, möge Dir die Tätigkeit als Präsidentin des Quartiervereins in Deiner Heimatgemeinde Riehen genauso viel Erfüllung bereiten wie Deine künstlerischen Herausforderungen und lass' uns zwischendurch einmal anrufen dürfen, wenn wir nicht mehr weiter wissen.

Heidi Hoyermann

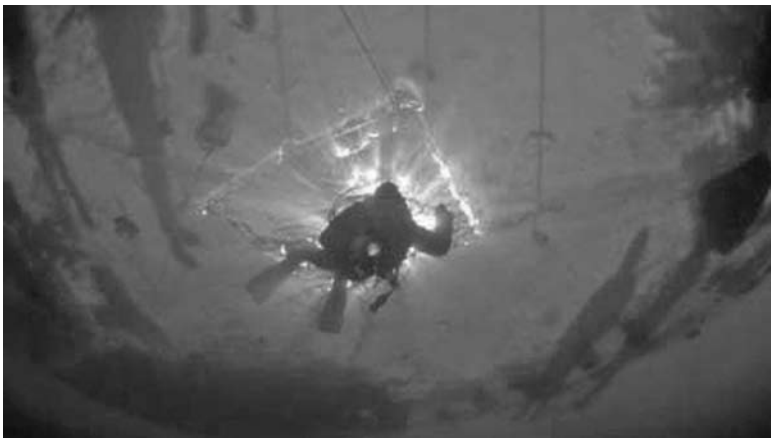
Eistauchen

Wenn man das Gefühl hat, dass Tauchen eine aufwändige und spezielle Sportart ist (meine Ausrüstung wiegt im Normalfall ca. 60 Kilo), so ist das Eistauchen die Quadratur davon. Zur Tauchausrüstung hinzu kommt noch viel Sicherungsmaterial (Leinen, Leitern) und Werkzeug zum Aufbrechen der Eisschicht (Bohrer, Axt, Motorsäge). Des Weiteren muss man je nachdem amtliche Bewilligungen und Erlaubnis der privaten Grundbesitzer einholen. So ein Unternehmen muss also gut vorbereitet und organisiert sein. Und da ein zugefrorenes Gewässer nicht gerade vor der Haustüre liegt, ergeben sich lange Anfahrtswege.

Tauchgang im Silvaplanersee

Nach zwei Wochen Vorbereitung und einer halben Tagesreise ist es endlich soweit, wir stehen am Ufer des Silvaplanersees und besprechen, wo und wie das Eisloch gemacht werden soll. Zum Glück haben wir zwei erfahrene Eistaucher dabei. Die etwa 50 m vom Ufer eine geeignete Stelle aussuchen und mit einem Eisbohrer beginnen, ein erstes Loch zu bohren. Danach gilt es zuerst einmal, ein entsprechend großes Loch zu sägen. Es kann niemand sagen, dass es einem beim Eistauchen nicht auch warm werden kann! Das Eis hat immerhin eine Stärke von gut 10 cm! Nach einer weiteren halben Stunde sind wir als erstes Tauchpaar fertig ausgerüstet.

Die Sicherungsleinen werden angeschlossen, wir sind bereit zum Abtauchen. Mit viel Adrenalin im Blut und tüchtigem Herzklopfen steigen wir ins eiskalte Wasser und lassen uns auf 3 Meter sinken.



Nach dem Einstieg

Fertig zum Einstieg

Nach dem gegenseitigen Durchchecken der Tauchausrüstung (funktioniert alles, ist alles dicht?) schaue ich mich ein erstes Mal richtig um. Im Schein der Taucherlampe ist alles in einem bläulichen weissen Licht. Faszinierend und mystisch!

Wir gleiten in fast vollkommener Schwerelosigkeit langsam auf den Grund in 15 Metern Tiefe zu. In dieser Tiefe ist fast schon kein Tageslicht mehr vorhanden, es ist jetzt blauschwarz und absolut still. Ich höre nur mein eigenes Herz schlagen,

Faszination unter Eis

mein Atmen und das Rauschen der ausgeatmeten Luft. Mit Handzeichen verständigen wir uns, dass wir wieder auftauchen bis unter die Eisschicht. Wir beobachten fasziniert das Blasenspiel unserer ausgeatmeten Luft unter dem Eis.

Direkt unter dem Eis

Ich probiere, kopfüber unter dem Eis zu gehen. Nach mehreren Anläufen gelingt es mir, ein eigenartiges Gefühl. Nach ein paar Schritten verliere ich den Orientierungssinn und das Gleichgewicht, es wird mir flau im Magen. Ich probiere wieder, meine normale Tauchposition einzunehmen (den Kopf oben und die Beine unten), aber das geht nicht so einfach.

Wir tauchen ja mit Trockentauchanzügen, bei denen man Druckluft von der Tauchflasche direkt in den Anzug pumpen kann (einerseits zur Wärmeisolation, andererseits zum Tarieren). Da die Luft unter Wasser immer den Weg nach oben sucht, habe ich jetzt alle Luft in den Beinen, die ich eigentlich nach unten nehmen will. Aber das geht nicht. Ich hänge mit dicken Elefantenfüssen unter dem Eis und kann mich nicht drehen, da das Ablassventil für die Luft an der rechten Schulter ist. Mit Hilfe meines Tauchpartners gelingt es mir, mich flach unter die Eisschicht zu legen und das Ablassventil zu betätigen. Nach diesem Experiment ist unser Luftvorrat zur Hälfte verbraucht, also das Zeichen, den Tauchgang zu beenden und zum Einsiegsloch zurückzukehren. Aber wo ist dieses verflixte Einstiegsloch? Wir haben beide überhaupt keine Orientierung mehr. Aber zum Glück haben wir ja unsere Sicherungsleinen, die an der Oberfläche je von einem weiteren Taucher geführt und gesichert werden. So finden wir rasch wieder unser Einstiegsloch, wo wir erwartet werden. Wir ziehen unsere Geräte im Wasser aus und reichen sie unseren Sicherungsleuten. So schaffen wir den Ausstieg und beginnen sofort begeistert zu erzählen.

Nach zwei Stunden sind wir wieder umgezogen und haben alles weg- und aufgeräumt. Ziemlich müde machen wir uns zu unserer Unterkunft in St. Moritz auf.

Am nächsten Tag gehen wir noch in den Marmorera-Stausee zu einem zweiten Eistauchgang. Dort können wir vom Ufer aus unter das Eis tauchen. Die Sicht ist aber sehr schlecht. Es ist trübe und der Tauchgang ist ein absoluter Blindflug. Enttäuscht brechen wir ab und nehmen den langen Heimweg unter die Räder.

Mein letzter Eistauchgang war im Lago del Naret, ganz hinten im Maggiatal. Unendlich schön, aber ebenso unendlich aufwändig.

Was macht eigentlich die Faszination des Eistauchens aus? Für mich ist es die perfekte Abgeschiedenheit, die Quadratur der Stille und Einsamkeit. Unter dem Eis wird man sich der eigenen Wenigkeit und Verletzlichkeit bewusst.

Armin Bieri

Gedanken zu Advent und Weihnachten

Advent fällt in die dunkle Jahreszeit, in die Zeit, die dem kürzesten Tag entgegen geht. Symbolisch zünden wir Woche für Woche eine Kerze mehr an, bis dann kurz nach dem 21. Dezember am Weihnachtsbaum viele Kerzen ein warmes Licht verbreiten. Dieses zunehmende Licht kennen wir aus vielen Kulturen. So feiern die Juden ‚Chanukka', ihr Lichtfest zu dieser Zeit. Es ist erstaunlich, was Weihnachten für einen hohen Stellenwert in unserer Gesellschaft geniesst. Dies nicht nur wegen ihrer Schattenseiten, dem Konsum, sondern weil wir uns anrühren lassen, unsere Herzen und Seelen berührt werden. Advent und Weihnachten könnte als seelische Lichttherapie gesehen werden.

Wenn wir das menschliche Leben betrachten, sehen wir solch rhythmisches Leben von hell und dunkel ebenfalls. Kaum jemand wird sagen können, dass er oder sie nie im Leben auch dunkle, schwierige, bedrückte, depressive Momente hat kennen lernen müssen. Es sind nicht die angenehmen Zeiten, Phasen, die wir lieber überspringen, auslassen möchten. Es fällt uns leichter, die Höhen und Höhepunkte zu leben. Diese können (und sollen!) wir mit jeder Faser unseres Körpers und jedem Hauch unserer Seele geniessen. Doch wenn wir in Therapie und Beratung und noch viel mehr in das Leben von Menschen und in unser Leben schauen, so sehen wir, dass gerade die dunklen und schwierigen Zeiten in unserem Leben uns letztlich vorangebracht haben. Mit Voranbringen meine ich das innere Wachsen, nicht das äussere, die Seele, nicht die Lohntüte.

Der Advent ist eine Zeit der Hoffnung. Die grösste und letzte Chiffre für Hoffnung können wir Jesus Christus nennen, Messias oder mit den anderen Religionen Gott, das grosse Licht.

Im Uni-Spital gehören die Pole Hoffnung und Verzweiflung zum Alltag. Nicht nur auf der Notfall- und der Intensivstation sind Menschen mit Extremsituationen konfrontiert. Unzählige Menschen kommen aus der Fülle ihrer Leben in dunkle Verzweiflung, Seelennot, Wut und Angst.

Der Vater findet seine vierjährige Tochter, einen Wildfang, auf dem Boden des Tenns liegend. Offensichtlich ist sie vom Dachboden gefallen. Sie ist nicht ansprechbar. Die herbeigerufenen Ambulanzfahrer lassen den Rettungshelikopter kommen. Der Bruder flüchtet in der Not in den Wald. Die Mutter kommt mit der Tochter ins USB. Auf einen Schlag ist nichts mehr, wie es war. Die Tochter wird mit Hightech diagnostiziert; als Seelsorger begleite ich die Mutter mit Hightouch. In diesem Falle gibt es, zum Glück oder Gott sei Dank, Entwarnung.

In der Onkologie ist der Absturz nicht so abrupt, der Ausgang aber oft unklar und offen. Eine Frau, die längere Zeit wegen ihrer Magenschmerzen in Behandlung ist, erfährt, dass sie Magenkrebs hat. Die Entfernung des Magens sichert vorerst das Überleben. Wirkliche Sicherheit gibt es aber in diesem Bereich keine; die Ängste bleiben; ohne Magen zu leben, muss gelernt werden; das Leben erfährt eine Änderung.

«Das Sinken geschieht um des Steigens willen», sagt eine jüdische Weisheit. Und Paul Tillich: *«Die Grenze ist der eigentliche Ort der Erkenntnis».* Ich wage zu behaupten, dass an keinem Ort der Welt (ausser in den kirchlichen Gottesdiensten) so viel gebetet wird, wie im Uni-Spital. Wo die Not am Grössten ist, ist die Hoffnung am Nötigsten. Wo die Tage kürzer werden, muss der Dunkelheit Licht beigegeben werden. Die Aufgabe der Arztes/der Ärztin ist es, in einem Menschen die Krankheit zu suchen. Hat er sie gefunden, kann er oft nicht aus der Hoffnung heraus sprechen, sondern muss Klartext reden. *«Die wahre Humanität liegt in der Bekämpfung der Krankheit und nicht in der Behandlung von Kranken»*, konnte Virchow noch sagen. Die heutige Ärztegeneration würde das nicht mehr unterschrieben. Die Aufgabe des Seelsorgers, meine Aufgabe, ist es, den Menschen in der Krankheit zu sehen, über seine Verzweiflung, Wut und Ängste zu reden, dabei die Hoffnung aber nie aussen vor zu lassen. Wie das konkret aussieht, muss die einzelne Situation, der einzelne Mensch zeigen. Wir verlassen hier auch den Pfad der manchmal nur zu tristen Gewissheit, und leben und handeln aus einem Glauben heraus, der schwierig zu kommunizieren ist. *«Wir können in keinen Abgrund fallen, ausser in die Hände Gottes»*, sagt Nietzsche (ausgerechnet!). In unserer jüdisch-christlichen Kultur soll niemand in seinem Leiden, in seiner Verzweiflung, mit seinen Diagnosen und Ängsten allein gelassen sein. *«Der Arzneien grösste aber ist die Liebe!»*, sagte Paracelsus. Das ist Weihnachten.

Jürg Merz
Jürg Merz ist evangelisch-reformierter Spitalpfarrer am Universitätsspital Basel

Der Personaldienst der Universität Basel stellt sich vor

Interview mit Ulrich Pfister, stv. Personalleiter der Universität Basel, und Cinzia D'Intino, Personalassistentin für die Medizinische Fakultät an der Universität Basel

DBM Facts: Vielleicht erzählt Ihr einmal, wie lange Ihr schon an der Uni seid, etwas über Euren persönlichen Werdegang, warum es Euch das Personalwesen angetan hat.

CD: Ich bin seit 1998 an der Uni.

DBM Facts: Was hast Du vorher gemacht?

CD: Nach meiner KV- Lehre war ich zehn Jahre bei einer Versicherungsgesellschaft in Basel im Personaldienst tätig. Anschliessend hat mir der damalige Personalleiter der Uni meinen jetzigen Job angeboten. Seitdem bin ich hier, wo es mir nach wie vor gefällt.
Im Jahr 2000 habe ich mich zur Personalfachfrau mit Fachausweis weitergebildet.

DBM Facts: Ueli, vielleicht erzählst Du jetzt einmal von Dir.

UP: Ich bin jetzt zwölf Jahre hier. Ursprünglich komme ich nicht aus dem Personalwesen. Ich war bei einer Ver-

sicherungsgesellschaft zunächst Leiter der Betriebsorganisation, danach der Assistent der Geschäftsleitung. Mit der Autonomie der Universität Basel im 1996 hat man erstmals einen Personalleiter gesucht, vorher war der Personaldienst des Kantons Basel-Stadt für die Personalbelange zuständig. Als Daniel Fischer-Ahr als Personalleiter der Uni angestellt wurde, hat er mich angefragt, ob ich an einer Stelle im Personalwesen interessiert sei. Der Aufbau einer neuen Personalorganisation war für mich eine Herausforderung, die ich gerne angenommen habe.

DBM Facts: Du hast dann im Personalwesen ganz neu angefangen ...

UP: Ja. Vor meiner Anstellung in der Versicherungsbranche war ich zwölf Jahre in der Unternehmensberatung tätig. Ich hatte Mandate in den unterschiedlichsten Branchen und Arbeitsgebieten. Als ich hier meine Arbeit aufgenommen habe, traf ich ein leeres Büro, das Mobiliar habe ich selbst mitgebracht. Der Aufbau einer neuen Personalorganisation war eine echte Herausforderung. Im 2000 wurde das kantonale Abrechnungssystem durch SAP abgelöst. Ab 2003 hat die Uni zudem die Nationalfonds und Drittmittelverwaltung von der STG übernommen, was zur Folge hatte, dass zusätzlich weitere 700 Personen durch unseren zentralen Personaldienst angestellt und verwaltet werden mussten.

DBM Facts: Ihr seid wirklich durch Zufall zur Uni und ins Personalwesen gekommen ...

UP: Ich hätte nie gedacht, dass ich nach meinem Studium wieder einmal zurück an die Uni komme. ...

DBM Facts: Hättest Du Dir mit 25 wahrscheinlich auch nicht gewünscht ... Du bist von Haus aus Betriebswirt?

UP: Ja. Ich habe Betriebswirtschaft studiert.

DBM Facts: Cinzia, kannst Du einmal beschreiben, was Deine Funktion ist?

CD: Ich bin Personalassistentin. Ich betreue die Mitarbeitenden der Medizinischen Fakultät und bin Ansprechpartnerin für die Angestellten und die Organisationseinheiten in allen personellen Belangen.

DBM Facts: Und arbeitest 50% ...

CD: Ja, ich betreue rund 500 Personen.

DBM Facts: Ueli, was sind Deine Hauptaufgaben?

UP: Neben den Budget- und Controlling-Aufgaben sowie der Führung des Personaldienstes stehe ich den Mitarbeitenden, den Organisationseinheiten und externen Stellen beratend zur Seite.
Die Fragestellungen sind vielschichtig, die Antworten darauf erfordern oft taktisches Geschick und Sensibilität.
Zur Zeit beschäftigen wir uns mit einer kritischen Überprüfung der Personalprozesse und der Optimierung unseres Verwaltungssystems. Der Anteil an administrativen Aufgaben wächst ständig und zwingt uns die Prozesse neu zu überdenken, damit wir mit den bestehenden Ressourcen das vielseitige Tagesgeschäft effizient und effektiv bewältigen können.

DBM Facts: Was sind für Dich die grössten Herausforderungen?

UP: Eine Herausforderung ist, die Organisation, die jetzt schon 13 Jahre alt ist, auf Vordermann zu bringen. Das wird mich die nächsten zwei Jahre beschäftigen. Die andere Herausforderung ist das Tagesgeschäft. Das kennt man nicht im Voraus.

DBM Facts: Wie versteht Ihr Euren Job?

CD: Im Dienst der Mitarbeitenden, aber gleichzeitig der Linie. Ich versuche, beiden gerecht zu werden und das ist nicht immer einfach.

UP: Das unterstütze ich auch auf jeden Fall. Denn einerseits ist man Arbeitgebervertreter, andererseits hat der Personaldienst auch eine soziale Verantwortung wahrzunehmen.

DBM Facts: Was wünscht Ihr Euch konkret von den Führungsbeauftragten und Mitarbeitenden?

CD: Rechtzeitige Informationen sind die Voraussetzung, um die Geschäftsvorfälle termingerecht erledigen zu können.

DBM Facts: Was würdest Du Dir wünschen, Ueli?

UP: Das Einhalten der Prozesse und eine gewisse Termindisziplin. Die Administration wird auch aufgrund neuer gesetzlicher Bestimmungen immer aufwendiger und komplexer. Es ist nicht einfach, den Mitarbeitenden und den Organisationseinheiten zu vermitteln, dass diese Anforderungen von staatlichen Stellen an unsere Administration gestellt werden. Die Uni selbst ist nicht überreglementiert.

DBM Facts: Was könntet Ihr Euch beruflich sonst noch vorstellen, wenn Ihr jetzt nicht hier im Personalwesen wäret ...

CD: Die Personalarbeit gefällt mir gut und ist sehr abwechslungsreich und dies in einem bestens funktionierendem Team. Ich fühle mich wohl im jetzigen Umfeld.

UP: Mir geht es genauso.

DBM Facts: Herzlichen Dank für dieses Gespräch.

Gino Pancera, Schreinerei ... oder das Erdmännchen des USB

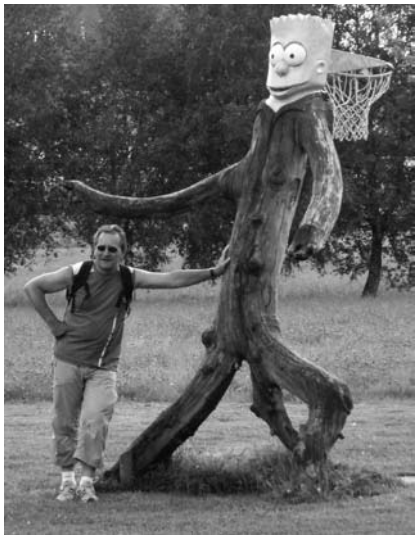
Ursprünglich komme ich vom Theater, wo ich lange als Bühnenhandwerker tätig gewesen bin. Obwohl ich die Bühne liebe und ich mich heute immer mal wieder als Sänger der Basler Liedertafel auf einer wieder finde, war die Hektik sehr gross und ich wünschte mir eine Arbeit mit regulären Arbeitszeiten. Nach zwei Jahren kam dann die Nachricht, dass das damalige Kantonsspital Basel einen Handwerker suchte. Ich weiss es noch wie heute. Als ich mich vorstellen ging, lag meine Frau gerade in den Wehen mit unserem zweiten Sohn. Und ich hatte Glück, sie nahmen mich. Meine Aufgaben waren allgemeine Unterhaltsarbeiten, Revisionen im Klinikum 2, im Zentrum für Lehre und Forschung, in den Operations- und Hörsälen, in der Ökonomie und Pathologie und auch im Holsteinerhof.

Über die Schreinerarbeiten habe ich viele Menschen kennen gelernt. Nie vergessen werde ich den Lieblingsbesprechungstisch von Daniel

Scheidegger, an den sich keiner herantraute, und den Umbau in der Nephrologie mit Christina Wolf-Heidegger, der uns eine Woche und viele Nerven gekostet hat. Auch im ZLF habe ich unterschiedliche Charaktere angetroffen : Bei Radek Skoda gab es kein Entrinnen, er hat mich immer gleich geschnappt, wenn er mich sah und mich über den neuesten Stand des Umbaus informiert, Alex Eberle hat mir gleich das «Du» angeboten und bei Fritz Bühler bleibt mir seine Warmherzigkeit in Erinnerung. Ed Palmer hat mir sogar einmal geholfen, eine Tür einzuhängen! Mit Herrn Conti habe ich überdies einmal ein Bier getrunken und Frau Ziegler ein Bild übergeben. Das waren noch Zeiten, das war noch Werkstatt.

Privat bin ich seit 23 Jahren verheiratet und habe zwei Söhne, Yves ist auf dem Weg, Schauspieler zu werden, und Marc pendelt als Architekt und Sänger zwischen Basel und Zürich. In meiner Freizeit singe und musiziere ich für mein Leben gern, sind Bilder meine Anziehungspunkte, fahre ich Velo, schwimme ich und gehe ich gerne Bergwandern, mal mit und mal ohne Hund. Und Ende April gehe ich in Pension.

Später wurden viele Arbeiten extern vergeben. In den 21 Jahren habe ich vier Vorgesetzte und viele Veränderungen erlebt, aber das ZLF war für mich immer ein Zufluchtsort. So haben sich in der Werkstatt viele gewundert, wenn ich mittwochs «mit den Forschern» joggen gegangen bin. Mit Armin Bieri, der mir immer ein guter Kollege und Sportler war, und Verena Jäggin, die uns auf Trab gebracht hat. Manchmal bin ich auch für das «Schyssdräggzügli» des ZLF bei der Sola-Stafette gestartet.

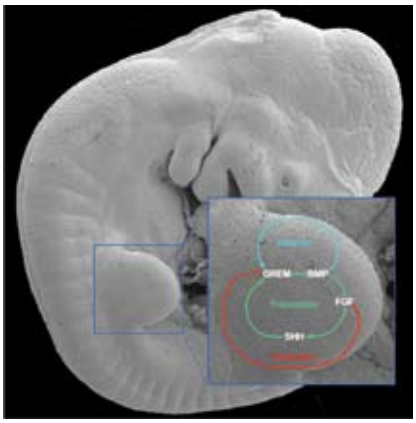


Danke, Gino!

Fröhlich, aufgestellt, motiviert, hilfsbereit und freundlich – so haben wir Dich all die Jahre am ZLF erlebt. Mit Deiner Kompetenz, Deiner Kreativität und Deinem Humor hast Du uns manchen Umzug, viele handwerkliche Probleme und unser Leben am USB erleichtert! Danke, Gino!

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



... gibt uns Rolf Zeller einen Einblick in sein Forschungsgebiet Developmental Genetics

... erfahren wir von Christian De Geyter mehr über die Forschungsaktivitäten im Labor Gynaecological Endocrinology

... erzählt uns Chitraganda Acharya, warum ihr die Zeit in Basel so gefallen hat

... dürfen wir dabei sein, wenn Vivian Kiefer auf den Philippinen Hilfe vor Ort leistet

550 JAHRE UNIVERSITÄT BASEL
WISSEN BEWEGT UNS

... stimmen wir uns auf die 550 Jahr-Feier der Universität Basel ein


23
22
24
20
19
6
21
DBM
CHRISTMAS
PARTY