



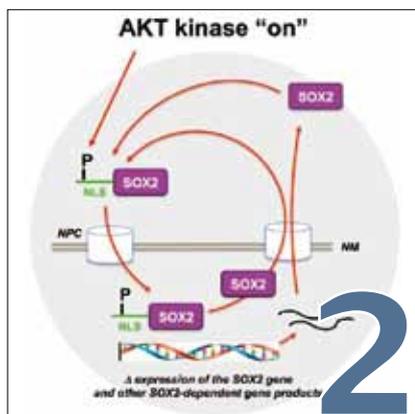
D B M

FACTS

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

**Stem Cells and Hematopoiesis | Hei senn eich dahaam
| Grosse Ferien!**

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Stem Cells and Hematopoiesis
from Claudia Lengerke



**Farewell lecture of
Albert Urwyler**



Malen mit Licht
von Ronny Nienhold



Hei senn eich dahaam
von Katharina Leonards und
Florian Marquardsen



Grosse Ferien!

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IMPRESSUM

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Heidi Hoyerermann

Übersetzungen

Paula Cullen, Thérèse Resink

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Eric Spaety, Morf Bimo Print AG, Binningen

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Niklaus Vogt

Administration

Manuela Bernasconi

Fotos

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Redaktion DBM Facts
 Departement Biomedizin
 Hebelstrasse 20
 4031 Basel
 heidi.hoyerermann@usb.ch

EDITORIAL



Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Im August wird das DBM feierlich sein 15jähriges Jubiläum mit einem internationalen Symposium und anschliessendem Fest begehen (Seite 8).

Wir freuen uns, Sven Cichon als Vertreter der Medizinischen Querschnittsfunktionen in der DBM-Leitung begrüßen zu dürfen. Er tritt die Nachfolge von Albert Urwyler an, der per Juni 2015 aus dem Gremium ausscheidet. Wir danken Albi Urwyler für seine vielen Beiträge und grosse Unterstützung des DBM sowohl in der DBM-Leitung als auch während seiner Zeit als Dekan der Medizinischen Fakultät. Wir freuen uns, dass er wissenschaftlich am DBM noch weiter tätig sein wird (Seite 9)!

In der vorliegenden Ausgabe erfahren Sie mehr über die Aktivitäten der Forschungsgruppe "Stem Cells and Hematopoiesis" von Claudia Lengerke (ab Seite 2). Wir präsentieren Ihnen die neuesten Publikationen (ab Seite 12), Roy Allenspach stellt sich die für den Monat Juni berechnete Frage Biosafety oder BBQ (ab Seite 10), wir sehen die Welt mit den Augen eines Fotografen (ab Seite 32) und lernen die älteste deutsche Stadt kennen (ab Seite 34). Neue Jobs für Forschungsgruppenleiter finden Sie auf Seite 42.

Eine spannende Lektüre und schöne Ferien (vielleicht auch einmal anders – siehe Seite 38)!

Dear Readers

In August we will celebrate 15 years of the DBM with an international symposium followed by celebratory festivities (page 8).

We are delighted to welcome Sven Cichon as representative of the "Medizinische Querschnittsfunktionen" to the DBM executive committee. He joins as successor to Albert Urwyler who retired from the committee in June 2015. Sincerest thanks to Albi Urwyler for his many contributions to, and his great support of, the DBM, as well as the DBM executive committee, and also for the time he spent as the Dean of the Medical Faculty. We are delighted that he will continue to remain scientifically active at the DBM (page 9)!

In this issue you can find out more about the activities of Claudia Lengerke's "Stem Cells and Hematopoiesis" research group (from page 2). We present the latest publications (from page 12); Roy Allenspach asks a rather apt question for June: biosafety or barbecue? (from page 10); we see the world through the eyes of a photographer (from page 32); and get to know the oldest German city (from page 34). New positions for research group leaders can be found on page 42.

Enjoy reading and wishing you all happy holidays (perhaps even something different – see page 38)!

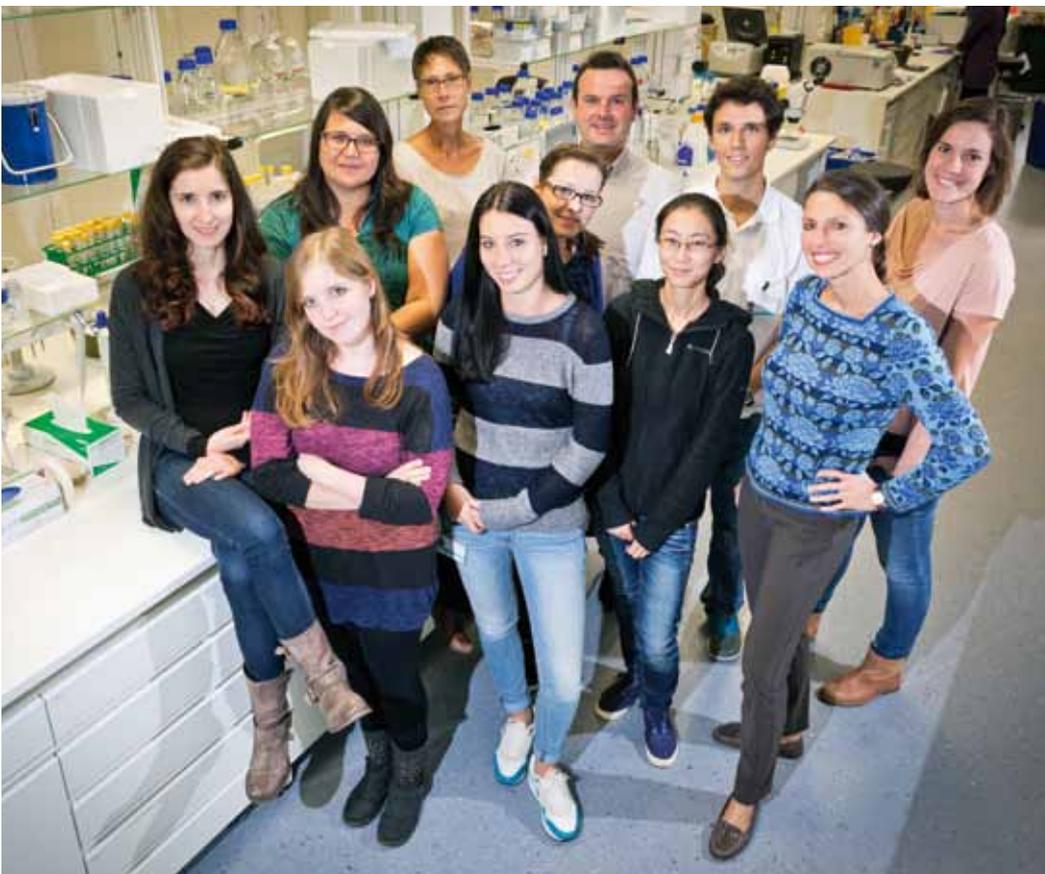
Stem Cells and Hematopoiesis

Our research group relocated from Tübingen (Germany) to Basel in August 2013. Since then several new team members have joined. We enjoy the international atmosphere of our lab and the institute, and the close exchange with the neighbouring research groups. Our research focuses on stem cell mechanisms in regeneration and disease. We hypothesize that stemness pathways contribute to cancer initiation, therapy resistance and relapse. By analysing stem cell specific features and looking at cancer and cancer therapies from a stem cell perspective, we aim to develop alternative treatment approaches. We are especially interested in leukemia and in the oncogenic roles of transcriptional factors regulating stem cells during development (EVI1, CDX2, SOX2). Additional to conventional work with murine and human cells, we use the zebrafish model to investigate these questions. In the following sections individual projects of our research group members are outlined.

The blood group:

Elisa Alghisi & Martina Konantz (Postdocs)

Martina's and Elisa's projects focus on the elucidation of the cellular and molecular mechanisms controlling hematopoietic stem cells (HSCs) in embryonic development. The projects take advantage of the zebrafish as a new tool to study blood cell development and differentiation. The zebrafish (*Danio rerio*) is a small freshwater teleost fish that has a short generation time and provides large numbers of offspring. During the last decade, the zebrafish has emerged as a powerful model organism for developmental biology studies and is also increasingly used in translational research. In spite of anatomical dissimilarities, major blood cell types and genetic pathways controlling hematopoiesis appear evolutionary conserved between fish and mammals and discoveries made from zebrafish blood screens have



The Stem cells and Hematopoiesis group (from left to right): Anna Lenard, Martina Konantz, Melanie Neutzner, Thorsten Schäfer, Matyas Ecsedi, Tamara Pereboom (back); Elisa Alghisi, Joëlle Müller, Anna Paczulla, Hui Wang, Claudia Lengerke (front).

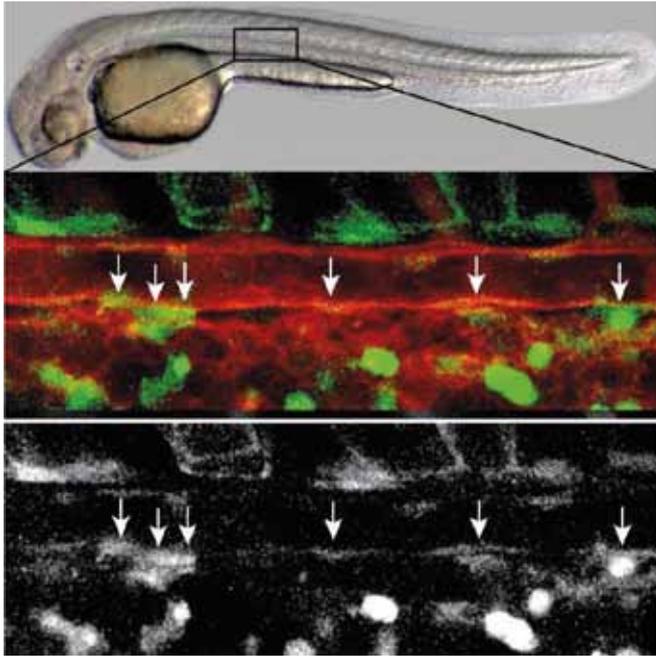


Figure 1: In the zebrafish embryo, HSC also emerge from the ventral wall of the dorsal aorta of the AGM region. By using a double transgenic line (*Tg(cmyb:GFP;kdr1:mKate-CAAX)*), we are able to monitor the *in vivo* formation and emergence of these cells (white arrows).

been already successfully translated to clinical trials in humans (North et al.; 2007; Goessling et al., 2011). Besides its amenability for screens, major advantages of the zebrafish model are its optical transparency and the extra-uterine development allowing *in vivo* observation of developmental processes such as the birth of HSCs from endothelial cells in the aorta-gonado-mesonephros region of the dorsal aorta (Figure 1).

Intriguing questions emerging from these studies that are followed up by our research group include (1) which endothelial cells are capable of transitioning to hematopoietic stem cells and (2) which molecular cues are involved in this process. Regarding the latter, previous reports identify a major role of the NOTCH pathway in hematopoietic stem cell emergence, and VEGF and SHH signalling as involved upstream regulators of NOTCH. Martina's on-going research project points out the *ecotropic viral integration site 1 (EVI1)* gene as an independent novel player inducing hematopoietic fate in endothelial cells by fine-tuning NOTCH levels. Currently, the molecular mechanisms involved in this process are investigated in more detail, for example by Elisa's proj-

ect analysing potential contributions of the *trichorhino-phalangeal syndrome 1 (trps1)* gene – a GATA family transcriptional factor – to *evi1*-induced hematopoiesis.

While *EVI1* has not yet been reported to play a role in early HSC specification, previous reports indicate important roles of *EVI1* in adult hematopoietic and leukemic stem cell biology. Indeed, the *EVI1* gene has originally been identified as a retroviral insertion site in myeloid tumors in AKXD mice and since then, emerged as one of the most potent oncogenes and molecular predictors of adverse outcome in myeloid leukemia (Mucenski et al., 1988). Recently, we could show that *EVI1* also regulates lymphatic blood cells, enhancing for example apoptosis resistance and *in vivo* leukemogenicity in acute lymphoblastic leukemia cells and influencing the biology of chronic lymphatic leukemia cells (Konantz et al., 2013, Vasyutina et al., 2015). To further investigate the role of *EVI1* in leukemia, Elisa is currently generating zebrafish models for *EVI1*-overexpression. Specifically, she takes advantage of the established Gal4-UAS transgenic system to induce the overexpression of the zebrafish *evi1* homologue into defined zebrafish blood cell types using specific hematopoietic promoters. Ideally, these transgenic models will provide a platform for comparing the transforming potential of *evi1* overexpression on immature versus specialized blood cells, and eventually may inform on the cell of origin of *evi1* overexpressing leukemias. Prospectively, this system shall be used to explore functionally potential cooperating genetic events observed in *EVI1* overexpressing human leukemia, such as the recently reported RAS pathway mutations. Moreover, the model can potentially be employed for drug screens with the aim of identifying new molecular pathways involved in *evi1*-induced malignant transformation and molecules specifically targeting these pathways or *evi1* itself.

Anna Lenard (Postdoc)

Novel therapies that emerge from screens need to first undergo safety assessment before they move on to the first clinical trials. Hematologic findings are one of the most common side effects encountered in this pre-clinical safety testing. The consequences of direct or indi-

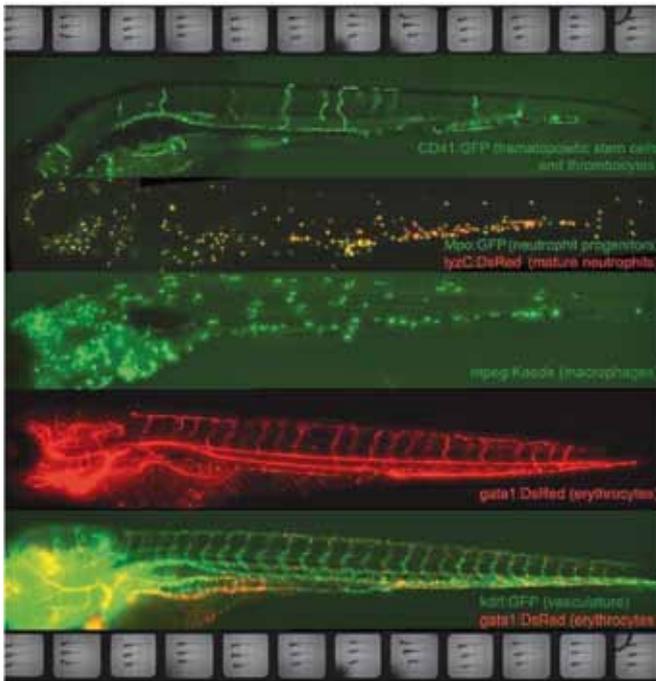


Figure 2: Various transgenic lines that fluorescently label blood cells and can be used to monitor the effects of drug treatment both microscopically and after dissociation into single cells via flow cytometry.

rect damage to blood cells and their precursors can be potentially life threatening, and hence, hematotoxicity can lead to the termination of a promising drug candidate. Current hematotoxicity testing employs *in vitro* models with a cell viability read-out. However, this approach only allows a limited read-out and, for example, does not capture effects on later maturation stages of blood cell progenitors. As part of the Roche postdoctoral fellowship program, Anna uses her zebrafish and live imaging experience to establish a zebrafish-based hematologic toxicity assessment model together with the Roche Preclinical Safety Department.

Using flow cytometry and high-content *in vivo* imaging of fluorescent reporter expression, she analyzes the effects of drug exposure on defined hematopoietic lineages with regard to cell numbers, distribution and activity. She is currently establishing various transgenic zebrafish lines labeling different types and stages of blood cells. Double transgenic combinations thereby allow analysis of different cell types in one embryo, for example progenitors and mature cells of the same or unrelated lineages (Figure 2).

Anna Paczulla (PhD student)

Anna's project focuses on the role of the caudal-type homeobox (*CDX*) gene family member *CDX2* in acute myeloid leukemia (AML). *CDX* genes were shown to regulate embryonic hematopoiesis via downstream *HOX* genes and interactions with the *WNT* signaling pathway. While no longer expressed in adult hematopoietic stem and progenitor cells, *CDX2* is aberrantly up-regulated via yet unknown mechanisms in the majority of acute myeloid leukemias. Anna explores the molecular regulation and functional relevance of *CDX2* expression in human AML and its importance for leukemia induction in healthy hematopoietic cells. Some of her recent findings point out interesting and unsuspected roles of *CDX2* on leukemic cell adhesion via non-cell autonomous interactions with the bone marrow niche (Figure 3). Anna currently explores the molecular mechanisms underlying these effects, which apparently involve the *WNT* signaling pathway. She further studies the interaction of human AML cells with the bone marrow niche using different experimental conditions and murine xenograft transplantation models.

Using zebrafish as xenograft models for human cancer cells:

Joëlle Müller (Master student)

Joëlle, a master student in the lab, explores, together with Martina, the zebrafish as a xenograft model. Human cancer cells have been shown to grow upon xenotransplantation in zebrafish embryo or adult fish. Embryo xenotransplantations especially provide important advantages when compared to conventional murine models, since they allow early assessment of *in vivo* tumorigenicity within few days as well as *in vivo* visualization of tumor-induced angiogenesis and invasiveness (Konantz et al., 2013). Potential draw-backs are the environmental differences in niches and growth factors as well as temperature (29°C for zebrafish, 35°C for xenotransplanted zebrafish) between zebrafish and humans. Currently, Martina and Joëlle have successfully transplanted several solid tumor cells including primary

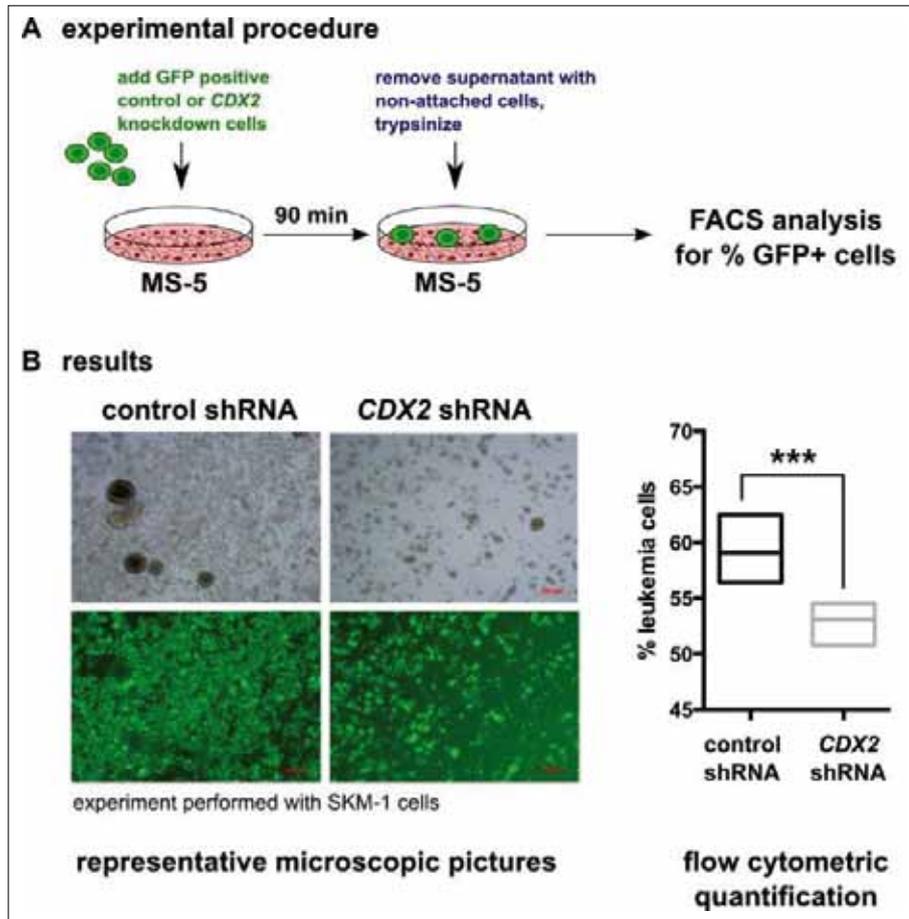


Figure 3: Adhesion assays using MS5 stromal cells reveal lower adhesion capacity of CDX2 knockdown GFP positive cells as compared to control transduced GFP-positive SKM1 cells. Experimental procedure: SKM1 cells were transduced with GFP-control or CDX2 shRNA GFP-lentiviruses to obtain control and respectively knockdown cells. Effectively transduced cells were selected by FACS and plated on a MS5 bone marrow stroma cell monolayer. After 90 minutes of co-culture the supernatant was removed and the cells that remained attached were trypsinized together with MS5 cells and analyzed via microscopy (A) and flow cytometry (B) for GFP positive cells.

material and leukemic cell lines and explored tumor induction using different methods (microscopy, qRT-PCR, FACS and/or histopathology, see figure 4). Next to optimizing the experimental transplant conditions and

readout, they investigate whether engraftment in fish correlates with disease characteristics and can be modulated by treatments with small molecules added to the water or specific genetic manipulations. Furthermore,

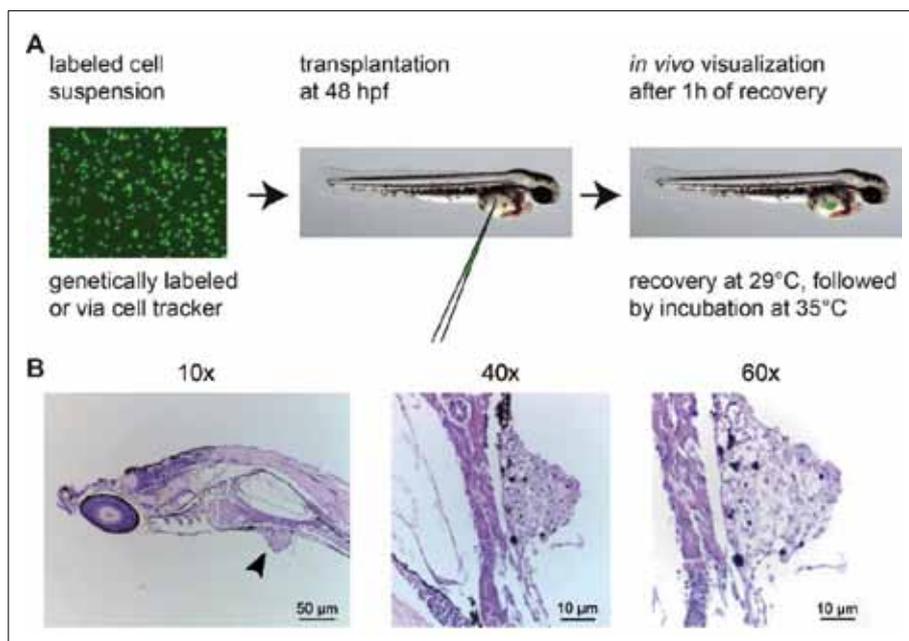


Figure 4: Human acute myeloid leukemia cells form tumors upon xenotransplantation into zebrafish embryo. Experimental Procedure: (A) Human cancer cells are either genetically or transiently labeled via different cell tracker for long term tracing of living cells (CM-DiI, Vybrant® DiO, Molecular probes®, Invitrogen). Cells are then transplanted into the yolk of 48 hpf old zebrafish embryos. After 1 hour of recovery at 29°C, fish are screened for positive fluorescence at the injection site. Fish are then transferred to 35°C and incubated for the next 3-5 days. (B) Growth of human cancer cells can then be monitored via histopathological stainings (H&E staining) or fluorescence microscopy, flow cytometry and qRT-PCR (not shown).

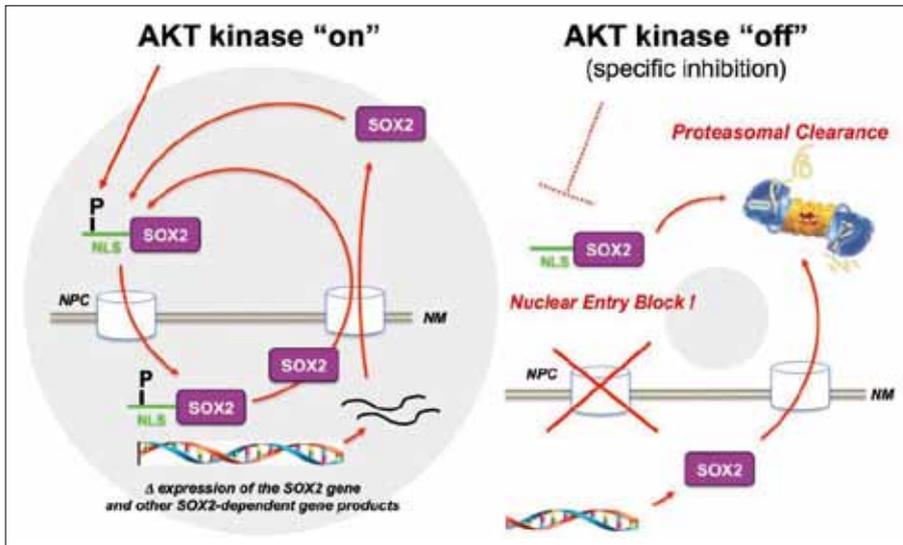


Figure 5: AKT kinase determines breast carcinoma cell clonogenicity via regulation of SOX2 subcellular localization and protein turnover.

the relationship between tumor cells and host cells such as macrophages in investigated in this model. Our research group also used this model in collaborations with other researchers (Viola Heinzlmann, Francis Jacob at the DBM and Sven Perner, University of Bonn).

The breast cancer team:

Hui Wang (PhD student), Thorsten Schäfer (Postdoc) & Tamara Pereboom (Technician)

Projects started in the research consortia at our previous facility in Tübingen involved research on cancer stem cells in other tumor models such as breast carcinoma (BC). BC is the most common type of malignant disease and one of the leading causes of cancer death in women worldwide. In spite of recent progresses in therapy, BC patients carry a life-long risk of disease recurrence. BC relapse is thought to originate from clonogenic breast carcinoma stem cells that metastasize, survive anti-tumor therapies and eventually re-initiate disease. Understanding the molecular mechanisms defining breast carcinoma stem cells may lead to the discovery of molecules effectively targeting this population.

EV11 gene activation has also been observed in solid cancers including breast carcinoma. In her research project, Hui investigates in detail the expression, functional roles and molecular partners of *EV11* in breast car-

cinoma. By performing *EV11* knockdown experiments using lentiviral particles, she found that *EV11* promotes cell proliferation and apoptosis resistance. Interestingly, estrogen exposure can rescue *EV11*-mediated growth inhibition suggesting that the two factors act on a common downstream pathway. Moreover these data imply that *EV11* expression is especially relevant for the growth of estrogen receptor negative breast carcinomas, which could be indeed confirmed analysing survival data in a larger cohort of breast carcinoma patients in collaboration with Sven Perner' group in Bonn and the University Hospital Zürich (Z. Varga & H. Moch). Next to further elucidation of the molecular mechanisms of *EV11*-driven cell growth, Hui's future areas of investigation include the role of *EV11* in bone marrow metastasis of human breast carcinoma cells.

Next to his recent interest in exploring biochemical aspects of *EV11* regulation in collaboration with the blood group and Hui, Thorsten investigates, together with Hui and Tamara, the regulation of the transcriptional master regulator *SOX2* (*sex determining region Y - Box 2*) in breast carcinoma stem cells. *SOX2* is a key regulator of pluripotency in embryonic stem cells and plays important roles in early organogenesis. More recently, *SOX2* expression was documented in various cancers and suggested as a breast carcinoma stem cell marker (Bareiss et al., 2013). Thorsten and Hui used a reporter assay with a stem cell-specific regulatory *SOX2* enhancer and identified the kinase AKT as an upstream regulator of *SOX2* expres-

sion in breast carcinoma stem cells. SOX2 and pAKT are co-expressed in putative breast carcinoma stem cells, and depletion of either of the two reduces breast carcinoma clonogenicity. Mechanistically, Thorsten showed that AKT physically interacts with SOX2 to modulate its subcellular distribution and thereby modulating protein stability (Figure 5). These data indicate promising applications for AKT-inhibitors in the treatment of SOX2-positive breast carcinoma patients.

Tamara Pereboom and Melanie Neutzner

Next to providing experimental support for different projects in the lab, Tamara is managing our primary cells database and, together with Melanie, organizes administratively our research laboratory.

Claudia Lengerke

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Dissertationen

Am 5. März 2015 konnte **Erez Dror** von der Forschungsgruppe Diabetes Research (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg

beenden. Er widmete sich in seiner Doktorarbeit dem Thema "Physiological synergy between IL-1 β and insulin on glucose disposal and macrophage activity".

Auszeichnungen

Venia docendi verliehen

In ihrer Sitzung am 15. April 2015 hat die Regenz der Universität Basel **Aimée Zuniga** von der Forschungsgruppe Developmental Genetics (Departement Biomedizin Mattenstrasse) die Venia docendi für Experimentelle Medizin verliehen. In ihrer Sitzung vom 20. Mai 2015 hat die Regenz **Adrian Egli** von der Forschungsgruppe Applied Microbiology Research (Departement Biomedizin Hebelstrasse) und **Giandomenica Iezzi**

von der Forschungsgruppe Cancer Immunotherapy (Departement Biomedizin Hebelstrasse) ebenfalls jeweils die Venia docendi für Experimentelle Medizin verliehen, **Min Jeong Kim** von der Forschungsgruppe Molecular Nephrology (Departement Biomedizin Hebelstrasse) erhielt die Venia docendi für Nephrologie. Sie sind damit befugt, den Titel eines Privatdozenten zu führen.

Das DBM gratuliert ganz herzlich!



15 years Department of Biomedicine

Anniversary Symposium

August 21, 2015

8:00 – 17:30

Grosser Hörsaal, ZLF

Elaine Fuchs, Rockefeller University

Markus Heim, DBM

Catherine Lubetzki, Inserm Paris

Ivan Martin, DBM

Erich Nigg, Biozentrum

Stuart Orkin, Harvard Medical School

Ed Palmer, DBM

Renato Paro, D-BSSE

Erika Pearce, Washington University

Tania Rinaldi, DBM

Keynote Lecture

Geoffrey West, Santa Fe Institute



Universität
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Universitätsspital
Basel

Farewell lecture of Albert Urwyler



With his farewell lecture “Anästhesie 2030 – mehr, schneller, besser?” (Anaesthesia 2030 – more, faster, better?) on May 21st 2015 Albert Urwyler formally said cheerio to the USB. While the Department of Anaesthesia has to face the future without one of their best – if not the very best – clinicians, the DBM can continue to count on Albi. Having concluded his many other long-standing functions as Dean, Chief Physician, Deputy Head of the Department of Anaesthesia and member of the DBM governing body, Albi will now further pursue and reinforce his research activities in the laboratory of Perioperative Patient Safety. Albi, we will be delighted to see you more often in the DBM.



Biosafety vs BBQ

Wie konnte es nur so weit kommen? Es ist Wochenende, meine Familie ist weg und ich hätte ein bisschen Zeit für mich. Ich könnte mir auf BBC ein Rugby Spiel anschauen, ich könnte einfach in den Garten sitzen und die Sonne geniessen oder ein gutes Buch lesen. Ich könnte mich mit Freunden in der Stadt treffen. Aber nein, ich sitze zuhause vor dem Computer und mache mir Gedanken zu einem Artikel, den ich für die DBM Facts schreiben soll. Das Einzige, das es einigermaßen erträglich macht, hab ich vor etwa zwei Stunden auf den Grill gelegt.

Das Erste, was ich mich fragte, war: Was kann ich zum Thema Biosicherheit schreiben? Dann musste ich mit einem Schmunzeln an die zwei meist gehörten Sätze denken, die ich am DBM bis jetzt gehört habe. Wann immer ich jemanden, der ohne grünen Kittel in einem BSL2 Labor arbeitete, darauf ansprach, bekam ich als Antwort zu hören: «Sorry. You are right» oder «Ich hab das Zellkulturlabor erst gerade betreten.» Egal, ob jemand seine Zellen durch das Mikroskop betrachtete oder an der biosafetybench sass und seine Zellen teilte. Gebetsmühlenartig und mit grosser Überzeugung: «Ich habe das Zellkulturlabor erst gerade betreten.» Was mich aber immer wieder erstaunte: Ich habe noch nie jemanden beim Arbeiten in einem BSL2 Labors ohne Handschuhe gesehen. Ein Schelm, wer da was Böses denkt.

Auf keinen Fall möchte ich hier jemanden an den Pranger stellen oder Euch ein schlechtes Gewissen einreden. Und ich denke, man hat sogar bis zu einem gewissen Punkt Verständnis, wenn es gefühlte 30°C in einem BSL2 Labor hat. Aber nichts desto trotz gibt es die Biosicherheitsrichtlinien aus einem guten Grund. Sie existieren nicht, um Euch das Leben schwer und kompliziert zu machen. Viel mehr sollt Ihr und die Umwelt vor den Organismen, mit denen Ihr in den BSL2 Labors arbeitet, geschützt werden. Durch die Massnahmen, die wir am DBM haben, soll letztlich eine Sicherheitskultur entstehen, bei der die Regeln ganz normal in den Laboralltag übergehen.

Wie ich aber kürzlich an einem Kurs zum Thema Arbeitssicherheit gelernt habe, wird es trotz allen Regeln und Richtlinien, Eurer Professionalität und Vorsicht früher oder später zu einem Unfall in einem BSL2 Labor kommen. Nach SUVA (Schweizerische Unfallversicherungsanstalt) ist es einfach eine Frage der Wahrscheinlichkeit. Je öfter etwas gemacht wird, desto grösser wird die Wahrscheinlichkeit, dass etwas schief läuft. Dass es zu einem Unfall kommt, können wir leider nicht verhindern. Aber wir können mit unserem täglichen Verhalten sehr wohl die Wahrscheinlichkeit verringern. Und dies ist mit sehr geringem Aufwand und ein bisschen Disziplin möglich. Setzt einfach die Regeln, die wir am DBM betreffend Biosicherheit haben, so pragmatisch wie möglich in Eurem Arbeitsalltag um und alles wird gut.

In diesem Sinn auf zu meinem Grill:

Spare Ribs mit einer sticky sauce

Die Silberhaut von der Knochenseite der Ribs entfernen und das Fett trimmen. Jeden Knochen auf der Unterseite leicht einschneiden. Die Zutaten für den Dry Rub gut vermischen, die Spare Ribs mit dem Dry Rub bestreuen und in Frischhaltefolie einwickeln. Über Nacht im Kühlschrank marinieren.

Für den Rub braucht Ihr: 3EL grobes Meersalz, 3EL smoked Paprika (im Globus erhältlich), 2EL brauner Rohrzucker, 2TL Zwiebelpulver, 1TL Knoblauchpulver, 1TL Piment, 1TL frisch gemahlener schwarzer Pfeffer, ¼ TL frisch geriebener Muskat und ½ TL Zimtpulver.

Die Zutaten für den Finishing Glaze in einen Kochtopf geben, gut umrühren, kurz aufkochen lassen und 20 Minuten köcheln lassen, hierbei immer wieder umrühren.



Für den Glaze braucht Ihr: 1 Tasse Tomatenketchup, ¼ Tasse brauner Rohrzucker, ¼ Tasse Honig, 1EL Apfelloessig, 1EL grobkörniger Senf, 1EL Zitronensaft, Abrieb einer Zitrone, 1EL Worcestershiresauce, 1TL Zwiebelpulver, ½TL Knoblauchpulver, ½TL Meersalz, ½TL frisch gemahlener schwarzer Pfeffer und ¼ TL Cayennepfeffer. Die Ribs verbringen mindestens 4 Stunden im Grill (geht auch im Backofen). Die Temperatur sollte die gesamte Garzeit zwischen 110° und 130° Celsius gehalten werden.

Die Spare Ribs auswickeln und mit der Fleischseite nach unten (indirekte Hitze) in den Grill legen. Nach 45 Minuten die Ribs wenden und weitere 45 Minuten im Grill lassen.

Die Spare Ribs vom Grill nehmen und die einzelnen Racks in Alufolie wickeln. Pro Rack 2–3 EL Apfelsaft oder Ananassaft mit in die Folie geben. Nun die Spare Ribs in der Alufolie für weitere 1,5 Stunden in den Grill legen. Die Spare Ribs aus der Alufolie nehmen und dünn mit dem warmen Finishing Glaze bepinseln, mindestens weitere 60 Minuten grillen und darauf achten, dass sie nicht zu dunkel werden. Ab und zu erneut mit dem Finishing Glaze bepinseln.

Die Ribs im sogenannten «Cadillac Cut» servieren – ein Knochen mit jeweils Fleisch rechts und links davon.

Roy Allenspach

PNAS

PNAS

cgi/doi/10.1073/pnas.1418549112

IF 9.809

T-bet- and STAT4-dependent IL-33 receptor expression directly promotes antiviral Th1 cell responses

Claudia Baumann^{a,b,1}, Weldy V. Bonilla^{c,1}, Anja Fröhlich^{a,b}, Caroline Helmstetter^{a,b}, Michael Peine^{a,b}, Ahmed N. Hegazy^d, Daniel D. Pinschewer^{c,2}, and Max Löhning^{a,b,2}

During infection, the release of damage-associated molecular patterns, so-called “alarmins,” orchestrates the immune response. The alarmin IL-33 plays a role in a wide range of pathologies. Upon release, IL-33 signals through its receptor ST2, which reportedly is expressed only on CD4⁺ T cells of the Th2 and regulatory subsets. Here we show that Th1 effector cells also express ST2 upon differentiation *in vitro* and *in vivo* during lymphocytic choriomeningitis virus (LCMV) infection. The expression of ST2 on Th1 cells was transient, in contrast to constitutive ST2 expression on Th2 cells, and marked highly activated effector cells. ST2 expression on virus-specific Th1 cells depended on the Th1-associated transcrip-

tion factors T-bet and STAT4. ST2 deficiency resulted in a T-cell-intrinsic impairment of LCMV-specific Th1 effector responses in both mixed bone marrow-chimeric mice and adoptive cell transfer experiments. ST2-deficient virus-specific CD4⁺ T cells showed impaired expansion, Th1 effector differentiation, and antiviral cytokine production. Consequently, these cells mediated little virus-induced immunopathology. Thus, IL-33 acts as a critical and direct cofactor to drive antiviral Th1 effector cell activation, with implications for vaccination strategies and immunotherapeutic approaches.

^aExperimental Immunology, Department of Rheumatology and Clinical Immunology, Charité-Universitätsmedizin Berlin, 10117 Berlin, Germany;

^bGerman Rheumatism Research Center Berlin, 10117 Berlin, Germany;

^cDivision of Experimental Virology, Department of Biomedicine, University of Basel, Basel, Switzerland; and

^dTranslational Gastroenterology Unit, Nuffield Department of Clinical Medicine, Experimental Medicine Division, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, United Kingdom

¹C.B. and W.V.B. contributed equally to this work.

²D.D.P. and M.L. contributed equally to this work.

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Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer

Marco Archetti^a, Daniela A. Ferraro^b, and Gerhard Christofori^b

The extensive intratumor heterogeneity revealed by sequencing cancer genomes is an essential determinant of tumor progression, diagnosis, and treatment. What maintains heterogeneity remains an open question because competition within a tumor leads to a strong selection for the fittest subclone. Cancer cells also cooperate by sharing molecules with paracrine effects, such as growth factors, and heterogeneity can be maintained if subclones depend on each other for survival. Without strict interdependence between subclones, however, nonproducer cells can free-ride on the growth factors produced by neighboring producer cells, a collective action problem known in game theory as the “tragedy of the commons,” which has been observed in microbial cell populations. Here, we report that similar dynamics occur in cancer cell populations.

Neuroendocrine pancreatic cancer (insulinoma) cells that do not produce insulin-like growth factor II (IGF-II) grow slowly in pure cultures but have a proliferation advantage in mixed cultures, where they can use the IGF-II provided by producer cells. We show that, as predicted by evolutionary game theory, producer cells do not go extinct because IGF-II acts as a nonlinear public good, creating negative frequency-dependent selection that leads to a stable coexistence of the two cell types. Intratumor cell heterogeneity can therefore be maintained even without strict interdependence between cell subclones. Reducing the amount of growth factors available within a tumor may lead to a reduction in growth followed by a new equilibrium, which may explain relapse in therapies that target growth factors.

^aSchool of Biological Sciences, University of East Anglia, Norwich Research Park, Norwich NR4 7TJ, United Kingdom; and

^bDepartment of Biomedicine, University of Basel, CH-4058 Basel, Switzerland

Blood

blood

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Deletion of *Stat3* in hematopoietic cells enhances thrombocytosis and shortens survival in a *JAK2-V617F* mouse model of MPN

Jean Grisouard¹, Takafumi Shimizu¹, Adrian Duek¹, Lucia Kubovcakova¹, Hui Hao-Shen¹, Stephan Dirnhofer², and Radek C. Skoda¹

The acquired somatic *JAK2-V617F* mutation is present in >80% of patients with myeloproliferative neoplasms (MPNs). *Stat3* plays a role in hematopoietic homeostasis and might influence the *JAK2-V617F*-driven MPN phenotype. We crossed our transgenic *SclCre;V617F* mice with a conditional *Stat3* knockout strain and performed bone marrow transplantations into lethally irradiated recipient mice. The deletion of *Stat3* increased the platelet numbers in *SclCre;V617F;Stat3^{fl/fl}* mice compared with *SclCre;V617F;Stat3^{fl/+}* or *SclCre;V617F;Stat3^{+/+}* mice. *Stat3* deletion also normalized *JAK2-V617F*-induced neutrophilia. Megakaryocyte progenitors were elevated, especially in the spleen, and a slight increase in

myelofibrosis was noted. We observed increased mRNA expression levels of *Stat1* and *Stat1* target genes and augmented phosphorylation of *Stat1* protein in bone marrow and spleen of *JAK2-V617F* mice after *Stat3* deletion. The survival of *Stat3*-deficient mice expressing *JAK2-V617F* was reduced. Inflammatory bowel disease, previously associated with shortened survival of *Stat3*-deficient mice, was less prominent in the bone marrow transplantation setting, possibly by limiting deletion of *Stat3* to hematopoietic tissues only. In conclusion, deletion of *Stat3* in hematopoietic cells from *JAK2-V617F* mice did not ameliorate the course of MPN, but rather enhanced thrombocytosis and shortened the overall survival.

¹ Department of Biomedicine, Experimental Hematology, and

² Institute of Pathology, University Hospital Basel, Basel, Switzerland

Diabetes

diabetes

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Angiotensin II Induces Interleukin-1 β -Mediated Islet Inflammation and β -Cell Dysfunction Independently of Vasoconstrictive Effects

Nadine S. Sauter^{1,2}, Constanze Thienel^{1,2}, Yuliya Plutino¹, Kapil Kampe², Erez Dror^{1,2}, Shuyang Traub^{1,2}, Katharina Timper^{1,2}, Benoit Bédât^{3,4}, Francois Pattou⁵, Julie Kerr-Conte⁵, Andreas W. Jehle^{2,6}, Marianne Böni-Schnetzler^{1,2} and Marc Y. Donath^{1,2}

Pathological activation of the renin-angiotensin system (RAS) is associated with the metabolic syndrome, and the new onset of type 2 diabetes can be delayed by RAS inhibition. In animal models of type 2 diabetes, inhibition of the RAS improves insulin secretion. However, the direct effects of angiotensin II on islet function and underlying mechanisms independent of changes in blood pressure remain unclear. Here we show that exposure of human and mouse islets to angiotensin II induces interleukin (IL)-1-dependent expression of IL-6 and MCP-1, enhances β -cell apoptosis, and impairs mitochondrial function and insulin secretion. In vivo,

mice fed a high-fat diet and treated with angiotensin II and the vasodilator hydralazine to prevent hypertension showed defective glucose-stimulated insulin secretion and deteriorated glucose tolerance. Application of an anti-IL-1 β antibody reduced the deleterious effects of angiotensin II on islet inflammation, restored insulin secretion, and improved glycemia. We conclude that angiotensin II leads to islet dysfunction via induction of inflammation and independent of vasoconstriction. Our findings reveal a novel role for the RAS and an additional rationale for the treatment of type 2 diabetic patients with an IL-1 β antagonist.

¹ Clinic of Endocrinology, Diabetes, and Metabolism, University Hospital Basel, Basel, Switzerland

² Department of Biomedicine, University of Basel, Basel, Switzerland

³ Cell Isolation and Transplantation Center, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland

⁴ University of Geneva School of Medicine, Geneva, Switzerland

⁵ University Lille Nord de France, Lille, France

⁶ Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland

Cancer chemotherapy agents target intratumoral dendritic cells to potentiate antitumor immunity

Philipp Müller¹, Kea Martin¹, Sebastian Theurich², Michael von Bergwelt-Baildon², and Alfred Zippelius^{1,3}

Cytotoxic drugs capable of killing cancer cells in conjunction with targeted conversion of tumor resident, tolerogenic dendritic cells (DCs) into efficient antigen presenting cells (APCs) are highly complementary therapeutic routes to boost antitumor immunity. Our data suggest that the microtubule-depolymerizing compounds Dolastatin 10 and Ansamitocin P3 may serve as prototypes for a class of agents that display this binary mode of action.

The field of cancer immunotherapy is moving forward at an accelerated pace and was honorably selected as Breakthrough of the Year in 2013 by the editors of Science. Following many disappointments and decades long struggles to successfully implement cancer immunotherapy from the bench to the bedside the concerted efforts of basic and clinical sci-

entists have begun to pay off in the form of efficacious clinical treatment regimens. Ipilimumab, a fully humanized antibody targeting cytotoxic T lymphocyte associated protein 4 (CTLA-4) as well as anti-PD-1 and -PD-L1 (the ligand of PD-1) blocking antibodies targeting the programmed cell death 1 (PD-1) immune checkpoint, have stimulated objective and durable anticancer responses in patients with treatment-refractory solid tumors, including melanoma and cancers of the lung, and kidney. These clinical successes highlight the potential of immune-based therapies in oncology. Nevertheless, only a fraction of patients respond and most of the responders eventually relapse. Possible explanations include immune effector cell paucity at the tumor site, as well as the molecular and cellular composition of the tumor microenvironment, both of which may pose a major hurdle for contriving antitumor immunity.

¹ Cancer Immunology & Biology; Department of Biomedicine; University Hospital Basel and University of Basel; Switzerland;

² Department I of Internal Medicine and Cologne Interventional Immunology; University Hospital Cologne; Germany;

³ Department of Medical Oncology; University Hospital Basel; Switzerland

Multispecific *Aspergillus* T Cells Selected by CD137 or CD154 Induce Protective Immune Responses Against the Most Relevant Mold Infections

Claudia Stuehler¹, Justyna Nowakowska¹, Claudia Bernardini^{1,2}, Max S. Topp⁴, Manuel Battegay², Jakob Passweg³, and Nina Khanna^{1,2}

Background. *Aspergillus* and *Mucorales* species cause severe infections in patients after hematopoietic stem cell transplantation (HSCT). Induction of antifungal CD4⁺ T-helper type 1 (T_H1) immunity is an appealing strategy to combat these infections. Immunotherapeutic approaches are so far limited because of a lack of antigens inducing protective T cells, their elaborate production, and the need of targeting a broad spectrum of pathogenic fungi.

Methods. We examined the response to different *Aspergillus fumigatus* proteins in healthy individuals and patients after HSCT and compared rapid selection protocols for fungus-specific T cells based on CD137 or CD154 expression.

Results. The *A. fumigatus* proteins Crf1, Gel1, and Pmp20 induced strong T_H1 responses in healthy individuals. T cells specific for these antigens expanded in patients with active invasive aspergillosis, indicating their contribution to infection control. T_H1 cells specific for the 3 proteins can be selected with similar specificity within 24 hours, based on CD137 or CD154 expression. These cells recognize naturally processed *A. fumigatus* and the multispecific T-cell lines, directed against all 3 proteins, especially those selected by CD154, additionally cross-react to different *Aspergillus* and *Mucorales* species.

Conclusions. These findings may form the basis for adoptive T-cell transfer for prophylaxis or treatment in patients with these devastating infections.

¹ Infection Biology Laboratory, Department of Biomedicine,

² Division of Infectious Diseases and Hospital Epidemiology, Departments of Biomedicine and Clinical Research, and

³ Division of Hematology, University Hospital of Basel, Switzerland; and

⁴ Division of Hematology, Department of Internal Medicine II, University of Wuerzburg, Germany

Monoamine transporter and receptor interaction profiles of novel psychoactive substances: Para-halogenated amphetamines and pyrovalerone cathinones

Anna Rickli^a, Marius C. Hoener^b, Matthias E. Liechti^a

Abstract

The pharmacology of novel psychoactive substances is mostly unknown. We evaluated the transporter and receptor interaction profiles of a series of para-(4)-substituted amphetamines and pyrovalerone cathinones. We tested the potency of these compounds to inhibit the norepinephrine (NE), dopamine (DA), and serotonin (5-HT) transporters (NET, DAT, and SERT, respectively) using human embryonic kidney 293 cells that express the respective human transporters. We also tested the substance-induced efflux of NE, DA, and 5-HT from monoamine-loaded cells, binding affinities to monoamine receptors, and 5-HT_{2B} receptor activation. Para-(4)-substituted amphetamines, including 4-methylmethcathinone (mephedrone), 4-ethylmethcathinone, 4-fluoroamphetamine, 4-fluoromethamphetamine, 4-fluoromethcathinone (flepheprone), and 4-bromomethcathinone, were relatively more serotonergic (lower DAT:SERT ratio) compared with their analogs amphetamine, methamphetamine, and methcathinone. The 4-methyl, 4-ethyl, and 4-bromo groups

resulted in enhanced serotonergic properties compared with the 4-fluoro group. The para-substituted amphetamines released NE and DA. 4-Fluoroamphetamine, 4-fluoromethamphetamine, 4-methylmethcathinone, and 4-ethylmethcathinone also released 5-HT similarly to 3,4-methylenedioxyamphetamine. The pyrovalerone cathinones 3,4-methylenedioxy-pyrovalerone, pyrovalerone, α -pyrrolidinoverophenone, 3,4-methylenedioxy- α -pyrrolidinopropiophenone, and 3,4-methylenedioxy- α -pyrrolidinobutiophenone potently inhibited the NET and DAT but not the SERT. Naphyrone was the only pyrovalerone that also inhibited the SERT. The pyrovalerone cathinones did not release monoamines. Most of the para-substituted amphetamines exhibited affinity for the 5-HT_{2A} receptor but no relevant activation of the 5-HT_{2B} receptor. All the cathinones exhibited reduced trace amine-associated receptor 1 binding compared with the non- β -keto-amphetamines.

^a Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland

^b Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switzerland

High-Resolution Breakpoint Analysis Provides Evidence for the Sequence-Directed Nature of Genome Rearrangements in Hereditary Disorders

Michal B. Kovac^{1,2,3,*}, Monika Kovacova^{4,*}, Hynek Bachraty⁵, Katarina Bachrata⁶, Salvatore Piscuoglio^{1,2,7}, Pierre Hutter⁸, Denisa Ilencikova⁹, Zdena Bartosova¹⁰, Ian Tomlinson³, Benno Roethlisberger¹¹, and Karl Heinimann^{1,2}

Abstract: Although most of the pertinent data on the sequence-directed processes leading to genome rearrangements (GRs) have come from studies on somatic tissues, little is known about GRs in the germ line of patients with hereditary disorders. This study aims at identifying DNA motifs and higher order structures of genome architecture, which can result in losses and gains of genetic material in the germ line. We first identified candidate motifs by studying 112 pathogenic germ-line GRs in hereditary colorectal cancer patients, and subsequently created an algorithm, termed recombination type ratio, which correctly predicts the propensity of rearrangements with respect to homologous versus non-homologous recombination events.

Introduction

Computational biology is likely to be instrumental in refining our understanding of the design of natural biological systems. This scientific discipline assumes a block-based structure of genomes of living organisms,

such that biological functions are encoded in shorter DNA motifs that are selected through evolution. As evolution cannot exist without an adaptation, it is also expected that some DNA motifs evolved to generate diversity of structures on which selection could operate.

¹ Research Group Human Genomics, Department of Biomedicine, University of Basel, Basel, Switzerland;

² Medical Genetics, University Hospital Basel, Basel, Switzerland;

³ The Wellcome Trust Centre for Human Genetics, University of Oxford, Old Road Campus, Oxford, UK;

⁴ Institute of Mathematics and Physics, Faculty of Mechanical Engineering, Slovak University of Technology, Bratislava, Slovakia;

⁵ Department of Software Technologies, Faculty of Management Science and Informatics, University of Zilina, Zilina, Slovakia;

⁶ Department of InfoCom Networks, Faculty of Management Science and Informatics, University of Zilina, Zilina, Slovakia;

⁷ Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York City, New York;

⁸ Institut Central des Hopitaux Valaisans, Service de Génétique Médicale, Sion, Switzerland;

⁹ Pediatric Department, University Children Hospital, Comenius University, Bratislava, Slovakia;

¹⁰ Medical Genetics, St. Elizabeth Cancer Institute, Bratislava, Slovakia;

¹¹ Kantonsspital Aarau, Tellstrasse, Aarau, Switzerland

* These authors contributed equally to this work.

The Phenotypic and Genotypic Spectra of Ichthyosis With Confetti Plus Novel Genetic Variation in the 3' End of *KRT10* From Disease to a Syndrome

Iris Spoerri, PhD; Michela Brena, MD; Julie De Mesmaeker, PhD; Nina Schlipf, PhD; Judith Fischer, MD, PhD; Gianluca Tadini, MD; Peter H. Itin, MD; Bettina Burger, PhD

Importance Ichthyosis with confetti (IWC) is a genodermatosis caused by dominant negative mutations in the gene encoding keratin 10 (*KRT10*). We investigated clinical and genetic details of a substantial number of patients with IWC in order to define major and minor criteria for diagnosis of this rare disorder.

Observations Parallel clinical investigation of 6 patients with IWC revealed a novel spectrum of phenotypes. We found several features that qualify as major criteria for diagnosis, which are clearly and consistently associated with the condition. These included malformation of ears, hypoplasia of mammillae, and dorsal acral hypertrichosis. Genetic analysis

of patients revealed several different frameshift mutations in intron 6 or exon 7 of *KRT10*. Analysis of this locus in 17 unrelated control individuals revealed 2 novel polymorphisms of *KRT10*.

Conclusions and Relevance We present for the first time to our knowledge the spectrum of clinical variability of IWC in 6 patients with confirmed mutations in *KRT10*. From this, we have extracted major and minor criteria to aid early and correct clinical diagnosis. Ectodermal malformations, present in all patients, suggest a novel classification of IWC as a syndrome. There is remarkable genetic variation at the IWC disease locus within control individuals from the general population.

Author Affiliations:

Research Group of Dermatology, Department of Biomedicine, University Hospital Basel, Basel, Switzerland (Spoerri, De Mesmaeker, Burger); Section of Dermatology, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico di Milano, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy (Brena, Tadini); Dermatology, University Hospital Basel, Basel, Switzerland (Itin); Institute of Human Genetics, University Medical Center Freiburg, Freiburg, Germany (Schlipf, Fischer).

Raptor ablation in skeletal muscle decreases Cav1.1 expression and affects the function of the excitation–contraction coupling supramolecular complex

Rubén J. Lopez¹, Barbara Mosca^{1,2}, Susan Treves^{1,2}, Marcin Maj¹, Leda Bergamelli², Juan C. Calderon³, C. Florian Bentzinger⁴, Klaas Romanino⁴, Michael N. Hall⁴, Markus A. Rüegg⁴, Osvaldo Delbono⁵, Carlo Caputo³ and Francesco Zorzato^{1,2}

The protein mammalian target of rapamycin (mTOR) is a serine/threonine kinase regulating a number of biochemical pathways controlling cell growth. mTOR exists in two complexes termed mTORC1 and mTORC2. Regulatory associated protein of mTOR (raptor) is associated with mTORC1 and is essential for its function. Ablation of raptor in skeletal muscle results in several phenotypic changes including decreased life expectancy, increased glycogen deposits and alterations of the twitch kinetics of slow fibres. In the present paper, we show that in muscle-specific raptor knockout (RamKO), the bulk of glycogen phosphorylase (GP) is mainly associated in its cAMP-non-stimulated form with sarcoplasmic reticulum (SR) membranes. In addition, ³[H]-ryanodine and ³[H]-PN200-

110 equilibrium binding show a ryanodine to dihydropyridine receptors (DHPRs) ratio of 0.79 and 1.35 for wild-type (WT) and raptor KO skeletal muscle membranes respectively. Peak amplitude and time to peak of the global calcium transients evoked by supramaximal field stimulation were not different between WT and raptor KO. However, the increase in the voltage sensor-uncoupled RyRs leads to an increase of both frequency and mass of elementary calcium release events (ECRE) induced by hyperosmotic shock in flexor digitorum brevis (FDB) fibres from raptor KO. The present study shows that the protein composition and function of the molecular machinery involved in skeletal muscle excitation–contraction (E–C) coupling is affected by mTORC1 signalling.

¹ Departments of Anesthesia and of Biomedicine, Basel University Hospital, Hebelstrasse 20, 4031 Basel, Switzerland

² Department of Life Sciences, General Pathology section, University of Ferrara, Via Borsari 46, 44100 Ferrara, Italy

³ Laboratorio de Fisiología Celular, Centro de Biofísica y Bioquímica, Instituto Venezolano de Investigaciones Científicas (IVIC), Apartado 20632, 1020A Caracas, Venezuela

⁴ Biozentrum, University of Basel, CH-4056 Basel, Switzerland

⁵ Department of Internal Medicine, Section on Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157, U.S.A.

Characterization of excitation–contraction coupling components in human extraocular muscles

Marijana Sekulic-Jablanovic¹, Anja Palmowski-Wolfe², Francesco Zorzato^{1,3}, and Susan Treves^{1,3}

Excitation–contraction coupling (ECC) is the physiological mechanism whereby an electrical signal detected by the dihydropyridine receptor, is converted into an increase in $[Ca^{2+}]$, via activation of ryanodine receptors (RyRs). Mutations in *RYR1*, the gene encoding RyR1, are the underlying cause of various congenital myopathies including central core disease, multiminicore disease (MmD), some forms of centronuclear myopathy (CNM) and congenital fibre-type disproportion. Interestingly, patients with recessive, but not dominant, *RYR1* mutations show a significant reduction in RyR protein in muscle biopsies as well as ophthalmoplegia.

This specific involvement of the extraocular muscles (EOMs) indicates that this group of muscles may express different amounts of proteins involved in ECC compared with limb muscles. In the present paper, we report that this is indeed the case; in particular the transcripts encoding RyR3, cardiac calsequestrin (CSQ2) and the $\alpha 1$ subunit of the cardiac dihydropyridine receptor are up-regulated by at least 100-fold, whereas excitation-coupled Ca^{2+} entry is 3-fold higher. These findings support the hypothesis that EOMs have a unique mode of calcium handling.

¹ Departments of Anesthesia and Biomedizin, Basel University Hospital, Hebelstrasse 20, 4031 Basel, Switzerland

² Eye Hospital, Basel University Hospital, Mittlere Strasse 91, 4031 Basel, Switzerland

³ Department of Life Sciences and Biotechnology, General Pathology section, University of Ferrara, Via Borsari 46, 44100 Ferrara, Italy

Immune Screening Identifies Novel T Cell Targets Encoded by Antisense Reading Frames of HIV-1

Christoph T. Berger^{a,b}, Anuska Llano^c, Jonathan M. Carlson^d, Zabrina L. Brumme^{e,f}, Mark A. Brockman^{e,f}, Samandhy Cedeño^c, P. Richard Harrigan^f, Daniel E. Kaufmann^{a,g}, David Heckerman^d, Andreas Meyerhans^{h,i}, Christian Brander^{c,i,j,k}

Cytotoxic-T lymphocyte (CTL) responses to epitopes in alternative HIV reading frames have been reported. However, the extent of CTL responses to putative proteins encoded in antisense reading frames is unknown. Using sequence alignments and computational approaches, we here predict five potential antisense HIV proteins and characterize common CTL responses against them. Results suggest that antisense-derived sequences are commonly transcribed and translated and could encode functional proteins that contain important targets of anti-HIV cellular immunity.

Virus-specific CD8⁺ cytotoxic-T lymphocyte (CTL) responses are important in the control of HIV infection (1–3). Accumulating evidence indicates that in addition to CTL responses targeting known structural and

nonstructural HIV proteins, CTL responses to epitopes in alternative reading frames (ARFs) of HIV can contribute to *in vivo* immune selection pressure (4–6). Importantly, these CTL responses are not limited to ARFs in the sense direction, but may also target antisense-encoded ARFs (5, 6). Antisense transcription of known host genes in human and rodent cells has been extensively described (7–10), and the existence of an antisense protein (ASP) in HIV was first proposed more than 20 years ago (10–12). The extent to which such viral antisense transcripts encode functional proteins remains largely unknown.

^a Ragon Institute of MGH, MIT and Harvard, Boston, Massachusetts, USA;

^b Translational Immunology, Department of Biomedicine, University Hospital Basel, Basel, Switzerland;

^c IrsiCaixa AIDS Research Institute-HIVACAT, Hospital Germans Trias I Pujol, Badalona, Spain;

^d Microsoft Research, Seattle, Washington, USA;

^e Simon Fraser University, Burnaby, BC, Canada;

^f British Columbia Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada;

^g University of Montreal Hospital Research Center (CRCHUM), Montreal, QC, Canada;

^h Infection Biology Group, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain;

ⁱ Institutio Catalana de Recerca i Estudis Avancats (ICREA), Barcelona, Spain;

^j University of Vic and Central University of Catalonia, Vic, Catalonia, Spain;

^k Autonomous University of Barcelona, Barcelona, Catalonia, Spain

Altered emotionality and neuronal excitability in mice lacking KCTD12, an auxiliary subunit of GABA_B receptors associated with mood disorders

F Cathomas^{1,2,*}, M Stegen^{3,*}, H Sigrist¹, L Schmid¹, E Seifritz^{2,4}, M Gassmann³, B Bettler³ and CR Pryce^{1,4}

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, is fundamental to brain function and implicated in the pathophysiology of several neuropsychiatric disorders. GABA activates G-protein-coupled GABA_B receptors comprising principal GABA_{B1} and GABA_{B2} subunits as well as auxiliary KCTD8, 12, 12b and 16 subunits. The *KCTD12* gene has been associated with bipolar disorder, major depressive disorder and schizophrenia. Here we compare *Kctd12* null mutant (*Kctd12*^{-/-}) and heterozygous (*Kctd12*^{+/-}) with wild-type (WT) littermate mice to determine whether lack of or reduced KCTD12 expression leads to phenotypes that, extrapolating to human, could constitute endophenotypes for neuropsychiatric disorders with which *KCTD12* is associated.

Kctd12^{-/-} mice exhibited increased fear learning but not increased memory of a discrete auditoryconditioned stimulus. *Kctd12*^{+/-} mice showed increased activity during the inactive (light) phase of the circadian cycle relative to WT and *Kctd12*^{-/-} mice. Electrophysiological recordings from hippocampal slices, a region of high *Kctd12* expression, revealed an increased intrinsic excitability of pyramidal neurons in *Kctd12*^{-/-} and *Kctd12*^{+/-} mice. This is the first direct evidence for involvement of KCTD12 in determining phenotypes of emotionality, behavioral activity and neuronal excitability. This study provides empirical support for the polymorphism and expression evidence that *KCTD12* confers risk for and is associated with neuropsychiatric disorders.

¹ Preclinical Laboratory for Translational Research into Affective Disorders (PLaTRAD), Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Zurich, Switzerland;
² Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Zurich, Switzerland;
³ Department of Biomedicine, Institute of Physiology, University of Basel, Basel, Switzerland and
⁴ Neuroscience Center, University and ETH Zurich, Zurich, Switzerland.
 * The two first authors contributed equally to this work.

An Improved Cartilage Digestion Method for Research and Clinical Applications

Matteo Centola, PhD¹, Beatrice Tonnarelli, PhD¹, Jeanine Hendriks, PhD², Mirella van den Doel, BS², Sandra Feliciano, BS¹, Adam Papadimitropoulos, PhD^{1,3}, Elia Piccinini, PhD^{1,3}, Jeroen Geurts, PhD⁴, Ivan Martin, PhD¹, and Andrea Barbero, PhD¹

Enzymatic isolation of chondrocytes from a cartilage biopsy is the first step to establish *in vitro* models of chondrogenesis or to generate cell-based grafts for cartilage repair. Such process is based on manually operated procedures and typically results in yields lower than 20% of the total available cells. In this study, we hypothesized that, as compared to conventionally used protocols, the enzymatic digestion of human articular cartilage in the presence of ascorbic acid 2-phosphate (AscA2P) or of sodium chloride (NaCl), in combination with the use of a perfusion bioreactor system, leads to a higher and more reproducible yield of cell populations with high proliferation and chondrogenic capacity. The addition of AscA2P within the enzymatic digestion medium did not significantly increase the cell yield, but resulted in a significant decrease of the intradonor variability in cell yield (-17.8% ± 10.7%, *p* = 0.0247) and in a

significant increase of the proliferation rate of the isolated chondrocytes (+ 19.0% ± 1.4%, *p* < 0.05) with respect to the control group. The addition of NaCl during cartilage digestion did not modulate cell yield. When the cartilage digestion was further performed under direct perfusion flow, beneficial synergistic effects were achieved, with an overall increase of 34.7% ± 6.8% (*p* < 0.001) in the cell yield and an average decrease of 57.8% ± 11.2% (*p* < 0.01) in the coefficient of variation with respect to the control group. Importantly, by implementing this strategy it was possible to retrieve clonal subpopulations more efficiently capable of undergoing chondrogenesis, both *in vitro* and *in vivo*. Our findings bear relevance for the preparation of human chondrocytes for laboratory investigations, and in the perspective of efficient and streamlined manufacturing of cell/tissue grafts for articular cartilage repair.

Departments of
¹ Surgery and of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland.
² CellCoTec BV, Bilthoven, The Netherlands.
³ Celtec Biotek AG, Basel, Switzerland.
⁴ Orthopaedic Department, Osteoarthritis Research Center Basel, University Hospital Basel, Basel, Switzerland.

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2012

Ivan Martin, PhD^{1,2}, Hilary Ireland, MSc^{1,2}, Helen Baldomero, MSc³ and Jakob Passweg, MD³

Following the coordinated efforts of five established scientific organizations, this report describes activity in Europe for the year 2012 in the area of *cellular and engineered tissue therapies*, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. Three hundred thirteen teams from 33 countries responded to the cellular and engineered tissue therapy survey: 138 teams from 27 countries provided data on 2157 patients, while a further 175 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (36%; 80% autologous), cardiovascular disorders (25%; 95% autologous), hematology/oncology, predominantly prevention or treatment of graft versus host disease and HSC graft enhancement (19%; 1% autologous), neurological disorders (3%; 99% autologous), gastrointestinal disorders (1%; 71% au-

tologous), and other indications (16%; 79% autologous). Autologous cells were predominantly used for musculoskeletal/ rheumatological (42%) and cardiovascular (34%) disorders, whereas allogeneic cells were mainly used for hematology/oncology (60%). The reported cell types were mesenchymal stem/stromal cells (49%), HSC (28%), chondrocytes (11%), dermal fibroblasts (4%), keratinocytes (1%), and others (7%). In 51% of the grafts, cells were delivered after ex vivo expansion, whereas cells were transduced or sorted in 10% and 16%, respectively, of the reported cases. Cells were delivered intra-organ (35%), intravenously (31%), on a membrane or gel (15%), or using 3D scaffolds (19%). The data are compared with those collected since 2008 to identify trends in the field and discussed in the light of recent publications and ongoing clinical studies.

Departments of
¹ Surgery and

² Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland.

³ European Group for Blood and Marrow Transplantation, Activity Survey Office, University Hospital Basel, Basel, Switzerland.

Mitochondrial function in neuronal cells depends on p97/VCP/Cdc48-mediated quality control

Lei Fang¹, Charles Hemion¹, Ana C. Pinho Ferreira Bento¹, Claudia C. Bippes¹, Josef Flammer² and Albert Neutzner^{1,2}

Maintaining mitochondrial function is essential for neuronal survival and offers protection against neurodegeneration. Ubiquitin-mediated, proteasome-dependent protein degradation in the form of outer mitochondrial membrane associated degradation (OMMAD) was shown to play roles in maintenance of mitochondria on the level of proteostasis, but also mitophagy and cell death. Recently, the AAA-ATPase p97/VCP/Cdc48 was recognized as part of OMMAD acting as retrotranslocase of ubiquitinated mitochondrial proteins for proteasomal degradation. Thus, p97 likely plays a major role in mitochondrial maintenance. Support for this notion comes from mitochondrial dysfunction associated with amyotrophic lateral sclerosis and hereditary inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD) caused by p97 mutation. Using SH-SY5Y cells stably expressing p97 or dominant-negative p97^{Q0} treated with mitochondrial toxins rotenone, 6-OHDA, or A β -peptide as model for neuronal cells suffering

from mitochondrial dysfunction, we found mitochondrial fragmentation under normal and stress conditions was significantly increased upon inactivation of p97. Furthermore, inactivation of p97 resulted in loss of mitochondrial membrane potential and increased production of reactive oxygen species (ROS). Under additional stress conditions, loss of mitochondrial membrane potential and increased ROS production was even more pronounced. Loss of mitochondrial fidelity upon inactivation of p97 was likely due to disturbed maintenance of mitochondrial proteostasis as the employed treatments neither induced mitophagy nor cell death. This was supported by the accumulation of oxidatively-damaged proteins on mitochondria in response to p97 inactivation. Dysfunction of p97 under normal and stress conditions in neuron-like cells severely impacts mitochondrial function, thus supporting for the first time a role for p97 as a major component of mitochondrial proteostasis.

¹ Department of Biomedicine, University of Basel, Basel, Switzerland

² Department of Ophthalmology, University of Basel, Basel, Switzerland

PI3K signalling is required for a TGF β -induced epithelial–mesenchymal-like transition (EMT-like) in human melanoma cells

Natalie C. Schlegel¹, Anina von Planta¹, Daniel S. Widmer², Reinhard Dummer² and Gerhard Christofori¹

Abstract: Epithelial to mesenchymal transition (EMT) is a programme defined in epithelial cells and recognized as playing a critical role in cancer progression. Although melanoma is not a cancer of epithelial cells, hallmarks of EMT have been described to play a critical role in melanoma progression. Here, we demonstrate that long-term TGF β exposure can induce a dedifferentiated EMT-like state resembling a previously described invasive phenotype (EMT-like). TGF β -induced EMT-like is marked by the downregulation of melanocyte differentiation markers, such as MITF, and

the upregulation of mesenchymal markers, such as N-cadherin, and an increase in melanoma cell migration and cell invasion. Pharmacological interference shows the dependency of TGF β -induced EMT-like on the activation of the PDGF signalling pathway and the subsequent activation of PI3K in human melanoma cells. Together, the data provide novel insights into the transcriptional plasticity of melanoma cells that might contribute to tumor progression in patients and propose avenues to therapeutic interventions.

¹ Department of Biomedicine, University of Basel, Basel, Switzerland;

² Department of Dermatology, University Hospital Zürich, Switzerland

Anti-Inflammatory/Tissue Repair Macrophages Enhance the Cartilage-Forming Capacity of Human Bone Marrow-Derived Mesenchymal Stromal Cells

Sergio B. Sesia^{1,2,*}, Ralph Duhr^{1,*}, Carolina Medeiros Da Cunha¹, Atanas Todorov¹, Stefan Schaeeren¹, Elisabetta Padovan¹, Giulio Spagnoli, Ivan Martin¹, and Andrea Barbero¹

Macrophages are key players in healing processes. However, little is known on their capacity to modulate the differentiation potential of mesenchymal stem/stromal cells (MSC). Here we investigated whether macrophages (Mf) with, respectively, pro-inflammatory and tissue-remodeling traits differentially modulate chondrogenesis of bone marrow derived-MSC (BM-MSC). We demonstrated that coculture in collagen scaffolds of BM-MSC with Mf derived from monocytes polarized with M-CSF (M-Mf), but not with GM-CSF (GM-Mf) resulted in significantly higher glycosaminoglycan (GAG) content than what would be expected from an equal number of BM-MSC alone (defined as chondro-induction). Moreover, type II collagen was expressed at significantly higher levels in BM-MSC/M-Mf as compared to BM-MSC/GM-Mf constructs, while type X collagen expression was unaffected. In order to understand the pos-

sible cellular mechanism accounting for chondro-induction, developing monoculture and coculture tissues were digested and the properties of the isolated BM-MSC analysed. We observed that as compared to monocultures, in coculture with M-Mf, BM-MSC decreased less markedly in number and exhibited higher clonogenic and chondrogenic capacity. Despite their chondro-inductive effect in vitro, M-Mf did not modulate the cartilage tissue maturation in subcutaneous pockets of nude mice, as evidenced by similar accumulation of type X collagen and calcified tissue. Our results demonstrate that coculture of BM-MSC with M-Mf results in synergistic cartilage tissue formation in vitro. Such effect seems to result from the survival of BM-MSC with high chondrogenic capacity. Studies in an orthotopic in vivo model are necessary to assess the clinical relevance of our findings in the context of cartilage repair.

¹ Departments of Surgery and of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland

² Department of Pediatric Surgery, University Children's Hospital of Basel (UKBB), Basel, Switzerland

* These authors contributed equally to this work

Interactions between Bupropion and 3,4-Methylenedioxymethamphetamine in Healthy Subjects

Yasmin Schmid*, Anna Rickli*, Antonia Schaffner, Urs Duthaler, Eric Grouzmann, Cédric M. Hysek, and Matthias E. Liechti

Abstract

3,4-Methylenedioxymethamphetamine (MDMA; “ecstasy”) is a popular recreational drug. The aim of the present study was to explore the role of dopamine in the psychotropic effects of MDMA using bupropion to inhibit the dopamine and norepinephrine transporters through which MDMA releases dopamine and norepinephrine. The pharmacodynamic and pharmacokinetic interactions between bupropion and MDMA in 16 healthy subjects were investigated using a double-blind, placebo-controlled, crossover design. Bupropion reduced the MDMA-induced elevations in plasma norepinephrine concentrations and the heart rate response to

MDMA. In contrast, bupropion increased plasma MDMA concentrations and prolonged its subjective effects. Conversely, MDMA increased plasma bupropion concentrations. These results indicate a role for the transporter-mediated release of norepinephrine in the cardiostimulant effects of MDMA but do not support a modulatory role for dopamine in the mood effects of MDMA. These results also indicate that the use of MDMA during therapy with bupropion may result in higher plasma concentrations of both MDMA and bupropion and enhanced mood effects but also result in lower cardiac stimulation.

Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland (Y.S., A.R., A.S., U.D., C.M.H., M.E.L.); and Biomedicine Service, University Hospital Lausanne, Lausanne, Switzerland (E.G.)

*These authors contributed equally to this work

Glucosylceramide synthase inhibitors differentially affect expression of glycosphingolipids

Shahidul Alam, André Fedier, Reto S Kohler, and Francis Jacob

Abstract

Glucosylceramide synthase (GCS) catalyzes the first committed step in the biosynthesis of glucosylceramide (GlcCer)-related glycosphingolipids (GSLs). Although inhibitors of GCS, PPMP and PDMP have been widely used to elucidate their biological function and relevance, our comprehensive literature review revealed that the available data are ambiguous. We therefore investigated whether and to what extent GCS inhibitors affect the expression of lactosylceramide (LacCer), neolacto (nLc4 and P_1), ganglio (GM1 and GD3) and globo (Gb3 and SSEA3) series GSLs in a panel of human cancer cell lines using flow cytometry, a commonly applied method investigating cell-surface GSLs after GCS inhibition. Their

cell-surface GSL expression considerably varied among cell lines and more importantly, sublethal concentrations (IC_{10}) of both inhibitors preferentially and significantly reduced the expression of Gb3 in the cancer cell lines IGROV1, BG1, HT29 and T47D, whereas SSEA3 was only reduced in BG1. Unexpectedly, the neolacto and ganglio series was not affected. LacCer, the precursor of all GlcCer-related GSL, was significantly reduced only in BG1 cells treated with PPMP. Future research questions addressing particular GSLs require careful consideration; our results indicate that the extent to which there is a decrease in the expression of one or more particular GSLs is dependent on the cell line under investigation, the type of GCS inhibitor and exposure duration.

Gynecological Research Group, Department of Biomedicine, University Hospital Basel, University of Basel, Hebelstrasse 20, Basel 4031, Switzerland



Therapeutic efficacy of the F8-IL2 immunocytokine in a metastatic mouse model of lung adenocarcinoma

Sébastien Wieckowski^a, Teresa Hemmerle^{b,c}, Spasenja Savic Prince^d, Béatrice Dolder Schlienger^a, Sven Hillinger^e, Dario Neri^{b,c}, Alfred Zippelius^{a,f}

Abstract

Objectives: Antibody–cytokine fusion proteins (immunocytokines) represent a novel class of armed antibodies in oncology. In particular, IL2- and TNF-based immunocytokines targeting the EDB domain of fibronectin and the A1 domain of tenascin-C have demonstrated promising anti-tumor activity and are currently investigated in Phase I and Phase II clinical trials. To advance the development of immunocytokines for NSCLC, we here report on the therapeutic efficacy of F8-IL2, an immunocytokine directed against the alternatively spliced EDA domain of fibronectin in a fully immunocompetent, orthotopic model of NSCLC, and the characterization of the target antigen expression in human NSCLC specimens.

Materials and methods: We evaluated the therapeutic efficacy of the F8-IL2 immunocytokine utilizing a K-ras mutant, p53 deficient metastatic mouse model of NSCLC derived from the latest generation of genetically engineered and conditional tumor models. In parallel, we assessed the presence of the EDA domain of fibronectin by immunofluorescence in lung biopsies obtained from patients with NSCLC.

Results: The EDA domain of fibronectin was broadly expressed in lung metastases obtained from our model. Treatment with F8-IL2 induced

substantial local changes within immune effector cell populations and demonstrated promising therapeutic efficacy as monotherapy. The target of F8-IL2, the EDA domain of fibronectin, was present in all human lung adenocarcinoma specimens tested.

Conclusion: Both the therapeutic efficacy in a metastatic mouse model of NSCLC and the extensive presence of the EDA domain of fibronectin in human NSCLC biopsies support the rational development of therapies based on the F8-IL2 immunocytokine for the treatment of NSCLC.

^a Cancer Immunology and Biology, Department of Biomedicine, University Hospital Basel, University of Basel, Hebelstrasse 20, CH-4031 Basel, Switzerland

^b Department of Chemistry and Applied Biosciences, ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

^c Philochem AG, Libernstrasse 3, CH-8093 Otelfingen, Switzerland

^d Institute of Pathology, University Hospital Basel, Schönebeinstrasse 40, CH-4003 Basel, Switzerland

^e Department of Thoracic Surgery, University Hospital Zürich, Schmelzbergstrasse 12, CH-8091 Zürich, Switzerland

^f Medical Oncology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

Development and validation of a rapid turboflow LC-MS/MS method for the quantification of LSD and 2-oxo-3-hydroxy LSD in serum and urine samples of emergency toxicological cases

Patrick C. Dolder^{1,2}, Matthias E. Liechti², Katharina M. Rentsch¹

Abstract Lysergic acid diethylamide (LSD) is a widely used recreational drug. The aim of the present study is to develop a quantitative turboflow LC-MS/MS method that can be used for rapid quantification of LSD and its main metabolite 2-oxo-3-hydroxy LSD (O-H-LSD) in serum and urine in emergency toxicological cases without time-consuming extraction steps. The method was developed on an ion-trap LC-MS/MS instrument coupled to a turbulent-flow extraction system. The validation data showed no significant matrix effects and no ion suppression has been observed in serum and urine. Mean intraday accuracy and precision for LSD were 101 and 6.84 %, in urine samples and 97.40 and 5.89 % in serum, respectively. For O-H-LSD, the respective values were 97.50 and 4.99 % in urine and 107 and 4.70 % in serum. Mean interday accuracy and precision for LSD were 100 and 8.26 % in urine and 101 and 6.56 % in serum, respectively.

For O-H-LSD, the respective values were 101 and 8.11 % in urine and 99.8 and 8.35 % in serum, respectively. The lower limit of quantification for LSD was determined to be 0.1 ng/ml. LSD concentrations in serum were expected to be up to 8 ng/ml. 2-Oxo-3-hydroxy LSD concentrations in urine up to 250 ng/ml. The new method was accurate and precise in the range of expected serum and urine concentrations in patients with a suspected LSD intoxication. Until now, the method has been applied in five cases with suspected LSD intoxication where the intake of the drug has been verified four times with LSD concentrations in serum in the range of 1.80–14.70 ng/ml and once with a LSD concentration of 1.25 ng/ml in urine. In serum of two patients, the O-H-LSD concentration was determined to be 0.99 and 0.45 ng/ml. In the urine of a third patient, the O-H-LSD concentration was 9.70 ng/ml.

¹ Laboratory Medicine, University Hospital, Petersgraben 4, 4031 Basel, Switzerland

² Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital and University of Basel, Hebelstrasse 20, 4031 Basel, Switzerland

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All Akt Isoforms (Akt1, Akt2, Akt3) Are Involved in Normal Hearing, but Only Akt2 and Akt3 Are Involved in Auditory Hair Cell Survival in the Mammalian Inner Ear

Yves Brand^{1,2}, Soledad Levano^{1,2}, Vesna Radojevic^{1,2}, Arianne Monge Naldi³, Cristian Setz^{1,2}, Allen F. Ryan^{4,5,6}, Kwang Pak^{4,6}, Brian A. Hemmings⁷, Daniel Bodmer^{1,2}

Abstract

The kinase Akt is a key downstream mediator of the phosphoinositide-3-kinase signaling pathway and participates in a variety of cellular processes. Akt comprises three isoforms each encoded by a separate gene. There is evidence to indicate that Akt is involved in the survival and protection of auditory hair cells in vitro. However, little is known about the physiological role of Akt in the inner ear—especially in the intact animal. To elucidate this issue, we first analyzed the mRNA expression of the three Akt isoforms in the inner ear of C57/BL6 mice by real-time PCR. Next, we tested the susceptibility to gentamicin-induced auditory hair cell loss in isoform-specific Akt knockout mice compared to wild-types (C57/BL6) in vitro. To analyze the effect of gene deletion in vivo, hearing and cochlear microanatomy were evaluated in Akt isoform knockout animals. In this study, we found that all three Akt isoforms are expressed in the cochlea. Our results further indicate that Akt2 and Akt3 enhance hair cell resistance to ototoxicity, while Akt1 does not. Finally, we determined that untreated Akt1 and Akt2/Akt3 double knockout mice display significant hearing loss, indicating a role for these isoforms in normal hearing. Taken

together, our results indicate that each of the Akt isoforms plays a distinct role in the mammalian inner ear.

¹ Department of Biomedicine, University Hospital Basel, Hebelstrasse 20, 4031 Basel, Switzerland,

² Clinic for Otolaryngology, Head and Neck Surgery, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland,

³ Inner Ear Research, Clinic for Otolaryngology, Head and Neck Surgery, University Hospital Zürich, Frauenklinikstrasse 24, NORD 2, 8091 Zürich, Switzerland,

⁴ Departments of Surgery/ Otolaryngology, UCSD School of Medicine, 9500 Gilman Drive MC0666, La Jolla, CA 92093, United States of America,

⁵ Department of Neurosciences, UCSD School of Medicine, 9500 Gilman Drive MC0666, La Jolla, CA 92093, United States of America,

⁶ San Diego VA Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161, United States of America,

⁷ Mechanisms of Cancer Program, Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

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Serpine2/PN-1 Is Required for Proliferative Expansion of Pre-Neoplastic Lesions and Malignant Progression to Medulloblastoma

Catherine Vaillant¹, Paola Valdivieso^{1,*}, Sandro Nuciforo^{1,*}, Marcel Kool², Alexandra Schwarzentruher-Schauerte¹, H el ene M ereau¹, Erik Cabuy³, Johannes A. Lohrbus⁴, Stefan Pfister², Aim e Zuniga¹, Stephan Frank⁵, Rolf Zeller¹

Abstract

Background

Medulloblastomas are malignant childhood brain tumors that arise due to the aberrant activity of developmental pathways during postnatal cerebellar development and in adult humans. Transcriptome analysis has identified four major medulloblastoma subgroups. One of them, the Sonic hedgehog (SHH) subgroup, is caused by aberrant Hedgehog signal transduction due to mutations in the *Patched1* (*PTCH1*) receptor or downstream effectors. Mice carrying a *Patched-1* null allele (*Ptch1*^{Δ/+}) are a good model to study the alterations underlying medulloblastoma development as a consequence of aberrant Hedgehog pathway activity.

Results

Transcriptome analysis of human medulloblastomas shows that *SERPINE2*, also called Protease *Nexin-1* (*PN-1*) is overexpressed in most medulloblastomas, in particular in the SHH and WNT subgroups. As siRNA-mediated lowering of *SERPINE2/PN-1* in human medulloblastoma DAOY cells reduces cell proliferation, we analyzed its potential involvement in medulloblastoma development using the *Ptch1*^{Δ/+} mouse model. In *Ptch1*^{Δ/+} mice, medulloblastomas arise as a consequence of aberrant Hedgehog pathway activity.

¹ Developmental Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland,

² Division of Pediatric Neuro-Oncology, German Cancer Research Center DKFZ, Heidelberg, Germany,

³ Single Cell Genomics, Friedrich Miescher Institute, Basel, Switzerland,

⁴ Neuropathology Unit, Department of Clinical Pathology, University Hospital Geneva, Geneva, Switzerland,

⁵ Division of Neuropathology, Institute of Pathology, University of Basel, Basel, Switzerland

* These authors contributed equally to this work.

Efficient Uptake of Blood-Borne BK and JC Polyomavirus-Like Particles in Endothelial Cells of Liver Sinusoids and Renal Vasa Recta

Jaione Simon-Santamaria¹, Christine Hanssen Rinaldo^{2,3}, Piotr Kardas⁴, Ruomei Li¹, Ivana Malovic¹, Kjetil Elvevold¹, Peter McCourt¹, Bård Smedsrød¹, Hans H. Hirsch^{4,5,*}, Karen Kristine Sørensen^{1,*}

Abstract

Liver sinusoidal endothelial cells (LSECs) are specialized scavenger cells that mediate high-capacity clearance of soluble waste macromolecules and colloid material, including blood-borne adenovirus. To explore if LSECs function as a sink for other viruses in blood, we studied the fate of virus-like particles (VLPs) of two ubiquitous human DNA viruses, BK and JC polyomavirus, in mice. Like complete virions, VLPs specifically bind to receptors and enter cells, but unlike complete virions, they cannot replicate. ¹²⁵I-labeled VLPs were used to assess blood decay, organ-, and hepatocellular distribution of ligand, and non-labeled VLPs to examine cellular uptake by immunohisto- and -cytochemistry. BK- and JC-VLPs rapidly distributed to liver, with lesser uptake in kidney and spleen. Liver uptake was predominantly in LSECs. Blood half-life (~1 min), and tissue distribution of JC-VLPs and two JC-VLP-mutants (L55F and S269F) that lack sialic acid binding affinity, were similar, indicating involvement of non-sialic acid receptors in cellular uptake. Liver uptake was not mediated by scavenger receptors. In spleen, the VLPs localized to the red pulp marginal zone reticuloendothelium, and in kidney to the endothelial lining of vasa recta segments, and the transitional epithelium of renal pelvis. Most VLP-pos-

itive vessels in renal medulla did not express PV-1/Meca 32, suggesting location to the non-fenestrated part of vasa recta. The endothelial cells of these vessels also efficiently endocytosed a scavenger receptor ligand, formaldehyde-denatured albumin, suggesting high endocytic activity compared to other renal endothelia. We conclude that LSECs very effectively cleared a large fraction of blood-borne BK- and JC-VLPs, indicating a central role of these cells in early removal of polyomavirus from the circulation. In addition, we report the novel finding that a subpopulation of endothelial cells in kidney, the main organ of polyomavirus persistence, showed selective and rapid uptake of VLPs, suggesting a role in viremic organ tropism.

¹ Department of Medical Biology, UiT – The Arctic University of Norway, Tromsø, Norway,
² Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø, Norway,

³ Department of Clinical Medicine, UiT – The Arctic University of Norway, Tromsø, Norway,

⁴ Department of Biomedicine, University of Basel, Basel, Switzerland,

⁵ Divisions of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Basel, Switzerland

* These authors contributed equally to this work.

Diffuse gastrointestinal bleeding and BK polyomavirus replication in a pediatric allogeneic haematopoietic stem cell transplant patient

M. Koskenvuo^a, I. Lautenschlager^b, P. Kardas^c, E. Auvinen^b, L. Mannonen^b, P. Huttunen^a, M. Taskinen^a, K. Vettenranta^a, H.H. Hirsch^{c,d}

Abstract

Patients undergoing haematopoietic stem cell transplantation (HSCT) are at high risk of severe gastrointestinal bleeding caused by infections, graft versus host disease, and disturbances in haemostasis. BK polyomavirus (BKPyV) is known to cause hemorrhagic cystitis, but there is also evidence of BKV shedding in stool and its association with gastrointestinal disease. We report putative association of BKPyV replication with high plasma viral loads in a pediatric HSCT patient developing hemorrhagic cystitis and severe gastrointestinal bleeding necessitating intensive care. The observation was based on chart review and analysis of BKPyV DNA loads in plasma

and urine as well as retrospective BKPyV-specific IgM and IgG measurements in weekly samples until three months post-transplant. The gastrointestinal bleeding was observed after a >100-fold increase in the plasma BKPyV loads and the start of hemorrhagic cystitis. The BKPyV-specific antibody response indicated past infection prior to transplantation, but increasing IgG titers were seen following BKPyV replication. The gastrointestinal biopsies were taken at a late stage of the episode and were no longer informative of BK polyomavirus involvement. In conclusion, gastrointestinal complications with bleeding are a significant problem after allogeneic HSCT to which viral infections including BKPyV may contribute.

^a Division of Hematology-Oncology and Stem Cell Transplantation, Children's Hospital, University of Helsinki, Finland

^b Department of Virology, Helsinki University Hospital (HUSLAB) and University of Helsinki, Helsinki, Finland

^c Transplantation & Clinical Virology, Department Biomedicine, University of Basel, Basel, Switzerland

^d Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis

Katrin E Hostettler^{1,2}, Jun Zhong¹, Eleni Papakonstantinou³, George Karakiulakis³, Michael Tamm^{1,2}, Petra Seidel¹, Qingzhu Sun¹, Jyotshna Mandal¹, Didier Lardinois⁴, Christopher Lambers⁵ and Michael Roth¹

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis. The kinase inhibitor nintedanib specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) significantly reduced the rate of decline of forced vital capacity versus placebo.

Aim: To determine the in vitro effect of nintedanib on primary human lung fibroblasts. **Methods:** Fibroblasts were isolated from lungs of IPF patients and from non-fibrotic controls. We assessed the effect of VEGF, PDGF-BB and basic FGF (bFGF) ± nintedanib on: (i) expression/activation of VEGFR, PDGFR, and FGFR, (ii) cell proliferation, secretion of (iii) ma-

trix metalloproteinases (MMP), (iv) tissue inhibitor of metalloproteinase (TIMP), and (v) collagen.

Results: IPF fibroblasts expressed higher levels of PDGFR and FGFR than controls. PDGF-BB, bFGF, and VEGF caused a pro-proliferative effect which was prevented by nintedanib. Nintedanib enhanced the expression of pro-MMP-2, and inhibited the expression of TIMP-2. Transforming growth factor-beta-induced secretion of collagens was inhibited by nintedanib.

Conclusion: Our data demonstrate a significant anti-fibrotic effect of nintedanib in IPF fibroblasts. This effect consists of the drug's anti-proliferative capacity, and on its effect on the extracellular matrix, the degradation of which seems to be enhanced.

¹ Pulmonary Cell Research, Department of Biomedicine, University Hospital Basel, Basel 4031, Switzerland

² Clinics of Respiratory Medicine, University Hospital Basel, Petersgraben 4, Basel 4031, Switzerland

Full list of author information is available at the end of the article.

Expression and localization of somatostatin receptor types 3, 4 and 5 in the wild-type, SSTR1 and SSTR1/SSTR2 knockout mouse cochlea

Vesna Radojevic^{1,2} & Daniel Bodmer^{1,2}

Abstract Somatostatin (SST) is a peptide hormone that exerts inhibitory effects mediated through binding to specific cell surface G protein-coupled receptors, of which five distinct subtypes (SSTR1-SSTR5) have been characterized. Our study performed on mouse cochlear hair cells shows the expression and localization of the three receptors (SSTR3-SSTR5) in wild-type (WT), single-knockout (SSTR1 KO) and double-knockout SSTR1/SSTR2 (DKO) mice. Similar SSTRs expression were observed in the inner

hair cells (IHC), outer hair cells (OHC) and supporting cells of cultivated P7 mouse organ of Corti (OC) explants as well as in cultivated cochlear neuroepithelial supporting cells (NEsc). We found differences in the expression of SSTR3-5 in WT, SSTR1 KO and DKO mouse cochlea, which might be explained as a compensatory effect in the cochlea after the loss of SSTR1 and/or SSTR2.

¹ Department of Biomedicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

² Clinic for Otolaryngology, Head and Neck Surgery, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

Induced PD-L1 Expression Mediates Acquired Resistance to Agonistic Anti-CD40 Treatment

Alfred Zippelius^{1,2}, Jens Schreiner¹, Petra Herzig¹, and Philipp Müller¹

Abstract

CD40 stimulation on antigen-presenting cells (APC) allows direct activation of CD8⁺ cytotoxic T cells, independent of CD4⁺ T-cell help. Agonistic anti-CD40 antibodies have been demonstrated to induce beneficial antitumor T-cell responses in mouse models of cancer and early clinical trials. We report here that anti-CD40 treatment induces programmed death ligand-1 (PD-L1) upregulation on tumor-infiltrating monocytes and macrophages, which was strictly dependent on T cells and IFN γ . PD-L1 expression could be counteracted by coadministration of antibodies blocking the PD-1 (programmed death-1)/PD-L1 axis as shown for T cells

from tumor models and human donors. The combined treatment was highly synergistic and induced complete tumor rejection in about 50% of mice bearing MC-38 colon and EMT-6 breast tumors. Mechanistically, this was reflected by a strong increase of IFN γ and granzyme-B production in intratumoral CD8⁺ T cells. Concomitant CTLA-4 blockade further improved rejection of established tumors in mice. This study uncovers a novel mechanism of acquired resistance upon agonistic CD40 stimulation and proposes that the concomitant blockade of the PD-1/PD-L1 axis is a viable therapeutic strategy to optimize clinical outcomes.

¹ Cancer Immunology and Biology, Department of Biomedicine, University Hospital Basel and University of Basel, Switzerland.

² Department of Medical Oncology, University Hospital Basel, Switzerland.

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Tarator (таратор)

Rezeptmenge für: 4 Personen
Zeitbedarf: 20 Minuten

Tarator ist eine erfrischende, sommerliche und kalt servierte Gurkensuppe aus dem Balkanraum.

Zutaten:

500 ml kalter (bulgarischer) Joghurt
300 ml kaltes Wasser
1 Salatgurke
1–5 Knoblauchzehen
1 Bund Dill
3 EL kaltgepresstes, natives Olivenöl
Weissweinessig
frisch gemahlener Pfeffer (optional)
Salz

Kochgeschirr:

1 Schneebesen, 1 grobe Reibe, 2 Schüsseln

Zubereitung:

Die Salatgurke unter kaltem Wasser abbrausen und mit einer groben Reibe in eine grosse Schüssel reiben.
Den Joghurt und das Wasser mit einem Schneebesen gut verrühren.
Die Knoblauchzehen schälen und fein zerreiben, etwas mit Salz bestreuen.
Die restlichen Zutaten, ausser dem Essig, mit dem Joghurt und der Gurke gut vermengen.
Die Suppe mit dem Weissweinessig abschmecken und kalt servieren.

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Cancer- and Immunobiology

Taya Kueng

Molecular Genetics

Fabiana Lueoend

Tumor Biology

Robert Reinhardt

Developmental Genetics

Ernst Emanuel Strehler

Tumor Biology

Fengyuan Tang

Tumor Biology

Stefan Weis

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Congratulations



Enea Di Marco

Geboren am 24.05.2015



Kurt Jonas Steinl

Geboren am 08.05.2015

Das DBM gratuliert ganz herzlich!



Elisaveta Kalinichenko

Geboren am 10.03.2015



Lilou Dasen

Geboren am 14.12.2014



Iris Eva Zippelius

Geboren am 02.03.2015



Iris Theodouli Thanasopoulou

Geboren am 19.03.2015

***Herzlich
willkommen,
allerseits!***

Malen mit Licht

So übersetzt Wikipedia das Wort Fotografie (photós = Licht, graphein = malen) aus dem Griechischen.



Im Laufe eines Tages ändert sich durch den Weg der Sonne das Licht deutlich. Besondere Stimmungen lassen sich in der Zeit um Sonnenaufgang und Sonnenuntergang einfangen. Wegen des relativ flach einfallenden oft gold-gelben Lichtes hat sich die Zeit nach dem Aufgang und vor dem Sonnenuntergang als «goldene Stunde» ihren Namen gemacht (Bild 1).

Das Licht um die Mittagszeit wird oft als schwierig bezeichnet, da sich durch die hochstehende Sonne sehr scharfe Schatten bilden. Vor allem bei der Personenfotografie sorgt das für Probleme, weil die Augen oft im Schatten der Augenbrauen verschwinden. Nachts und in dunklen Räumlichkeiten stellt einen die Abwesenheit von Licht vor ganz andere Herausforderungen. Hierzu ein kleines Paradoxon: Interessanterweise kann ein frontal ausgerichteter Blitz zur Mittagszeit die Gesichtsschatten wunderbar verschwinden lassen, wird aber in Kirchen und anderen schummrigen Situationen zum echten Stimmungskiller.

Da ich als PhD Student am DBM arbeite, komme ich hauptsächlich in den Morgen- oder Abendstunden zum Fotografieren. Oft sind es die Hunderunden, auf denen ich mit der Kamera unterwegs bin. Daher ist mein kleines Beagle-Meitli «Bisou» wohl mein häufigstes Motiv. Mit ihr als Model versuche ich ab und an auch, gezielt Regeln der Fotografie zu brechen. Eine dieser Regeln lautet zum Beispiel «Fotografiere nie gegen die Sonne». Hintergrund dieser Regel ist, dass jedes Objekt seinen Schatten in Richtung Kamera wirft und so seine Struktur und Farbe in eben diesem Schatten verschwinden. Mit maximal geschlossener Blende kann man jedoch sehr stimmungsvolle Bilder erzeugen, in denen alle Dinge wie ein Scherenschnitt vor dem Farbverlauf des Himmels wirken (Bild 2).





Natürlich muss man sich gerade in der Schweiz mit all ihren Sehenswürdigkeiten nicht auf den eigenen Hund als Motiv beschränken. Mit dem mediterranen Süden, dem Mittelland und den Alpen warten vielerlei Landschaften darauf, entdeckt zu werden. Auf unseren Wandertouren am Wochenende bin ich dann mit einem Weitwinkelobjektiv unterwegs. Dieses hilft, die Szenerie eines besonderen Aussichtspunktes im Panoramaformat aufzunehmen. Nun gibt es schon allerlei Bilder von immer denselben Bergspitzen, aber mit dem Mond im Rücken und den Sternen am Himmel, werden dieselben Berge wieder interessanter (Bild 3).

Malen mit Zeit

Neben dem Licht ist ein zweiter Faktor für die Fotografie von grosser Bedeutung. Dieser Faktor ist die Zeit. Gemeint ist die Belichtungszeit, die man der Kamera lässt, um das Bild aufzunehmen.

Am Tag reichen dem Fotoapparat oft Sekundenbruchteile um genügend Licht zu sammeln und eine Szene festzuhalten. Der Rotmilan von Bild 4 ist in den Wäldern um die Blindenhundeschule in Allschwil zu Hause. Oft kreisen drei oder vier von ihnen über den Feldern von Allschwil. Eine eintausendstel ($1/1000$) Sekunde hat gereicht, um ihn dabei aufzunehmen, wie er jene Beute unter die Lupe nimmt, die er kurz vorher bei einem Sturzflug aufgegriffen hat.



Unter anderem ist dieses Bild auch deswegen so scharf, weil die Aufnahmezeit so kurz war, dass Bewegungen der Kamera kaum eine Rolle gespielt haben. Je länger die Belichtungszeit, desto wichtiger ist, dass der Fotograf die Kamera still hält. Geübte Fotografen schiessen scharfe Bilder aus der Hand bis zu einer Belichtungszeit von $1/25$ Sekunden. Für alles, was länger dauert, legt man die Kamera besser auf eine Mauer oder schraubt sie auf ein Stativ. Dann sind den Belichtungszeiten keine Grenzen mehr gesetzt. Belichtungszeiten von mehreren Sekunden bis zu Minuten sind mit Stativ kein Problem mehr – der Akku der Kamera sollte dann aber geladen sein.



30 Sekunden lang hat die Kamera Licht für das Bild am Strand von Lausanne (Bild 5) gesammelt. Wer genau hinschaut, kann auch die Sterne des Sternbildes Orion erkennen. Um Sterne zu fotografieren, braucht man schon einen sehr sicheren Stand. Oft sind trotz Stativ einige Bilder verwackelt. Diese wandern in der Regel umgehend ins Datennirvana.

Mit ein bisschen Fantasie und Übung kann man aber auch bei längeren Belichtungszeiten mit Bewegung spielen. Bild 6 ist entstanden, als ich vom Hafen von Lausanne aus ein Bild von Evian-Les-Bains machen wollte. Irgendwann kam dann die Fähre dazwischen. Aufgrund ihrer Bewegung allerdings ist die Fähre unsichtbar, während ihre Lichter sehr deutlich zu sehen sind.



Spas macht auch, während einer längeren Belichtungszeit aus dem Bild heraus oder herein zu springen (Bild 7). Das Ergebnis ist eine Art Doppelbelichtung aus zwei Bildern: Ein Bild von einer Person liegt auf einem anderen Bild.

Natürlich funktionieren solche Experimente nicht immer beim ersten Mal. Oft genug stellt man sich das Ergebnis auch viel toller vor, als es am Ende im Bild aussieht. So oder so lernt man eigentlich immer wieder etwas dazu und als Ablenkung von der Arbeit reicht es alle mal.

Ronny Nienhold

Hei senn eich dahaam - Welcome to Germany's oldest

Test your knowledge about Trier – find the answers while reading

Why do you meet so many Chinese people with cameras in Trier?

.....

Which holy relic is to be found in the cathedral?

.....

How could Trier beat both the UEFA Cup and Champions league winners in one season?

.....

What is the main drink of the locals?

.....

What is the most popular phrase in local Trier slang?

.....

What are the main ingredients of a simple but delicious Trier specialty?

.....

Welcome to Trier, founded over 2000 years ago as Augusta Treverorum, today the oldest city of Germany. The city is located in the west of the state Rhineland- Palatinate, very near to the borders of Luxembourg and France. It lies on the bank of the river Moselle, in a valley surrounded by vineyards and embedded among the two mountain ranges of Eifel and Hunsrück. Its placement is one reason for Trier being a well known locality for wine connoisseurs. If you find time to go along the riverside by bike you can visit hundreds of villages famous for local wine makers, producing and selling their own wine at small local festivals.

The city has approximately 100.000 inhabitants making it very cosy. It is also a university city. The University of Trier, or, as it is better known, the Karl Marx-University, is known for many humanity disciplines, especially focussing on law and economics. Due to the high number of students joining the university every year, Trier can therefore be called a students' city with an above average number of bars. The reason for the university's name is the fact that Trier is the birth place of the famous German philosopher, economist and social-critic. His manifest is one of the pillars of the Chinese state-structure. As a result many Chinese

city Trier



people come to visit Trier every year and the house in which he was born is of particular interest and is always surrounded by a lot of Chinese travelers taking pictures. The school that Karl Marx attended still exists and is a well-known secondary school in Trier today.

The Roman remains in Trier are listed as a UNESCO world cultural heritage site and consist of 9 important historical sites. The most important one, and at the same time the town's landmark, is the black gate "Porta Nigra", a former Roman gate that kept enemies outside of the inner city area. Trier was founded at least 16 years before Christ. At the time, where Romans located and built up the city, it developed to be a focus point of the west-Roman Empire. Nowadays one can still visit the throne room, amphitheatre and some Roman baths. The Romans were known to already be very experienced and modern in their technical constructions which can be seen, for example, in the ancient remains of an under floor heating system.

Today the ground level of whole city is located several meters above that of old Roman times. The locals say that whenever they want to build a new house, and they have to dig a hole first, there will be always be some Roman items found that then delay the construction work – the city is still full of ancient material. Sometimes that can even

be something precious. In 1993, a hoard of gold coins weighing 18.5kg was found during building works in the center of Trier. It is the largest collection of gold coins from the great Roman empire and therefore a main exhibit in the historical museum of Trier. Another example of how old Roman walls and constructions have impaired the modern city structure is to be found in a big glassy cube on a central yard in the inner city. During street building works in the late 1980s a large area full of antique bath-walls was found. In the early 1990s it was decided to integrate the discovery into the city-picture by covering it with a big glass building. Today it is used for many official festivals and formal receptions.



Next to the Roman sights, we have the oldest bishops' cathedral where the holy robe worn by Jesus shortly before his crucifixion, is exhibited. It is kept in a reliquary and cannot be viewed most of the time. The last pilgrimages to see the robe took place in 2012, 1996 and 1959. In front of the cathedral you can find the cathedral stone. A famous legend says that in the middle ages the devil himself was asked



to help build a bar, but, when he saw that he had helped to build a church, he wrathfully dropped the last stone in front of the cathedral where it still lies today. It is like a magnet for many tourists.

After an exhausting sightseeing trip, we can recommend the beautiful wine-house „Oechsle“ in the city-center to get in touch with the bright wine-culture of Trier. Here you can combine a relaxing wine-tasting session with some delicious food.

In addition, during the main grape harvest time at the end of July / beginning of August there are a lot of large local wine-festivals taking place. There are also the old city festival and the pure wine-festivals at the riverside area of “Zurlauben” and in the little wine producing village of “Olewig”. Both are great opportunities to taste local wine and listen to all kinds of live-music embedded with a typical wine-yard flair. Although we have such a large choice of different wines, the locals have chosen a

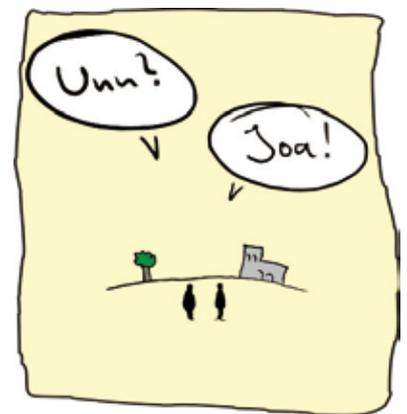


specific kind of cider called “Viez” as their main drink. We have included a nice recipe of a typical favourite dish of the most locals as well, that can be accompanied by either wine or cider. Pretty easy and very tasty.

For all of the impassioned sport fans among you, Trier is probably not the center of action in the field of international sports, although it hosts some important sport teams.

In addition to a successful woman handball club in the first national league, and a basketball club in the second national league, SV Eintracht Trier 05 is the number one soccer club in Trier. Honestly, the club does not play a great role in the bright history of the German Bundesliga, but it is probably the only club that beat both the winner of the UEFA CUP FC Schalke 04 and the winner of the UEFA Champions league Borussia Dortmund 09 in the season 1997/1998. How was that possible? Trier reached the semi-final of the national DFB Soccer cup during that season. It is considered as the greatest Cup-success in the club history.

The most valuable player at that time for Trier was Rudi Thömmes (1986 – 2004). He is probably regarded as one of the symbolic figures of the traditional club in Trier. Everyone in Trier knows him and his important goal against Dortmund in 1998.



If you get to know some typical locals, you will find them to be generally a bit stubborn and closed, but also very social on the other side. As in Basel, we celebrate “Fastnacht” in an extraordinarily festive manner. Everyone wears a costume and goes out on the streets to enjoy the parades, collect sweets and enjoy some drinks with friends. If you listen carefully to the locals, you will hear that they speak a strong dialect when compared to high-German.

Recipe Recipe

Trierer "Teerdisch"

1/2 kg sauerkraut
 1 kg potatoes (that we call "grombeeren")
 some little blood and liver sausages
 salt

Cook potatoes and sauerkraut separately. Mash the potatoes and mix it with sauerkraut, add a bit salt. Heat up the sausages and serve them with the mix. Alternatively: You can have meatballs or liver dumplings.



Recipe Recipe

If you do not know what to say, but you would like to be polite, ask "And?" and someone will reply with "Yes" and be very happy that you contribut-

ed. If you would like to express any deviation from the norm (good, bad, tasty, awful), you should try it with "oh leck". Really, try it!



Florian & Katharina

The authors of this article were both born in and grew up in Trier. They met 10 years ago in school and attended biology as one their main classes during their preparation for their university-entrance diploma. Katharina studied molecular biology in Maastricht (NL) whereas Florian studied biosciences in Giessen (D). In 2012, they met again during holidays in their hometown in the famous students' bar "Simplicissimus" where Katharina successfully tried to convince Florian with a glass of "Viez" to move to Basel.

Grosse Ferien!

Wir haben längst verlernt, was das Aus in Auszeit bedeutet Ein Plädoyer für einen neuen Urlaub

Drüben im Solarium ist ein neues Schild im Schaufenster. «Faken Sie das Urlaubsgefühl!» steht darauf. Daneben ist ein Paar in Badehosen freigestellt, das sich gegenseitig auf die knusprige Kruste schaut. Den Urlaub vortäuschen, darauf muss man erst mal kommen. Noch komischer ist, was das Schaufenster eigentlich sagt: Urlaub muss was abwerfen. Wozu wegfahren, wenn man nicht mindestens als ein anderer wiederkommt? Dieser verbreitete Anspruch ist schon Teil unserer Urlaubskrise. Ein anderer ist jene vermaledeite Woche vor dem Urlaub. Für gewöhnlich wird das ja die schlimmste Arbeitswoche des ganzen Halbjahrs. Der Klumpen Unbeantwortetes und Aufgeschobenes, den man über Monate jongliert hat, jetzt soll er doch noch schwinden. Alle Kanäle, auf denen im Büroalltag gesendet wird, müssen vorbereitet sein auf die Unterbrechung, sie sollen möglichst wenig weiterleiten. Die Angst vor der unwägbarer Störung des heiligen Urlaubs kennt nur eine Abhilfe: Alles fertigmachen. Deshalb ist die letzte Arbeitswoche so produktiv wie drei normale, man schreit, finished, delegiert wie nie und kollabiert final, weil noch was Neues reinkommt.



Gerade Menschen, die sich ihren Arbeitsalltag besonders frei eingerichtet haben, erleben die letzten Tage vor den Ferien als quälendes Endzeit-Szenario. Vielleicht, weil das eine der wenigen Deadlines ist, die nicht aufgeschoben werden kann. Spät am Freitagabend, wenn alle anderen schon gegangen sind, formuliert man im ungewohnten Beisein des Reinigungspersonals die Abwesenheitsnotiz. Meist wird es ein harsches Konstrukt aus Selbstbezeichnung und Erschöpfung: «E-Mails werden nicht gelesen / . . . nur in sehr dringenden Fällen ist da der Kollege / . . . meine geplante Rückkehr am. . . » Erst wenn es klingt, als begäbe man sich nackt ins Herz der Finsternis, ist es drastisch genug, erst dann wird jeder verstehen, was los ist: Man ist mal kurz nicht da. Man macht Urlaub. Herrgott, ist das anstrengend.

Vor allem im Sommer, denn das ist ja der Vorzeigurlaub, der Grand Slam der Freizeit, Sommerurlaub muss liefern. Möglicherweise haben wir diese fixe Idee von unseren Eltern übernommen, vielleicht aber auch einfach vom Dudelradio. Dort wird das Mantra von der bösen Arbeit und dem tollen Urlaub jeden Tag zementiert. Die Anrufer, die Moderatoren, die Hörer im Stau singen es non-stop im Chor: Montag bäh, Wochenende hurra, Arbeit bäh, Urlaub hurra und erst recht der Sommerurlaub, hee-ey, ab in den Süden! Der Kontrast zwischen Arbeitswelt und Freiheit wird da jeden Tag verstärkt. Wozu eigentlich, wem nützt diese Propaganda? Wer es auf dem Weg zu seiner Arbeit oft genug hört, hasst selbige pflichtgemäss und setzt sich für die nächsten Urlaube irre Erlebnis-Benchmarks. Ein Teufelskreis – je mehr man den Urlaub überhöht, desto unwahrscheinlicher wird, dass er die Erwartungen erfüllt, desto schlechter erholt kommt man nach Hause,



desto schneller ist die Arbeit wieder bäh. Recht bald hat einen das System so weit, dass man denkt, das Mallorca-Herumliegen, das Gran-Canaria-Wandern, das Thailand-Tingeln wäre das wahre Leben, das, wofür man arbeitet. Was dort eigentlich passiert, ist aber banal: Man schaltet sich für zehn Tage in den gleichen Urlaubsmodus wie die Geräte um einen herum. Der Urlaubsmodus ist aber auch nur das Arbeitsprogramm in einer soften, bunten und wenig belastbaren Beta-Version, massenhaft kopiert. In diesem Programm sammeln wir Auslandserfahrung, verbessern Sprachkenntnisse, optimieren Sport- und Hobby-Fähigkeiten und kurbeln den Devisenhandel an. Zurück im Büro fahren wir aus dem Standby wieder auf die Arbeitsoberfläche hoch. Wir waren nicht wirklich aus. Das Urlauben, wir beherrschen es eigentlich nicht gut. Der grösste Ausbruch besteht doch meistens darin, dass man sich schon um fünf Uhr nachmittags einen Longdrink servieren lässt oder selbst einschenkt. Da sitzt man dann und denkt von sich selbst als entschleunigter Person.

Es muss sich also etwas ändern. Nicht nur wegen der krampfhaft proaktiven Reiserei, nicht nur, weil die Studien sagen, dass sich vom fünften Tag an überhaupt erst ein vager Erholungseffekt einstellt, der dann aber im schlechtesten Fall nach drei Wochen Büro schon wieder weg ist. Nein, wir müssen unsere Urlaubsidee überarbeiten, weil sie die letzten sechzig Jahre nicht hinterfragt wurde. Wir absolvieren ihn letztlich immer noch so wie Heinz Erhardt, mit überfülltem Kofferraum und Pepita-Ehekrach, mit einem wohl-dosierten Hauch Exotik und buntem letzten Abend. Eine muffige, spiessige Kurzflucht. Dabei wissen wir eigentlich, was der bessere Urlaub wäre. Jeder von uns trägt ihn als vage Erinnerung in sich, als verblichenes Polaroid eines Sommers aus längst vergangener Zeit. Dieses Polaroid, es ist eine unscharfe Melange aus allen Sommerferien, in denen wir vielleicht zwischen sechs und zwölf Jahre alt waren und die Zeitläufte nur von vagem Interesse. Sechs Wochen Schulferien sind ja eine kolossale Sache, die meisten gestatten sich später nie wieder



im Leben eine solche Masse undefinierter Zeit am Stück, eine Spanne, in die man nichts hineinträgt und aus der man nichts wieder mitbringen muss als sich selbst. Verpflichtungen? Zero! Man diffundierte in den Sommer, der August war wie dunkler Honig in einem sehr großen Stundenglas, die Tage, die Wochen, man konnte sie einfach vergessen. Sicher, die Eltern entführten einen vielleicht in ihren Eltern-Urlaub, zwei Wochen, in denen sie um fünf Uhr einen Longdrink für sich und ein Eis fürs Kind bestellten. Aber dann ging es zurück, in die hitzestillen Städte und Dörfer mit ihrem angezählten Gartengrün und dort war man dann endgültig: lose, frei.

Man brauchte nicht viel. Das immer gleiche Handtuch, mit dem man zum Freibad radelte, die paar Freunde, die ähnlich sommersediert neben einem trotteten und ohne Verabredung am Steg sassen, einen Fußball vielleicht, ein bisschen Taschengeld. Das Wichtigste stellte sich unbemerkt ein: goldene Langweile und ein Anflug von Ewigkeit. Nicht so sehr, wenn man sich animieren lässt, die Alpen überquert, Wellen surft, auf Lanzarote Pilates lernt und Jetski ausleiht, erfährt man etwas über sich, sondern wenn man sich gepflegt langweilt. Wir erreichen den Zustand echter Langweile später im Leben aber nicht mehr, sie hat keine Lobby, und all die Systeme, die uns umgeben, sind darauf angelegt, sie zu bekämpfen. Aber die gute Langweile der Sommerferien, die Anfang vierte Woche in der endlosen Vormittagsstille des Elternhauses einsetzte, begleitet nur vom Brummseln der Stubenfliege am Fenster, war sie es nicht, die uns wieder auf null stellte? Wäre sie nicht auch heute den komischen Verben näher, die wir jedem Urlaub andichten: Runterkommen, abschalten, ausklinken? Sind damit nicht eigentlich Tage gemeint, in denen die grösste Aufregung das Trocknen der eigenen Fußspuren am sonnenwar-

men Beckenrand ist? Und zwar: Richtig viele Tage, richtig viele trocknende Fussspuren? Im Spiel gedacht – wie liesse sich dieses Sommerferiengefühl für Erwachsene wieder herstellen? Wichtig scheint die Einheit von Ort, Zeit und Handlung zu sein, was zufällig der Aristotelischen Forderung für ein gutes Drama entspricht. Aber als Kind war man eben meist an seinen Ort gebunden, man plante nicht in die Zukunft, man handelte

lokal und flog immer auf Sicht. Dann die Vertrautheit der Umgebung! Erst wenn die Füße die Trampelpfade auch in der Dämmerung von alleine finden, erst wenn man eins mit der Topografie ist und alle Codes kennt, lässt sich doch ruhig ich sein.

Das bedeutet nicht, dass man in der Vision von erwachsenen Sommerferien nicht verreisen soll, aber dann bitte auch mal: Irgendwo ankommen. Wir sprechen schliesslich von Ferien, nicht von einer Reise, nicht von einem Trip, nicht von einem Hopping. Zwei Wochen sind für Vertrautheit an einem neuen Ort zu kurz, wir sollten dieses Format endlich aufbrechen. Vier Wochen an einen Ort! Und das die nächsten fünf Sommer! Ist nicht so ungewöhnlich, Franzosen und Italiener halten es seit jeher so. Das merkt man deren Volkswirtschaften auch an, könnte man frozeln. Aber Amerikaner und Japaner machen so gut wie nie Urlaub und wirken wirtschaftlich auch ziemlich ausgebrannt.

Und vor hundertzwanzig Jahren waren wir urlaubs-mässig ja schon mal moderner, Stichwort Sommerfrische. Sommerfrischen hiessen ursprünglich nur die Behausungen, die zu eben jenem Zweck aufgesucht wurden. Einfache Bauernstuben, kleine Häuser, schlichte Quartiere. Man begab sich dorthin, bevor der Sommer seinen Zenit erreichte, und das war das Höchstmass an Bewegung, das man die nächsten Wochen oder Monate auf sich nahm. Der Rest ergab sich. Man fuhr nicht in die Sommerfrische, um ein anderer zu werden. Es war nicht die krasse Flucht, die heutigen Urlauben anhaftet, nicht das unbedingte Bestreben, für vierzehn Tage alles an Alltag, Klamotte, Sprache, Nachbarn hinter sich zu lassen. Nein, der Sommerfrischler blieb, wer er war, erledigte weiterhin Korrespondenz, kleidete sich weiterhin adrett, lud ein und besuchte reihum,

es gab ein paar Freunde, man lernte andere kennen, ein leichter Flirt, ein bisschen Tennis. Und weil man Jahr um Jahr wiederkam, wurde aus dem Fremdeln des ersten Aufenthalts mit den Jahren ein geborgenes Streicheln, eine Sommerheimat.

Luftveränderung ist ein schönes Wort. Mal ehrlich, wie viel Abenteuer mehr braucht der Mensch, als dass die Luft morgens ein bisschen verheissungsvoller riecht als sonst? Und dafür reichte schon immer eine Fahrt mit dem Eilzug aus der Stadt hinaus. Weil es kein Dudelradio gab, war die Arbeit damals vielleicht auch nicht ganz so verpönt. Künstler praktizierten im Urlaub einfach weiter, Fabrikbesitzer fuhren donnerstags zur Familie aufs Land und kehrten am Sonntag in die Stadt zurück, wer kein Geld hatte, half den Bauern bei der Ernte und schlief im Heu. Ziel war nicht das Ziel, sondern die verbrachte Zeit. Der vergessene Schriftsteller Ludwig Steub notierte damals: Jeder Torwart, jeder Milchmann geht aufs Land, und selbst die abgelegensten Berghöfe werden aufgesucht, um dort arkadisch zu leben und im Schatten der Holunderbüsche Trautmanns und anderer bayerischer Schriftsteller beliebteste Werke zu lesen. Ein kleines Arkadien, in dem man mit der leichten Muse im Schatten der Büsche liegt – damit ähnelt die klassischen Sommerfrische den grossen Ferien in der Polaroid-Erinnerung.



Klar, jetzt muss noch der Einwand behandelt werden. Vier Wochen am Stück weg, un-mö-glich! Aber käme es nicht wenigstens auf einen Versuch an, in einer Zeit, in der unsere Arbeitsstrukturen ohnehin aufweichen und die Technik die Gartenlaube oder die Terrasse auf Mykonos notfalls kurzfristig zu einem Schreibtisch machen können? Wäre nicht jetzt genau die Zeit, eine Renaissance der Sommerfrische einzuläuten, wo die Chefs doch mit Elternzeit, Teilzeitmodellen und dem Wunsch nach Work-Life-Balance Erfahrung gesammelt haben? Wäre es nicht ein Experiment wert, sich mal zwei Drittel Jahresurlaub zu sparen und gleichzeitig den Hass auf die Arbeit zu mildern, den Stress an den Wochenenden auszuschlafen, das Fernweh zur Not mit kurzen Städtereisen zu besänftigen und dafür etwas Großes zu bekommen: einen ganzen Sommer. Den Flieder auf- und verblühen sehen. Noch besser: Das ganze dahinstampfende Land mal einen Monat runterfahren, und jeder besucht den Ort aus seinem Sommerferien-Polaroid! Das ist nicht die künstliche Insel vor Dubai, das ist viel günstiger. München, Frankfurt, Berlin – Gone Fishing! Keine schlimme letzte Arbeitswoche, weil ja alle wegfahren oder es zumindest voneinander annehmen. Wir kämen vielleicht nicht so knusprig braun zurück wie die Herrschaften auf dem Solarium-Plakat, aber hallo, wir hätten endlich mal das Urlaubsgefühl nicht vorgetäuscht.

Von Max Scharnigg
(Süddeutsche Zeitung am Wochenende, 09.08.2014)

Anmerkung der Redaktion: Es gibt Texte, die vergisst man nicht. Dieser ist so schön, dass wir uns erlaubt haben, ihn nach der Erstveröffentlichung in der SZ nun auch in den DBM Facts zu publizieren.

Entering the ice cream business



A “refreshing” experience

“Stracciatella und Pistacchio im Cornet... bitte schön... das macht 4 Franken” – I live new emotions and find myself in a different dimension when, on a Saturday or Sunday afternoon, I help my wife Gabriella to sell the ice cream she produces (see <https://www.facebook.com/gabriellagelatoartigianale>).

Having a business in the field of Italian gastronomy has always been a dream for Gabriella, but I had always found good reasons to wait for more suitable times. Now that the children are grown up, that we could afford the necessary investment, that we could use the parterre apartment of our renovated farmer house, I could not find reasonable excuses: in mid-April we inaugurated an authentic Italian ice cream shop (“gelateria”)! Well... authentic is technically only partially correct: Gabriella does use Italian ingredients of the highest quality (e.g., sicilian Pistachios from Bronte, hazelnuts from Piemonte, lemon peel of fruits grown in my family garden on the ligurian coast). However, she is proud of combining them with regional dairy products (e.g., swiss Biofarm organic milk and yogurt from the Bruderholz in Oberwil, cream from the Manser Molki) or – upon availability – with locally picked fruits (e.g., fresh berries or cherries). The result therefore has to be acknowledged as a swiss-italian combination. By the way, synthetic emulgators, flavors, colourings and preservatives are banned from her recipes, so that her product complies with the strict definition of homemade, artisanal ice cream (“gelato artigianale”).

During the weekend, I truly enjoy standing behind the ice cream window for a few hours to serve the very diverse persons passing by the shop. The most difficult but most adorable customers are the children: their smile when – after several changes of mind on the taste selection – I give them the filled cup or cone is a unique source of gratification! The teenager coming with the girlfriend and offering her an ice cream softens me up, in the memory of similar moments I have lived a few years back... It's also not infrequent to meet managers working in the pharma industry and colleagues from the DBM or other research institutes, casually dressed after a hike or bike ride with their friends or family. Last week I even met an artist who traded a charcoal drawing against some vanilla ice cream. I had initially expressed con-



cerns to Gabriella about my garden being ‘invaded’ by strangers, but now I find it fascinating to see it as a meeting point or stop-over, where people feel welcomed and breath air of relax and friendliness. My dream? That one day I can offer an ice cream to Roger Federer: ultimately, he is from Oberwil and maybe he will decide to pass by...

The most rewarding aspect of this “refreshing” experience, however, is to see the enthusiasm, motivation and gratification of Gabriella. She is finally accomplishing what she had dreamt of and I am a living witness of the truth in the motto “Happy wife, happy life”! The children? They observe with curiosity and give us some tips on how to make things attractive for the market segment they represent, namely progymnasium students. So far, with the excuse that they have a lot of homework, they remain rather distant from the refrigerated window... unless they come to grab an ice cream as an afternoon snack.

As marketing is the soul of business, I have to conclude with an offer: gratis ice cream (medium size) to all of you who come to the shop with the personal copy of the DBM Facts. Don't worry, Radek... I'm not wasting the time of the DBM students... we'll sure have interesting scientific discussions there!

Ivan Martin

Today: Stefan Wieland, Hepatology

Here I am writing a short contribution to DBM Facts and wondering how I got here? This is not what was supposed to happen, but, I guess like for many others, life continuously surprises with unexpected turns and events... But let's not jump ahead and start from the beginning:

Growing up at one of the many lakes in Switzerland and playing in a wonderful backyard, I apparently developed an early curiosity for "what is in there..." for many things including those very bright and shiny flowers. In retrospect this almost seems like the beginning of a path to studying biology. But, not so fast. I was also fascinated by all things mechanical and went on to complete training as a "Maschinenmechaniker".



I really enjoyed handling the metal and building machines from the ground up. Not surprisingly, I was very much fascinated by the wonders of big machines especially the moon rocket Saturn V. Our neighbors (we had no TV) had to get up at 3 am in the morning so I could watch the moon landing of the Apollo 11 mission. But, with the big things came also the start of the era of miniaturization of such items as electronic circuits, including microprocessors. This was exciting too and as a member of a "computer club" we embarked on building our very own computer and used it for such mundane tasks as controlling an elevator or running an intricate model train system.

And when did I become a biologist you ask? Well, through all those

times, a love for anything nature related was always with me. Hence, I very much enjoyed road trips that included simultaneous tinkering with my car and taking in the beauties of, for example, the isle of Corsica. Professionally I eventually moved away from machines and computers, went back to school to acquire a "Matura" and then studied biology at the University of Zurich. As a "Werkstudent" I took on many different jobs including one that I presume has become completely obsolete in the internet era: at the time a few of us were selling the first batch of newly printed news papers shortly before midnight in the streets of Zurich under the heading "Tomorrow's News Paper". More importantly though, through one of my jobs I also got to know a "Chemielaborantin" and we



became and remained each other's life companions ever since.

I finished my studies in the relatively young discipline of molecular biology working on eukaryotic promoters, enhancers, transcrip-

tion factors and their interplay that were the hot topics of the day. Unexpectedly however, I took a turn again and started working with hepatitis B virus first in Zurich, then in Freiburg im Breisgau and then for a two-year postdoc experience

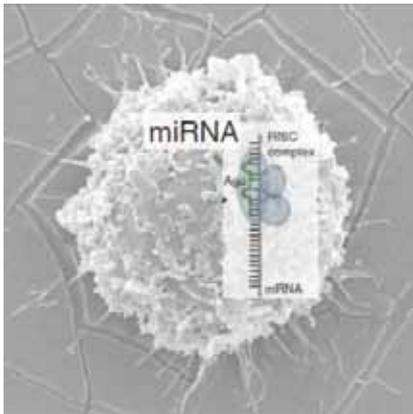
in Southern California. But, oops, my wife and I stayed in San Diego for almost 20 years enjoying life at and outside of work. We grew especially fond of the desert scenery and its special vegetation such as the Ocotillo (that doesn't really need support from my wife).



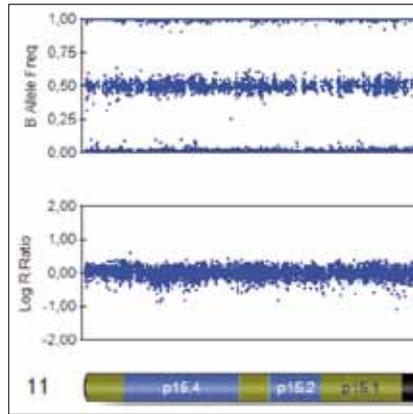
Through a story too long for this article, and lasting friendships, I was then given the exciting opportunity to bring my hepatitis virus knowledge to the DBM and hopefully contribute to the success of the lab and department while my wife acts as a pastor in a beautiful village im Baselbiet. Wait, wasn't she a Chemielaborantin? Well, she too remains continuously surprised by the unexpected turns and events life presents us with...

VORSCHAU PREVIEW

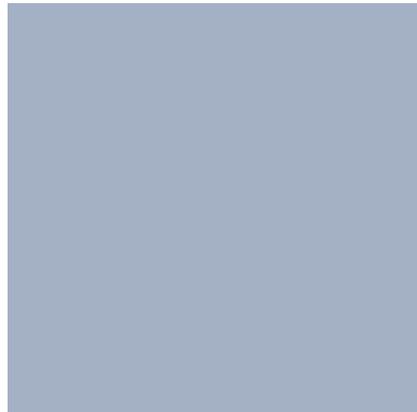
In der nächsten Ausgabe ...



... nimmt uns Lukas Jeker mit in die Forschungswelt der Molecular Immune Regulation



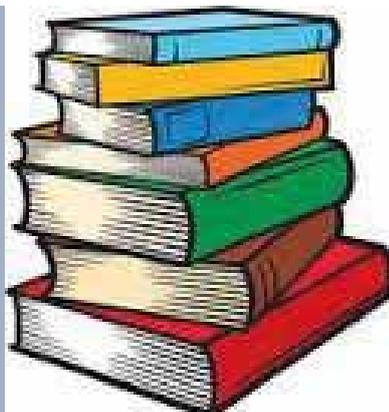
...arbeiten wir uns mit Stefan Herms durch riesige Mengen genetischer Daten



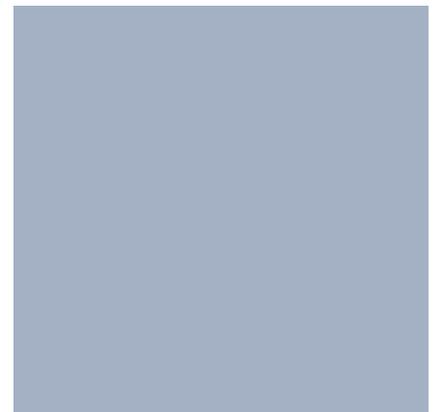
...lernen wir mit Ilija Lujic und Marc Bichsel, was Ausdauer ist



...stellt uns Mari Nakamura ihre Heimat Japan vor



...treffen wir mit Friederike Schulze Menschen, die noch Bücher lesen



Nehmt hin mit Weinen oder Lachen

Nehmt hin mit Weinen oder Lachen,
was euch das Schicksal gönnt:
Kein König kann euch glücklich machen,
wenn ihr es selbst nicht könnt.

(Friedrich von Bodenstedt, 1819-1892)

