DBM FACTS

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«Wir entscheiden alle Dinge gemeinsam» – Interview mit Magdalena Müller-Gerbl und Rolf Zeller | What molecules give the necessary instructions? | A Letter from Boston

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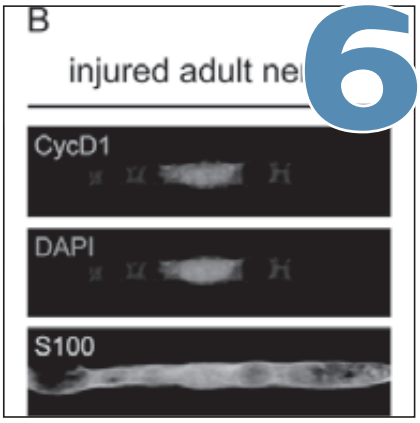

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IMPRESSUM

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Rat skeletal muscle stained for PECAM-1 (endothelium; red), α-SMA (smooth muscle; blue) and NG-2 (pericytes; green). Edin Mujagic, Cell and Gene Therapy

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Passend zur endlich einziehenden wärmeren Jahreszeit liegt nun auch die Frühjahrsausgabe der DBM-Facts vor Ihnen: Rolf Zeller und Magdalena Müller-Gerbl berichten über das Institut für Anatomie, Suzana Atanasoski beschreibt, wie sie mit ihrer Forschungsgruppe die Frage angeht, welche Moleküle die notwendigen Instruktionen für die Entwicklung des Nervensystems abgeben. Olivier Gasser lässt uns teilhaben an seinem zweijährigen Forschungsaufenthalt in Boston, während seine Familie in der Heimat geblieben ist. Wer den neuen Spitaldirektor, Dr. Werner Kübler, bei seinen Antrittsbesuch am DBM nicht erleben konnte, hat auf Seite 41 die Chance dazu.

Bei dieser Gelegenheit begrüssen wir ganz herzlich die neuen Forschungsgruppenleiter Olivier Pertz (SNF-Förderprofessur) und Daniel Bodmer (Tenure Track Assistenzprofessor für ORL) mit ihren Labors und wünschen Ihnen viel Erfolg.

Auf Seite 14 geben wir Ihnen Impressionen vom Besuch einer Delegation der Fudan Universität aus Shanghai am DBM in Basel wieder. Die neuesten Publikationen aus dem DBM finden Sie ab Seite 16.

Eine spannende Lektüre wünscht Ihnen
Radek Skoda

Dear Readers

To accompany the warmer days that have finally arrived, the spring edition of DBM-Facts is here: Rolf Zeller and Magdalena Müller-Gerbl give an account of the Institute for Anatomy; Suzana Atanasoski describes how, together with her research group, she approaches the questions regarding which molecules deliver the necessary instructions for the development of the nervous system. Olivier Gasser lets us share in the experience of his two-year research visit to Boston while his family stayed at home. For those who didn't get to meet the new hospital director, Dr. Werner Kübler, during his visit to the DBM, they can now do so on page 41.

On this occasion we would like to heartily greet the new research group leaders Olivier Pertz (SNF-Assistant Professor) and Daniel Bodmer (Tenure Track Assistant Professor for ORL) and their laboratories and wish them every success.

The impressions of a visiting delegation from the Fudan University from Shanghai to the DBM in Basel can be found on page 14.
The latest publications from the DBM can be found from page 16 onward.

Wishing you all an exciting read
Radek Skoda

Im Interview:

«Wir entscheiden alle Dinge gemeinsam»

Magdalena Müller-Gerbl und Rolf Zeller: Wie zwei erfahrene Professoren gemeinsam das Anatomische Institut leiten und alle dabei gewinnen

DBM: Herr Zeller, 2003 sind Sie Leiter des Anatomischen Instituts geworden als Nichtanatom. Warum hat man ausgerechnet Sie gewählt und warum haben Sie angenommen? Sie hatten doch eine gute Stelle als Ordinarius an der Universität Utrecht ...

RZ: Warum man mich gewählt hat, weiss ich auch nicht. Nein, eine Idee war sicher, im Rahmen dieser ganzen Reorganisation des DKBW die Forschung in der Vorklinik zu stärken. Damals wurden alle Stellen in den vorklinischen Instituten primär im Blick auf die Forschung hin besetzt. Da Anatomie und Embryologie historisch immer eng zusammengehörten, hat man mich als Entwicklungsgenetiker gewählt. Wichtig für meine Zusage war aber, dass die nächste Person, die berufen wird, ein Anatom sein muss. Ich war überzeugt, dass dann alles funktionieren würde. Und ich glaube, es funktioniert auch, sehr gut sogar. Frau Müller-Gerbl ist nicht nur Makroanatomin, sondern macht auch funktionelle Anatomie und Forschung. Das ist eine gute Konstellation. Wir diskutieren ja nicht nur über die Lehre und das Museum sondern auch über Forschung. Oder? Habe ich das so richtig gesagt?

MMG (lacht): Ab und zu einmal.

«Es gab schon Zweifel: Was passiert mit der Anatomie»

Haben Sie Probleme gehabt, anerkannt zu werden als Nichtanatom?

RZ: Soll ich ehrlich sein?

Aber bitte ...

RZ: Ja, würde ich schon sagen. Was man so hört, sind die meisten in der Zwischenzeit vom Gelingen überzeugt. Aber es gab schon Zweifel: Was passiert mit der Anatomie?

Ja, was passiert denn mit ihr? Wohin steuert sie? Ich nenne einmal die Neuberufung von Ihnen, Frau Müller-Gerbl, die Nachfolge von Lukas Landmann und Cordula Nitsch. Wo liegt der Fokus? Dienstleistung/Lehre oder Forschung? Wie geht ein Institut mit soviel Lehre um? Zusätzlich das Anatomische Museum?

RZ: Ich sage einmal ganz grob etwas und dann gehen wir ins Detail. Heute ist klar, an der Universität kann sich keine Einheit mehr nur über Dienstleistung und Lehre definieren. Das heisst, der Forschungsaspekt muss gestärkt werden. Wie gesagt, Anatomie und Embryologie hängen eng zusammen. Heute sind natürlich die Molekularbiologie, bildgebende Verfahren und Tissue Engineering wichtig. Vom Tissue Engineering kommen wir schnell zu den Stammzellen. In diesem grossen Gebiet können wir sicher nicht alles abdecken. Aber wir bewegen uns irgendwo zwischen Anatomie, Morphologie, bildgebenden Verfahren, also der Abbildung von Embryonen und Geweben, bis hin zur molekularen Zelllehre. Das ist ein weites Spektrum, sicherlich weiter als bei allen anderen, oder Magdalena?

MMG: Die Anatomie steht auf zwei Standbeinen. Zum einen die Lehre, zum anderen aber auch die Forschung. Unser Ziel ist es, einerseits eine qualitativ gute Lehre zu gewährleisten, und da gibt es einige Herausforderungen im Zusammenhang mit Bologna, zumal der Personalbestand, der uns zur Verfügung steht, nicht besonders üppig ist. Andererseits wollen wir auch eine qualitativ hochstehende Forschung machen.

Rolf Zeller
Jahrgang 1957

1980 bis 1984 PhD am Biozentrum, Universität Basel, bei Prof. E. M. De Robertis, 1985 bis 1989 Postdoktorand am Dept. of Genetics, Harvard Medical School, Boston, USA, bei Prof. P. Leder, 1989 bis 1998 Forschungsgruppenleiter am European Molecular Biology Laboratory, EMBL, Heidelberg, Deutschland, 1999 bis 2003 Ordinarius für Developmental Biology, Universität Utrecht, Niederlande, seit 2003 Ordinarius für Anatomie und Embryologie an der Universität Basel

Und was hat erste Priorität?

MMG: Ich würde das eine nicht ohne das andere wollen. Es besteht ja auch eine gewisse Wechselwirkung. Ich kann nur dann gute Lehre machen, wenn ich nicht nur Lehrbuchwissen weitergebe, sondern auch sagen kann «Leute, in diesem Gebiet da tut sich etwas». Und es passiert auch in der Anatomie noch etwas, obwohl oft die Frage kommt: «Was kann man denn heute in der Anatomie noch erforschen?»

Wenn man es prozentual ausdrücken wollte? Wie viel ist Lehre und wie viel Forschung?

MMG: Das hängt mit der Stelle zusammen, die man hat.

RZ: Das kann ich vielleicht kurz erklären. Wir haben damals noch mit Herrn Moroni entschieden, dass wir im Bereich Lehre Stellen, in Englisch würde man sagen für «Lecturers» schaffen, jetzt gibt es ja die Universitätsdozenten, die brauchen wir einfach. Die Anatomie deckt $^2/_3$ der gesamten Lehre der Vorklinik ab.

$^2/_3$?

MMG: Oder anders herum: Die Anatomie muss 2/3 der Lehre erbringen, das hängt damit zusammen, weil sie sich aus drei grossen Gebieten zusammensetzt: Makroskopie, Embryologie und Histologie.

RZ: Dafür haben wir jetzt drei Stellen, die vor allem in der Lehre verankert sind. Herr Beier, den Sie ja schon interviewt haben, Herr Stammler, der in der Gruppe von Magdalena Müller-Gerbl arbeitet, und Herr Haag-Wackernagel von der Integrativen Biologie, die in der Zwischenzeit in die Anatomie integriert wurde. Herr Stammler ist der Nachfolger von Herrn Spornitz, das heisst, wir haben auch die Forschungsgruppen reduziert. Wir sind immer noch im Umbruch. Wir haben zwei Extraordinariate zu besetzen, hier müssen wir schauen, dass die Betreffenden von ihrer Lehrleistung her ein Pensum haben, das sie auch noch forschen lässt. In diesem Zusammenhang haben wir den ganzen Präparationsbereich neu organisiert.

Das heisst ...

MMG: Wir sind dabei, eine Lehrsammlung aufzubauen und haben jetzt das Verfahren der Plastination etabliert, das kennen sie von Herrn Prof. von Hagens, wobei wir hier weniger kontroverse Exponate herstellen, aber das Wissen ist vorhanden.

«Präparieren heisst das Erfassen der Dreidimensionalität und das tatsächliche Begreifen der Strukturen»

Ist das überhaupt noch zeitgemäss im Zeitalter der Computersimulation?

MMG: Neuen Verfahren gegenüber sollte man immer offen sein, die Lehrmethoden ändern sich. Auch was die Manpower betrifft, die man benötigt, sollte man sich immer überlegen, was man vom Herkömmlichen braucht. Ich bin überzeugt, dass der Präparierkurs durch nichts zu ersetzen ist. Präparieren heisst das Erfassen der Dreidimensionalität und das tatsächliche Begreifen der Strukturen.

Magdalena Müller-Gerbl
Jahrgang 1958

1978 bis 1985 Medizinstudium an der Universität Freiburg/Breisgau, 1984 Approbation, 1985 Promotion, 1985 bis 1989 wissenschaftliche Angestellte am Anatomischen Institut der Universität Freiburg/Breisgau, bei Prof. R. Putz, 1989 wissenschahftliche Assistentin an der Anatomischen Anstalt der Ludwig-Maximilians-Universität München bei Prof. R. Putz, 1992 Habilitation für das Gesamtfach Anatomie, 1998 Ernennung zur ausserplanmässigen Professorin, 1999 Gastprofessur an der Harvard Medical School, 2001 bis 2007 verschiedene Gastdozenturen an der Universität Basel, seit 2007 Extraordinaria für Makroskopische Anatomie an der Universität Basel

Ist der Präparierkurs ein KO-Kriterium, weil viele Studierende das nicht können?

MMG: Nein, nein, gar nicht. Es wird ja nicht verlangt, dass die Studierenden am Ende des Kurses präparatorische Fähigkeiten haben. Am Ende wird Wissen geprüft. Der Anteil der Studierenden, der psychische Probleme im Umgang mit toten Menschen hat, ist verschwindend gering. Am Anfang haben sicher einige Studenten Schwierigkeiten, aber sie haben ja ein ganzes Semester Zeit, sich damit auseinanderzusetzen.

RZ: Ich musste mich ja auch dieser Thematik stellen. Wenn man realisiert hat, dass die Körper gespendet werden, die Menschen dieses also sehr bewusst tun, und wir uns nicht mehr im Mittelalter befinden, bekommt man einen natürlichen Zugang. Ähnlich wie Organspender stellen diese Menschen ihren ganzen Körper zur Verfügung.

MMG: Diese Auseinandersetzung mit dem Tod ist im gesamten Kontext eine wichtige Erfahrung. Man hat Berührungsängste gegenüber dem toten Menschen, auf der anderen Seite muss man etwas daran, nämlich den toten Körper, zergliedern. Es geht darum, die richtige Balance zu finden. Diese spielt auch später im Beruf eine grosse Rolle: Auf der einen Seite muss der Arzt sich das Mitgefühl mit dem Patienten bewahren, aber er darf nicht vor lauter Mitleid handlungsunfähig werden.

Wie viele Spender haben Sie pro Jahr?

MMG: 25.

Woher kommen sie?

MMG: Aus der Umgebung.

Und die Gründe? Erfährt man die?

MMG: Die erfährt man schon. Es gibt Menschen, die wir über Jahre betreuen, die immer wiederkommen und mit uns sprechen. Sie kommen und möchten wissen, wie alles funktioniert, es kursieren doch einige Gerüchte, z.B. dass man Geld dafür bekäme. Was die Menschen tatsächlich erhalten, ist ein Begräbnis, das von uns übernommen wird. Das ist sicher ein Grund. Andere sagen, die Medizin hat mir viel Gutes getan, ich möchte das zurückgeben. Andere wiederum möchten, dass ihr Körper nach dem Tod auch noch zu etwas nütze ist. Wieder andere möchten ihre Familie mit den Begräbniskosten nicht belasten.

Würden Sie es selbst auch tun?
MMG: Ich habe mir das noch nicht überlegt. Ich denke, das ist eine Altersfrage. Haben Sie schon einmal darüber nachgedacht?

Ich weiss, dass ich keine Organe spende.
MMG: Das ist etwas, das auch in einem früheren Stadium des Lebens eine Rolle spielen kann. Aber diese Auseinandersetzung mit dem Tod oder besser, das Sich-Gedanken-machen, was soll mit meinem Körper nach dem Tod geschehen, fängt erst in einem bestimmten Alter an. Wir wären sehr erstaunt und aufgeschreckt, wenn jemand mit 25 Jahren in die Anatomie käme, um seinen Körper zu vermachen. Da sind wir sehr vorsichtig. Bei Verdacht auf Depressionen und Selbstmordgedanken versuchen wir diese Menschen an entsprechende Fachleute weiterzuleiten.

Müssen Anatomen besondere Eigenschaften haben? Ich denke an einen Ihrer Präparatoren, der als Hobby das Halten von Pfeilgiftfröschen angibt ...
MMG: Nein, absolut nicht. Ich habe nichts dergleichen. Oft ist es gerade in der Anatomie Zufall, dass man dort hängen bleibt. Ich bin in Vorbereitung auf die Chirurgie-Ausbildung ein Jahr in die Anatomie gegangen und dann geblieben.

Wir sitzen hier in einem grossen Büro. Dabei sind Sie, Herr Zeller, die meiste Zeit in der Mattenstrasse. Wir leben Sie und das Institut mit dieser Aufteilung?
RZ (lacht): Das grosse Büro ist historisch bedingt, ich bin auch zufrieden mit einem kleinen. Am Anfang waren wir mit der ganzen Gruppe hier drin. Sie ist dann in das Zentrum für Biomedizin in der Mattenstrasse gekommen, in dem überall molekularbiologisch, genetisch gearbeitet wird. Dieses Umfeld ist für die Gruppe sehr wichtig. Mir war bewusst, dass ich diese Situation haben werde. Manchmal ist das ein Problem, wenn ich drüben bin und hier gebraucht werde. Dann muss ich halt herkommen, in der Zwischenzeit mache ich das in zehn Minuten mit dem Fahrrad.

Seit Magdalena da ist, haben wir eine duale Führung, was zwischen uns beiden gut funktioniert. Wir entscheiden eigentlich alle Dinge miteinander und wir informieren uns gegenseitig. Ich könnte ja auch im Ausland sein, wenn etwas passiert, dann kümmert sich Magdalena oder umgekehrt. Wir haben beide unsere speziellen Expertisen, aber wenn es um Aspekte geht, wie wir das Institut leiten, dann sind wir uns, auch wenn wir aus anderen Gebieten kommen, sehr ähnlich.

MMG: Dazu kommt, dass wir uns einfach gut verstehen. Rolf hat sich über das gewöhnliche Mass dafür eingesetzt, dass die Lehre gut ausgestattet ist.

RZ: Die ganze Lehre und das Leichenwesen sind jetzt gut organisiert. Das haben wir wirklich gemeinsam geschafft und relativ schnell. Es geht erstaunlich gut. Wenn Frau Pacek ein Problem hat, dann ruft sie mich an und wenn es nötig ist, komme ich rüber, oder sie legt mir Sachen hin und auf dem Nachhauseweg unterschreibe ich dann.

MMG: Und Du bist ja auch zu fixen Zeiten da.

RZ: Am Montag vormittag bin ich hier und unterhalte mich dann mit allen Mitarbeitenden aus dem technischen Bereich.

Sie haben auch Glück, dass Sie Frau Pacek haben, die das Haus kennt ...
RZ: Wir haben hier ein sehr gutes Team. Vom technischen Stab angefangen, über das Sekretariat, die Administration, das Leichenwesen, das Museum, ohne diese Mannschaft könnten wir es nicht machen. Ich gebe den Mitarbeitenden Freiheiten, dafür haben sie auch Verantwortung. Das ist schon richtig. Am Anfang war es wahrscheinlich schon komisch für die Mitarbeitenden, dass ich nicht immer einfach hier im Büro sitze und erreichbar bin. Aber, Magdalena, Du bist auch nicht immer vor Ort.

MMG: Ich bin natürlich schon mehr hier.

Radek Skoda, mein Chef, ist auch nicht immer erreichbar ...
RZ: Eben, Eigenverantwortung ist wichtig.

Frau Müller-Gerbl, Herr Zeller, herzlichen Dank für dieses Gespräch.

Das Interview führte Heidi Hoyermann-Welinsky
Photos: Verena Jäggin

Cell division and cell differentiation in the nervous system:

What molecules give the necessary instructions?

Suzana Atanasoski,
SNF Förderprofessur
Institute of Physiology
Department of Biomedicine

Regulating the choice between proliferation, growth arrest, and differentiation determines growth and size of organs during development and during regeneration following injury. In the past, we have been exploring the molecular mechanisms linking proliferation and differentiation in Schwann cells, the myelinating cells of the peripheral nervous system (PNS). We screened for proteins that are involved in the regulation of Schwann cell proliferation and myelination. These included proteins of the cell cycle machinery, as well as molecules of the neuregulin/erbB and TGFβ pathways. We subsequently tested the hypothesis that developmentally and injury-induced proliferation of Schwann cells is regulated by different molecular mechanisms. In summary, these studies led to the novel finding that Schwann cells can switch their requirements for cell cycle proteins and signaling pathways in vivo, dependent on their cell-cell contact and/or the extracellular environment. We anticipate that the conceptual framework and the molecular players are comparable in the peripheral and central nervous system (CNS). Thus, we have recently extended our studies and started testing the hypothesis that distinct cell cycle components as well as the TGFβ antagonist Ski are also key players in coordinating proliferation and differentiation in neural stem and progenitor cells in the CNS.

Cyclin D1 expression in peripheral neuropathies

Schwann cells are highly proliferative during development and after damage to peripheral nerves. Schwann cell proliferation is also a pathological characteristic of nerves in demyelinating peripheral neuropathies, such as Charcot-Marie-Tooth disease type 1A (CMT1A). Using array technology we identified differentially expressed transcripts in normal versus diseased nerves of animal models for CMT1A. Some of the identified transcripts, the cell cycle protein cyclin D1, the neuregulin receptor erbB2, and the protooncogene Ski, were investigated in more detail. D-type cyclins are required for the initial steps in cell division and nuclear import is essential for the function of cyclin D1 in promoting cell proliferation. Like normal myelinating Schwann cells in wildtype mice, remyelinating Schwann cells in CMT animal models show perinuclear cyclin D1 expression. Schwann cells with nuclear cyclin D1 expression are proliferating and are exclusively associated with demyelinated axonal segments. Supernumerary Schwann cells, however, do not express cyclin D1 and do not proliferate. Thus, cyclin D1 expression and its subcellular localization correlate directly with distinct physiological states of Schwann cells in animal models of CMT1A (Atanasoski et al., 2002).

Schwann cell proliferation during development and following nerve damage

Is proliferation during development and following nerve

injury driven by the same mechanisms? The molecular phenotype of "denervated", proliferating Schwann cells in axotomized nerves is similar to that of immature, proliferating Schwann cells in developing nerves. However, we challenged this common view by comparing the expression, regulation, and localization of various cell cycle proteins in Schwann cells of developing and adult peripheral nerves as well as following nerve injury. Our findings showed that, during normal development, proliferating Schwann cells expressed cyclin D1 in the perinuclear cytoplasm. In contrast, after injury to either immature or mature nerves, cyclin D1 became localized to the nuclei of proliferating Schwann cells (Fig. 1). Functional analysis using cyclin D1-deficient animals revealed that developmentally regulated proliferation of Schwann cells was not affected by the absence of cyclin D1, whereas injury-induced proliferation was impaired regardless of the maturation status of the Schwann cell. Our results demonstrated that not only do different cell types use various combinations of cyclins for cell cycle progression, but that a specific cell type can switch cyclin combinations in vivo dependent on its cell-cell contact and/or the extracellular environment (Atanasoski et al., 2001). We next analyzed the requirements for three members of the cyclin-dependent kinase (cdk) family in intact and injured peripheral nerves using cdk-deficient mice. Our findings showed that postnatal Schwann cell proliferation is uniquely controlled by cdk4 and, that following nerve injury, Schwann cells lacking cdk4 were unable to re-enter the cell cycle (Atanasoski et al., 2008). In addition, our recent results reveal an additional regulatory aspect, namely a striking difference in the requirement for a cell cycle protein, cdk4, in embryonic versus postnatal Schwann cell proliferation. Thus, it will remain a challenging task to dissect which mitogens, signaling pathways, and cell cycle proteins drive proliferation at distinct stages within the Schwann cell lineage, an issue important not only for understanding the basic biology of myelinated peripheral nerves but also in disease mechanisms of peripheral neuropathies and peripheral nerve tumors.

Neuregulin/erbB2 signaling in Schwann cells

Various signaling pathways have been implicated in the control of Schwann cell development. The best studied is the neuregulin/erbB signaling system that is required for survival and proliferation of cultured Schwann cells. In vivo, this pathway is critically important for survival and proliferation of immature Schwann cells, as well as for establishing correct myelin thickness during development of peripheral nerves. We therefore investigated whether erbB2 signaling is also essential for Schwann

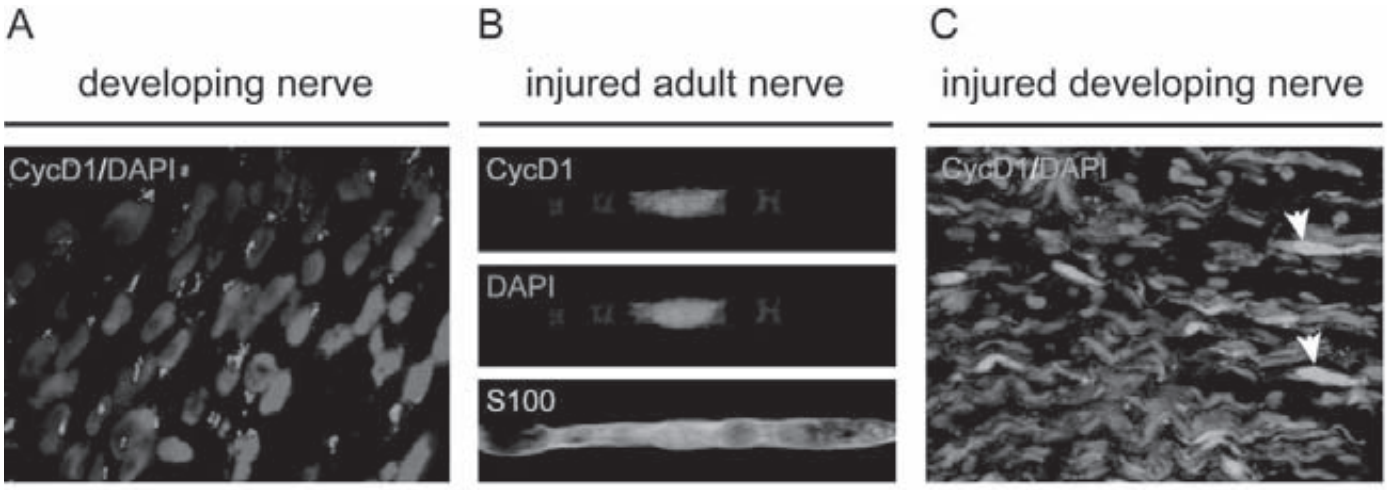

Figure 1: Subcellular Localization of Cyclin D1
A. Cyclin D1 is expressed in the perinuclear region of immature Schwann cells. B. Cyclin D1 is expressed in nuclei of proliferating Schwann cells in mature teased sciatic nerves 4 days post axotomy. C. Cyclin D1 is expressed in nuclei of immature Schwann cells (arrowheads) of developing sciatic nerves after injury.
DAPI, nuclear marker; S100, Schwann cell marker

cell proliferation and survival following nerve injury. We used inducible Cre-loxP technology to specifically delete erbB2 in adult Schwann cells, which allowed us to investigate its role without the potentially confounding effects of developmental alterations. Using this technology we showed that erbB2 expression was markedly reduced upon induction of erbB2 gene disruption, with no apparent effect on the maintenance of already established myelinated peripheral nerves. In contrast to findings in cell culture experiments, Schwann cell proliferation and survival were not impaired in mutant animals after nerve injury, despite reduced levels of cyclin D1 (Atanasoski et al., 2006). This unexpected but important observation challenged the current view that injury-induced processes are simply a recapitulation of the cellular events during normal development. It is likely that other signaling systems contribute to the regulation of Schwann cell proliferation and survival upon axonal damage and compensate for the loss of neuregulin/erbB function. TGFβ signaling might be a candidate, since it is involved in the regulation of Schwann cell proliferation, survival and differentiation.

TGFβ signaling in Schwann cells

In normal adult sciatic nerve, TGFβ is detected in the cytoplasm of Schwann cells. In vitro, treatment of purified Schwann cells with TGFβ results in a marked increase of their proliferation rate. Thus, Schwann cells are one of the few normal cell populations to respond mitogenically to TGFβ. Aside from its effects on proliferation, TGFβ blocks both Schwann cell myelination and the expression of many myelin-related molecules. We therefore investigated the role of the nuclear protein Ski as an inhibitor of the TGFβ/ BMP pathway. In agreement with its antagonistic role in TGFβ-signaling, we found that Ski overexpression inhibited TGFβ-mediated proliferation of Schwann cells and myelination was blocked in myelin-competent cultures derived from Ski-deficient mice (Fig. 2). We showed that Ski links the biologically interconnected events of proliferation and differentiation in postnatal Schwann cells, thereby contributing to the understanding of the molecular mechanisms that control nerve development, regeneration, and neuropathies (Atanasoski et al., 2004).

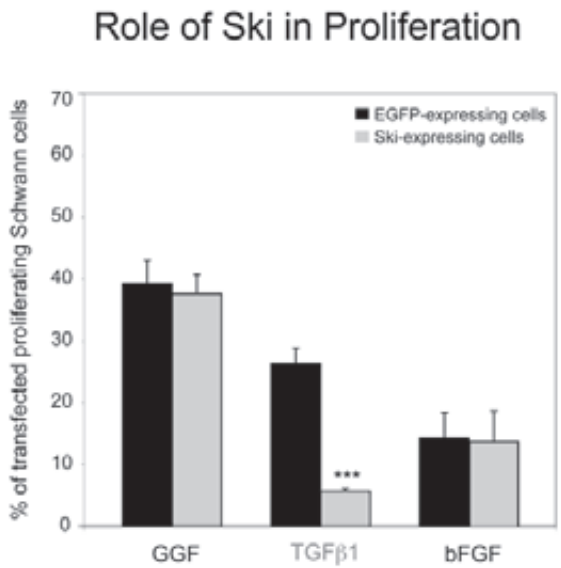

Figure 2A: Ski inhibits TGFβ1-mediated Schwann cell proliferation. Quantitative analysis of proliferation rates of Schwann cells grown in the presence of different mitogens (GGF, TGFβ1, or bFGF). Overexpression of Ski specifically decreased the proliferation capacity of cells grown in the presence of TGFβ1 (grey bars) in comparison to controltransfected cells (black bars). Data are mean values of three experiments ± SD.

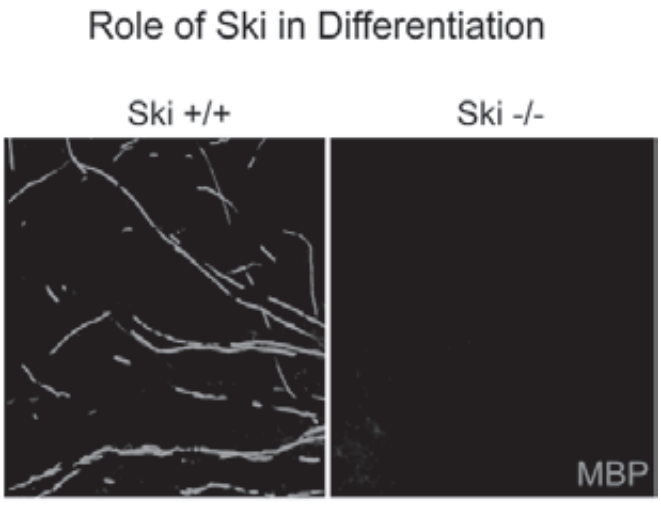

Figure 2B: Absence of myelin formation in dorsal root ganglia (DRG) of Ski-deficient mice. Expression of the myelin marker MBP in control (Ski+/+) and mutant (Ski-/-) DRG explant cultures. Note the complete absence of myelin in Ski-deficient samples.

Functional relevance of the proto-oncogene Ski in the CNS

The CNS develops from self-renewing, multipotent neural stem cells. These differentiate into neural progenitor cells, which eventually give rise to neurons, astrocytes, and oligodendrocytes. The identification of neural stem cells in the adult CNS suggested a capacity of these cells for self-repair after brain injury. However, there are profound differences between embryonic and adult neural stem/progenitor cells with respect to the markers they express, their location in the brain, and their proliferative capabilities. This raises the question of how proliferation is controlled in embryonic and adult neural stem/progenitor cells, and which signaling pathways influence maintenance and cell division in these two cell populations. To realize the potential medical benefit of neural stem cells in brain repair, it is imperative to understand the factors that regulate the expansion and differentiation of these cells. Our recent results show that Ski protein is expressed in germinal zones of developing mice, and that Ski-deficient neural progenitors (NPCs) are less proliferative than wild type cells in vivo and in vitro. Additional analyses suggest that Ski is required for keeping neural and oligodendrocyte progenitor cells (OPCs) in an undifferentiated state. These preliminary data constitute a solid basis for further analyses of the roles of Ski and the cell cycle machinery in both NPCs and OPCs during development, in the adult, and following injury. Knowledge of how these cells can be maintained and induced to differentiate into distinct cell types, may be of potential medical use in regenerative repair or cell replacement therapies. Our projects are expected to strengthen interactions between basic and applied research within and outside the Department of Biomedicine.

Suzana Atanasoski, SNF Förderprofessur
Institute of Physiology
Department of Biomedicine

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A Letter from Boston

Dear all,

I guess that only the minority of those reading this article will know me. I was quite surprised to recognize only half the people, at most, I saw the last time I visited the DF, which was last December. Nevertheless, in many ways, I know what most of you are experiencing. I completed my Ph.D. and first Post-Doc at the DF, spending a total of seven years there, which represents quite a bit of my life. I was asked to write something about the place I left Basel for, which is Boston (Massachusetts, USA), and what I have experienced since I moved to the U.S. nearly one and a half year ago. I have to admit that I did not fully realize, at the time, the benefit of spending some time abroad, in a new lab, a new city, a whole new environment. I did so because, as a scientist, you feel that you should do so, because most of us do. Having already spent a year in Australia for my diploma thesis, I knew I was in for a big change of lifestyle. All the more since this time I had to organize everything for my family, my wife, and my three year old son as well. My family has, since then, gained one French/German/American member, as my daughter was born may 2007 in Cambridge, MA. I have now been in Boston for a while, but unfortunately my family had to go back to Europe more than half a year ago for several reasons I will mention later.

I am not sure what I should preferentially narrate from my experience so far to provide you with an experience you might actually think about instead of just reading it. Some of you might be in a very similar situation to what I was at the time: Ph.D. students longing to finally put an end to being a student and thinking about how much they would earn in industry vs. what an academic career could possibly offer as a valuable trade-off, or post-docs finally realizing that the age-limits of the SNF are approaching rather quickly. Well, I can relate to these situations and I guess I could find as many answers/reactions as there are people reading this right now. Maybe it was for the challenge, maybe it was for the excitement, but I decided to give academia an honest and serious try, packed my belongings and took off for Boston to ramp up my publication list. The first few months were supposed to be solely dedicated

The whole family in front of Harvard Library

Anouk and Remy Gasser

to work, as my wife and I decided that it would be better if my family joined me later, a very good idea in retrospect. So I integrated into my new lab, the Partners AIDS Research Center at Massachusetts General Hospital, and started reading a whole lot about HIV, antigen presentation, and so forth, and got a very quick introduction to all projects that were currently up and running. I settled quickly, scientifically as well as logistically, which was partly due to the fact that I could take over the apartment and car of my colleague Florian Bihl, who also bequeathed me some unfinished projects I was very happy to take over as a quick-start.

As a European, Boston is arguably one of the most enjoyable cities in the United States. You get (almost) everything you are used to back in Europe, and you get it even on Sundays, which is very convenient if you work until late during the week. So I acclimatized quite quickly, to all but the freezing temperatures that you experience in the New England winter. In Boston you immediately realize the difference between the measured temperature and the one you actually feel when exposed to the wind (the so called "Wind-Chill"), in particular if you travel by bike to work, which I did. My family joined me February 2007, along with some heavy-duty clothes and shoes. My wife was pregnant with our second child, and so we could not rely on the experience gained from our first child, but had instead to look for new primary health-care providers, amongst (many) other things. Due to the cold temperatures, we spent our week-ends strolling around in malls, a U.S. feature my son began to love!

The pregnancy of my wife proceeded, fortunately, without complications. We were, however, both surprised by the differences in the standards of prenatal care (mainly compared to Germany). I was also a bit sceptical as to whether my wife's second pregnancy would have a somewhat profound influence on my ability to concentrate on my job, but I must admit that it was (again) a very pleasant experience. My wife is certainly of the kind that makes you directly relate to her hormonal status, but I must admit that I prefer getting lots of feedback rather than too little. After all, there are not many ways a man can witness the evolution of his child. Sharing the emotions, although intense at times, of my pregnant wife was certainly an aspect of the "being" of my children I would not want to miss. Anyway, we soon began to plan the birth, choosing the Mount Auburn Hospital for its very close proximity to Harvard Square, where we lived, and the good appraisal from people we talked to. Another bonus, we realized later, was the fact that some rooms had a magnificent view on the Charles River that runs through Boston. As mentioned, my work did not really suffer from the expected second child, the only sign being a cell phone that would follow me a bit more closely than it usually does. Back at home with my daughter, things were extremely easy compared to the same phase with my son. Indeed, she slept a lot and the nights were relatively calm. I could not dream of anything better. I had already pictured myself half asleep in front of painful 13 color flow cytometry acquisitions, but instead, I was only

PARC (Partners Aids Research Center) retreat

slightly drowsy, and did not really suffer from being a newly fledged father-of-two, this time the only "hint" being an ever present cup of java in my hands.

The best season to experience Boston is most likely spring and late autumn, the latter attracting more tourists due to the magnificent colours you experience all around the city, and even more so in the surroundings. The summer is usually marked by scorching heat and very high humidity, and last year was no exception. Therefore, in summer we sought shade and air-conditioning in malls again, just as we had in winter to get away from the cold (these places save your life ... believe me!!). It is hard to acclimatize to such different weather than we get in central Europe. The humidity is hard to deal with, especially for young children. The end of the summer sadly meant saying good bye to my wife and kids, since my son was about to enter kindergarten and my wife was eager to start working, which she could not do here since the U.S. do not grant total equivalence to veterinary or human medical degrees awarded by European Universities. Working "for free" to acquire skills was not really an option since childcare is outrageously expensive. Thus, it was kind of back to the start ... and I was alone in Boston again.

I believe that research in general, and maybe biomedical research in particular, demands a high level of dedication, that can be all the more difficult to put forth if you have a family. Pursuing an academic career, or the dream thereof until you realize that you are too old to be competitive, is sometimes linked to regular lab-, country- or even life-style-changes. Research kind of guides your life, and ultimately the ones of your family. The decision to let go of my family was a rational one, as the best for my research project(s) and career was not the best for them. Only now do I realize how risky the road can be to do what it takes, or the very least that it takes, to stay competitive. Being an endurance athlete, that once in a while wanders to the other side of "sanity" to compete in long-distance triathlons, I see a lot of similarities to the realm of athletics. In both cases people feel the urge to remove all distractions that prevent them from achieving greatness. For most dedicated scientists I saw, and still see, that a working week has typically seven days. Although the decision to live away from my family was, as alluded to, rather based on rational things, I have sometimes the feeling that, alone, I fall back to odd rituals, such as constantly thinking about work, or sports, or both (!), and this feeling is rather frightening as it mentally tears me even further away from my family than has already been achieved by spatial separation. I think being by myself for quite some time has helped me to put my life, and my job, into perspective. I do not know whether what I am saying even remotely reflects what you are thinking sometimes, but being constantly immersed in the realm of science is, from my viewpoint, slightly imbalanced. Starting a family, with all that comes with it, can turn daily schedules into mind-puzzling nightmares, but altogether (except maybe for the debilitating sleep deprivation) is the best way to keep both feet tightly anchored on solid ground. But I came to realize these changes are quite reversible. When you live together, you sometimes do not feel so compelled to assess how your job affects your family life; you just do what you have to do. The sole fact is that to live together takes care of most of the effort necessary to keep things alive. Living apart, however, is totally different. Not only

After birth at Mount Auburn Hospital with view on Charles River

Remy and Olivier at New England Zoo

do you have to increase the input, but you might even have to plan for it, mostly due to different time zones.

So far, from many perspectives, I have learned a lot in Boston. Scientifically, I found myself immersed in one of the most stimulating and thought-provoking environments I could have imagined. I guess that is the very reason that makes such a foreign experience so valuable for us scientists. Having only known Basel for most of my active scientific career, it was very refreshing to experience something totally different in terms of diversity and magnitude. I can only deeply encourage all of you, Ph.D. students and Post-Docs alike, to make that next step. This step might be a very humbling one, but I also believe that we all tend to underestimate our talents unless we truly and fully apply ourselves, even better it this happens in an inspiring setting. The feeling that will remain etched into my mind will be that the only goal worth pursuing in science is to reach for greatness relative to yourself while not losing the initial reason(s) you entered a scientific career in the first place. Very few will, while reaching for their personal best, become great relative to others.

From a personal viewpoint, that partly relates to work, I learned a few valuable lessons too. I think that I could get a glimpse of the factors that can undermine, or on the contrary boost, your confidence, your work (and ultimately your publication list!). Founding a family can be a difficult thing to accomplish for scientists, who, conceivably, have to keep a fair amount of flexibility to be able to deal with experimental scheduling and/or meltdowns. The awards you get in return cannot be summed up in the few words that I have left to complete this article, but I experienced the self-sabotaging thoughts that settle in once those are taken away from you. I find myself reinforced in the idea that there is certainly no ideal time point to start a family, as a scientist that follows an academic career, and I do not even dare to think about how it must be for women. At one point you just have to do it (or not) and then take it one step at a time. I had my fair share of experiences, for now, but do not ask me whether I would do something differently if I could turn back time, I simply do not know. Nothing of what I just wrote down would have been possible without the enormous support of my wife and family. This much I know.

Olivier Gasser

The whole family in Cambridge, at Charles River

Shanghai Symposium am DBM

Im Rahmen der Städtepartnerschaft Basel–Shanghai besuchte eine Delegation der Medizinischen Fakultät der Fudan Universität, Shanghai, das DBM. Am Freitag, den 7. März 2008, fand von 8.30 Uhr bis 16.45 Uhr im Zentrum für Lehre und Forschung ein Symposium zu Ehre der Gäste statt. Nach der Begrüssung durch Regierungsrat Dr. Carlo Conti eröffneten die beiden Dekane Prof. Albert Urwyler, Medizinische Fakultät der Universität Basel, und Prof. Xiaoyuan Feng, Medizinische Fakultät der Fudan Universität, Shanghai, das Symposium. Es folgten Vorträge von Zhenghong Yuan, Lu Hongzhou, Gao Qiang und Zheng Ping seitens der chinesischen Gäste und von Markus Heim, Manuel Battegay, Radek Skoda, Jean Pieters und Bernhard Bettler, die die Gastgeber vertraten. Das Symposium klang mit einem gemeinsamen Abendessen aus. Im Rahmen dieser Visite mit Blick auf die im Mittelpunkt stehende Forschung zu Viraler Hepatitis, HIV und Tuberkulose hatten die Gäste am Tag zuvor auch die Möglichkeit, einige Labors zu besuchen.

Dr. Carlo Conti

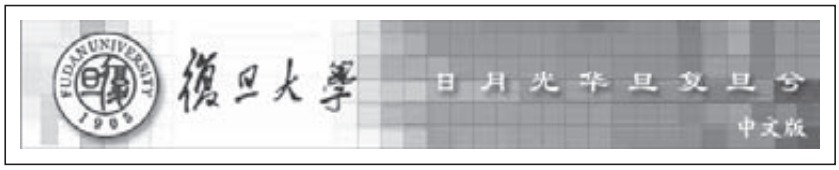
Prof. Albert Urwyler

Prof. Xiaoyuan Feng

Lunch Time: Schweizer Delikatessen . . .

. . . für internationales Publikum

Obere Reihe von links: Prof. Zhenghong Yuan, Prof. Markus Heim, Prof. Lu Hongzhou, Prof. Manuel Battegay
Mittlere Reihe von links: Prof. Radek Skoda Prof. Gao Qiang, Prof. Jean Pieters, Prof. Zheng Ping
Untere Reihe: Prof. Bernhard Bettler



Mit einem gemeinsamen Abendessen ging das Symposium zu Ende

Criteria for selecting papers presented in "DBM-Facts"

Please submit articles as pdf files to the Departmental Assistant, Manuela Bernasconi:
manuela.bernasconi@unibas.ch

We will try to include as many articles as possible in each issue. However, there are page constrains, which may force us to make a selection. The final decision will be made by the chair of the Department of Biomedicine according to following criteria:

- First priority will be given to articles published in high ranked journals that are authored by members of the Department of Biomedicine (first author, senior author and corresponding author from DBM).
- Articles published in low impact journals and articles where members of the Department of Biomedicine are only co-authors may also be included, but will receive lower priority.

The following publications do not qualify for inclusion in "DBM-Facts" (=most frequent reasons for rejection):

- Articles "in press" (please wait until the pdf is available with the correct volume, page numbers etc)
- Articles without mentioning of the DBM affiliation
- Articles where neither first author, nor senior author, nor corresponding author are from DBM
- Articles with purely clinical work without a clear contribution of the DBM laboratories
- Review articles (with very few exceptions, e.g. reviews in Cell, Science, Nature etc.)
- Book chapters

Please note that each issue of DBM-Facts will have a deadline for the submission of articles. Deadline for the next issue is May 23, 2008.
Radek Skoda

Nature nature 9, 162–176, 2008 IF31,4

Reviews Molecular Cell Biology: Lipid signalling in disease

M. P. Wymann[1], and Roger Schneiter[2]

Abstract:
Signalling lipids such as eicosanoids, phosphoinositides, sphingolipids and fatty acids control important cellular processes, including cell proliferation, apoptosis, metabolism and migration. Extracellular signals from cytokines, growth factors and nutrients control the activity of a key set of lipid-modifying enzymes: phospholipases, prostaglandin synthase, 5-lipoxygenase, phosphoinositide 3-kinase, sphingosine kinase and sphingomyelinase. These enzymes and their downstream targets constitute a complex lipid signalling network with multiple nodes of interaction and cross-regulation. Imbalances in this network contribute to the pathogenesis of human disease. Although the function of a particular signalling lipid is traditionally studied in isolation, this review attempts a more integrated overview of the key role of these signalling lipids in inflammation, cancer and metabolic disease, and discusses emerging strategies for therapeutic intervention.

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The New England Journal of Medicine | The NEW ENGLAND JOURNAL of MEDICINE | 205, 523–531, 2008 IF14,5

Intrathymic expression of Flt3 ligand enhances thymic recovery after irradiation

L. Kenins[1,3], J. W. Gill[2], R. L. Boyd[3], G. A. Holländer[2], and A. Wodnar-Filipowicz[1]

Abstract:
Hematopoietic stem cell transplantation (HSCT) requires conditioning treatments such as irradiation, which leads to a severely delayed recovery of T cell immunity and constitutes a major complication of this therapy. Currently, our understanding of the mechanisms regulating thymic recovery is limited. It is known that a subpopulation of bone marrow (BM)–derived thymic immigrant cells and the earliest intrathymic progenitors express the FMS-like tyrosine kinase 3 (Flt3) receptor; however, the functional significance of this expression in the thymus is not known. We used the BM transplant model to investigate the importance of Flt3 ligand (FL) for the regeneration of the T cell compartment. We show that FL is expressed in the adult mouse thymus on the surface of perivascular fibroblasts. These cells surround the proposed thymic entry site of Flt3 receptor–positive T cell progenitors. After irradiation, perivascular FL expression is up-regulated and results in an enhanced recovery of thymic cellularity. Thymic grafting experiments confirm an intrathymic requirement for FL. Collectively, these results show that thymic stromal cell–mediated FL–Flt3 receptor interactions are important in the reconstitution of thymopoiesis early after lethal irradiation and HSCT, and provide a functional relevance to the expression of the Flt3 receptor on intrathymic T cell progenitors.

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Blood | blood | 111, 3931–3940, 2008 IF10,4

Ratio of mutant *JAK2*-V617F to wild-type *Jak2* determines the MPD phenotypes in transgenic mice

R. Tiedt[1], H. Hao-Shen[1], M. A. Sobas[1,2], R. Looser[1], S. Dirnhofer[3], J. Schwaller[4], and R. C. Skoda[1]

Abstract:
An acquired somatic mutation in the *JAK2* gene (*JAK2*-V617F) is present in the majority of patients with myeloproliferative disorders (MPDs). Several phenotypic manifestations (polycythemia vera [PV], essential thrombocythemia [ET], and primary myelofibrosis) can be associated with the same mutation. We generated *JAK2*-V617F transgenic mice using a human *JAK2* gene with the sequences encoding the kinase domain placed in the inverse orientation and flanked by antiparallel loxP sites. Crossing mice of one transgenic line (FF1) with transgenic mice expressing Cre-recombinase under the control of the hematopoiesis specific Vav promoter led to expression of *JAK2*-V617F that was lower than the endogenous wild-type *Jak2*. These mice developed a phenotype resembling ET with strongly elevated platelet counts and moderate neutrophilia. Induction of the *JAK2*-V617F transgene with the interferon-inducible MxCre resulted in expression of *JAK2*-V617F approximately equal to wild-type *Jak2* and a PV-like phenotype with increased hemoglobin, thrombocytosis, and neutrophilia. Higher levels of *JAK2*-V617F in mouse bone marrow by retroviral transduction caused a PV-like phenotype without thrombocytosis. These data are consistent with the hypothesis that the ratio of mutant to wild-type *JAK2* is critical for the phenotypic manifestation. A similar correlation was also found in patients with MPD.

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Blood blood 111, 1428–1436, 2008 IF10,4

NKG2D ligand expression in AML increases in response to HDAC inhibitor valproic acid and contributes to allorecognition by NK-cell lines with single KIR-HLA class I specificities

S. Diermayr[1], H. Himmelreich[1], B. Durovic[1], A. Mathys-Schneeberger[1], U. Siegler[1,2], U. Langenkamp[1], J. Hofsteenge[2], A. Gratwohl[3], A. Tichelli[3], M. Paluszewska[4], W. Wiktor-Jedrzejczak[4], C. P. Kalberer[1], and A. Wodnar-Filipowicz[1]

Abstract:
This study exploited alloreactivity of natural killer (NK) cells for augmenting the recognition of human acute myeloid leukemia (AML). To circumvent the inhibitory effect of killer immunoglobulin receptor (KIR) signaling, we generated NK-cell lines with single KIR specificities for major human leukocyte antigen (HLA) class I allotypes. We demonstrated efficient cytolysis of KIR-HLA class I–mismatched primary AML blasts even at low effector-to-target ratios. To define the impact of tumor-associated activating NKG2D-ligands (NKG2D-L), 66 AML patients at diagnosis were analyzed. NKG2D-L were selectively expressed on monoblastic cells in AML M4 and M5 yet absent or weakly expressed on myeloblastic cells in all AML subtypes. Paucity of cell-surface NKG2D-L was not the result of shedding because levels of soluble ULBP1 ligand measured in AML plasma were in the normal range. Notably, purified NKG2D-L$^+$ monoblastic cells were more susceptible to NK-mediated killing than NKG2D-L$^-$ myeloblastic cells. Accordingly, induction of cell-surface NKG2D-L by treatment with the histone deacetylase inhibitor, valproic acid, rendered cells more sensitive to NK cytolysis. These data suggest that adoptive transfer of selected populations of alloreactive HLA class I–mismatched NK cells in combination with pharmacologic induction of NKG2D-L merits clinical evaluation as novel approaches to immunotherapy of human AML.

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Blood blood 111, 3863–3866, 2008 IF10,4

Clonal heterogeneity in polycythemia vera patients with *JAK2* exon12 and *JAK2*-V617F mutations

S. Li[1], R. Kralovics[2], G. De Libero[3], A. Theocharides[4], H. Gisslinger[2], and R. C. Skoda[1]

Abstract:
We studied the lineage distribution of *JAK2* mutations in peripheral blood of 8 polycythemia vera (PV) patients with exon 12 mutations and in 21 PV patients with *JAK2*-V617F. Using a quantitative allele discrimination assay, we detected exon 12 mutations in purified granulocytes, monocytes, and platelets of 8 patients studied, but lymphoid cells showed variable involvement and the mutation was absent in T cells. Endogenous erythroid colonies grew in all patients analyzed. One patient displayed erythroid colonies homozygous for the exon 12 mutation with evidence for mitotic recombination on chromosome 9p. In some patients with exon 12 mutations or *JAK2*-V617F, a proportion of endogenous erythroid colonies were negative for both JAK2 mutations. One patient carried 2 independent clones: one with an exon 12 mutation and a second with *JAK2*-V617F. The finding of clonal heterogeneity is compatible with the hypothesis that additional clonal events are involved in the pathogenesis of PV.

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Blood blood 111, 1735–1738, 2008 IF10,4

Clinical stem-cell sources contain $CD8^+CD3^+$ T-cell receptor–negative cells that facilitate bone marrow repopulation with hematopoietic stem cells

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Abstract:
Clinical observations in patients undergoing bone marrow transplantation implicate the involvement of $CD8^+$ cells in promoting the stem-cell engraftment process. These findings are supported by mouse transplant studies, which attributed the engraftment-facilitating function to subpopulations of murine $CD8^+$ cells, but the analogous cells in humans have not been identified. Here, we report that clinical stem-cell grafts contain a population of $CD8^+CD3^+$ T-cell receptor– negative cells with an engraftment facilitating function, named candidate facilitating cells (cFCs). Purified cFC augmented human hematopoiesis in NOD/SCID mice receiving suboptimal doses of human $CD34^+$ cells. In vitro, cFCs cocultured with $CD34^+$ cells increased hematopoietic colony formation, suggesting a direct effect on clonogenic precursors. These results provide evidence for the existence of rare human $CD8^+CD3^+TCR^-$ cells with engraftment facilitating properties, the adoptive transfer of which could improve the therapeutic outcome of stem-cell transplantation.

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Blood blood 110, 3862–3870, 2007 IF 10,4

Increased TSLP availability restores T- and B-cell compartments in adult IL-7–deficient mice

S. Chappaz[1], L. Flueck[1], A. G. Farr[2], A. G. Rolink[1], and D. Finke[1]

Abstract:
Interleukin 7 (IL-7) plays a crucial role in adult lymphopoiesis, while in fetal life its effect can be partially compensated by TSLP. Whether adult hematopoietic progenitor cells are unresponsive to TSLP or whether TSLP is less available in adult microenvironments is still a matter of debate. Here, we show that increased TSLP availability through transgene (Tg) expression fully restored lymphopoiesis in IL-7–deficient mice: it rescued B-cell development, increased thymic and splenic cellularities, and restored double-negative (DN) thymocytes, β and T-cell generation, and all peripheral lymphoid compartments. Analysis of bone marrow chimeras demonstrated that hematopoietic progenitor cells from adult wild-type mice efficiently differentiated toward B- and T-cell lineages in lethally irradiated IL-7 deficient mice provided TSLP Tg was expressed in these mice. In vitro, TSLP promoted the differentiation of uncommitted adult bone marrow progenitors toward B and T lineages and the further differentiation of DN1 and DN2 thymocytes. Altogether, our results show that adult hematopoietic cells are TSLP responsive and that TSLP can sustain long-term adult lymphopoiesis.

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Stem Cells STEM CELLS 25, 1823–1829, 2007 IF 7,9

Three-Dimensional Perfusion Culture of Human Adipose Tissue-Derived Endothelial and Osteoblastic Progenitors Generates Osteogenic Constructs with Intrinsic Vascularization Capacity

A. Scherberich, R. Galli, C. Jaquiery, J. Farhadi, I. Martin

Abstract:
In this study, we aimed at generating osteogenic and vasculogenic constructs starting from the stromal vascular fraction (SVF) of human adipose tissue as a single cell source. SVF cells from human lipoaspirates were seeded and cultured for 5 days in porous hydroxyapatite scaffolds by alternate perfusion through the scaffold pores, eliminating standard monolayer (two-dimensional [2D]) culture. The resulting cell-scaffold constructs were either enzymatically treated to extract and characterize the cells or subcutaneously implanted in nude mice for 8 weeks to assess the capacity to form bone tissue and blood vessels. SVF cells were also expanded in 2D culture for 5 days and statically loaded in the scaffolds. The SVF yielded $5.9 \pm 3.5 \times 10^5$ cells per milliliter of lipoaspirate containing both mesenchymal progenitors ($5.2\% \pm 0.9\%$ fibroblastic colony forming units) and endothelial-lineage cells ($54\% \pm 6\%$ $CD34^+/CD31^+$ cells). After 5 days, the total cell number was 1.8-fold higher in 2D than in three-dimensional (3D) cultures, but the percentage of mesenchymal- and endothelial-lineage cells was similar (i.e., 65%–72% of $CD90^+$ cells and 7%–9% of $CD34^+/CD31^+$ cells). After implantation, constructs from both conditions contained blood vessels stained for human CD31 and CD34, functionally connected to the host vasculature. Importantly, constructs generated under 3D perfusion, and not those based on 2D-expanded cells, reproducibly formed bone tissue. In conclusion, direct perfusion of human adipose-derived cells through ceramic scaffolds establishes a 3D culture system for osteoprogenitor and endothelial cells and generates osteogenic-vasculogenic constructs. It remains to be tested whether the presence of endothelial cells accelerates construct vascularization and could thereby enhance implanted cell survival in larger size implants.

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Stem Cells STEM CELLS 25, 1178–1185, 2007 IF 7,9

A Cassette System to Study Embryonic Stem Cell Differentiation by Inducible RNA Interference

D. Wegmüller[1], I. Raineri[1], B. Gross[1], E. J. Oakeley[2], C. Moroni[1]

Abstract:
Although differentiation of pluripotent embryonic stem cells is restricted by a hierarchy of transcription factors, little is known about whether post-transcriptional mechanisms similarly regulate early embryoid differentiation. We developed a system where small hairpin (sh)RNAs can be induced in embryonic stem (ES) cells from a defined locus following integration by Flp recombinase-mediated DNA recombination. To verify the system, the key transcription factor Stat3, which maintains pluripotency, was downregulated by shRNA, and the expected morphological and biochemical markers of differentiation were observed. Induction of shRNA specific for the post-transcriptional regulator Brf1 (*Zfp36L1*) amplified the cardiac markers with strong stimulation of cardiomyocyte formation within embryoid bodies. These findings identify Brf1 as a novel potential regulator of cardiomyocyte formation and suggest that post-transcriptional mechanisms are of importance to early development and, possibly, to regenerative medicine. The inducible RNA interference system presented here should also allow assignment of function for candidate genes with suspected roles in ES cell development.

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Arthritis&Rheumatism Arthritis & Rheumatism 58, 197–208, 2008 IF 7,8

Engineered Cartilage Generated by Nasal Chondrocytes Is Responsive to Physical Forces Resembling Joint Loading

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Abstract:

Objective:

To determine whether engineered cartilage generated by nasal chondrocytes (ECN) is responsive to different regimens of loading associated with joint kinematics and previously shown to be stimulatory of engineered cartilage generated by articular chondrocytes (ECA).

Methods:

Human nasal and articular chondrocytes, harvested from 5 individuals, were expanded and cultured for 2 weeks into porous polymeric scaffolds. The resulting ECN and ECA were then maintained under static conditions or exposed to the following loading regimens: regimen 1, single application of cyclic deformation for 30 minutes; regimen 2, intermittent application of cyclic deformation for a total of 10 days, followed by static culture for 2 weeks; regimen 3, application of surface motion for a total of 10 days.

Results:

Prior to loading, ECN constructs contained significantly higher amounts of glycosaminoglycan (GAG) and type II collagen compared with ECA constructs. ECN responded to regimen 1 by increasing collagen and proteoglycan synthesis, to regimen 2 by increasing the accumulation of GAG and type II collagen as well as the dynamic modulus, and to regimen 3 by increasing the expression of superficial zone protein, at the messenger RNA level and the protein level, as well as the release of hyaluronan. ECA constructs were overall less responsive to all loading regimens, likely due to the lower extracellular matrix content.

Conclusion:

Human ECN is responsive to physical forces resembling joint loading and can up-regulate molecules typically involved in joint lubrication. These findings should prompt future in vivo studies exploring the possibility of using nasal chondrocytes as a cell source for articular cartilage repair.

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Cancer Research Cancer Research 67, 10840–10848, 2007 IF 7,7

Placental Growth Factor-1 Attenuates Vascular Endothelial Growth Factor-A–Dependent Tumor Angiogenesis during ß Cell Carcinogenesis

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Abstract:

Members of the vascular endothelial growth factor (VEGF) family are critical players in angiogenesis and lymphangiogenesis. Although VEGF-A has been shown to exert fundamental functions in physiologic and pathologic angiogenesis, the exact role of the VEGF family member placental growth factor (PlGF) in tumor angiogenesis has remained controversial. To gain insight into PlGF function during tumor angiogenesis, we have generated transgenic mouse lines expressing human PlGF-1 in the ß cells of the pancreatic islets of Langerhans (Rip1PlGF-1). In single-transgenic Rip1PlGF-1 mice, intra-insular blood vessels are found highly dilated, whereas islet physiology is unaffected. Upon crossing of these mice with the Rip1Tag2 transgenic mouse model of pancreatic ß cell carcinogenesis, tumors of double-transgenic Rip1Tag2;Rip1PlGF-1 mice display reduced growth due to attenuated tumor angiogenesis. The coexpression of transgenic PlGF-1 and endogenous VEGF-A in the ß tumor cells of double-transgenic animals causes the formation of low-angiogenic hPlGF-1/mVEGF-A heterodimers at the expense of highly angiogenic mVEGF-A homodimers resulting in diminished tumor angiogenesis and reduced tumor infiltration by neutrophils, known to contribute to the angiogenic switch in Rip1Tag2 mice. The results indicate that the ratio between the expression levels of two members of the VEGF family of angiogenic factors, PlGF-1 and VEGF-A, determines the overall angiogenic activity and, thus, the extent of tumor angiogenesis and tumor growth.

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Brain BRAIN 131, 288–303, 2008 IF7,6

Normal-appearing white matter in multiple sclerosis is in a subtle balance between inflammation and neuroprotection

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Abstract:
Multiple sclerosis is a chronic inflammatory disease of the CNS. Although progressive axonal injury and diffuse inflammatory damage has been shown in the chronic phase of the disease, little is known about the molecular mechanisms underlying these pathological processes. In order to identify these mechanisms, we have studied the gene expression profile in non-lesion containing tissue, the so-called normal-appearing white matter (NAWM). We performed differential gene expression analysis and quantitative RT-PCR on subcortical white matter from 11 multiple sclerosis and 8 control cases. Differentially expressed genes were further analysed in detail by in situ hybridization and immunofluorescence studies. We show that genes known to be involved in anti-inflammatory and protective mechanisms such as STAT6, JAK1, IL-4R, IL-10, Chromogranin C and Hif-1 are consistently upregulated in the multiple sclerosis NAWM. On the other hand, genes involved in pro-inflammatory mechanisms, such as STAT4, IL-1β and MCSF, were also upregulated but less regularly. Immunofluorescence colocalization analysis revealed expression of STAT6, JAK1, IL-4R and IL-13R mainly in oligodendrocytes, whereas STAT4 expression was detected predominantly in microglia. In line with these data, in situ hybridization analysis showed an increased expression in multiple sclerosis NAWM of HIF-1 in oligodendrocytes and HLA-DR in microglia cells. The consistency of the expression levels of STAT6, JAK1, JAK3 and IL-4R between the multiple sclerosis cases suggests an overall activation of the STAT6-signalling pathway in oligodendrocytes, whereas the expression of STAT4 and HLA-DR indicates the activation of pro-inflammatory pathways in microglia. The upregulation of genes involved in anti-inflammatory mechanisms driven by oligodendrocytes may protect the CNS environment and thus limit lesion formation, whereas the activation of pro-inflammatory mechanisms in microglia may favour disease progression. Altogether, our data suggests an endogenous inflammatory reaction throughout the whole white matter of multiple sclerosis brain, in which oligodendrocytes actively participate. This reaction might further influence and to some extent facilitate lesion formation.

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The Journal of Neuroscience *The Journal of Neuroscience* 28, 3333–3340, 2008 IF 7,5

The Role of Nerve- versus Muscle-Derived Factors in Mammalian Neuromuscular Junction Formation

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Abstract:
Neuromuscular junctions (NMJs) normally form in the central region of developing muscle. In this process, agrin released from motor neurons has been considered to initiate the formation of synaptic acetylcholine receptor (AChR) clusters (neurocentric model). However, in muscle developing in the absence of nerves and thus of agrin, AChR clusters still form in the muscle center. This raises the possibility that the region of NMJ formation is determined by muscle-derived cues that spatially restrict the nerve to form synapses from aneural AChR clusters, e.g., by patterned expression of the agrin receptor MuSK (muscle-specific kinase) (myocentric model). Here we examine at initial stages of synaptogenesis whether the responsiveness of myotubes to agrin is spatially restricted, whether the regions of NMJ formation in wild-type muscle and of aneural AChR cluster formation in agrin-deficient animals correlate, and whether AChR cluster growth depends on the presence of agrin. We show that primary myotubes form AChR clusters in response to exogenous agrin in their central region only, a pattern that can spatially restrict NMJ formation. However, the nerve also makes synapses in regions in which aneural AChR clusters do not form, and agrin promotes synaptic cluster growth from the first stages of neuromuscular contact formation. These data indicate that aneural AChR clusters per se are not required for NMJ formation. A model is proposed that explains either the neurocentric or the myocentric mode of NMJ formation depending on a balance between the levels of MuSK expression and the availability of nerve-released agrin.

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Nucleic Acids Research | Nucleic Acids Research | 35, 3859–3867, 2007 IF6,3

Cell cycle regulation as a mechanism for functional separation of the apparently redundant uracil DNA glycosylases TDG and UNG2

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Abstract:
Human Thymine-DNA Glycosylase (TDG) is a member of the uracil DNA glycosylase (UDG) superfamily. It excises uracil, thymine and a number of chemical base lesions when mispaired with guanine in double-stranded DNA. These activities are not unique to TDG; at least three additional proteins with similar enzymatic properties are present in mammalian cells. The successful co-evolution of these enzymes implies the existence of non-redundant biological functions that must be coordinated. Here, we report cell cycle regulation as a mechanism for the functional separation of apparently redundant DNA glycosylases. We show that cells entering S-phase eliminate TDG through the ubiquitin–proteasome system and then maintain a TDG-free condition until G2. Incomplete degradation of ectopically expressed TDG impedes S-phase progression and cell proliferation. The mode of cell cycle regulation of TDG is strictly inverse to that of UNG2, which peaks in and throughout S-phase and then declines to undetectable levels until it appears again just before the next S-phase. Thus, TDG- and UNG2-dependent base excision repair alternates throughout the cell cycle, and the ubiquitin–proteasome pathway constitutes the underlying regulatory system.

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European Journal of Immunology | European Journal of Immunology | 37, 1431–1441, 2007 IF 4,8

Differential alteration of lipid antigen presentation to NKT cells due to imbalances in lipid metabolism

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Abstract:
Deficiencies in enzymes of the lysosomal glycosphingolipid degradation pathway or in lysosomal lipid transfer proteins cause an imbalance in lipid metabolism and induce accumulation of certain lipids. A possible impact of such an imbalance on the presentation of lipid antigens to lipid-reactive T cells has only been hypothesized but not extensively studied so far. Here we demonstrate that presentation of lipid antigens to, and development of, lipid-reactive CD1d-restricted NKT cells, are impaired in mice deficient in the lysosomal enzyme ß-galactosidase (ßGal) or the lysosomal lipid transfer protein Niemann-Pick C (NPC) 2. Importantly, the residual populations of NKT cells selected in $ßGal^{-/-}$ and $NPC2^{-/-}$ mice showed differential TCR and CD4 repertoire characteristics, suggesting that differential selecting CD1d:lipid antigen complexes are formed. Furthermore, we provide direct evidence that accumulation of lipids impairs lipid antigen presentation in both cases. However, the mechanisms by which imbalanced lipid metabolism affected lipid antigen presentation were different. Based on these results, the impact of lipid accumulation should be generally considered in the interpretation of immunological deficiencies found in mice suffering from lipid metabolic disorders.

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Molecular Cancer Research Molecular Cancer Research 6, 468–482, 2008 IF 4,8

Modulation of Endocrine Pancreas Development but not β-Cell Carcinogenesis by Sprouty4

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Abstract:
Sprouty (Spry) proteins modulate signal transduction pathways elicited by receptor tyrosine kinases (RTK). Depending on cell type and the particular RTK, Spry proteins exert dual functions: They can either repress RTK-mediated signaling pathways, mainly by interfering with the Ras/Raf/mitogen-activated protein kinase pathway or sustaining RTK signal transduction, for example by sequestering the E3 ubiquitin-ligase c-Cbl and thus preventing ubiquitylation, internalization, and degradation of RTKs. Here, by the inducible expression of murine Spry4 in pancreatic β cells, we have assessed the functional role of Spry proteins in the development of pancreatic islets of Langerhans in normal mice and in the Rip1Tag2 transgenic mouse model of β-cell carcinogenesis. β cell–specific expression of mSpry4 provokes a significant reduction in islet size, an increased number of cells per islet area, and impaired islet cell type segregation. Functional analysis of islet cell differentiation in cultured PANC-1 cells shows that mSpry4 represses adhesion and migration of differentiating pancreatic endocrine cells, most likely by affecting the subcellular localization of the protein tyrosine phosphatase PTP1B. In contrast, transgenic expression of mSpry4 during β-cell carcinogenesis does not significantly affect tumor outgrowth and progression to tumor malignancy. Rather, tumor cells seem to escape mSpry4 transgene expression.

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Molecular and Cellular Neuroscience 37, 519–527, 2008 IF4,6

Postnatal Schwann cell proliferation but not myelination is strictly and uniquely dependent on cyclin-dependent kinase 4 (cdk4)

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Abstract:
Peripheral myelin formation depends on axonal signals that tightly control proliferation and differentiation of the associated Schwann cells. Here we demonstrate that the molecular program controlling proliferation of Schwann cells switches at birth. We have analyzed the requirements for three members of the cyclin-dependent kinase (cdk) family in Schwann cells using cdk-deficient mice. Mice lacking cdk4 showed a drastic decrease in the proliferation rate of Schwann cells at postnatal days 2 and 5, but proliferation was unaffected at embryonic day 18. In contrast, ablation of cdk2 and cdk6 had no significant influence on postnatal Schwann cell proliferation. Taken together, these findings indicate that postnatal Schwann cell proliferation is uniquely controlled by cdk4. Despite the lack of the postnatal wave of Schwann cell proliferation, axons were normally myelinated in adult cdk4-deficient sciatic nerves. Following nerve injury, Schwann cells lacking cdk4 were unable to re-enter the cell cycle, while Schwann cells deficient in cdk2 or cdk6 displayed proliferation rates comparable to controls. We did not observe compensatory effects such as elevated cdk4 levels in uninjured or injured nerves of cdk2 or cdk6-deficient mice. Our data demonstrate that prenatal and postnatal Schwann cell proliferation are driven by distinct molecular cues, and that postnatal proliferation is not a prerequisite for the generation of Schwann cell numbers adequate for correct myelination.

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Molecular and Cellular Neuroscience 37, 599–609, 2008 IF4,6

Altered peripheral myelination in mice lacking $GABA_B$ receptors

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Abstract:
Emerging evidence implicates γ-aminobutyric acid type B ($GABA_B$) receptors in peripheral nervous system (PNS) functions. In order to elucidate which biochemical, morphological and functional parameters of peripheral nerve fibers depend on $GABA_B$ receptors we studied $GABA_{B1}$-deficient mice, which are devoid of functional $GABA_B$ receptors. Here, we show that $GABA_{B1}$-deficient mice exhibit morphological and molecular changes in peripheral myelin, including an increase in the number of irregular fibers and increases in the expression levels of the myelin proteins PMP22 and P0. Moreover, the number of small myelinated fibers and small neurons of the lumbar dorsal root ganglia is higher in $GABA_{B1}$-deficient mice than in wild-type littermates. We further show that $GABA_{B1}$-deficient mice exhibit gait alterations and reduced allodynia. In summary, our findings implicate $GABA_B$ receptors in the PNS myelination process and raise the possibility that PNS alterations contribute to the sensory phenotypes of $GABA_{B1}$-deficient mice.

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The Journal of Nutrition JN THE JOURNAL OF NUTRITION 138, 519-525, 2008 IF4,0

Chronic treatment with red wine polyphenol compounds mediates neuroprotection in a rat model of ischemic cerebral stroke

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Abstract:
In this study, we investigated the in vivo effects of red wine polyphenol compounds (RWPC) in rats that were submitted to middle cerebral occlusion as an experimental model of stroke. Male Wistar rats were given RWPC [30 mg/(kg x d) dissolved in drinking water] or water for 1 wk before being subjected to transient middle cerebral artery occlusion followed by reperfusion. Sham-operated rats were subjected to transient occlusion in which the filament was not completely introduced. The release of amino acids and energy metabolites were monitored by intracerebral microdialysis. The volume of the ischemic lesion was assessed 24 h after reperfusion. Proteomic analysis of brain tissue was performed to study the effects of ischemia and RWPC on specific protein expression. Treatment with RWPC completely prevented the burst of excitatory amino acids that occurred in response to ischemia in untreated rats and significantly reduced brain infarct volumes. Rats chronically treated with RWPC, however, had lower basal concentrations of energy metabolites, including glucose and lactate in the brain parenchyma, compared with untreated rats. Chronic RWPC treatment significantly enhanced the residual cerebral blood flow during occlusion and reperfusion in rats subjected to transient occlusion compared with untreated rats. This effect resulted from arterial vasodilatation, as the internal diameters of several arteries were significantly enlarged after RWPC treatment. Proteomic studies revealed the modulation by RWPC of the expression of proteins involved in the maintenance of neuronal caliber and axon formation, in the protection against oxidative stress, and in energy metabolism. These findings provide an experimental basis for the beneficial effects of RWPC on the neurovascular unit during stroke.

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Tissue Engineering **Tissue Engineering** 13, 2021–2028, 2007 IF 3,7

Three-Dimensional Cell Culture and Tissue Engineering in a T-CUP (Tissue Culture Under Perfusion)

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Abstract:
The aim of this study was to develop and validate a simple and compact bioreactor system for perfusion cell seeding and culture through 3-dimensional porous scaffolds. The developed Tissue Culture Under Perfusion (T-CUP) bioreactor is based on the concept of controlled and confined alternating motion of scaffolds through a cell suspension or culture medium, as opposed to pumping of the fluid through the scaffolds. Via the T-CUP, articular chondrocytes and bone marrow stromal cells could be seeded into porous scaffolds of different compositions and architectures (chronOS™, Hyaff ®-11, and Polyactive™) at high efficiency (greater than 75%), uniformity (cells were well distributed throughout the scaffold pores), and viability (greater than 97%). Culture of articular chondrocytes seeded into 4-mm thick PolyactiveTM scaffolds for 2 weeks in the T-CUP resulted in uniform deposition of cartilaginous matrix. Cultivation of freshly isolated human bone marrow nucleated cells seeded into ENGipore ceramic scaffolds for 19 days in the T-CUP resulted in stromal cell-populated constructs capable of inducing ectopic bone formation in nude mice. The T-CUP bioreactor represents an innovative approach to simple, efficient, and reliable 3D cell culture, and could be used either as a model to investigate mechanisms of tissue development or as a graft manufacturing system in the context of regenerative medicine.

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Journal of Neurophysiology **Journal of Neurophysiology** 98, 3791–3795, 2007 IF3,7

Functional Mapping of $GABA_B$-Receptor Subtypes in the Thalamus

D. Ulrich, V. Besseyrias and B. Bettler

Abstract:
The thalamus plays an important role in attention mechanisms and the generation of brain rhythms. -Aminobutyric acid type B ($GABA_B$) receptors are known to regulate the main output neurons of the thalamus, the thalamocortical relay (TCR) cells. However, the contributions of the two predominant $GABA_B$-receptor subtypes, $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$, to the control of TCR cell activity are unknown. Here, we used genetic and electrophysiological methods to investigate subtype-specific $GABA_B$ effects at the inputs to TCR cells. We found that mainly $GABA_{B(1a,2)}$ receptors inhibit the release of glutamate from corticothalamic fibers impinging onto TCR cells. In contrast, both $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors efficiently inhibit the release of GABA from thalamic reticular nucleus (TRN) neurons onto TCR neurons. Likewise, both $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors efficiently activate somatodendritic K^+ currents in TCR cells. In summary, our data show that $GABA_{B(1b,2)}$ receptors cannot compensate for the absence of $GABA_{B(1a,2)}$ receptors at glutamatergic inputs to TCR cells. This shows that the predominant association of $GABA_{B(1a,2)}$ receptors with glutamatergic terminals is a feature that is preserved at several brain synapses. Furthermore, our data indicate that the cognitive deficits observed with mice lacking $GABA_{B(1a,2)}$ receptors could to some extent relate to attention deficits caused by disinhibited release of glutamate onto TCR neurons.

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Journal of Cellular Physiology | Cellular Physiology | 213, 490–494, 2007 | IF 3,6

The Chromatin of Differentiating Erythroblasts is Cleaved into Large Size Fragments Independent of Caspase Activated DNase and Apoptosis Inducing Factor

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Abstract:
Erythroblast cell differentiation involves self-controlled and limited nuclear proteolysis prior nucleus loss. Early evidence suggests that apoptotic-like pathways are activated during this process. The chromatin of developing erythroblasts becomes fragmented in vivo, however, the exact mechanisms and molecules involved remain elusive. In this study, erythroblasts were differentiated in culture from CD34-enriched umbilical cord blood progenitor cells and the characteristics of DNA fragmentation were examined. This analysis shows that the chromatin of differentiating erythroblasts is cleaved into discrete fragments of 50-200 kb. This process most likely involves one or several endonucleases as we detect in vivo double strand DNA cleavage. However, major players of the apoptotic DNA degradation, caspase activated DNase and apoptosis inducing factor, are not activated in these cells. Therefore, our data suggests that erythroblast chromatin degradation may involve enzymes distinct form those active in apoptotic cells

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Journal of Neuroimmunology | Journal of Neuroimmunology | 194, 153–164, 2008 | IF2,9

Natalizumab alters transcriptional expression profiles of blood cell subpopulations of multiple sclerosis patients

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Abstract:
Natalizumab, the most recently approved treatment for relapsing multiple sclerosis (MS) exerts its action through binding to alpha4 integrins. We studied longitudinally gene expression profiles in peripheral blood of MS patients, treated with natalizumab for more than 2 years. The majority of altered genes relates to immune response, signal transduction, adhesion and metabolism. Not only gene expression relevant for T lymphocytes was altered, but also genes regulating B-lymphocyte, neutrophil and erythrocyte functions. Understanding these different gene effects and their interrelationships will provide more insights into additional mechanisms of action of natalizumab and possibly allow better prediction of adverse events

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Cytokine CYTOKINE 41, 29–37, 2008 IF 2,4

LPS induces interleukin-6 and interleukin-8 but not tumor necrosis factor-α in human adipocytes

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Abstract:
Adipose tissue-derived cytokines are presumably involved in obesity-associated pathologies including type 2 diabetes and atherosclerosis. Here we studied the lipopolysaccharide (LPS)-induced expression dynamics of tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), IL-8 and IL-10 in human adipose tissue biopsies, in preadipocyte-derived adipocytes, and in mesenchymal stem cell (MSC)-derived adipocytes. TNF, IL-6, IL-8 and IL-10 secretions by adipose tissue explants were increased 5.5-, 19.5-, 3.5- and 12.5-fold, respectively, by LPS (1 μg/mL) administration. Concordantly, IL-6 and IL-8 release was dose-dependently induced in MSC-derived adipocytes by LPS (>10 pg/mL). In contrast, TNFα and IL-10 remained undetectable even at the highest LPS dose (1 μg/mL) after 24 h. In MSC- and preadipocyte-derived adipocytes, respectively, exposure to LPS evoked a weak and transient induction of TNF mRNA whereas induction of IL-6 and IL-8 mRNA were pronounced and sustained for at least 24 h. Basal glucose uptake, lipolysis and IL-6 mRNA were induced by exogenous TNFα (10 ng/mL) but not by IL-6 (10 ng/mL), IL-8 (100 ng/mL) and IL-10 (20 ng/mL). In this adipocyte model TNFα induces well known metabolic effects, but together with previous reports these data suggest that inflammation-induced TNFα may derive from non-adipocyte sources in adipose tissue, likely to be macrophages.

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Brain Research BRAIN RESEARCH 1203, 177–188, 2008 IF2,3

Effect of 17β-estradiol on functional outcome, release of cytokines, astrocyte reactivity and inflammatory spreading after spinal cord injury in male rats

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Abstract:
TThe effect of 17β-estradiol on the secondary damage following spinal cord injury (SCI) was examined in male rats subjected to moderate compression. Two doses of 17β-estradiol (0.1 or 4 mg/kg) were injected i.p. immediately after spinal cord compression. Functional outcome was observed during 4 weeks following injury with two different tests. Release of cytokines (IL-1, IL-1β and IL-6) was assessed 6 h, 3 days and 1 week post-injury. Reactive astrocytes expressing the glial fibrillary acidic protein GFAP and vimentin, and diffusion of CD68-positive inflammatory cells were examined from 3 days to 4 weeks following SCI. Treatment with 17β-estradiol significantly increased locomotor function from the first week until 4 weeks post-SCI. The injured spinal cord of 17β-estradiol-treated rats expressed more IL-1, IL-1β and IL-6 than controls 6 h after injury. Moreover, 17β-estradiol-treated rats showed reactive astrocytes as soon as 3 days following SCI, with increased GFAP expression, smaller lesion areas and more limited diffusion of CD68-positive cells after 1 week post-injury compared to controls. The number of CD68-positive cells was also reduced in 17β-estradiol-treated rats one week post-SCI. However, these differences between 17β-estradiol-treated and control rats disappeared after 4 weeks. These results suggest that 17β-estradiol protects the spinal cord by stimulating early cytokines release and astroglial responses. These stimulations may prevent the area of damage from expanding and inflammatory cells to spread in the surrounding tissue during the critical first week following SCI. Although transient, these effects improved the locomotor recovery that was sustained over 4 weeks after injury

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Cryobiology CRYOBIOLOGY 54, 99–105, 2007 IF 2,2

Impact of freezing/thawing procedures on the post-thaw viability of cryopreserved human saphenous vein conduits

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Abstract:
Background:
Cryopreserved human blood vessels are important tools in reconstructive surgery. However, patency of frozen/thawed conduits depends largely on the freezing/thawing procedures employed.
Methods:
Changes in tone were recorded on rings from human saphenous vein (SV) and used to quantify the degree of cryoinjury after different periods of exposure at room temperature to the cryomedium (Krebs–Henseleit solution containing 1.8 M dimethyl sulfoxide and 0.1 M sucrose) and after different cooling speeds and thawing rates following storage at –196 °C.
Results:
Without freezing, exposure of SV to the cryomedium for up to 240 min did not modify contractile responses to noradrenaline (NA). Pre-freezing exposure to the cryomedium for 10–120 min attenuated significantly post-thaw maximal contractile responses to NA, endothelin-1 (ET-1) and potassium chloride (KCl) by 30–44%. Exposure for 240 min attenuated post-thaw contractile responses to all tested agents markedly by 62–67%. Optimal post-thaw contractile activity was obtained with SV frozen at about –1.2 °C/min and thawed slowly at about 15 °C/min. In these SV maximal contractile responses to NA, ET-1 and KCl amounted to 66%, 70% and 60% of that produced by unfrozen controls. Following cryostorage of veins for up to 10 years the responsiveness of vascular smooth muscle to NA was well maintained.

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Journal of Receptors and Signal Transduction Journal of Receptors and Signal Transduction 27, 383–409, 2007 IF2,0

Dimeric DOTA-α-Melanocyte-Stimulating Hormone Analogs: Synthesis and In Vivo Characteristics of Radiopeptides with High In Vitro Activity

J.-P. Bapst, S. Froidevaux, M. Calame, H. Tanner, A. N. Eberle

Abstract:
Dimeric analogs of α-melanocyte-stimulating hormone (-MSH) labeled with radiometals are potential candidates for diagnosis and therapy of melanoma by receptor-mediated tumor targeting. Both melanotic and amelanotic melanomas (over-)express the melanocortin-1 receptor (MC1-R), the target for α-MSH. In the past, dimerized MSH analogs have been shown to display increased receptor affinity compared to monomeric MSH, offering the possibility of improving the ratio between specific uptake of radiolabeled α-MSH by melanoma and nonspecific uptake by the kidneys. We have designed three linear dimeric analogs containing a slightly modified MSH hexapeptide core sequence (Nle-Asp-His-d-Phe-Arg-Trp) in parallel or antiparallel orientation, a short spacer, and the DOTA chelator for incorporation of the radiometal. In vitro, all three peptides were more potent ligands of the mouse B16-F1 melanoma cell melanocortin-1 receptor (MC1-R) than DOTA-NAPamide, which served as standard. The binding activity of DOTA-diHexa(NC-NC)-amide was 1.75-fold higher, that of diHexa(NC-NC)-Gly-Lys(DOTA)-amide was 3.37-fold higher, and that of DOTA-diHexa(CN-NC)-amide was 2.34-fold higher. Using human HBL melanoma cells, the binding activity of diHexa(NC-NC)-Gly-Lys(DOTA)-amide was sixfold higher than that of DOTA-NAPamide. Uptake by cultured B16-F1 cells was rapid and almost quantitative. In vivo, however, the data were less promising: tumor-to-kidney ratios 4 hr postinjection were 0.11 for [^{111}In]DOTA-diHexa(NC-NC)-amide, 0.26 for diHexa(NC-NC)-Gly-Lys([^{111}In]DOTA)-amide, and 0.36 for [^{111}In]DOTA-diHexa(CN-NC)-amide, compared to 1.67 for [^{111}In]DOTA-NAPamide. It appears that despite the higher affinity to the MC1-R of the peptide dimers and their excellent internalization in vitro, the uptake by melanoma tumors in vivo was lower, possibly because of reduced tissue penetration. More striking, however, was the marked increase of kidney uptake of the dimers, explaining the unfavorable ratios. In conclusion, although radiolabeled α-MSH dimer peptides display excellent receptor affinity and internalization, they are no alternative to the monomeric DOTA-NAPamide for in vivo application.

Laboratory of Endocrinology, Department of Research, University Hospital and University Children's Hospital, Basel, Switzerland

BMC Infectious Diseases 7:25, 2007 IF 1,9

Adjuvant TACE inhibitor treatment improves the outcome of TLR2$^{-/-}$ mice with experimental pneumococcal meningitis

H. Echchannaoui[1], S. L. Leib[2] , U. Neumann[3] and R. MA Landmann[1]

Abstract:

Background: *Streptococcus (S.) pneumoniae* meningitis has a high lethality despite antibiotic treatment. Inflammation is a major pathogenetic factor, which is unresponsive to antibiotics. Therefore adjunctive therapies with antiinflammatory compounds have been developed. TNF484 is a TNF-alpha converting enzyme (TACE) inhibitor and has been found efficacious in experimental meningitis. Toll-like receptor 2 (TLR2) contributes to host response in pneumococcal meningitis by enhancing bacterial clearing and downmodulating inflammation. In this study, TNF484 was applied in mice, which lacked TLR2 and exhibited a strong meningeal inflammation.

Methods: 10^3 CFU S. *pneumoniae* serotype 3 was inoculated subarachnoidally into C57BL/6 wild type (wt) mice or TLR2$^{-/-}$, CD14$^{-/-}$ and CD14$^{-/-}$/TLR2$^{-/-}$ mice. Severity of disease and survival was followed over 9 days. Response to antibiotics (80 mg/kg ceftriaxone i.p. for 5 days) and/or TACE inhibitor treatment (1 mg/kg s.c. twice daily for 4 days) was evaluated. Animals were sacrificed after 12, 24, and 48 h for analysis of bacterial load in cerebrospinal fluid (CSF) and brain and for TNF and leukocyte measurements in CSF.

Results: TLR2$^{-/-}$ mice were significantly sicker than the other mouse strains 24 h after infection. All knockout mice showed higher disease severity after 48 h and died earlier than wt mice. TNF release into CSF was significantly more elevated in TLR2$^{-/-}$ than in the other strains after 24 h. Brain bacterial numbers were significantly higher in all knockout than wt mice after 24 h. Modulation of outcome by antibiotic and TACE inhibitor treatment was evaluated. With antibiotic therapy all wt, CD14$^{-/-}$ and TLR2$^{-/-}$/CD14$^{-/-}$ mice, but only 79% of TLR2$^{-/-}$ mice, were rescued. TACE inhibitor treatment alone did not rescue, but prolonged survival in wt mice, and in TLR2$^{-/-}$ and CD14$^{-/-}$ mice to the values observed in untreated wt mice. By combined antibiotic and TACE inhibitor treatment 95% of TLR2$^{-/-}$ mice were rescued.

Conclusion: During pneumococcal meningitis strong inflammation in TLR2-deficiency was associated with incomplete responsiveness to antibiotics and complete response to combined antibiotic and TACE inhibitor treatment. TACE inhibitor treatment offers a promising adjuvant therapeutic strategy in pneumococcal meningitis.

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Fundamental & Clinical Pharmacology 21, 67–74, 2007 IF1,8

Intraindividual comparison of human radial and internal thoracic arteries in vitro and the effect of preoperative calcium blocker therapy

M. T.R. Grapow[1,2], D. C. Reineke[1,2], T. Kern[1,2], C. Antona[3], G. Gelpi[3], E. Santoli[3], H.-R. Zerkowski[1,2], T. P. Carrel[1,2,4], E. Müller-Schweinitzer[1,2]

Abstract:

TThe patency rate of radial artery (RA) conduits is considerably lower than that of internal thoracic artery (ITA) grafts and the evidence suggests that this is due to a clinically suspected higher incidence of vasospasm. The aim of this study was, therefore, to compare intraindividually the pharmacological reactivity of RA with that of ITA. Both RA and ITA were taken from the same patients and investigated in parallel. Changes in tone were monitored isometrically on ring preparations from both arteries in organ baths with modified Krebs–Henseleit solution containing 1.25 mm calcium chloride at 1 g passive preload. In intraindividual comparisons maximal receptor-mediated contractile responses to noradrenaline and endothelin-1 and endothelium-dependent acetylcholine-induced relaxant responses revealed no differences between both arteries. By contrast, depolarization-induced contractions to potassium chloride (KCl) appeared to be significantly higher in RA than in ITA. Further analysis, however, revealed that this difference was due to preoperative calcium entry blocker (Ca^{2+}eB) therapy. Compared with control tissues, maximal responses to KCl were significantly attenuated in the ITA but unchanged in RA when arteries were obtained from patients with preoperative Ca^{2+}eB therapy. The present results suggested that functional responses to pharmacological stimuli of both RA and ITA were quite similar. Preoperative Ca^{2+}eB therapy, however, attenuated markedly responses to KCl of the ITA leaving those of RA unchanged. These results, demonstrating a lower sensitivity to Ca^{2+}eB of RA, therefore suggested that in addition to Ca^{2+}eB other classes of drug may be more effective at reducing the propensity of RA conduits to vasospasm

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Dr. Werner Kübler zu Besuch am Departement Biomedizin

Getreu seinem Motto, alle Bereiche des USB zu Beginn seiner Amtszeit näher kennen zu lernen, stattete der neue Spitaldirektor dem Departement Biomedizin (DBM) am Donnerstag, den 28.02.2008, seinen Antrittsbesuch ab. Zunächst traf Werner Kübler sich mit Leiter Radek Skoda, anschliessend lernte er auf einem Rundgang die Infrastruktur des DBMs kennen, um sich dann mit dem Stab des Departements auszutauschen. Es folgte ein Gespräch mit den Forschungsgruppenleitern und ein Abschlusstreffen mit Radek Skoda. Zum Schluss konnten alle Mitarbeitenden beim Apéro im Seminarraum Werner Kübler in ungezwungener Atmosphäre kennen lernen. Sein Fazit: Das DBM sei ein wichtiger Bestandteil des Universitätsspitals, es sei gut organisiert, er danke uns allen, die wir unter diesen engen Platzverhältnissen so engagiert bei der Arbeit seien, wünsche uns viel wissenschaftlichen Erfolg und menschlich gute Arbeitsbedingungen!

Dissertationen

Seit dem 30. Oktober 2007 trägt **Katri Waldhauser** von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin USB) den Doktortitel. Sie hat sich in ihrer Dissertation mit dem Forschungsgebiet «Mitochondrial toxicity of drugs» auseinandergesetzt.

Ebenfalls im Oktober hat **Michèle Ecker** von der Forschungsgruppe Neural-Immune Interactions (Institut für Physiologie) ihre Dissertandenzeit erfolgreich abgeschlossen. Sie hat ihre Dissertation dem Thema «Charakterisierung leistungsphysiologischer Parameter bei Eishockeyspielern am Beispiel der Schweizerischen Nationalmannschaft» gewidmet.

Am 2. November 2007 hat sich **Andrea Knapp** von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin USB) erfolgreich den Fragen des Dissertationskomitees gestellt. Sie hat sich in ihrer Dissertation mit «Characterization of in vitro and in vivo models for the investigation of hepatotoxicity» beschäftigt.

Daniel Wegmüller von der Forschungsgruppe Experimental Oncology (Institut für Medizinische Mikrobiologie) hat am 12. Dezember 2007 seine Dissertationszeit erfolgreich abgeschlossen. Das Thema seiner Doktorarbeit war: «Investigation of the Posttranscriptional Regulator BRF 1 in Embryonic Stem Cells by Inducible RNA-Interference».

Am 17. Dezember 2007 hat sich **Sanja Kais** von der Forschungsgruppe Molecular Genetics (Institut für Biochemie und Genetik) erfolgreich dem Dissertationskomitee präsentiert. Das Thema ihrer Doktorarbeit lautete: «Regulatory Aspects of DNA Double-Strand Break Repair in the Yeast Saccharomyces cerevisiae».

Am 18. Dezember 2007 hat **Hatice Karaüzüm** von der Forschungsgruppe Infection Biology (Departement Biomedizin USB) erfolgreich ihre Dissertation verteidigt. Der Titel ihrer Doktorarbeit lautete: «The Impact of Glycopeptide- and Methicillin-Resistance on Staphylococcus aureus and its Virulence in Localized and Systemic Infections».

Der 31. Januar 2008 beendete für **Barbara Biermann** von der Forschungsgruppe Synaptic Plasticity (Institut für Physiologie) erfolgreich ihre Dissertationszeit. Sie befasste sich in ihrer Doktorarbeit mit dem Thema «The sushi domains and their role in $GABA_B$ receptor compartmentalization».

Herzlichen Glückwunsch an alle!

Habilitation

Pia März von der Forschungsgruppe «Neural Immune Interactions» (Institut für Physiologie) hat sich am 3. September 2007 auf dem Gebiet der Physiologie habilitiert. Das Thema ihrer Habilitation lautete: «The Role of Cytokines in Neuroprotection: Identification of New Regulatory Proteins».

SNF-Förderprofessur für Simona Rossi

Simona Rossi Girard von der Forschungsgruppe Transplantation Immunology and Nephrology (Departement Biomedizin USB) hat eine SNF-Förderprofessur erhalten. Ihr Projekt lautet: «Treg and tolerance induction: single player game or teamwork?»

Herzlichen Glückwunsch!

Beförderungen

Per 1. Juli 2007 ist **Gennaro De Libero** von der Forschungsgruppe Experimental Immunology (Departement Biomedizin USB) zum Extraordinarius für Tumorimmunologie, speziell die Funktion von T-Zellen und natürlichen Killerzellen, an der Medizinischen Fakultät der Universität Basel ernannt worden.

Ebenfalls zum 1. Juli 2007 hat die Medizinische Fakultät der Universität Basel **Ivan Martin** von der Forschungsgruppe Tissue Engineering (Departement Biomedizin USB und Institut für Chirurgische Forschung und Spitalmanagement am USB) zum Extraordinarius für Tissue Engineering berufen.

Preise

Pfizer-Forschungspreis 2008 an Andreas Wicki und François Lehembre

Andreas Wicki und François Lehembre von der Forschungsgruppe Tumor Biology (Institut für Biochemie und Genetik) haben den Pfizer-Forschungspreis 2008 im Bereich der Grundlagenforschung Onkologie erhalten. Der Preis ist mit 30 000 Fr. dotiert.

Pfizer-Forschungspreis 2008 an Gideon Hönger und Stefan Schaub

Gideon Hönger von der Forschungsgruppe Transplantation Immunology and Nephrology (Departement Biomedizin USB) und Stefan Schaub von der Abteilung Nephrologie USB haben den Pfizer-Forschungspreis 2008 im Bereich Urologie und Nephrologie erhalten. Das Preisgeld beträgt 30 000.- Fr.

SAKK-Amgen Research Award 2007 an Andreas Wicki und Christoph Mamot

Der o.g. Preis wird von der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) für ein geplantes Forschungsprojekt verliehen. Die Wahl fiel auf Andreas Wicki (Onkologie USB) und Christoph Mamot von der Forschungsgruppe Medical Oncology (Departement Biomedizin USB) für ihr Forschungsprojekt mit Immunliposomen. Der Preisgeld beträgt 50 000 Fr.

Ernennung

Alex Eberle wird Fellow am Collegium Helveticum

Alex Eberle von der Forschungsgruppe Endocrinology (Departement Biomedizin USB) wird zum Mitglied des Collegium Helveticum ernannt. Damit öffnet sich das bisher auf Universität und ETH Zürich zugeschnittene Collegium für eine offizielle Mitgliedschaft der Universität Basel.

Auszeichnung

Radek Skoda von der Forschungsgruppe Experimental Hematology (Departement Biomedizin USB) erhielt die grosse Auszeichnung, am 8. Dezember 2007 in Atlanta die begehrte Ham-Wasserman Lecture der American Society of Hematology (ASH) halten zu dürfen. Der Titel von Radek Skodas Ham-Wasserman Lecture, die er vor einem Publikum von über 10 000 Wissenschaftlern aus aller Welt gab, lautete: «The Molecular Basis of the Myeloproliferative Disorders».

Immunomeetings **Mondays, 12.30 – 13.30 ZLF, Room 313**

Date	Speaker	Group
05.05.	Nabil Bosco	Molecular Immunology
19.05.	Anthony Collmann	Experimental Immunology
26.05.	Giandomenica Iezzi	Surgical Research
02.06.	Jürg Schifferli	Immunonephrology
09.06.	Mathias Schmaler	Infection Biology
16.06.	Stephane Chappaz	Developmental Immunology
23.06.	Radhi P. Velayutham	Pediatric Immunology

Peptidseminar

Friday, 23 May 2008, 10.45, Department of Chemistry, Kleiner Hörsaal Organische Chemie, St. Johanns Ring 19, Ground Floor

Prof. Dr. Emanuel Escher, Department of Pharmacology, University of Sherbrooke, Canada

„GPCR Structures and Activation Mechanisms through Reactive Receptor Probes“

DEPARTEMENT BIOMEDIZIN USB

Chitrangada Acharya
Tissue Engineering

Eline Angevaare
Infectious Diseases

Evelyne Furger
Clinical Pharmacology

Heinz Hermann
Infectious Diseases

Roland Huber
Neurooncology

Simon Jörger
Exp. Hematology

Richard Kühl
Infection Biology

Clémentine Le Magnen
Oncology Surgery

Helena Lima
Tissue Engineering

Gabriela Oser
Exp. Hematology

Pankaj Shende
Cardiobiology

Adetola Adesida
Tissue Engineering

Laurent Brault
Childhood Leukemia

Sandra Feliciano
Tissue Engineering

Jean Grisouard
Metabolism

Anne-Geraldine Guex
Tissue Engineering

Sinan Güven
Tissue Engineering

Stefanie Hamm
Immunobiology

Giandomenica Iezzi
Oncology Surgery

Anne-Kathrin John
Infectious Diseases

Carolyn King
Transpl. Immnunology

Shanshan Lin
Hepatology

Martin Peier
Vascular Biology

Ramin Radpour
Prenatal Medicine

Robert Steinert
Gastroenterology

Raoul Droeser
Oncology Surgery

Edin Mujagic
Cell and Gene Therapy

Nasser Sadr
Tissue Engineering

Elia Piccinini
Tissue Engineering

INSTITUT FÜR BIOCHEMIE UND GENETIK

Michel Letzelter
Cell migration and neuritog.

Adeline Stiefvater
Developmental Immunology

Ulrike Hopfer
Tumor Biology

Lukas Mannhart
Tumor Biology

Olivier Pertz
Cell migration and neuritog.

Claudia Suenderhauf
Dev. and Mol. Immunology

Nicole Salvisberg
Dev. and Mol. Immunology

INSTITUT FÜR ANATOMIE

Olivia Gugger
Developm. Neurob. & Regen.

Catherine Vaillant
Developmental Genetics

Daniel Limacher
Technical Support

INSTITUT FÜR PHYSIOLOGIE

Nancy Gerits
Synaptic Plasticity

Nicoletta Sustreanu
FG Atanasoski

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN USB

Sandrine Aeppli, Infectious Diseases
Anne-Sophie Benischke, Clinical Pharmacology
Claudia Bittel, Clinical Pharmacology
Stephanie Eckert, Clinical Pharmacology
Regina Krattinger, Endocrinology
Barbara Lüscher, Clinical Pharmacology
Tobias Schindler, Clinical Pharmacology
Nadine Vogt, Clinical Pharmacology
Louis Hofstetter, Infection Biology
Alexander Kutz, Childhood Leukemia
Vincent Mosimann, Molecular Nephrology
Eva Seiler, Infectious Diseases
Ralph Verstappen, Tissue Engineering
Svenja Zietzling, Neurobiology
Inés Kaufmann, Prenatal Medicine
Arne Mehrkens, Tissue Engineering

INSTITUT FÜR ANATOMIE

Lisa D'Amato, Development Genetics
Alan Daspond, Development Genetics
Marco Osterwalder, Developmental Genetics

INSTITUT FÜR BIOCHEMIE UND GENETIK

Petra Schmidt, Tumor Biology
Duttu Vallabhapurapu, Developmental Immunology

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Stefanie Fellmann, Transplantation Virology
Monika Kübler, Technical Support
Romana Ledermann, Molecular Diagnostics
Manuela Schneiter, Serology/Virology

INSTITUT FÜR PHYSIOLOGIE

Elisabeth Strittmatter, Technical Support
Nidhi Gakhar-Koppole, Synaptic Plasticity

Austritte:

DEPARTEMENT BIOMEDIZIN USB

Chantal Schlatter-Häner, Clinical Pharmacology
Ralph Tiedt, Experimental Hematology
Danila Ivanov, Signaling
Cuddapah Sunku Chennakesava, Molecular Nephrology
Verena Christen, Hepatology
Mark Daniels, Transplantation Immunology
Andrea Knapp, Clinical Pharmacology
Philippe Linscheid, Metabolism
Xaver Huber, Oncology Surgery
Arina Mathys, Experimental Hematology
Zorana Radic, Clinical Pharmacology
Tea Rekhviasvili, Prenatal Medicine
Song Li, Prenatal Medicine
Emma Teixeiro Pernas, Transplantation Immunology
Anja Zahno, Clinical Pharmacology
Ying Li, Prenatal Medicine

INSTITUT FÜR ANATOMIE

Udo Spornitz, Electron Microscopy
Bart Hendriks, Functional Neuroanatomy
Jacob Dziuballe, Technical Support

INSTITUT FÜR BIOCHEMIE UND GENETIK

Dorit Hässler, Developmental and Molecular Immunology
Sanja Kais, Molecular Genetics
Beat Hostettler, Animal Care Facility
François Lehembre, Tumor Biology
Tibor Schomber, Tumor Biology
Gertraud Orend, Tumor-Stroma Interactions
Anne-Catherine Feutz, Tumor-Stroma Interactions
Yundan Jia, Tumor-Stroma Interactions
Martial Kammerer, Tumor-Stroma Interactions
Katrin Lange, Tumor-Stroma Interactions

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Charles Betz, Experimental Oncology
Sohrab Bodaghi, Transplantation Virology
Sabine Eckervogt, Animal Care Facility
Salome Erhardt, Experimental Oncology
Georg Funk, Transplant. Virology
Anna Hirsch, Transplantation Virology
Doris Löw, Serology/Virology
Erwin Kump, Experimental Immunology
Peter Erb, Experimental Immunology
Elvira Zlauwinen, Technical Support

INSTITUT FÜR PHYSIOLOGIE

Barbara Biermann, Synaptic Plasticity
Franziska Schatzmann, Synaptic Plasticity
Gongda Xue, Synapse Formation
Margot Stauffer, Technical Support

Congratulations

Theodosia-Penelope Kyriakakis-Buron
Geboren am
6.10.2007

Leandro Gianni' Barrera
Geboren am
8.1.2008

Livia Noreen Bettler
Geboren am 2.12.2007

Nils Oliver Molle
Geboren am
20.1.2008

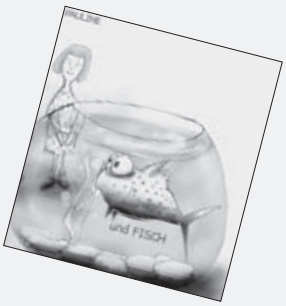
Herzlich willkommen, allerseits!

Pauline had the fish as a pet !

Under the close scrutiny of our Controller Gerry Brunner, Manuela Bernasconi drew the winning answer to the Christmas puzzle from the 28 correct submissions.

And the winner is: Margrit Kacy.

Many congratulations and enjoy your visit to the cinema! (The cinema ticket will be sent to the winner by post).



Whoever else would like to win 2 cinema tickets must correctly solve our next puzzle. The editoral office look forward to your replies, which should be sent to **dbmfacts@unibas.ch**.

The closing date for submission is **31.5.2008**.

DBMFacts-Rätsel

Wo befindet sich der Geheimagent?

Ein britischer Geheimagent erwacht aus einer Ohnmacht. Er befindet sich in einer fensterlosen, kahlen Zelle, mit einem Bett mit zwei Decken, einem Waschbecken mit Wasserhahn, einem Tisch und einem Hocker sowie einem Plastikeimer. Er erinnert sich, von gegnerischen Spionen betäubt und offensichtlich entführt worden zu sein. Er wäscht sich den Kopf, um klare Gedanken zu fassen zu können und setzt sich auf den Hocker.

Entweder er befindet sich noch in England oder er ist bereits nach Argentinien gebracht worden. Für sein Verhalten bei dem nun kommenden Verhör wäre es sehr wichtig zu wissen, in welchem der beiden Länder er sich befindet. An keinem der Gegenstände im Zimmer kann er das Herstellungsland erkennen und was würde es schon heissen, wenn auf der Bettdecke stünde «Made in China»?

Doch plötzlich hat er eine Idee, wie er sofort feststellen kann, in welchem Land er sich aufhält. Welche?

Tipp: Mit dieser Methode könnte man aber nicht feststellen, ob man sich gerade in England oder Polen befindet!

Enigma

Where is the secret agent?

A British secret agent awakes from unconciousness. He finds himself in a windowless, bare cell that contains a bed with two covers, a washbasin with a tap, a tabe and a stool, as well as a plastic basin. He remembers being drugged by a hostile spy who obviously abducted him. He washes his face in order to clear his thoughts and sits down on the stool. He is either still in England or has already been brought to Argentina. His behaviour in the forthcoming interrogation will depend on which of the two lands he is. He can't recognise the country of origin of any of the objects in the room, and the „Made in China" label on the bed cover doesn't tell him anything.

Then suddenly he realises how he can immediately determine which land he is in. What is his idea ?

Tip: One cannot use this method to determine if one is currently in England or Poland.

Heute: **Andreas Schäuble**

Es ist mir ein Vergnügen, mich hier im Rahmen dieser Reihe vorstellen zu können. Wenn man die bisherigen Vorstellungen im früheren DFacts durchsieht, stellt man fest, dass die Uni Basel wahrhaftig international ist.

Womit wir beim Anfang sind: Meine Herkunft. Oder mein bis heute immer währendes «Da-Sein». Denn ich kann weder mit einer Herkunft aus Übersee, noch mit exotischen Kochrezepten aus einer ebensolchen Heimat aufwarten. Vom «Ditscheriduu» weiss ich nur, dass es aus Australien stammt, aus Holz ist, und dass ein Ton entsteht, wenn man richtig hinein bläst. Ich gebe es zu. Ich bin halt nur ein ganz normaler Basler Bebbi ...

...dessen Verhalten hingegen manchmal sicher auch ein wenig «strange» wirkt.

Umso mehr bin ich aber durchaus stolz darauf, in unserer Stadt und an dieser Uni zu leben und mitzuwirken. Erst recht da unser Institut für Medizinische Mikrobiologie mit Forschungs- und Diagnostik-Laboratorien in einem grossartigen, historischen Haus untergebracht ist, dessen Bestimmung allerdings annodazumal eine deutlich andere war als heutzutage. Das Stachelschützenhaus war schliesslich ursprünglich ein an die Stadtmauer gebauter Armbrustschützen-Stand!

Seit inzwischen neun Jahren bin ich, zusammen mit meinem Team, in unserem Institut zuständig für Technik und Infrastruktur. Und bei dieser Gelegenheit will ich wieder einmal eine Lanze brechen für die Gruppierung derer, die oftmals unbeachtet, teilweise wörtlich, im Untergrund tätig sind. Vieles wird dort, vom übrigen «daily business» unbemerkt, für das Funktionieren eines Betriebs und dessen Erfolg geleistet.

Soweit der kleine Überblick zum Beruf, denn, frei nach Wilhelm Busch: «Es rast die Zeit, wir rennen mit.» (Wie schnell doch unser bisschen Leben schwindet!)

Daher noch ein kurzer Blick in mein «anderes», privates Leben. Ich bin verheiratet, habe einen erwachsenen Sohn, und immer noch einen enormen Hunger aufs und wahnsinnig viel Freude am Leben.
Das war der kurze Blick.
Und was ich sonst so treibe, sehen Sie ja auf den Fotos!

Vielleicht treffen wir uns einmal?
Bis dahin wünsche ich allen Gesundheit, Zeit und Glück!

Karate-Do Shotokan

by Martine Calame-Christe with the help of Michel Calame

Karate entered my life somewhat by chance. While doing my PhD work at the University of Neuchâtel, I was looking for a new physical activity when I learned that a colleague was a Karate trainer : a beginner course would start the week later. I thought : «Why not try ». The week after, I joined the course without knowing that I was starting a true love story with Karate, which now lasts since 17 years.

Historical perspective

The origins of Karate go back to the 6th century, rooting in China, where the buddhist monk Boudhidharma developed a fighting technique using fists and feet. This martial art was later exported to Okinawa, the main island of the Ryu-Kyu archipelago.

In 1429, while still under Chinese domination, the population of Okinawa was forced to abandon wearing and using weapons. This lead the people to develop the art of bare-hands fighting. The secrecy then kept around these techniques make it delicate to establish a clear historical development of karate: the great masters of the ancient times remain largely unknown. Matsumura Sokon was the first official master developing a true karate school on the island of Okinawa. Among his numerous students were Azato and Itosu. Itosu played a central role for the evolution of traditional karate, adapting this art to the requirements of a more modern world. A great pedagogue and katas specialist (a kata is a codified sequence of specific movements), he convinced the authorities to include what was then called Okinawa-Te (or Tode) in the normal physical education courses at secondary schools. It will however not be before the first trip of Gichin Funakoshi that Tode will become known outside Okinawa.

Gichin Funakoshi

In 1922, Okinawa had become a Japanese province. Funakoshi, then a student from Azato and Itosu, took a trip to Tokyo to perform a Tode demonstration. His presentation met such a great success, generating a wealth of requests for real courses from the participants, that Funakoshi decided to stay in the city and teach his art. As of 1930, Funakoshi started to use the ideogram Kara meaning "empty " or "bare" instead of To, which designed China and appended the suffix do. Karate-do, the way of the bare hand was born, replacing the ancient Tode, China's hand. In 1935, he opened his own dojo: the shotokan. Shotokan means the school of the Shoto house, with Shoto being he name used by Funakoshi to sign his writings. Gishin Funakoshi taught only 15 katas to his students: Heian (shodan, nidan, sandan, yondan, godan), tekki (shodan, nidan, sandan), bassaï daï, kanku daï ; hangetsu, enpi, jiin, jitte and gankaku. Others masters from Okinawa came to Japan, organizing seminars and teaching additional katas. Funakoshi however remained very attached to the traditional teaching, opposing the practice of kumite (combat) and refusing to organize competitions. His son, Yoshitaka, took the lead over the technical aspects of the Shotokan dojo in 1938. Wiping out the Chinese origins, he more and more enriched the shotokan with Japanese influences.

空手道

Left: Gishin Funakoshi. Right: the ideogram "karate".

Even before his death in 1958, the shotokan karate introduced by Gishin Funkoshi branched in various versions. Otsuka Hinori created the Wado-Ryu, Egami Shiregu the Shotokaï, while Funakoshi Yoshitaka crated the new Shotokan Ryu. Yoshitaka also established the grade system: the Kyus (9 to 1) and the dans (1 to 10). He developed free fighting following various technical and strategical criteria in order to improve its efficiency, thereby introducing the kumite. Karate started to spread in western Europe after World War II.

Karate today

The practice of karate nowadays englobes different aspects:

Kihon

Basic training of the techniques, performed alone by repeating each technique sequentially, alternating executions on the left and right side. The quest for perfection in each movement, technically and physically, is the goal sought after here, served by a deep mental concentration.

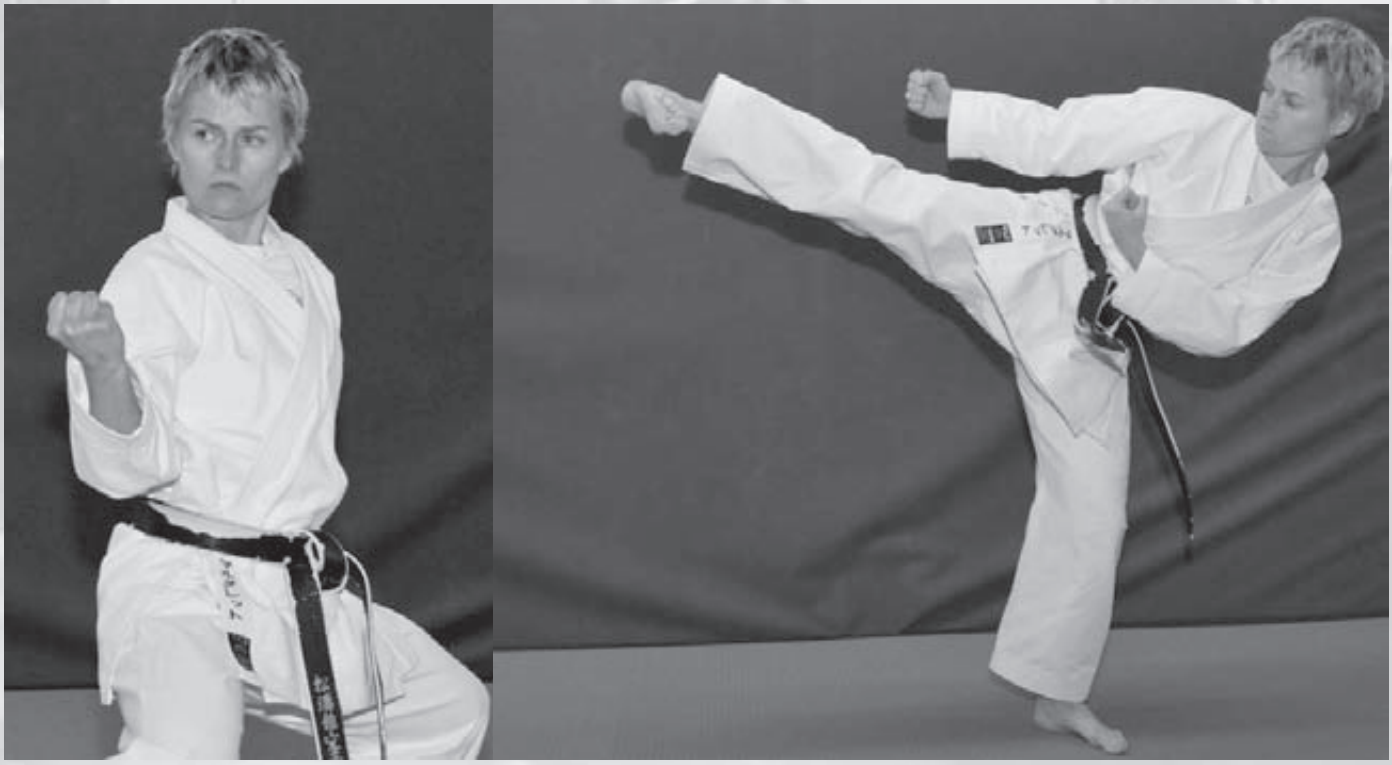
Katas

Sequence of predetermined actions, encompassing defense, attack and counter-attacks movements. The precise body positioning and motion simulates a fighting against a few adversaries.

Kumite

Literally, it means "grouping hands", that is, working together and not alone anymore. The notion of kumite can adopt different forms in karate, from a very codified form to free fighting. The fight can be pre-defined (kihon-kumite), limited to a fixed number of attacks (e.g.: ippon-kumite for one attack, sambon kumite for three), flexible (ju kumite), without contact (kunde kumite) or free (jiyu kumite).

Shall you look for a karate club in the region Basel, you'll find many. It's a popular sport and art and you will have to try to find the style and group suiting you. Karate is opened to everyone; you'll simply need a bit of patience, some will and the virus of karate will take care of the rest!



Currently I'm training with the shotokan section of the Budo Arts Club Basel **(www.budoarts.ch)**. The section is under the supervision of Sensei (master) Pavao Piacun, 8th Dan of karate **(www.karate-do-bern.ch)**. We are seven trainers in Basel (between 1st to 2nd Dan) taking care of the Tuesday and Friday trainings.

Sensei Piacun come once a month to Basel to give a special, top training while he gives another "month training" in Bern, at the Marudojo **(www.marudojo.ch)**. Dedicated Kata and Kumite trainings also take place at the Honbu dojo (Sensei Piacun's dojo). Finally, a one week spring camp as well as a two weeks summer camp take place every year in Croatia, offering a great combination of beach and karate.

Sensei Pavao Piacun

Budo Arts logo

A beginner's course in Shotokan karate will soon be advertised on the web page of our club; if you feel like trying, do not hesitate to pay us a visit and join our sympathetic team.

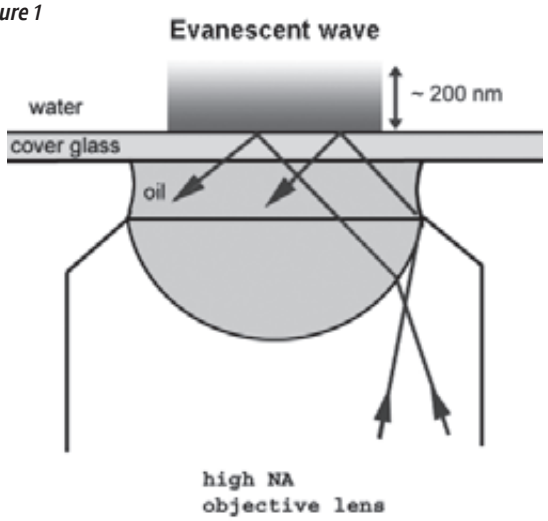
TIRF: using evanescent waves for high resolution membrane fluorescence imaging

Total Internal Reflection Fluorescence (TIRF) microscopy is a relatively new technology, used to monitor membrane associated events including vesicular transport, protein surface membrane targeting, synaptic vesicle fusion, surface membrane receptor assembly, $[Ca^{2+}]_i$ signals occurring on or very close to the plasma membrane, at very high resolution. It offers several advantages over conventional line scanning confocal microscopy, including the possibility of acquiring data from an ultrathin optical section and offers a spatial resolution of 100–200 nm which is 5 times that of a confocal microscope, with a high signal-to-noise ratio and concomitantly it yields information regarding time and space.

Principle of TIRF microscopy:

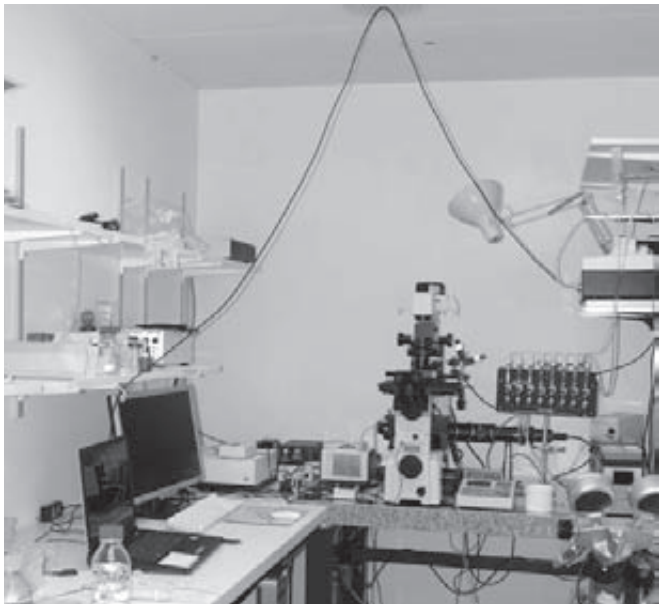
The physical phenomenon of total internal reflection has been known for many years and has been used for many different applications, including on-line molecular interaction detection (BIAcore). In microscopy TIRF requires the use of special objectives with a high numerical aperture; the physical principle is that the incident angle of the laser illumination is greater than the critical angle θ and this results in total internal reflection, producing an evanescent wave immediately adjacent to the coverglass-specimen interface (see figure 1). This evanescent wave (which reaches maximally 100 nm into the specimen after which its energy drops off exponentially) is used to excite single molecules in the thin section in contact with the coverglass. Obviously, the TIRF microscope can not replace a confocal microscope since it can not be used to scan through optical sections (for example in a tissue), but can only be applied to events occurring at the plasma membrane.

Figure 1



TIRF microscope set up at the DBM USB

The most critical aspect of working with TIRF is that one has to be sure that the focus is at (and maintained at) the glass-specimen contact site. In order to adjust the focus at the glass-specimen interface, our microscope is equipped with a SRIC (Surface Reflective Interference Contrast) filter. This filter makes all sections in contact with glass appear as black shadows. This is useful because it allows us to check whether our cells are truly adherent to the glass and to focus on the sites of adherence. Once we have selected the cell of interest, the perfect focus system is activated. The perfect focus system detects the boundary surface between the cover glass and the aqueous solution of the sample using a near infrared light beam and controls the focus using the boundary surface as reference position. The perfect focus system corrects the focus continually in or-



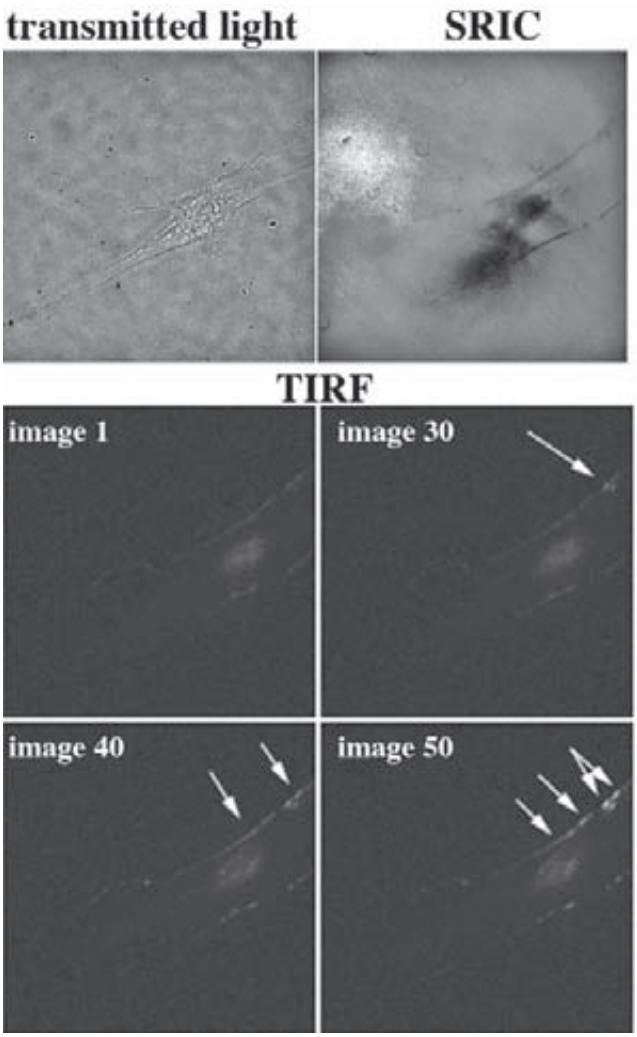
der to compensate for the small changes (drift) occurring during an experiment, especially during time lapse experiments. In addition, the TIRF microscope set up in the DBM USB is equipped with 2 lasers: one excites fluorochromes at 405 nm and the other at 488nm; this allows us to follow changes in the fluorescence of FITC-, YFP/GFP-, Alexa fluor488, fluo-4, blue/white ER tracker just to mention a few of the fluorescent compounds we routinely use. Images are acquired via cooled, back-illuminated C.C.D. camera with on-chip electron gain multiplication (C9100-13 Hamamatsu) which can provide high sensitivity and subarray (64 x 64 pixel, 1 pixel=6.14 µm, binning 1) frame images at rate of 166 s^{-1}. The TIRF microscope is also equipped with (1) a temperature-controlled chamber and with (2) computer-controlled fast drug delivery system. The TIRF microscope set up also allows activation of excitable cells by electrical field stimulation.

Example of an experiment
(or what we study with the TIRF microscope)

Our lab is interested in studying calcium homeostasis in muscle cells from normal individuals and patients affected by neuromuscular disorders affecting the ryanodine receptor sarcoplasmic reticulum Ca^{2+} release channel. An important aspect of Ca^{2+} metabolism concerns where the Ca^{2+} giving rise to a transient comes from; under some experimental conditions, the transient is mainly due to release from intracellular stores, while in others it is due both to release from intracellular stores and to influx from the extracellular medium, via opening of Ca^{2+} channels on the plasma membrane. Therefore it is important to be able to discriminate between the two kinds of Ca^{2+} signals; the TIRF microscope allows us to discriminate between these two kinds of Ca^{2+} events. The figure 2 shows Ca^{2+} influx in a human myotube. The top panel on the right shows the region of adherence of the myotube to the glass, as observed with the SRIC filter. This focal plane was selected and maintained with the perfect focus system and the same cell was subsequently imaged in time lapse for fluo-4 fluorescence changes after stimulation with KCl which mimics the electrical depolarization normally responsible for activating ryanodine receptor mediated Ca^{2+} release. The arrows on the bottom panels show areas on the cell's plasma membrane where increase in Ca^{2+} occur.

Francesco Zorzato

Figure 2



Fussball EM

Henri Delaunay-Pokal

Der neue Henri Delaunay-Pokal, den der Sieger 2008 erstmals in den Händen halten wird, hat den Namen und die Form der ursprünglichen Trophäe behalten, doch er ist modernisiert worden, um der Bedeutung des wichtigsten europäischen Nationen-Turniers gerecht zu werden.

Das Problem war, dass er zum Beispiel viel kleiner ist als die Trophäen der UEFA Champions League oder des UEFA-Pokals. Also wurde entschieden, den neuen Pokal zu vergrössern.

Kleinere Änderungen

Der neue Pokal erinnert in seinem Aussehen schon sehr an die alte Trophäe. Allerdings wurde eine kleine Figur, die auf der Rückseite des Originalpokals mit einem Ball jongliert, genauso entfernt wie der Marmor-Sockel. Dafür wurde der silberne Boden vergrößert, um den Pokal zu stabilisieren. Die Namen der siegreichen Nationen, die auf dem Sockel standen, wurden nun auf der Rückseite des Pokals eingraviert. Dieser besteht aus Sterling Silber, wiegt acht Kilogramm und ist 60 Zentimeter hoch.

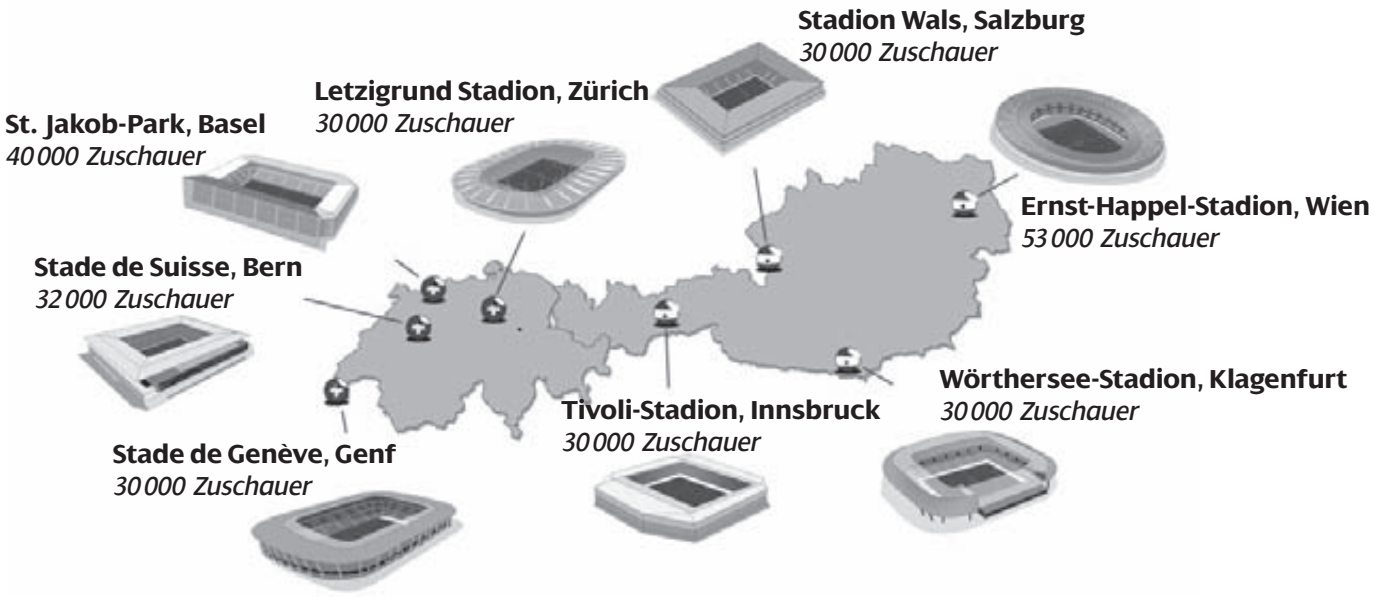
Quelle: uefa.com

Gruppe A			
Schweiz	Tschechien	Portugal	Türkei

Gruppe B			
Österreich	Kroatien	Deutschland	Polen

Gruppe C			
Niederlande	Italien	Rumänien	Frankreich

Gruppe D			
Griechenland	Schweden	Spanien	Russland



VORSCHAU PREVIEW

In der nächsten Ausgabe . . .

. . . sind wir dabei, wenn die Rettungsspezialisten der REGA ihren Jahrescheck am Helikopter absolvieren

Und ausserdem

. . . gibt uns Antonius Rolink einen Einblick in den Forschungsbereich Developmental and Molecular Immunology

. . . berichtet Primo Schär aus seiner Forschungsgruppe Molecular Genetics

. . . lässt Gabriela Kuster Pfister uns teilhaben an ihrer Forschungsarbeit in Myocardial Research

Wer wird Europameister?

GRUPPENSPIELE

7.6.	18.00	Schweiz–Tschechien
	20.45	Portugal–Türkei
8.6.	18.00	Österreich–Kroatien
	20.45	Deutschland–Polen
9.6.	18.00	Rumänien–Frankreich
	20.45	Holland–Italien
10.6.	18.00	Spanien–Russland
	20.45	Griechenland–Schweden
11.6.	18.00	Tschechien–Portugal
	20.45	Schweiz–Türkei
12.6.	18.00	Kroatien–Deutschland
	20.45	Österreich–Polen
13.6.	18.00	Italien–Rumänien
	20.45	Holland–Frankreich
14.6.	18.00	Schweden–Spanien
	20.45	Griechenland–Russland
15.6.	18.00	Schweiz–Portugal
	20.45	Türkei–Tschechien
16.6.	18.00	Polen–Kroatien
	20.45	Österreich–Deutschland
17.6.	18.00	Holland–Rumänien
	20.45	Frankreich–Italien
18.6.	18.00	Griechenland–Spanien
	20.45	Russland–Schweden

VIERTELFINAL

19.6. 20.45	Match 25	Sieger Gr. A–Zweiter Gr. B
19.6. 20.45	Match 26	Sieger Gr. B–Zweiter Gr. A
19.6. 20.45	Match 27	Sieger Gr. C–Zweiter Gr. D
19.6. 20.45	Match 28	Sieger Gr. D–Zweiter Gr. C

HALBFINAL

25.6. 20.45	Match 29	Sieger 25–Sieger 26
26.6. 20.45	Match 30	Sieger 27–Sieger 28

FINAL

29.6. 20.45	Sieger 29–Sieger 30

Mitmachen und ein Ticket für ein Heimspiel des FC Basel gewinnen.
Wer wird Europameister? Die Redaktion freut sich über jede Zuschrift unter dbmfacts@unibas.ch. Einsendeschluss ist der 6.6.2008.

Frühling *Theodor Fontane (1819–1898)*

Nun ist er endlich gekommen doch
In grünem Knospenschuh;
«Er kam, er kam ja immer noch»,
Die Bäume nicken sich's zu.

Sie konnten ihn all erwarten kaum,
Nun treiben sie Schuss auf Schuss;
Im Garten der alte Apfelbaum,
Er sträubt sich, aber er muss.

Wohl zögert auch das alte Herz
Und atmet noch nicht frei,
Es bangt und sorgt: »Es ist erst März,
Und März ist noch nicht Mai.«

O schüttle ab den schweren Traum
Und die lange Winterruh':
Es wagt es der alte Apfelbaum,
Herze, wag's auch du.