DBM FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Periodical Information of the Department of Biomedicine

«Ich möchte die Macht der Fakultät geben» – Interview mit Albert Urwyler | mRNA turnover and oncogenesis | Diffuse or not diffuse . . . Why is transport important for drug action?

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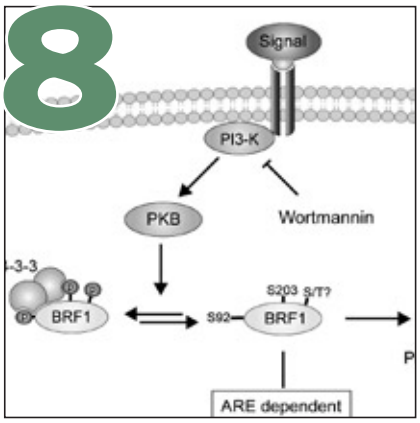

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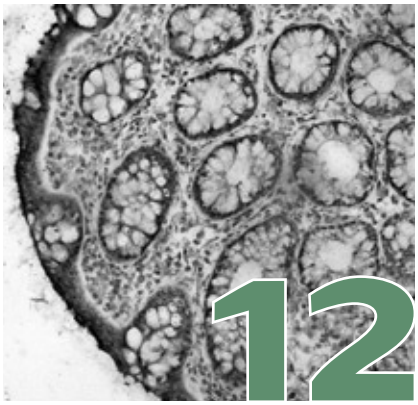

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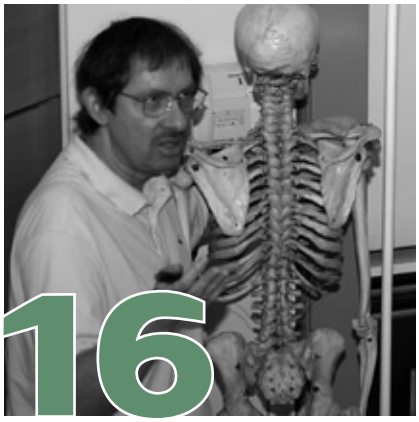

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Das neue Logo des Departements Biomedizin wurde von Frau Eleni Kougionis entworfen. Sie gewann innerhalb des ausgeschriebenen Wettbewerbs den ersten Preis. Frau Kougionis macht eine Ausbildung zur Polygrafin an der Schule für Gestaltung, Basel. Momentan ist sie im zweiten Lehrjahr.

IMPRESSUM

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Das Departement Klinisch Biologische Wissenschaften (DKBW) hat am 01.12.2007 seinen Namen geändert. Es heisst jetzt neu «Departement Biomedizin» (englisch Department of Biomedicine). Es umfasst die gesamte Laborforschung der Medizinischen Fakultät. Damit muss auch das «Departement Forschung» umbenannt werden. Wir heissen ab jetzt «Departement Biomedizin, Universitätsspital Basel». Neu finden sich nun auch die Institute der ehemaligen Vorklinik (Institut für Anatomie, Institut für Biochemie und Genetik, Institut für Medizinische Mikrobiologie und Institut für Physiologie) und auch die Laborforschung des Universitäts Kinderspitals Beider Basel unter dem gemeinsamen Dach des Departements Biomedizin wieder. In diesem Zusammenhang wurde auch ein neues Logo entworfen (siehe Impressum).
Im Neuen Jahr wird Frau Rita Ziegler, Direktorin des Universitätsspitals Basel, nach Zürich wechseln. Frau Ziegler hat wesentlich zur Gestaltung des neuen Departements Biomedizin beigetragen und hat die biomedizinische Forschung am Spital immer tatkräftig unterstützt. Ich bedanke mich an dieser Stelle herzlich dafür.
Passend zum Namenswechsel hier die erste Ausgabe der erweiterten Dfacts, die ab jetzt neu «Departement Biomedizin Facts» (DBM Facts) heissen. Mit einem von Thomas Stebler neugestalteten Layout soll der neue Newsletter ab jetzt über die Aktivitäten des gesamten Departements berichten. Lassen Sie sich überraschen – in der ersten Ausgabe berichtet Albert Urwyler über seine ersten hundert Tage als Dekan der Medizinischen Fakultät, bringt uns Christoph Moroni seine Forschung über «mRNA Tumor and Oncogenesis» näher, führen uns Heike Gutmann und Jürgen Drewe in die Thematik «Diffuse or not diffuse ... Why is transport important for drug action?» ein, erleben wir einen Vormittag im Dozentenleben des Konstantin Beier und hören wir, was Andreas Papassotiropoulos als seinen Tätigkeitsschwerpunkt sieht. Einen Überblick über die Forschungsaktivitäten aller beteiligten Labors geben die Publikationen, die den wissenschaftlichen Teil abrunden. Darauf folgt ein buntes Allerlei im Mitarbeiterteil. Wer sich u.a. mit Albert Einstein messen möchte, hat beim Weihnachtsrätsel eine reelle Chance dazu.

Eine spannende Lektüre und schöne Festtage wünscht Ihnen
Radek Skoda

Dear Readers

The Department of Clinical and Biological Research (DKBW) has changed its name from the 1st of December 2007 on. It is called now „Department of Biomedicine" and assembles the Laboratories of Research of the Medical Faculty. Therefore the „Department Research" will be re-named as „Department of Biomedicine, University Hospital Basel". The former pre-clinical institutes (Institute of Anatomy, Institute of Biochemistry and Genetics, Institute of Medical Microbiology and Institute of Physiology) and the Research Laboratories of the Basel University Childrens Hospital will be included into the Department of Biomedicine.
You can find the new logo in the Impressum.
Rita Ziegler, the director of the University Hospital Basel will start her new position in Zürich. Mrs. Ziegler was essentially involved in the planning of the new Department and always supported the biomedical research in the hospital. I say thank you for everything she did for us.
Here you will find the first issue of the expanded Dfacts which is re-named as „Department of Biomedicine Facts" (DBM Facts). With a new layout, designed by Thomas Stebler; the new newsletter is supposed to inform about the activities of the entire Department. Just see what happens. In the first issue Albert Urwyler informs us about his first 100 days as Dean of the Medical Faculty, Christoph Moroni gives us some understanding about his research in the field of „mRNA tumor and oncogenesis", Heike Gutmann and Jürgen Drewe induct us into the topic „Diffuse or not diffuse ... Why is transport important for drug action?", Konstantin Beier leads us through the life as a lecturer and we can read how Andreas Papassotiropoulos describes his main focus. The list of the latest publications gives you an overview about the research activities of the contributing labs. At the end you find a bunch of different things from the staff-members and last not least ...the „Christmas enigma" – there will be a good chance to compete with Albert Einstein!

Have an enjoyable read and Merry Christmas and a Happy New Year
Radek Skoda

«Ich möchte die Macht der Fakultät geben»

Prof. Albert Urwyler, Dekan der Medizinischen Fakultät, über seine 100 ersten Tage im Amt

In Journalistenkreisen nennt man es ein Kamingespräch, wenn komplexe Themen im kleinen Rahmen diskutiert werden. Die Interviewpartner sollten in der Hierarchie gleichrangig sein und vom Typ her gut zusammen passen. DBM Facts konnte Prof. Regine Landmann, Vorsitzende der Gleichstellungskommission der Medizinischen Fakultät, Forschungsgruppenleiterin am DF und ehemalige Leiterin desselben, als Interviewende gewinnen. Sie traf den neuen Dekan der Medizinischen Fakultät, Prof. Albert Urwyler, hundert Tage nach dessen Amtseinführung zum Gespräch. Und der Dekan nahm sich Zeit.

Am 8. November 2007 warst Du als Dekan der Medizinischen Fakultät 100 Tage im Amt. Gibt es ein Adjektiv, mit dem Du beschreiben kannst, wie Du Dich jetzt fühlst?
Also gesundheitlich fühle ich mich gut.

Das ist schön.
Finanziell geht es mir auch gut.

(lacht)
Ich habe nur ein Problem. Ich muss meine Agenda in den Griff bekommen. Nach drei Monaten kann ich langsam erkennen, wie ich die Prioritäten und Postprioritäten setzen will.

Hast Du Dir das Leben als Dekan so vorgestellt, wie es jetzt in der Realität ist?
Ich habe ein bisschen damit gerechnet.

Wo bist Du momentan am meisten gefordert?
Die höchste Anforderung ist, den Fakultätsmitgliedern und damit der Organisation gerecht zu werden. Alles auf einen guten Nenner zu bringen im Verhältnis zu den vorgesetzten Instanzen. Da fühle ich mich ein wenig als Vermittlungsperson in beiden Richtungen.

Das ist sicher eine schwierige Aufgabe ...
Das ist eine Herausforderung. Du verfügst über mehr Information und bekommst früher Einsicht in die Geschäfte, damit musst Du einerseits die Interessen der Politik und der Universität der Fakultät schmackhaft machen, andererseits ist es Deine Aufgabe, die Interessen der Fakultät in den oberen Instanzen anzubringen, die

wiederum die Einsicht in die Fakultät nicht haben. Das Scharnier ist aber auch spannend, oder?

Das ist spannend, ja.
Kannst Du noch einen Grund nennen, warum Du Dich für dieses Amt beworben hast?
Ich möchte zum Nutzen der Organisation etwas erreichen. Ich wollte gerne auf einem höheren Niveau und in einem komplexeren Umfeld noch einmal die Funktion ausfüllen, die ich in der Anästhesie in Teilbereichen schon länger übernommen habe.

Ist nicht der grosse Unterschied, dass die beiden Ebenen Universität/Rektorat wie auch das Gesundheitsdepartement viel politischer Entscheidungen treffen als Du es in Deinem fachlichen Umfeld gewohnt bist?
Richtig. Im universitären Bereich ist der schwierige Teil die Nachhaltigkeit von gewissen Dingen.

Politik ist im Schnitt sehr strategie- und personenbezogen. Dort wird oft leider nicht sehr langfristig gedacht ...
In der Politik geht es kurzfristig um Wiederwahl, Prozentanteile einer Partei. Wenn wir einmal anfangen, einen Struktur- und dann einen Berufungsbericht zu schreiben und es nicht übertreiben wollen, sind wir schnell bei drei Jahren, bis die Person dann wirklich da ist ...

Genau.
Und wir könnten uns noch ein bisschen länger Zeit lassen, dann wäre je nachdem die Qualität noch ein bisschen besser. Dann haben wir uns nach drei bis fünf Jahren auf eine Person festgelegt, die dann die nächsten zwanzig Jahre das Fach prägt ...

Das steht dem Tempo in der Politik komplett entgegen. Glaubst Du, die Geschwindigkeit unserer Entscheide in der Universität hat auch in der Zukunft ihren Wert? Oder möchtest Du eine andere Gangart vorschlagen?
Die Fakultät muss sich die Fragen im Vorhinein stellen und nicht abwarten, welche Themen bei ihr auf den Tisch kommen. Wir haben bereits damit angefangen, indem wir eine Liste erstellt haben von Leuten, von denen wir erwarten, dass sie bis 2010 in Pension gehen. Jetzt können wir überlegen, wo und wann in welcher Form Aufträge für Strukturberichte erstellt werden sollen.

Auch bei der translationalen Forschung müssen wir nicht warten, bis uns von aussen etwas aufgezwungen

wird. Wir können sie nach und nach entwickeln, in unsere strategischen Pläne aufnehmen. Man könnte statt einzelnen professoralen Strukturberichten Berichte für grössere Gebilde ausarbeiten. Dann hat man eine gewisse Idee, wie man einen Forschungsschwerpunkt in den nächsten fünf bis zehn Jahren entwickelt. Da können wir wirklich proaktiv etwas tun.

Man muss aber auch kommunizieren, dass man in der Fakultät nicht immer einen Businessplan anwenden kann. Siehst Du das fakultätsübergreifend auch im Hinblick auf die Phil II-Fakultät? Ich habe viel Kontakt zu ihr und stelle fest, dass es oft Stoppstrassen auf beiden Seiten gibt. Beim systembiologischen Projekt, das ja jetzt vom SNF stimuliert wird, hat das Dekanat ja auch ein bisschen eine Vermittlungsfunktion. Wie stellst Du Dich dazu? Da geht es ja ganz konkret um Forschungsförderung.

Das ist eine schwierige Frage. Nach hundert Tagen habe ich mit einem solch langfristigen Geschäft noch keine Erfahrungen. An anderen Orten hat man die Problematik gelöst, indem man die beiden Fakultäten miteinander verschmolzen hat. Ob das in Basel so funktioniert, möchte ich aufgrund der organisatorischen Langsamkeit in Frage stellen. Dann gibt es noch die Möglichkeit, die Angelegenheit auf Dekanatsebene anzusiedeln. Wenn man dies möchte, braucht man hauptamtliche Dekane. Ich selbst bin ein Anhänger vom Milizsystem, ansonsten ist das Dekanat nur noch eine Verwaltungsstelle und weit weg von der Front. Man kann diskutieren, wie lange ein Dekan im Amt sein sollte, es gibt verschiedene Varianten. Bei drei Jahren mit eventueller Verlängerung könnte es sicherlich möglich sein, sich auf Dekanatsebene mit der Phil II zusammenzusetzen. In einer attraktiven Universität muss es immer möglich sein, dass sich die Forschenden selbst Kooperationsmodelle über Fakultätsgrenzen hinweg anstreben, Dekanat und Universität unterstützen solche Aktivitäten.

Ich würde gerne noch etwas zur Zusammenarbeit Basel-Bern hören. Was wird Realität? Was ist machbar? Was ist Papierbekenntnis? Was schwebt Dir persönlich vor?

Ich habe ja gestern eine kurze Einstimmung auf Basel-Bern gegeben. Man muss ganz klar sehen, die Initiative ist von der Politik ausgegangen. Es ging in erster Linie darum, die Spitzenmedizin in Basel und Bern zu erhalten und der Forderung der Zürcher nach Alleinherrschaft einen Riegel vorzuschieben. Politisch gesehen ist das für unser Land mit seiner kantonalen Struktur ein sehr geschickter Weg. Wir haben in unserem Land immer diese Politik gehabt: Konsens, vielleicht klein, aber fein, manchmal auch ein bisschen provinziell, aber dafür stimmt die Lebensqualität.

Was heisst das für uns als Fakultät?

Die Politik will Kooperation sehen, primär im klinischen Bereich. Es gibt zwei Modelle, ein so genanntes Vorsteher- und ein Partnerschaftsmodell. Wir müssen uns innerhalb der Fakultät und mit der Berner Fakultät zusammen überlegen, welcher Option wir den Vorzug geben. Im Vorstehermodell koordiniert eine Person, die von Basel oder Bern sein kann, die Zusammenarbeit. Das Partnerschaftsmodell geht davon aus, dass man nicht an beiden Orten den gleichen Schwerpunkt hat. Man ergänzt sich gegenseitig. Diese Diskussion findet jetzt in

der Mikrobiologie und Pathologie statt, in der Herz- und Neurochirurgie ist man bereits in der Schlussphase neuer Berufungen. In der Ethik und Geschichte hat man sich schon geeinigt. Es ist schon viel passiert. Deshalb habe ich dieses Thema gestern in die Fakultät gebracht.

Das ist ein positiver Aspekt im Rahmen des Konkordanzgedankens. Das schliesst gut ab. Du hast gesagt, es geht um die klinischen Einheiten. Nun zum Thema Klinische Forschung versus Grundlagenforschung. Wo möchtest Du die Forschung sehen?

Übersetzen wir das einmal in die Frage: Wo setzen wir Schwerpunkte? Oder in die Frage, die uns am meisten Schwierigkeiten bereitet: Priorität oder Postpriorität? Ich bin der Überzeugung, eine Fakultät lebt von intelligenten und motivierten Menschen, egal, ob sie sich für klinische oder Grundlagenforschung interessieren. Deshalb muss die Autonomie der einzelnen Personen relativ gross gehalten werden. Forschung ist im Grunde nicht planbar.

«Das ist eine Frage der Kultur im System»

Der Politik ist das nicht ganz klar, sie mag eher planbare Forschung, sie versucht sie zum Teil auch zu beeinflussen, soll sie auch, aber wir müssen auf der anderen Seite schauen, dass wir selber unsere eigenen Schwerpunkte setzen. Das ist eine Frage der Kultur im System. Wenn wir die Vergangenheit anschauen, wie sich die Medizinische Fakultät entwickelt hat, dann ist das ein bisschen wie in der Katholischen Kirche mit ihren Bischöfen und dem Kirchenvolk – die Macht unterhält sich selbst und ist hierarchisch etabliert.

Wir müssen eine Möglichkeit finden, wie wir uns als Gemeinschaft mit Einbezug aller engagierten Mitglieder der Fakultät bewegen können, nur so können wir unsere Prioritäten selbst bestimmen. Ich möchte die Macht der Fakultät geben. Das Informationsdefizit ist ein Problem in diesem Zusammenhang. Ich bin dabei, die entscheidenden Informationen transparent aufzubereiten, so dass die Fakultät mitreden kann. So kommen wir diesbezüglich vorwärts. Wichtig ist auch eine enge Verbindung zwischen den Grundlagenwissenschaften und der

klinischen Medizin. Beide Seiten müssen wissen, was auf beiden Seiten passiert. Verständnis, gegenseitiges Interesse und Vernetzung haben ein enormes Entwicklungspotential. Das ist der Weg, den ich mit der Fakultät gehen möchte.

Ich spüre, dass wir mit unseren Anliegen von Dir getragen werden. Du gibst uns die Freiheit nach unserem besten Wissen und Gewissen die Neugierde zu fördern, die die Lehre und Forschung braucht. Und wir wissen, dass Du diese Freiheit zum Besten nutzt. Ich sehe das als Dein Vermächtnis, das Du in zwei Jahren schon gelebt sehen möchtest.

Gibt es etwas, dass Du den Leserinnen und Lesern mit auf den Weg geben möchtest?

Es gibt schon noch Dinge, die wir noch nicht angesprochen haben und die mir wichtig sind. Ich wünsche mir, dass die Organisation sich entwickelt, insbesondere die Funktionsträger.

Das Wichtigste sind ja die Selektion und die Auswahlkriterien. Du kannst ja nicht befehlen, sondern nur mitgestalten.

Man kann nie abschätzen, wie sich jemand entwickelt. Wer erfolgreich sein will, braucht Motivation, Engagement und eine gewisse Menge Intelligenz. Wer die Universität geschafft hat, hat soviel Intelligenz, dass man ihn auch fördern kann. Motivation und Engagement merkt man relativ schnell, hier muss man mit entsprechenden Programmen ansetzen. Da haben wir sicher Verbesserungspotential. Ebenso, was die Unsicherheit der Gruppierung II betrifft: Sie trägt die Hauptlast in Lehre und Forschung. Man muss den Menschen klar sagen, auf was sie sich einlassen. Von Seiten der Organisation könnte man weniger Ordinariatsstellen besetzen. Damit verteilt man das Geld weniger breit und erreicht, dass man in den priorisierten Gebieten mehr bieten kann. Wenn man bedenkt, dass ein Extraordinariat eine Normausstattung von 770.000 Franken und ein Ordinariat von 1.1 Mio. Franken haben sollten, müssen wir genau überlegen, wo wir uns warum was leisten wollen. Das ist viel Geld. Und dann ist da noch die Frage der Evaluation von Personen und Projekten. Man evaluiert heute ziemlich aus dem hohlen Bauch heraus anstatt vorgängig klare Kriterien zu definieren. Besser wäre es, die Bewerber an den vorher ausgearbeiteten Kriterien zu messen. Das Anforderungsprofil für eine Professur zu erstellen, ist relativ einfach und das Auswahlverfahren sollte ausschliesslich darauf basieren.

Du sprichst zwei ganz wichtige Dinge an. Einerseits möchtest Du eine Struktur in die Evaluation bringen, indem man bestimmte Kriterien festlegt, andererseits plädierst Du dafür, die alten Kategorien aufzubrechen. Damit erreicht man eine sinnvollere Verteilung der Mittel. Aber hast Du nicht auch das Gefühl, dass Du damit zugleich das Problem des Mangels an Frauen in der Gruppierung I aufhebst oder zumindest milderst, da eine Person nicht mehr gleichzeitig vier Funktionen haben muss wie Klinikleiter, Manager, Koordinator Lehre und Forschung? Das ist aus meiner Sicht für eine Frau mit Kindern einfach nicht machbar. Aber wenn man anfängt, Funktionen innerhalb einer Professur aufzuteilen, in dem Moment wird es möglich sein, dass

Frauen auch Professuren haben. Könntest Du Dir solch eine Entwicklung vorstellen? Es gibt ja Pilotprojekte am Kinderspital Zürich. Das ist doch sicher möglich, ohne dass damit die Qualität in der Klinik auf der Strecke bleibt.

Also gut, das habe ich auch im Kopf. Du gehst natürlich von einem anderen Punkt aus, aber am Schluss muss es zusammenpassen. Wir befinden uns in einem kompetitiven und selektiven System, in dem Exzellenz gefordert ist. Wir müssen international kompetitiv sein, es wäre unrealistisch, dies zu verneinen. Aber wir sollten uns so organisieren, dass die Aufgaben für Menschen im System machbar sind. Ich bezweifle, dass Druck das richtige Mittel ist. Jeder hat eine Leistungskurve, sie geht nach oben, irgendwann bist Du top und dann geht sie wieder runter.

«Du kannst nicht Transatlantik fliegen und jeden Abend zu Hause sein»

Und jetzt zu Deiner anderen Frage, die passt indirekt natürlich dazu. Man muss sich wirklich überlegen, wie viel man in Personalunion machen kann. Gewisse Probleme sehe ich in verschiedenen Fächern der klinischen Medizin, in denen ein hoher Anteil an Verfügbarkeit gefragt ist, Dienstleistung wird 7 x 24 Stunden gefordert. Wenn man in diesen Bereich geht und noch eine akademische Karriere machen möchte, kann man ein normales Privatleben vergessen. Das ist aber auch wieder eine Frage der Transparenz: Du kannst auch nicht Jumbojet-Kapitänin sein, Transatlantik fliegen und jeden Abend zu Hause sein. Das geht einfach nicht. In unserem Bereich gibt es bestimmt Möglichkeiten. Man kann z.B. Klinik und Forschung in einem Tandemkonzept zwischen zwei Personen miteinander verbinden. Wir brauchen Menschen in der Klinik, die forschungsorientiert sind,

aber nicht unbedingt selbst im Labor forschen und andere in der Grundlagenforschung, die klinisch orientiert sind, und im Labor forschen. Ich kann auch nicht am Patienten arbeiten und gleichzeitig im Labor führend sein. Von der Vorstellung, „Hans Dampf in allen Gassen" sein zu können, müssen wir wegkommen. Irgendwo ist man dann doch nicht so gut, meistens an allen Orten nicht. Und das ist weder für die Menschen noch für das System befriedigend.

Albi, vielen Dank für das Gespräch.

Fotos: Verena Jäggin

mRNA turnover and oncogenesis

In this summary of the research of the "Experimental Oncology" group at the Institute of Medical Microbiology in this first issue of DBM-Facts, I show, partly from an historical perspective, how following a basic oncological question led us into the field of posttranscriptional gene regulation, an area which has recently become of considerable importance in cell biology, including oncology. Over the years this work has involved many excellent team members (see below) to whom I am grateful, and several of whom, I am pleased to state, are currently in responsible positions in the Department of Biomedicine.

Tumor cells with a posttranscriptional lesion

Overexpression of critical genes ("oncogenes") is a hallmark of cancer, and the corresponding proteins are actual (Glivec, Novartis), or potential, drug targets. The IL3 gene encoding the haematopoietic growth factor interleukin-3 (IL-3) is an oncogene in rare human B-cell lymphomas involving a well known oncogenic mechanism: chromosome translocation (here between chromosomes 5 and 14), which juxtaposes the IL-3 gene next to the transcriptionally active immunoglobulin heavy chain gene, resulting in overexpression of IL-3 with autocrine stimulation. This is a classical transcriptional mechanism. We

Back row (from left): Christoph Moroni, Martin Schmidlin, Marco Colombi, Daniel Wegmüller, Klaus Molle

Front row (from left): Ji-Lu Min, Don Benjamin, Anke Thiemeyer, Charles Betz, Verena Sustreanu

were intrigued when we originally discovered, in experiments studying the ras oncogene, haemapoetic tumor cells that overexpressed IL-3, but with an intact IL3 gene showing no signs of DNA rearrangements. As it turned out, the defect was not at the transcriptional level but resulted from increased mRNA stability of the IL-3 mRNA, in other words, the tumor cell had a problem in mRNA turnover. This was at the time a little explored area and led us and others to many interesting basic questions: why are some (e.g. IL-3) transcripts labile and turn over in less than 30min, while others (housekeeping genes) are very stable? What protects a mRNA from degradation, what is the trigger of decay and what stabilizes a transcript? Is this process regulated, and if so how? What is the relevance for oncogenesis?

How is mRNA turnover achieved and regulated?

A key finding was made in the lab some 15 years ago by Ola Filipowicz, (now a Professor in Experimental Hematology at the DBM) who found that raising calcium concentrations led to an immediate halt in the ongoing turnover of certain mRNAs (11). This gave us a pharmacological tool to study the question: how does calcium and cell activation stabilize mRNA? It turned out that calcium activate certain signaling pathways via ionophores, and both pharmacological (inhibitors) and genetic (dominant-negative constructs) evidence from several labs, including ours (5), pointed, at that time, to the fact that protein kinases can act as stabilizers of mRNA, presumably by phosphorylating yet to be identified RNA binding proteins.

BRF1 (part 1): Isolation of an ARE-binding protein

It was known that a short nonamer sequence (present in most cytokines) called the ARE (AU-rich element) is responsible for the short half-life of IL-3 mRNA. Fine mapping of the IL-3 ARE by Georg Stoecklin and by Sinuhe Hahn (8) clarified the role of this element in turnover. (For his work Georg, now a group leader in Heidelberg obtained the freshly created Faculty prize for the best thesis; Sinuhe established his own lab at the DBM and is Professor in the Prenatal Medicine lab). The question was: which proteins bind to the ARE, and are these proteins and thus mRNA turnover regulated by phosphorylation. Later work by Georg Stoecklin with Marco Colombi generated the first cellular mutants in the field

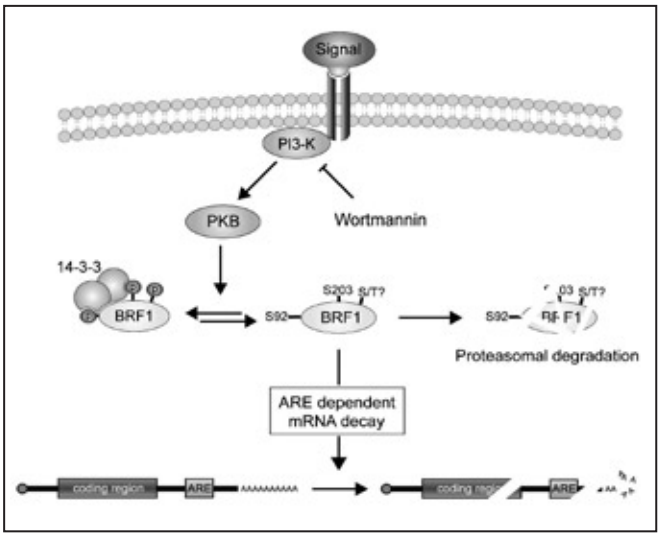

Figure 1: Regulation of mRNA decay by PKB via Brf1
In its unphosphorylated state BRF1 promotes degradation of mRNA and the protein itself is at the same time turning over rapidly. Upon phosphorylation by PKB, BRF1 interacts with 14-3-3, a scaffolding protein, and is thereby kept in an inactive state and protected from proteasomal degradation.

of mRNA decay (9), and isolated the missing gene following gene transfer using a cDNA library packaged in retroviruses (7). The gene identified was BRF1, a zinc finger protein and close relative of the TTP gene, a known post-transcriptional regulator of the cytokine TNF, and this confirmed that we were on the right track. Later work by Martin Schmidlin, Min Lu and by Don Benjamin showed that BRF1 becomes phosphorylated by protein kinase B on two specific serines, and this event is sufficient to abrogate mRNA decay (1, 6). Thus, a first goal was achieved: we understood that an extracellular signal can activate the PKB pathway, leading, in addition, to known PKB effects such as anti-apoptosis, growth etc., and also to an immediate block in the decay of specific ARE-containing mRNAs via phosphorylation of BRF1. The current model is shown in Figure 1. Other key papers in this historical summary by current DBM-members were the description of transcriptional and posttranscriptional mechanisms in autocrine tumors (3) by Hans Hirsch, now Professor at the IMM and the cloning of a calcium channel and tumor marker (2) by Martin Buess.

Brf1 (part 2): Downregulation in embryonal stem cells

Regulators of gene expression, whether transcriptional or posttranscriptional, are likely to play a role in cellular

differentiation. In the hope of finding a cellular system where Brf1 may regulate cell differentation via mRNA turnover we turned to mouse embryonic stem cells, where established protocols allow controlled triggering of differentiation into cells of all three germinal layers: ectoderm, mesoderm, endoderm. The approach taken by Daniel Wegmüller in his PhD thesis was to establish in ES cells a cassette system, where a small hairpin RNA (shRNA) of choice can be induced by a tetracycline analogue to trigger RNA interference. This approach was successful and allowed specific downregulation of Brf1 in ES cells with an unexpected result: we observed stimulation of cardiomyocyte formation either scored microscopically as "beating bodies" or by biochemical markers (10). We propose that certain ARE-containing transcripts, under negative control by Brf1, suppress cardiomyocyte formation, but when Brf1 levels drop, their mRNA levels rise and favour differentiation into cardiomyocytes. The system also allows one to study the effect of any suspected ES cell regulator, is validated with Stat3, and is available on request.

Brf1 (part 3): The first posttranscriptional oncoprotein?

As pointed out above, oncoproteins can be generated by chromosomal translocation and gene fusion, as shown with the classical Philadelphia translocation generating the bcr-abl fusion protein. Acute leukemias show a multiplicity of additional translocation genes frequently affecting genes for transcription factors, which acquire altered (oncogenic) specificity. Are posttranscriptional regulatory genes also altered in cancer cells by chromosome translocation? We were intrigued when in late 2006, Professor Siebert, a leading human geneticist from Kiel contacted us as his team had found that certain human B-cell lymphomas contain as a frequent signature event, an internal deletion in chromosome 14 (which carries both the heavy chain locus, and the Brf1 gene), and that the major breakpoint occurred in the first intron of Brf1! cDNA cloning experiments and functional analysis were carried out in parallel in Kiel and our lab by Marco Colombi, and the following picture emerged: the deletion juxtaposes Brf1, truncated at the N-terminal, to a region in the H-chain locus. An internal (cryptic) AUG serves as a novel start codon to generate a mutated Brf1 truncated at the aminoterminus (Figure 2). Is this allele found in the tumors functional, and is it oncogenic? Having established reporter systems for mRNA turnover in the lab, the first question could be answered positively, the tumor allele promotes ARE-dependent mRNA degradation. Is this sufficient for oncogenicity? Hardly, as one mutation is generally not sufficient to transform a cell, but we speculate that an altered distribution of ARE-containing transcripts may reflect a step towards oncogenicity, similar to an altered expression profile following mutation of a transcription factor. How can we test this hypothesis? We turned again to our ES cells.

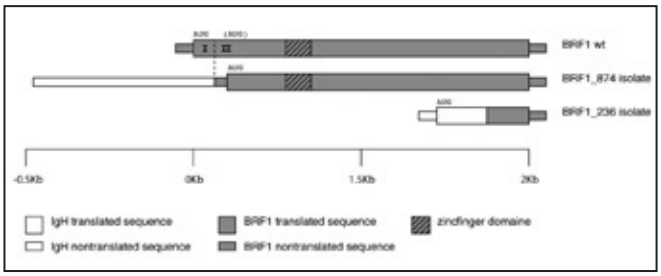

Figure 2: Fusion transcripts between IgH and Brf1 loci found in B-cell lymphomas (Collaboration with R. Siebert, Kiel).
Schematic representation of transcripts from wt Brf1 (top) and two lymphoma-derived alleles following intrachromosomal deletion. In isolate 874, a splicing event froma H-chain donor site targets the acceptor site of exon 2, and the protein utilizes an internal inframe AUG (shown in wt in brackets). In isolate 236, a cryptic splice site within Brf1 exon II is utilized.

Brf1 (part 4): Expressing the putative oncoprotein in ES cells

As the ES cell system was ongoing work in the lab, Daniel Wegmüller and Nicoletta Sustreanu quickly established, using published protocols, how blood cells could be generated from ES cells. While experiments are now aimed at establishing whether or not the putative oncogenic variant form of Brf1 accelerates cell division and/or antagonizes apoptosis or cellular senescence, an interesting observation was made by Marco Colombi and Martin Schmidlin: when Brf1 constructs (both wild-type and the lymphoma derived variant) are introduced into fibrosarcoma cells as a control the protein is expressed, and its functional role can be revealed via targeted mRNA reporter decay. When, however, the same constructs are introduced into undifferentiated ES cells the mRNA is expressed, but no protein is made. Unexpectedly, we stumbled over a form of translational control.

Our current data suggest that two regions in the gene are required to overcome a translational inhibition signal, which, interestingly, is operative in undifferentiated pluripotent ES, but not in other cells. Food for thought and further experimentation! It will be interesting to see how, in comparison, haematopoietic stem cells obtained ex vivo would behave: do they also show translation suppression? Do they express the Brf1 proteins? Will they be able to reveal an oncogenic event? In the meantime, the oncogenic role of the novel Brf1 fusion gene remains to be established.

An applied project: IL-3 dependence and TOR pathway activation

For many of the projects we used IL-3 dependent mouse PB-3c mast cells, which enabled many aspects of mRNA turnover, as described above, to be revealed, particularly the link to autocrine oncogenicity involving transcriptional and posttranscriptional effects of the IL3 locus. More recently, we made an observation with the potential for translational research. We found that cells can be transformed to IL-3 independence by a frame shift mutagen, and that the mechanism is recessive and acts by loss-of-function (4). Interestingly, the transformed cells display exquisite sensitivity to the TOR-pathway inhibitor rapamycin, to which parental cells are insensitive. Indeed, mutants have constitutive high activity of TOR (for example phosphorylation of p70 S6 kinase). As the TOR pathway is of considerable interest as a potential drug target, and as rapamycin derivatives are in clinical testing for certain cancers, our dual cell system (rapamycin-sensitive mutant/insensitive precursor) represents an attractive system for a high throughput screen for inhibitors of the TOR pathway. Currently, over 100'000 compounds are being tested with Dr. U. Regenass (Actelion), and potential hits will be characterized on our collection of independent mutants. Our system should also allow us to reveal compounds that are not inhibitory per se, but are able to confer rapamycin sensitivity to cells (rapamycin sensitizers). Preliminary evidence by Charles Betz and Klaus Molle indicates that loss of the genes TSC2 and PTEN sensitizes cells to rapamycin. These findings may have relevance for chemotherapeutic strategies involving the TOR pathway.

Outlook

The "RNA world" – as it is appreciated today – encompasses far more than the export of nuclear gene copies, it has regulatory properties and with microRNA serves as a network connecting many biological functions, with growth regulation being a prominent example. The elucidation of how this network works will keep more than one generation of students and postdocs busy – inside and outside the Department of Biomedicine!

Christoph Moroni, Experimental Oncology, Institute of Medical Microbiology

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Diffuse or not diffuse ... Why is transport important for drug action?

Drug transport across biological membranes

Membranes separate different parts of the body, the so-called compartments. They allow for concentration gradients between compartments. These gradients are important for vital cell functions, such as electrical excitation. Some of the compartments, such as the brain, require essentially different concentrations of ions, transmitters and signal molecules. In addition to separation, membranes also allow the controlled transport of certain compounds, which are not able to cross the membranes purely by passive diffusion. This selective transport is mediated by a variety of transport proteins. These transport proteins act as transporters for many drugs and several classes of drug transporter have been

Back row (from left):
Birk Poller,
Jürgen Drewe,
Felix Hammann

Front row (from left):
Heike Gutmann,
Angelika Maier,
Ursula Behrens

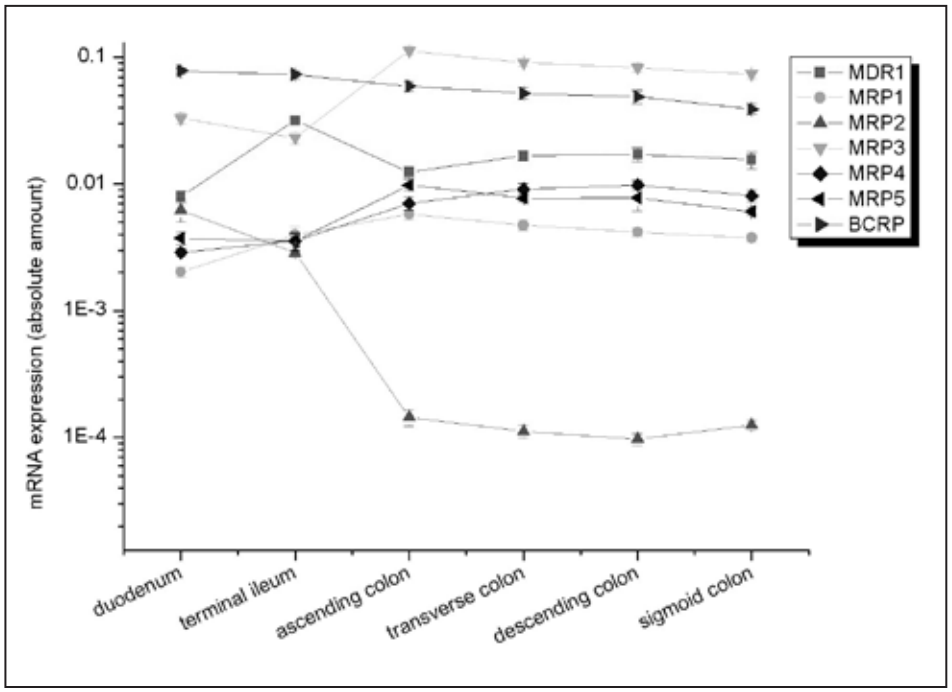

Figure 1
Expression of all transporter protein genes in different gut segments normalized to the villin expression. MDR1, MRP1, MRP2, MRP3, MRP4, MRP5 and BCRP. Data represent means (±SEM) of biopsies from 10 health subjects, except duodenum, where biopsies from 9 subjects were used.

characterized. Among them, the ATP-binding cassette (ABC) transporter superfamily is of high importance.

The ABC transporter superfamily is a group of integral membrane proteins involved in the ATP-dependent transport of compounds across intracellular or cellular membranes and which thereby affects uptake, tissue distribution and elimination of drugs. ABC-transporters play an important role in drug pharmacokinetics, but also in the elimination of toxic (endogeous and exogenous) compounds. The ABC-transporter family is an evolutionary old superfamily and is defined on the basis of structural similarities. About 48 human ABC genes have been identified so far, and these have been divided into seven distinct subfamilies on the basis of their sequence homology and domain organization. All ABC transporters are membrane-bound and are involved in the transport of substrates across biological membranes, either plasma membranes or membranes of intracellular compartments. The typical ABC transporter is build of two halves, each half consisting of 6–11 membrane-spanning helices and one nucleotide binding domain. ABC-transporters are found in many species, bacteria and yeast and they possess a highly conserved sequences homology between species. The latter suggests an essential biological function.

Transport proteins like P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and several multidrug resistance related proteins (MRP1–5) are well-known and important members of the ABC transporter family. They were first detected overexpressed in human cancer, where they mediate drug resistance to cancer therapy. In general they affect drug transport at the level of intestinal drug absorption, in limiting the distribution of drugs towards different tissues such as CNS (blood-brain barrier) and contribute to active elimination of drugs in liver and kidney.

Genetic polymorphisms of transporters

As with many other genes, genetic polymorphisms of transporters have been described and these have some effect on drug transport and availability at the site of action (e.g. pharmacological function). Three major polymorphisms of P-glycoprotein have been described in humans. Although significant impacts on drug effect in HIV patients and on the bioavailability of orally taken digoxin have been described, the clinical significance of these polymorphisms is still controversially discussed. Currently, we are evaluating the significance of different ABC-transporter polymorphisms (including P-glycopro-

tein) in inflammatory bowel diseases.

Drug-drug interaction

Transporter activity can be affected by different drugs: drugs utilizing the same transport protein may compete with each other for the binding site resulting in a decreased transport rate for the drug with the lower binding affinity. Other drugs (such as the cyclosporine derivative PSC388) inhibit transporter function without being transported themselves. In addition, drugs such as rifampicin, St. John's wort, phenytoin and nelfinavir induce the gene expression of transporters. These processes can lead to clinically significant drug-drug interaction, especially during polypharmacy.

To investigate the mechanisms of intestinal transporter function and regulation in vitro, we established several models consisting of intestinal human cell lines (Pfrunder et al, 2002). With these cell culture systems, we investigated several drugs as well as natural compounds and their effect on modulation of ABC transporter function and/or expression.

The drug interaction potential of different natural drugs was investigated in several projects: the effects of a) green tea extracts on MRP2 function and b) the natural antidepressant hypericum perforatum (Netsch et al, Planta Med 2005, Gutmann et al, 2006). The relevance of the in vitro effects of the latter study were subsequently investigated in vivo in a clinical study. It was reported that women to whom a low-dose oral contraceptive and St John's wort were administered concomitantly exhibited significantly more intracyclic bleeding and diminished levels of contraceptive drugs than those who took oral contraceptives alone (Pfrunder et al, 2003).

In another project, the mechanisms of a clinically observed interaction of flucloxacillin and cyclosporine was investigated in vitro and in vivo in rats. We showed that flucloxacillin was able to induce intestinal P-glycoprotein and CYP3A activity. This may explain why higher doses of cyclosporine are needed during concomitant flucloxacillin treatment (Huwyler et al., Curr Drug Metab., 2006).

ABC transporter and their role in the intestine

Our research group is interested in the importance of ABC transporter for the intestinal absorption of drugs, in addition to other applications. Efflux transporters such as P-glycoprotein, BCRP and several MRPs are located in the intestinal wall and form a barrier against cel-

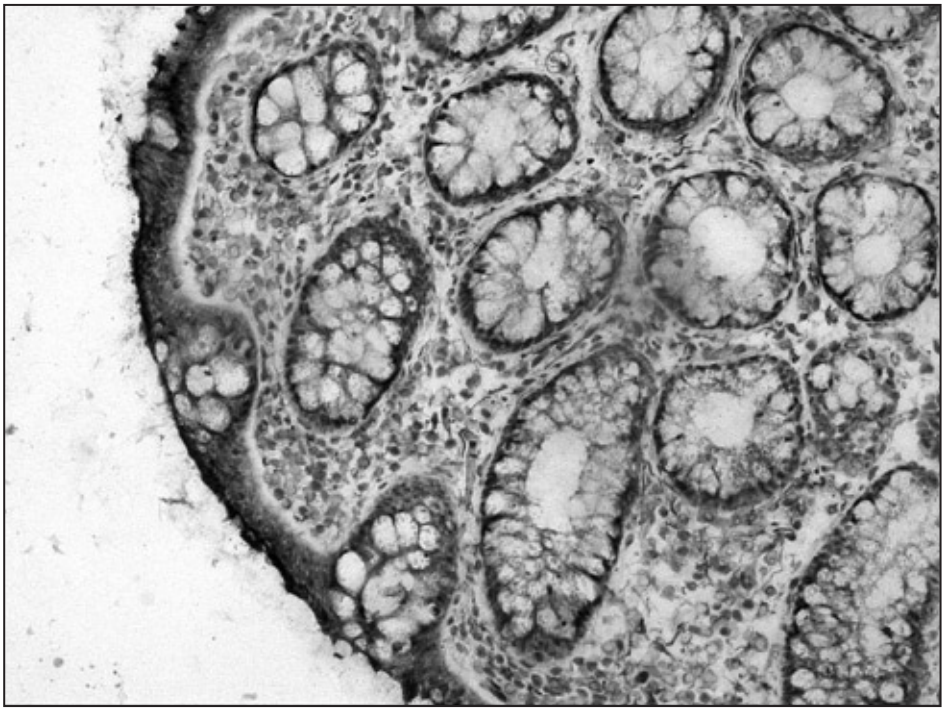

Figure 2
Immunohistochemical staining of BCRP protein on the apical membrane of healthy human duodenal epithelial cells using the BCRP antibody BXP-21.

lular accumulation of toxins and thereby limit drug absorption. Due to their broad substrate specificity, they influence the pharmacokinetics of many chemically unrelated substances such as HIV therapeutics, anticancer agents, and a variety of other drugs. Here, mechanisms that modulate cellular and tissue uptake are of special interest.

Another topic of interest is the absorption enhancement of drugs (by galenical formulation or drug targeting) that have a limited intestinal transport due to ABC transporter action. One example we studied was the influence of surfactants on talinolol permeability in vitro. The results were subsequently compared and validated in vivo in an open-label three way cross-over study. In this study, we confirmed our in vitro results that the surfactant TPGS inhibits P-glycoprotein and, as a consequence, significantly increases the bioavailability of talinolol (Bogman et al. CPT, 2005).

To assess possible drug targeting strategies, we systematically investigated the topographical distribution of ABC transporters in tissue biopsies taken along the human intestinal tissue tract (Pgp, BCRP and MRP1–5 gene).

Changes in ABC transporter expression and activity

Changes in ABC-transporter expression under disease conditions and a subsequent impact on drug uptake and distribution are also of interest. The clinical effect of drugs may be changed either by up- or down-regulation of ABC transporter genes.

Cancer chemotherapy is, for example, seriously limited by the development of multidrug resistance (MDR). This is characterized by overexpression of ABC transporter (such as P-gp, MRP, LRP, and BCRP) mediated efflux of a broad range of anticancer drugs through the membrane of cancer cells. Several new compounds that reverse MDR transporter mediated drug resistance are currently under clinical trials for specific forms of advanced cancers. Some of these modulators have been investigated by us in vitro.

Expression of transporters is also changed in other diseases, such as obstructive cholestasis and inflammatory bowel disease. In contrast to MDR in oncology, reduced duodenal BCRP (a transporter for bile acids and numerous drugs) expression was found in patients with obstructive cholestasis (Zimmermann et al, Digestion 2006). In addition to ABC transporter changes, the apical sodium dependent bile acid transporter ASBT (non-ABC transporter of bile acids) is also significantly down-regulated in this disease (Hruz et al, Gut, 2006).

ABC transporters in inflammatory bowel diseases

In a current project, we are investigating the expression patterns of several ABC transporters in biopsies of patients with inflammatory bowel diseases such as ulcerative colitis (UC) and Crohn's disease (CD). We were able to show that UC patients exhibit a decreased expression of certain transporters in inflamed, but not in uninflamed, sites of the mucosa. A decreased expression of these transporters could substantially contribute to the accumulation of carcinogens in enterocytes. This in turn might partly explain the observation that patients with UC have a higher risk of developing colorectal carcinoma. Furthermore, down-regulation could influence the pharmacokinetics and effects of anti-inflammatory drugs used in the treatment of UC.

Conclusion

We have been able to show that ABC transporters are able to influence the absorption, distribution and elimination of drugs and thereby modulate therapeutic effects. They therefore constitute a clinically important source of severe drug-drug interactions. Knowledge of the impact of transporters can help to explain clinically observed drug-drug interactions and might help to improve safety of individual drug therapy in the future.

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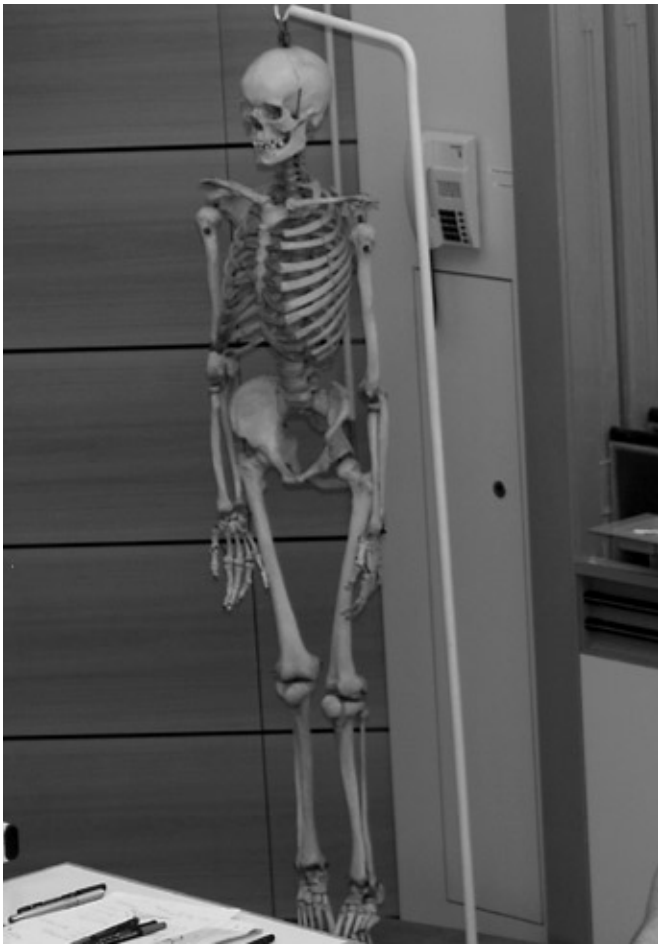
«Ich liebe es, Vorlesung zu halten ...»

Ein Vormittag im Dozentenleben des Konstantin Beier



Mittwochmorgen, 8.00 Uhr, ein fensterloser Hörsaal mit dem Charme der 70er Jahre im Institut für Anatomie. Nur das Handyverbot an der Wand gibt einem das Gefühl im Jahr 2007 zu sein. Die ersten Studierenden der Sportwissenschaft trudeln ein. Der Saal füllt sich unüberhörbar mit Leben. Um zehn nach acht kommt Prof. Konstantin Beier, gelbes Poloshirt, helle Hose. «Die Mediziner sind braver», wirft er mir im Vorübergehen zu, «die Sportstudenten sind eine gute Übung.»

Stimmt, das Rascheln im Hintergrund nimmt nicht ab. Beier nimmt das Mikrophon und wiederholt den Stoff der letzten Vorlesung. Thema: Das Fussskelett. Oberes und unteres Sprunggelenk, die Achse derselben, Unterschenkelmuskeln, Achillessehne. Ich denke an Michael Ballack und die Studenten hoffentlich an den Musculus gastrocnemius, der anscheinend mehr weisse Fasern aufweist als der Musculus soleus, der wiederum mehr rote hat. Wir erfahren, Langläufer haben rote Muskeln, weisse sind eher Sprintermuskeln. «Sie kennen weisse und rote Fasern, wenn Sie Geflügel essen», erklärt er, «eine Gans ist ein ausdauernder Flieger, also hat sie rote Fasern. Ein Huhn fliegt höchstens einmal auf den Zaun, das spricht für weisse Fasern.» Tierversuche einmal anders. Anschliessend werfen wir einen tiefen Blick auf unsere Wadenmuskeln, später malen wir eine Skizze aus: Hallux (grün), Flexus hallucis longus (orange), Metatarsalia (lila), Beier erklärt klar und anschaulich, lernen möchte man das nicht, aber es ist interessant.

Und es wird noch besser: Wir sehen, wie man sich einen 52jährigen Universitätsgelehrten mit Spreizfuss vorzustellen hat. «Dann latschen Sie auf der nicht dafür

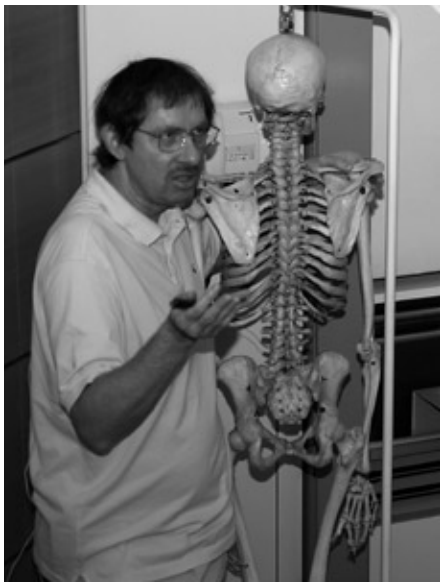
designten Mittelfläche ...» Spricht's und «bewegt» sich durch den Hörsaal. Dann sind wir dran: «Stellt Euch auf die Stufe und wackelt mit den Zehen, fühlt Ihr Eure Sehnen?» Alle sollen ihre Sehnen fühlen: «Jetzt macht mal!» Wir fühlen unsere Sehnen, die sich entzünden können. Erinnerungen werden wach an die Sehnenscheidenentzündungen in jenen Zeiten, als man im Deutschunterricht zu Heinrich Manns «Untertan» noch stricken durfte. «Die Sehne, die zum Musculus extensor hallucis longus zieht, muss ja um die Ecke», holt mich der Vollblutdidaktiker aus meinen Erinnerungen. Lateinische Bezeichnungen und viele Folien folgen, u.a. auch über die «alte Kellnerkrankheit», die immer dann auftritt, «wenn man mit schlechten Schuhen über den Boden latscht oder wie ein Verrückter joggt». Die Sportstudenten hören's wohl.

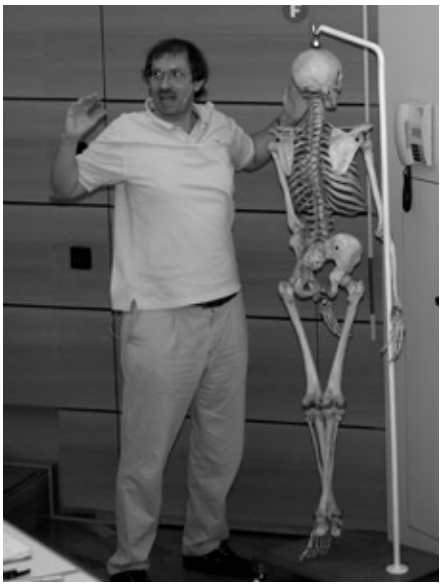
«Wir sind Endorphin-Junkies»

Von neun bis viertel nach neun ist Pause. «Oder sollen wir länger Pause machen und dafür nachspielen?» Ein Kaffee muss sein. «Wer bei den Sportstudenten durch ist, kann überall Vorlesungen halten», erklärt Beier mir. Mir gefällt seine Art zu unterrichten: Die Vorlesung kommt ganz locker daher, das bedeutet aber eine präzise Vorbereitung und das Zeug zu einem guten Didaktiker. Es folgt Beier im Steppergang, Beier beim Ausfall des N. fibularis, was man auch als «Storchengang» bezeichnet. Wir liegen flach vor Lachen und wissen nicht, welche Muskeln gerade bei uns aktiv sind. Gut, dass ein Skelett gerade neben der Tafel steht, da lässt sich manches – auch ohne Muskeln und Bänder – noch einmal seriös diskutieren. Beier malt, schreibt, gestikuliert, zeigt, erklärt. Wir sind beim Pfannenband. «Wollen Sie den lateinischen Namen?» «Nein», tönt es aus dem Hörsaal. Weiter geht's mit der «Marschfraktur». «Stellt Euch vor, 100 km Marsch beim Schweizer Militär, die latschen nur noch auf ihren Bändern, aber wir haben ja einen Willen, wir sind Endorphin-Junkies ...» «Hab ich noch irgendwelche Dias?» Er zeigt Hohl-, Platt- und Klumpfüsse.

Wir haben noch sechs Minuten, um mit den oberen Extremitäten anzufangen. Das Skelett muss wieder ran: «Das Schlüsselbein ist mit dem Acromion gelenkig verbunden...» Ich höre, es handelt sich um ein echtes Gelenk, obwohl es nicht so aussieht. Hätte ich ihn in Chemie gehabt, hätte ich dieses verhasste Fach vor dem Abitur nicht abgewählt, der hätte bestimmt der letzten Formel noch etwas abgewonnen, denke ich. Die Vorlesung ist zu Ende, ich habe viel gelernt, unter anderem auch, mich von dem Vorurteil zu verabschieden, dass Menschen, die Sport studieren, nicht nur irgendwelche Klimmzüge am Reck machen.

Wir laufen den Rhein entlang. Nach Sankt Johann, am Volta-Platz vorbei. Zeit, für ein kurzes privates Gespräch. Ich frage ihn nach den Gottesdiensten, die er für die Menschen organisiert, die ihren Körper der Anato-





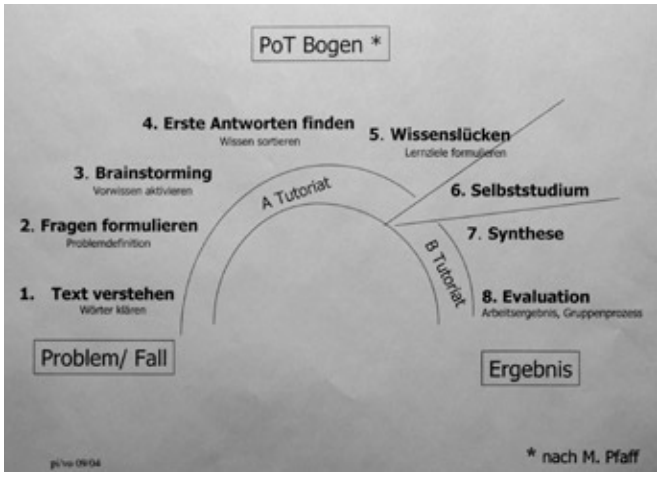
mie vermacht haben. Er habe Gesang studiert, erzählt er mir, habe in verschiedenen Chören mitgesungen, u. a. auch im Heidelberger Opernchor, und liebe Opern. Jedes Jahr stelle er aus dem Präparationskurs einen Chor zusammen und übe mit ihm Lieder von Mendelssohn, Choräle von Bach etc. ein, wie er es aus seiner Heidelberger Zeit kenne. Viele Angehörige der Toten würden zum Gottesdienst in der Peterskirche kommen, der von Pfarrern mit vorbereitet werde.

Wenn er nicht Vorlesung gibt, kümmert er sich um seine Forschungsgruppe Histologie am Anatomischen Institut, die er sowohl in der Forschung wie auch in der Dienstleistung sieht. Als Biologe, der Ahnung von Lehre habe, stehe man zwischen allen Stühlen. Er habe sich für den Schwerpunkt Lehre entschieden. Zum Glück für die Studierenden.

Wir nähern uns unserem Ziel: Ein altes Bürogebäude am Rhein, die sogenannte Brain-Box. Über ausgetretene, mit grauem Teppichboden belegte Stufen geht es in den dritten Stock. Neun Gruppen von Medizinstudenten sind ebenfalls zum Unterricht eingetroffen. Im Aufenthaltsraum erkenne ich die Professoren Bettler, Brenner und Otten. Jeder von ihnen muss zwei Gruppen hintereinander betreuen.

Konstantin Beier ist zunächst für Gruppe 36 zuständig. Sechs Männer, eine Frau. Im Tutoriatsraum prangt mir der sogenannte POT (problemorientiertes Tutoriat)-Bogen entgegen, ich erfahre mehr über die einzelnen Stufen der Problemlösung, artikuliert vom Studiendekanat, das muss es ja wissen. «Pünktlichkeit ist der Respekt vor der Lebenszeit meiner Mitmenschen», lese ich da. Ich frage mich, was die kaputten Treppenstufen draussen mir gegenüber sind. Konstantin Beier geht die Teilnehmerliste durch. «Soll ich rumlaufen?» Er beantwortet sich die Frage gerade selbst: «Nein, dann muss ich mich ja bücken». Ein Argument, das man bei seiner Grösse nachvollziehen kann.

Wir sitzen im Kreis und versuchen Stufe 1 zu bewältigen, die da lautet: Text verstehen. Wir verstehen: «Patientin kommt in die Sprechstunde mit folgenden



Beschwerden, die sich im Laufe der letzten ein bis zwei Jahre langsam entwickelten: Müdigkeit, keine Unternehmenslust, Gewichtszunahme von 7 kg, habe häufig allgemeines Kältegefühl, verspürt eine «Muskelsteifigkeit und Myalgien nach Belastung etc.» Einer meldet sich, er schreibt freiwillig Protokoll, jede Gruppe hat eine Funktionsliste. «Wer möchte die Diskussion leiten?» Bologna fordert eine weitere Funktion. Die Medizinstudentin meldet sich mutig. Wir sprechen Hochdeutsch. «Was sind Myalgien?» «Muskelschmerzen» tönt es aus dem Plenum. «Wer geht an die Wandtafel?» Ein Student ist schnell bestimmt.

Nächster Schritt: Brainstorming. Das Studiendekanat hätte seine Freude an uns. «Wir sind im Themenblock Endokrinologie», meint ein Student, «der Fall könnte mit Hormonen zu tun haben.»

«Denkt ganzheitlich, wenn es auch schwer ist!»

Der gebürtige Leipziger, der Leiter dieses Themenblocks ist, hört sich alles aufmerksam an. Auf der Tafel erscheinen Stichworte wie: Schilddrüsenhormone, Hypokalzämie, Parathormon, Kalziumphosphat, Cushing-Syndrom. Beier greift kurz ein: «Sehen Sie die gesamte Systematik» und lässt weiter diskutieren. Seine Art, mit den Studenten umzugehen, gefällt mir, kompetent, freundlich und mit einer Leichtigkeit, die motiviert. Während die Studierenden weiter über T3/T4, den Wärme- und Energiehaushalt und Jodmangel nachdenken, lasse ich meinen Blick durch den Raum gleiten. Ein paar leere Regale, die Tür mit geriffeltem Glasfenster, ein orangenes und ein gelbes DIN A3 Blatt mit besagten Problemlösungsstrategien, nebendran ein einsamer Klebstreifen, der Teppichboden ist braun und fleckig, die Stühle scheinen einmal eierschalenfarben gewesen zu sein, Erinnerungen an Sofia/Bulgarien werden wach, doch Beier holt mich mit «Wenn der Patient kommt, ist er nicht im Themenblock Endokrinologie» jäh aus meinem Rückblick. «Denkt ganzheitlich, wenn es auch schwer ist!»

Wir formulieren unsere Lernziele. Dinge, die wir nicht wissen: Wirkungsweise Schilddrüsenhormone, Regelkreise, die Ursachen von Jodmangel». Wir sind bei Schilddrüsenfehlfunktionen. «Im Hochgebirge hat alles zuwenig Jod», erklärt Beier uns, «der Bergkäse, das Fleisch von Tieren». « Habt Ihr in den bayrischen, österreichischen und Schweizer Alpen noch nie das Kompliment gehört ‚Hat die Frau aber einen schönen Kropf?'». Die Stimmung ist gut, da nimmt man auch die Hausaufgabe in Kauf, sich zu überlegen, was man als Krankheit sicherlich ausschliessen kann. In einer Woche geht es weiter, zwischendrin haben die Studenten noch eine Vorlesung über die Schilddrüse. Ich habe Glück und das Lösungsblatt.

In der Pause um 11.15 Uhr treffen wir auf den Autor des Falles, Marius Kränzlin, man fachsimpelt unter Kollegen, während am Haus die Güterzüge vorbeidonnern. Um 11.45 Uhr geht es weiter. Die zweite Gruppe ist erschienen. Sofort kehrt Ruhe ein. Medizinstudenten sind ein anderer Menschenschlag. Der gleiche Fall, wieder nach Schema F. Doch Beier variiert, bringt Schwung. Ich frage mich, wie das in einer Gruppe abläuft, in der der Dozent todlangweilig ist. Beiers einzigstes Arbeitsinstrument: Ein blauer Filzstift. Nicht umsonst ist er schon einmal zum besten Dozierenden des zweiten Jahreskurses in der Humanmedizin gewählt worden.

Heidi Hoyermann-Welinsky
Fotos: Verena Jäggin

Interview with Andreas Papassotiropoulos

Professor for Molecular Psychology and Head of Life Sciences Training Facility (LSTF), Biocenter

Dear Prof. Papassotiropoulos, you have been recently appointed professor for Molecular Psychology, a newly established position at the University Basel...
Yes, that is correct. The rationale behind this position is to give psychology, and also psychiatry, the chance to capitalize on the new developments in biology and especially in genetics. Many psychological traits and phenotypes are strongly related to biology.

Could you briefly describe your focus of research and how you came to work in this field?
By training I am a clinician, or more specifically a psychiatrist and psychotherapist. During my residency as a psychiatrist I was involved in genetic studies of Alzheimer's disease, which is a classical polygenic disease. My research focus at that time was to identify genes related to the risk for the development of Alzheimer's disease, which still remains one of my important fields of interest. However, I realized that we were trying to explain the genetics of 'bad memory' without even having a clue about the genetics of physiological memory in humans. Therefore, the genetics of human memory capacity became my other field of interest. By identifying genes related to physiological memory capacity, we can also address the question whether they are related to memory disorders.

In many of your publications you are doing SNP association studies. What is the impact of SNP genotyping on diagnosis and therapy of polygenic diseases?
Polygenic, genetically complex diseases cannot really be diagnosed by genetics. Nevertheless, we are currently experiencing a real revolution in the genomic area, which is due to technological achievements and the possibility to perform genome-wide association studies. More and more important association studies are being published, and some of them identify polymorphisms strongly related to what we originally thought to be a polygenic disease but that turns out to be, at best, oligogenic. Let me give you one example: In 2005 one of the first hypothesis-free genome scans was done on macular degeneration. It turned out that only one polymorphism within the gene encoding complement factor H was strongly related to macular degeneration. The rest of the genome wasn't. This study shed a new light on the pathophysiology of this disease. Several other

large studies have been recently published on diabetes, obesity, glaucoma, etc. So it becomes more and more clear that human genetics is a great tool to understand biology. The time is right to do large-scale association studies.

Andreas Papassotiropoulos, M.D., Professor of Molecular Psychology

36 years old, married, 3 children
***1996** M.D. thesis at the Bonn University Medical School, Bonn, Germany;*
***1996 – 2000** Postdoctoral Fellow at the Departments of Psychiatry and Neurology, University of Bonn;*
***2000 – 2007** Research Group Leader Clinical Genetics, Division of Psychiatry Research, University of Zürich, Switzerland;*
***2000 – 2004** Deputy Clinical Director, Division of Psychiatry Research, University of Zürich;*
***2003** Visiting Scientist, Laboratory of Neurogenetics, National Institute of Aging, Bethesda/MD, USA;*
***2003 – 2007** Research Professor, Division of Psychiatry Research, University of Zürich;*
***2004 – present** Scientific Advisor, Translational Genomics Research Institute (TGen), Phoenix/AZ, USA;*
***2007 – present** Full Professor and Director, Division of Molecular Psychology; Head of Life Sciences Training Facility, Biozentrum, University of Basel*

You were talking of technological achievements. Which new technologies are you using and also introducing to the institute?

We are fortunate enough to build upon the already existing Affymetrix platform which was initially established for expression studies. However, the same platform can be used for genome-wide association studies. Back in Zürich we were the first to perform a genome-wide scan with half a million polymorphisms by using the 500k SNP chip from Affymetrix. We are now proud to be probably the first in Europe to have established the new SNP chip 6.0, which contains roughly 1 million polymorphisms and, in addition, 1 million probes for copy number variations. While we are talking, we are hybridizing the first 200 chips and I am very eager to see the first results.

You have a pyrosequencing machine in your lab. What are the differences compared to conventional (Sanger) sequencing and for which kind of applications is it used?

Pyrosequencing was originally developed for medium throughput SNP analysis. It is a direct sequencing of the SNP region and enables control of the sequence 5' and 3' of the SNP. It is also very well suitable for insertion/deletion analysis. In addition, pyrosequencing is ideal for epigenetic, i.e. methylation studies. We are currently optimizing the protocols for such studies.

Are you currently dedicating all your time to research, or are you also seeing patients?
For the first years in Basel I decided not to see patients because I want to establish a solid research fundament. In addition to research I have teaching duties, for example the new lecture and master projects in molecular psychology.

You are involved in the 'Sesam' project (Swiss Etiological Study of Adjustment and Mental health), which was debated extensively in the press. What is the aim of that project and specifically of the part you are conducting?
My interest within Sesam is to perform genetic association studies in adult psychiatric diseases, such as depression and anxiety, in order to understand better the biology behind these disorders.

Are there any particular hobbies that the readership of DBM Facts should know of?
Back in Greece I went to a classical guitar school, so whenever there is time left I play the guitar. Otherwise, my family and my job don't allow too much time for hobbies.

Thank you for this interesting and informative interview.

The interview was made by Ralph Tiedt

Interview with Philippe Demougin

Leading Technician LSTF

What kind of services does the Life Sciences Training Facility offer?
We offer access and training for tools (procedures, instruments, software) which are aimed at the study of gene expression and DNA variations at genome-wide level. Our core competence is the use of the Affymetrix platform. Affymetrix is a Californian company which provides ready-to-use microarrays of high quality and very high density. Using this technology one can, within a couple of days, interrogate the level of expression of all annotated genes at once within a group of tested cells (in culture or in a tissue) in order to compare them to a reference group of cells. The LSTF is also providing training in the use of the Genopyting arrays including the recently released 6.0 version which interrogates close to 1 million Single Nucleotide Polymorphisms (SNPs) and as many Copy Number Variations markers.
The LSTF is involved in all aspects of service maintenance. The LSTF trains the researchers who perform all steps (from nucleic acid purification to data analysis).

The researcher is in charge of his project, performs the work at the bench and ultimately analyses its own data. We provide state of the art instruments and software and the training to make a good use of them and the user does the job.

If I want to perform a microarray experiment, how do I get started?

Each project is unique and we strongly encourage users to contact us as early as possible in order to plan the experimental design and to address technical issues, such as sample preparation and storage. In principle it is best is to get in touch with me via e-mail ***(philippe.demougin@unibas.ch)*** or telephone ***(+41 61 267 2178)*** in order to plan an appointment, so that we can meet and discuss. Among other things we'll discuss the experimental design, the proper way of isolating nucleic acid (DNA or RNA), and the cost and schedule of the experiment in particular. Once the user has total RNA or genomic DNA isolated, the procedure is very standardized and takes about a week until hybridization and scanning. The purpose of the LSTF is not to generate benefits. The user is charged for what he uses. We provide all reagents and consumables, except the Genechips, for these procedures and charge the user accordingly.

So the chips have to be bought by the user...

Yes, the user buys the chips, but at prices negotiated by us. In fact all academic institutes in Switzerland using Affymetrix arrays are part of what we call the Swiss Array Consortium (SAC). The price of one array is very much dependant on how many arrays a laboratory uses per year. Since we are essentially a single client, we have good prices. Researchers in Switzerland have the opportunity to purchase arrays at a preferential price because the SAC is the largest academic client in Europe. The user orders the array using a code we give him and then brings them to the facility for hybridization when needed. The LSTF makes, what remain expensive experiments, more affordable than ever.

How about the data analysis?

For gene expression studies, there are free programs available (the most known one being "R" from the Bioconductor consortium), but they are usually for people who have skills in programming languages. The LSTF provides free access to the commercial software package GeneSpring GX, from Agilent, which is user-friendly, with a standard interface. We have 2 licenses and 2 workstations where you can sit and analyze your data. Special computer skills are not necessary for one to be able to filter differentially expressed genes and to apply statistical tools to check their significance.

Thanks a lot for this information.

The interview was made by Ralph Tiedt

Ein Blick ins Reagenzglas

Das DKBW organisierte einen «Tag der offenen Tür» anlässlich des 50-jährigen Jubiläums der Krebsliga beider Basel.

Anlässlich des 50-jährigen Jubiläums der Krebsliga beider Basel fand am 25. August 2007 ein «Tag der offenen Tür» für die Mitglieder der Krebsliga beider Basel im Zentrum für Lehre und Forschung statt. Die Krebsliga beider Basel ist ursprünglich als Verein zur Unterstützung der Krebsforschung gegründet worden. Noch heute dienen über 50% der Spenden und Einnahmen zur Förderung der Krebsforschung in der Region Basel. Die restlichen Mittel werden in Präventionskampagnen, verschiedenen Dienstleistungen für Krebsbetroffene und Kurse zur Information über Krebs eingesetzt. Die Mitglieder der Krebsliga sind oft selbst von der Krankheit Krebs betroffen oder kennen jemanden in ihrem näheren Umfeld, der an der Krankheit leidet. Durch ihre Spenden hoffen sie, dass dieses Leiden eines Tages geheilt oder zumindest die Lebensqualität erhöht werden kann.

Als Dank für die jahrelange finanzielle Unterstützung wollte die Krebsliga in ihrem Jubiläumsjahr den Mitgliedern etwas Besonderes bieten und bat das DKBW, exklusiv den Mitgliedern, der Krebsliga einen Blick ins «Reagenzglas» bzw. in die Forschungslabors zu gewähren. Anhand von konkreten Beispielen sollten die Forscher den Mitgliedern ihre Forschungsprojekte näher bringen und die Fortschritte in der Krebsforschung aufzeigen. Gerne war das DKBW bereit, einen «Tag der offenen Tür» für die Mitglieder der Krebsliga zu organisieren.

Das Interesse der Mitglieder an diesem Anlass war gross und sie nutzten die einmalige Gelegenheit, Forscher persönlich kennen zu lernen. Die 150 Teilnehmer reisten trotz sommerlichen Temperaturen aus verschiedenen Regionen der Schweiz an. Jeder Gast hatte an diesem Tag die Gelegenheit, drei verschiedene Forschungsgruppen

näher kennen zu lernen, ihnen Fragen zu stellen und sich mit den Forschern intensiv auszutauschen.
Für das DKBW war der «Blick ins Reagenzglas» ebenfalls eine Premiere, da zum ersten Mal Forschungsgruppen verschiedener Institute gemeinsam einen «Tag der offenen Tür» organisiert haben. Neben neun Forschungsgruppen des Departements Forschung haben fünf Forschungsgruppen des Zentrums für Biomedizin (ZBM) ihre Forschungsprojekte vorgestellt. Im Foyer des ZLF errichteten die Forschungsgruppen des ZBM Christofori, Schär, Heinimann, Orend und Holländer ihre «Forschungsstationen». Die Gruppen des Departements Forschung Eberle, Heim, Skoda, Filipowicz, Schwaller, Biedermann, Spagnoli, Merlo und Rochlitz gaben Einblick in ihre Labors im 3. und 4. Stock des ZLF.
Mit grossem Engagement veranschaulichten die Gruppen ihre Forschungsprojekte anhand von Postern und Computerpräsentationen. Die Gäste konnten entartete Krebszellen im Vergleich zu gesunden Zellen oder Schnitte durch ein humanes Melanom mit Hilfe von Mikroskopen betrachten. Experimente wie Mutationsscreens, das Sortieren fluoreszent markierter Zellen oder DNA Isolationen mit anschliessender Sequenzierung der DNA zur Identifikation von Mutationen wurden von den Forschern vorgeführt und näher erklärt. Am Beispiel des Vaterschaftstests wurde die Assoziation eines DNA-Profils mit der Veranlagung zu Krankheiten, wie zum Beispiel Darmkrebs, dargelegt. Sogar ein Darmpräparat ist eigens von der Pathologie zur Verfügung gestellt worden zur Veranschaulichung der Geschwürbildung entarteter Zellen und der daraus folgenden Zerstörung des Organs.
Die Mitglieder der Krebsliga waren begeistert und beeindruckt von den Präsentationen. Von vielen kam die Rückmeldung, dass sie zum ersten Mal verstanden hätten, wie Krebs entstehen kann und wie die Forscher es angehen, die Krebszellen zu bekämpfen, auszuhungern oder in die Apoptose zu treiben. Der Wunsch der Teilnehmer nach einem «nächsten Mal» war nicht zu überhören.....

Caroline Möller-Dossenbach
Fotos: Pablo Wünsch Blanco

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.
Radek Skoda

The New England Journal of Medicine | The NEW ENGLAND JOURNAL of MEDICINE | 356, 371–378, 2007 | IF 51,3

Lack of Association between Antimyelin Antibodies and Progression to Multiple Sclerosis

J. Kuhle[1], C. Pohl[2,3], M. Mehling[1], G. Edan[4], M. S. Freedman[5], H. P. Hartung[6], C. H. Polman[2,7], D. H. Miller[8], X. Montalban[9], F. Barkhof[7], L. Bauer[2], S. Dahms[2], R. Lindberg[1], L. Kappos[1] and R. Sandbrink[2]

Abstract:

Background: Patients with a single episode of neurologic dysfunction and brain magnetic resonance imaging (MRI) scans suggestive of multiple sclerosis are at high risk for clinically definite multiple sclerosis, but the outcome for individual patients is unpredictable. An increased risk of progression to clinically definite multiple sclerosis in patients with serum antibodies against myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) has been reported.

Methods: We measured serum anti-MOG and anti-MBP IgG and IgM antibodies in 462 patients with a first clinical event suggestive of multiple sclerosis and at least two clinically silent lesions on brain MRI. The patients were participating in a multicenter trial of treatment with interferon beta-1b. Antibodies were assessed by Western blot analysis at baseline, and the results compared with the time and rate of progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis as defined by an international panel (the McDonald criteria). Regular visits were scheduled for the assessment of neurologic impairment and for MRI before treatment and at months 3, 6, 9, 12, 18, and 24.

Results: No associations were found between the presence of anti-MOG and anti-MBP IgM and IgG antibodies and progression to clinically definite multiple sclerosis or a diagnosis of multiple sclerosis according to the McDonald criteria, either in the entire cohort or in any subgroups of the study population.

Conclusions: Serum antibodies against MOG and MBP, as detected by Western blot analysis, are not associated with an increased risk of progression to clinically definite multiple sclerosis in patients who have had a clinically isolated syndrome suggestive of multiple sclerosis.

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Nature nature 446, 735–736, 2007 IF 26,7

Cancer: Division of labour

Gerhard Christofori

Some genes are involved in the development of a new tumour; others specifically promote the dissemination of its cancerous cells to other organs. A set of four genes seems to be required for both processes.

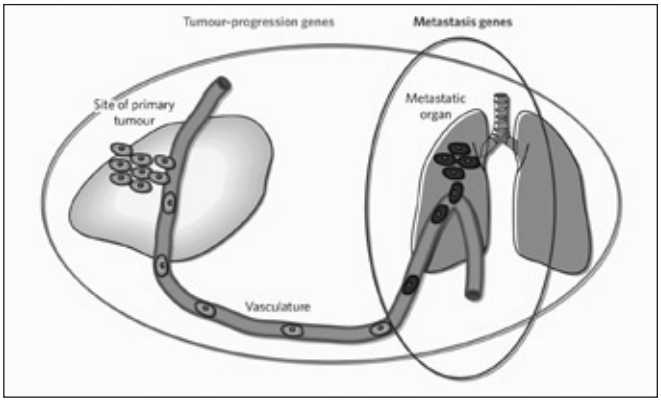

Figure 1: Roles of different genes in cancer.

Gupta et al.4 identify genes that are required for the growth of primary tumours, for intravasation and extravasation of tumour cells to the specific metastatic target organ (as exemplified here by the lung) and for metastatic outgrowth. These genes are required for the growth of the primary tumour and the many stages of metastasis, and can be classified as ‚tumour-progression genes'. By contrast, ‚metastasis genes' contribute exclusively to metastatic outgrowth.

[1] Gerhard Christofori is at the Institute of Biochemistry and Genetics, Department of Clinical–Biological Sciences (DKBW), University of Basel, Center for Biomedicine, Mattenstrasse 28, CH-4058 Basel, Switzerland

Immunity **Immunity** 26, 643–654, 2007 IF 18,3

Ectopic lymphoid-organ development occurs through interleukin 7-mediated enhanced survival of lymphoid-tissue-inducer cells

D. Meier[1,4], C. Bornmann[1,4], S. Chappaz[4], S. Schmutz[1], L. A. Otten[2], R. Ceredig[3], H.Acha-Orbea[2], D. Finke[1]

Abstract:
Development of Peyer's patches and lymph nodes requires the interaction between $CD4^+$ $CD3^-$ IL-7Rα^+ lymphoid-tissue inducer (LTi) and VCAM-1^+ organizer cells. Here we showed that by promoting their survival, enhanced expression of interleukin-7 (IL-7) in transgenic mice resulted in accumulation of LTi cells. With increased IL-7 availability, de novo formation of VCAM-1^+ Peyer's patch anlagen occurred along the entire fetal gut resulting in a 5-fold increase in Peyer's patch numbers. IL-7 overexpression also led to formation of multiple organized ectopic lymph nodes and cecal patches. After immunization, ectopic lymph nodes developed normal T cell-dependent B cell responses and germinal centers. Mice overexpressing IL-7 but lacking either RORγ, a factor required for LTi cell generation, or lymphotoxin $\alpha1\beta2$ had neither Peyer's patches nor ectopic lymph nodes. Therefore, by controlling LTi cell numbers, IL-7 can regulate the formation of both normal and ectopic lymphoid organs.

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The Journal of Experimental Medicine THE JOURNAL OF EXPERIMENTAL MEDICINE 204, 2553–2559, 2007 IF 14,5

A constant affinity threshold for T cell tolerance

D. Naeher[1], M. A. Daniels[1], B. Hausmann[1], P. Guillaume[2], I. Luescher[2], E. Palmer[1]

Abstract:
T cell tolerance depends on the T cell receptor's affinity for peptide/major histocompatibility complex (MHC) ligand; this critical parameter determines whether a thymocyte will be included (positive selection) or excluded (negative selection) from the T cell repertoire. A quantitative analysis of ligand binding was performed using an experimental system permitting receptor-coreceptor interactions on live cells under physiological conditions. Using three transgenic mouse strains expressing distinct class I MHC-restricted T cell receptors, we determined the affinity that defines the threshold for negative selection. The affinity threshold for self-tolerance appears to be a constant for cytotoxic T lymphocytes.

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Plos Medicine PLoS MEDICINE 4, 3, e96, 2007 IF 13,8

HIV Patients Developing Primary CNS Lymphoma Lack EBV-Specific CD4$^+$ T Cell Function – Irrespective of Absolute CD4$^+$ T Cell Counts

O. Gasser[1], F. K. Bihl[2], M. Wolbers[3], E. Loggi[2], I. Steffen[4], H. H. Hirsch[4], H. F. Günthard[5], B. D. Walker[2], C. Brander[2], M. Battegay[6], C. Hess[1]

Abstract:
Background: In chronic HIV infection, antiretroviral therapy–induced normalization of CD4$^+$ T cell counts (immune reconstitution [IR]) is associated with a decreased incidence of opportunistic diseases. However, some individuals remain at risk for opportunistic diseases despite prolonged normalization of CD4$^+$ T cell counts. Deficient Epstein-Barr virus (EBV)-specific CD4$^+$ T cell function may explain the occurrence of EBV-associated opportunistic malignancy – such as primary central nervous system (PCNS) lymphoma – despite recovery of absolute CD4$^+$ T cell counts.
Methods and Findings: Absolute CD4$^+$ T cell counts and EBV-specific CD4$^+$ T cell-dependent interferon-γ production were assessed in six HIV-positive individuals prior to development of PCNS lymphoma ("cases"), and these values were compared with those in 16 HIV-infected matched participants with no sign of EBV-associated pathology ("matched controls") and 11 nonmatched HIV-negative blood donors. Half of the PCNS lymphoma patients fulfilled IR criteria (defined here as CD4$^+$ T cell counts ≥500/μl blood). EBV-specific CD4$^+$ T cells were assessed 0.5–4.7 y prior to diagnosis of lymphoma. In 0/6 cases versus 13/16 matched controls an EBV-specific CD4$^+$ T cell response was detected ($p = 0.007$; confidence interval for odds ratio [0–0.40]). PCNS lymphoma patients also differed with regards to this response significantly from HIV-negative blood donors ($p < 0.001$, confidence interval for odds ratio [0–0.14]), but there was no evidence for a difference between HIV-negative participants and the HIV-positive matched controls ($p = 0.47$).
Conclusions: Irrespective of absolute CD4$^+$ T cell counts, HIV-positive patients who subsequently developed PCNS lymphoma lacked EBV-specific CD4$^+$ T cell function. Larger, ideally prospective studies are needed to confirm these preliminary data, and clarify the impact of pathogen-specific versus surrogate marker-based assessment of IR on clinical outcome

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Hepatology *Hepatology* 46, 558–565, 2007 IF 10,4

Activation of endoplasmic reticulum stress response by hepatitis viruses up-regulates protein phosphatase 2A

V. Christen, S. Treves, F. H. T. Duong, M. H. Heim

Abstract:
The up-regulation of protein phosphatase 2 A (PP2A) is an important factor leading to an inhibition of IFN signaling caused by viral protein expression. Here, we describe the molecular mechanism involved in PP2Ac up-regulation by HCV and HBV. HCV and HBV protein expression in cells induces an ER stress response leading to calcium release from the ER. HCV protein expression induces CREB activation, probably through calcium/calmodulin-dependent protein kinase. CREB binds to a CRE element in the promoter of PP2Ac and induces its transcriptional up-regulation. Because PP2Ac is involved in many important cellular processes including cell-cycle regulation, apoptosis, cell morphology, development, signal transduction and translation, its up-regulation during ER stress has potentially important implications.

Department of Research, University Hospital Basel, Basel, Switzerland

Blood *blood* 110, 375–379, 2007 IF 10,4

Leukemic blasts in transformed JAK2-V617F–positive myeloproliferative disorders are frequently negative for the JAK2-V617F mutation

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Abstract:
To study the role of the JAK2-V617F mutation in leukemic transformation, we examined 27 patients with myeloproliferative disorders (MPDs) who transformed to acute myeloid leukemia (AML). At MPD diagnosis, JAK2-V617F was detectable in 17 of 27 patients. Surprisingly, only 5 of 17 patients developed JAK2-V617F–positive AML, whereas 9 of 17 patients transformed to JAK2-V617F–negative AML. Microsatellite analysis in a female patient showed that mitotic recombination was not responsible for the transition from JAK2-V617F–positive MPD to JAK2-V617F–negative AML, and clonality determined by the MPP1 polymorphism demonstrated that the granulocytes and leukemic blasts inactivated the same parental X chromosome. In a second patient positive for JAK2-V617F at transformation, but with JAK2-V617F–negative leukemic blasts, we found del(11q) in all cells examined, suggesting a common clonal origin of MPD and AML. We conclude that JAK2-V617F–positive MPD frequently yields JAK2-V617F–negative AML, and transformation of a common JAK2-V617F–negative ancestor represents a possible mechanism.

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The Embo Journal | EMBO JOURNAL | 26, 2832–2842, 2007 | IF 10,1

Increased tumor cell dissemination and cellular senescence in the absence of β_1-integrin function

A. Kren[1], V. Baeriswyl[1], F. Lehembre[1], C. Wunderlin[1], K. Strittmatter[1], H. Antoniadis[1], R. Fässler[2], U. Cavallaro[3] and G. Christofori[1]

Abstract:
Integrins are transmembrane receptors that bind extracellular matrix proteins and enable cell adhesion and cytoskeletal organization, as well as transduction of signals into cells, to promote various aspects of cellular behavior, such as proliferation or survival. Integrins participate in many aspects of tumor biology. Here, we have employed the Rip1Tag2 transgenic mouse model of pancreatic β cell carcinogenesis to investigate the role of β_1-integrin in tumor progression. Specific ablation of β_1-integrin function in pancreatic β cells resulted in a defect in sorting between insulin-expressing β cells and glucagon-expressing α cells in islets of Langerhans. Ablation of β_1-integrin in β tumor cells of Rip1Tag2 mice led to the dissemination of tumor cell emboli into lymphatic blood vessels in the absence of ongoing lymphangiogenesis. Yet, disseminating β_1-integrin-deficient β tumor cells did not elicit metastasis. Rather, primary tumor growth was significantly impaired by reduced tumor cell proliferation and the acquisition of cellular senescence by β_1-integrin-deficient β tumor cells. The results indicate a critical role of β_1-integrin function in mediating metastatic dissemination and preventing tumor cell senescence.

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Journal of Allergy and Clinical Immunology | The Journal of Allergy and Clinical Immunology | 119, 98–105, 2007 | IF 8,8

Disease-specific expression and regulation of CCAAT/enhancer-binding proteins in asthma and chronic obstructive pulmonary disease

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Abstract:
Background: CCAAT/enhancer-binding proteins (C/EBPs) control cell proliferation; lack of C/EBPα correlates with increased proliferation of bronchial smooth muscle cells (BSMCs) of asthmatic patients.
Objective: We sought to assess disease-specific expression of C/EBPα, β, δ, and ε and the effects of budesonide (10 8 mol/L) and formoterol (10 8 mol/L).
Methods: Expression and function of C/EBPα, β, δ, and ε BSMCs of control subjects (n = 9), asthmatic patients (n = 12), and patients with chronic obstructive pulmonary disease (COPD; n = 10) were determined.
Results: The control group expressed C/EBPα, β, δ, and ε, which were upregulated by serum (5%). Budesonide completely inhibited C/EBPα and β expression; formoterol increased C/EBPα expression (2-fold). C/EBPδ and ε expression were not affected by the drugs. The asthmatic group did not appropriately express C/EBPα. Basal levels of C/EBPβ, δ, and ε were upregulated by serum (5%). Budesonide and formoterol increased C/EBPβ levels (3.4-fold and 2.5-fold, respectively), leaving C/EBPα, δ, and ε levels unaffected. The COPD group normally expressed C/EBPα, β, and ε, which were upregulated by serum treatment (5%). Basal levels of C/EBPδ were downregulated by serum in 7 of 10 BSMC lines. Budesonide inhibited C/EBPα and β expression, upregulated C/EBPδ (3.2-fold), and had no effect on C/EBPε. Formoterol upregulated C/EBPα expression (3-fold) but not the other C/EBPs. Protein analysis and electrophoretic mobility shift assay confirmed the disease-specific expression pattern of C/EBPα in asthmatic patients and C/EBPδ in patients with COPD.
Conclusions: The expression and regulation of C/EBPs in BSMCs of asthmatic patients and patients with COPD seems disease specific. Budesonide and formoterol modulate C/EBP expression in a drug- and disease-specific pattern.
Clinical implications: The data could provide a method to discriminate between asthma and COPD at an early disease stage.

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Reduction of BMP4 activity by gremlin 1 enables ureteric bud outgrowth and GDNF/WNT11 feedback signalling during kidney branching morphogenesis

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Abstract:
Antagonists act to restrict and negatively modulate the activity of secreted signals during progression of embryogenesis. In mouse embryos lacking the extra-cellular BMP antagonist gremlin 1 (*Grem1*), metanephric development is disrupted at the stage of initiating ureteric bud outgrowth. Treatment of mutant kidney rudiments in culture with recombinant gremlin 1 protein induces additional epithelial buds and restores outgrowth and branching. All epithelial buds express *Wnt11*, and *Gdnf* is significantly upregulated in the surrounding mesenchyme, indicating that epithelial-mesenchymal (e-m) feedback signalling is restored. In the wild type, *Bmp4* is expressed by the mesenchyme enveloping the Wolffian duct and ureteric bud and *Grem1* is upregulated in the mesenchyme around the nascent ureteric bud prior to initiation of its outgrowth. In agreement, BMP activity is reduced locally as revealed by lower levels of nuclear pSMAD protein in the mesenchyme. By contrast, in *Grem1*-deficient kidney rudiments, pSMAD proteins are detected in many cell nuclei in the metanephric mesenchyme, indicative of excessive BMP signal transduction. Indeed, genetic lowering of BMP4 levels in *Grem1*-deficient mouse embryos completely restores ureteric bud outgrowth and branching morphogenesis. The reduction of BMP4 levels in *Grem1* mutant embryos enables normal progression of renal development and restores adult kidney morphology and functions. This study establishes that initiation of metanephric kidney development requires the reduction of BMP4 activity by the antagonist gremlin 1 in the mesenchyme, which in turn enables ureteric bud outgrowth and establishment of autoregulatory GDNF/WNT11 feedback signalling.

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ANNALS OF SURGERY ANNALS OF SURGERY 244, 978–985, 2006 IF 7,7

Precultivation of Engineered Human Nasal Cartilage Enhances the Mechanical Properties Relevant for Use in Facial Reconstructive Surgery

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Abstract:
Objective: To investigate if precultivation of human engineered nasal cartilage grafts of clinically relevant size would increase the suture retention strength at implantation and the tensile and bending stiffness 2 weeks after implantation.

Summary Background Information: To be used for reconstruction of nasal cartilage defects, engineered grafts need to be reliably sutured at implantation and resist to bending/tension forces about 2 weeks after surgery, when fixation is typically removed.

Methods: Nasal septum chondrocytes from 4 donors were expanded for 2 passages and statically loaded on 15 × 5 × 2-mm size nonwoven meshes of esterified hyaluronan (Hyaff-11). Constructs were implanted for 2 weeks in nude mice between muscle fascia and subcutaneous tissue either directly after cell seeding or after 2 or 4 weeks of preculture in chondrogenic medium. Engineered tissues and native nasal cartilage were assessed histologically, biochemically, and biomechanically.

Results: Engineered constructs reproducibly developed with culture time into cartilaginous tissues with increasing content of glycosaminoglycans and collagen type II. Suture retention strength was significantly higher (3.6 ± 2.2-fold) in 2-week precultured constructs than in freshly seeded meshes. Following in vivo implantation, tissues further developed and maintained the original scaffold size and shape. The bending stiffness was significantly higher (1.8 ± 0.8-fold) if constructs were precultured for 2 weeks than if they were directly implanted, whereas tensile stiffness was close to native cartilage in all groups.

Conclusion: In our experimental setup, preculture for 2 weeks was necessary to engineer nasal cartilage grafts with enhanced mechanical properties relevant for clinical use in facial reconstructive surgery.

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Cancer Research **Cancer Research** 67, 6163–6173, 2007 IF 7,7

Endothelin Receptor Type B Counteracts Tenascin-C–Induced Endothelin Receptor Type A–Dependent Focal Adhesion and Actin Stress Fiber Disorganization

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Abstract:
Tenascin-C, an extracellular matrix molecule of the tumor-specific microenvironment, counteracts the tumor cell proliferation–suppressing effect of fibronectin by blocking the integrin 5ß1/syndecan-4 complex. This causes cell rounding and stimulates tumor cell proliferation. Tenascin-C also stimulates endothelin receptor type A (EDNRA) expression. Here, we investigated whether signaling through endothelin receptors affects tenascin-C–induced cell rounding. We observed that endothelin receptor type B (EDNRB) activation inhibited cell rounding by tenascin-C and induced spreading by restoring expression and function of focal adhesion kinase (FAK), paxillin, RhoA, and tropomyosin-1 (TM1) via activation of epidermal growth factor receptor, phospholipase C, c-Jun NH2-terminal kinase, and the phosphatidylinositol 3-kinase pathway. In contrast to EDNRB, signaling through EDNRA induced cell rounding, which correlated with FAK inhibition and TM1 and RhoA protein destabilization in the presence of tenascin-C. This occurred in a mitogen-activated protein kinase/extracellular signal-regulated kinase kinase–dependent manner. Thus, tumorigenesis might be enhanced by tenascin-C involving EDNRA signaling. Inhibition of tenascin-C in combination with blocking both endothelin receptors could present a strategy for sensitization of cancer and endothelial cells toward anoikis.

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The Journal of Neuroscience ***The Journal of Neuroscience*** 27, 3260–3267, 2007 IF 7,5

Basic Fibroblast Growth Factor Modulates Density of Blood Vessels and Preserves Tight Junctions in Organotypic Cortical Cultures of Mice: A New In Vitro Model of the Blood–Brain Barrier

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Abstract:
This study was performed to examine the maintenance of blood vessels in vitro in cortical organotypic slice cultures of mice with special emphasis on basic fibroblast growth factor (FGF-2), which is known to promote angiogenesis and to preserve the integrity of the blood–brain barrier. Slices of neonatal day 3 or 4 mouse brain were maintained for 3, 7, or 10 d in vitro (DIV) under standard culture conditions or in the presence of FGF-2. Immunohistochemistry for factor VIII-related antigen or laminin revealed a relative low number of blood vessels under standard conditions. In contrast, moderate FGF-2 concentrations increased the number of vessels: with 0.5 ng/ml FGF-2 it was 1.4-fold higher after DIV 3 or 1.5-fold after DIV 7 compared with controls; with 5 ng/ml it was almost doubled in both cases. With an excess of 50 ng/ml, FGF-2 vessels were reduced after DIV 3 or similar to controls after DIV 7. FGF receptor 1 was preferentially found on endothelial cells; its immunolabeling was reduced in the presence of the ligand. Cell death detected by an ethidium bromide analog or the apoptosis marker caspase-3 was barely detectable during the 10 d culture period. Immunolabeling of the tight junction proteins ZO-1 (zonula occludens protein 1), occludin, claudin-5, and claudin-3 revealed evidence for structural integrity of the blood–brain barrier in the presence of moderate FGF-2 concentrations. In conclusion, FGF-2 maintains blood vessels in vitro and preserves the composition of the tight junction. Hence, we propose FGF-2-treated organotypic cortical slices as a new tool for mechanistic studies of the blood–brain barrier.

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Journal of Neurology | Journal of Neurology | 254, 160–168, 2007 | IF 7,5

Antimyelin antibodies in clinically isolated syndromes correlate with inflammation in MRI and CSF

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Abstract: OBJECTIVE: We investigated the correlation of antimyelin oligodendrocyte glycoprotein-(anti-MOG) and anti-myelin basic protein antibodies (anti-MBP) in serum of CIS patients with inflammatory signs in MRI and in CSF and, as previously suggested,the incidence of more frequent and rapid progression to clinically definite MS (CDMS). METHODS: 133CIS patients were analysed for anti-MOG and anti-MBP (Western blot). Routine CSF and cranial MRI (quantitatively and qualitatively) measures were analyzed. 55 patients had a follow-up of at least 12 months or until conversion to CDMS. RESULTS: Patients with anti-MOG and anti-MBP had an increased intrathecal IgG production and CSF white blood cell count($p = 0.048$ and $p = 0.036$). When anti-MBP alone, or both antibodies were present the cranial MRI showed significantly more T2 lesions ($p = 0.007$ and $p = 0.01$,respectively). There was a trend for more lesion dissemination in anti-MBP positive patients ($p = 0.076$).Conversely, anti-MOG- and/or anti-MBP failed to predict conversion to CDMS in our follow-up group ($n = 55$). Only in female patients with at least one MRI lesion ($n = 34$) did the presence of anti-MOG correlate with more frequent ($p = 0.028$) and more rapid ($p = 0.0209$) transition to CDMS. CONCLUSIONS: Presence of anti-MOG or anti-MBP or both was not significantly associated with conversion to CDMS in our CIS cohort. However, patients with anti-MOG and anti-MBP had higher lesion load and more disseminated lesions in cranial MRI as well as higher values for CSF leucocytes and intrathecal IgG production. Our data support a correlation of anti-MOG and anti-MBP to inflammatory signs in MRI and CSF. The prognostic value of these antibodies for CDMS, however, seems to be less pronounced than previously reported.

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Oncogene | Oncogene | 26, 2290–2298, 2007 | IF 6,6

Tumor progression induced by the loss of E-cadherin independent of β-catenin/Tcf-mediated Wnt signaling

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Abstract:
E-cadherin-mediated cell–cell adhesion is frequently lost during the development of malignant epithelial cancers. Employing a transgenic mouse model of β-cell carcinogenesis (Rip1Tag2) we have previously shown that the loss of E-cadherin is a rate-limiting step in the progression from adenoma to carcinoma. However, the mere loss of cell adhesion may not be sufficient and additional signals are required to cause tumor cells to permeate the basal membrane and to invade surrounding tissue. Besides being an important component of the E-cadherin cell-adhesion complex, β-catenin plays a critical role in canonical Wnt signaling. We report here that β-catenin-mediated Wnt signaling does not contribute to tumor progression in Rip1Tag2 mice. E-cadherin downregulates β-catenin/Tcf-mediated transcriptional activity by sequestrating β-catenin into E-cadherin cell-adhesion complexes even in the presence of activated Wnt signaling. Upon loss of E-cadherin expression, β-catenin is degraded and Tcf/β-catenin-mediated transcriptional activity is not induced. Moreover, forced expression of constitutive-active β-catenin or genetic ablation of Tcf/β-catenin transcriptional activity in tumor cells of Rip1Tag2 transgenic mice does not affect tumor progression. Together, the data indicate that signals other than β-catenin/Tcf-mediated Wnt signaling are induced by the loss of E-cadherin during tumor progression in Rip1Tag2 transgenic mice.

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Journal of Cell Science | Journal of Cell Science | 120, 2232–2240, 2007 | IF 6,4

Ca^{2+} signaling through ryanodine receptor 1 enhances maturation and activation of human dendritic cells

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Abstract:
Increases in intracellular Ca^{2+} concentration accompany many physiological events, including maturation of dendritic cells, professional antigen-presenting cells characterized by their ability to migrate to secondary lymphoid organs where they initiate primary immune responses. The mechanism and molecules involved in the early steps of Ca^{2+} release in dendritic cells have not yet been defined. Here we show that the concomitant activation of ryanodine receptor-induced Ca^{2+} release together with the activation of Toll-like receptors by suboptimal concentrations of microbial stimuli provide synergistic signals, resulting in dendritic cell maturation and stimulation of T cell functions. Furthermore, our results show that the initial intracellular signaling cascade activated by ryanodine receptors is different from that induced by activation of Toll-like receptors. We propose that under physiological conditions, especially when low suboptimal amounts of Toll-like receptor ligands are present, ryanodine receptor-mediated events cooperate in bringing about dendritic cell maturation.

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The Journal of Immunology | The Journal of Immunology | 177, 8806–8812, 2006 | IF 6,3

Cyclooxygenase Regulates Cell Surface Expression of CXCR3/1-Storing Granules in Human $CD4^+$ T Cells

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Abstract:
Efficient migration of $CD4^+$ T cells into sites of infection/inflammation is a prerequisite to protective immunity. Inappropriate recruitment, on the other hand, contributes to inflammatory pathologies. The chemokine/chemokine receptor system is thought to orchestrate T cell homing. In this study, we show that most circulating human $CD4^+$ T cells store the inflammatory chemokine receptors CXCR3 and CXCR1 within a distinct intracellular compartment. Equipped with such storage granules, $CD4^+$ T cells coexpressing both receptors increased from only 1% ex vivo to ~30% within minutes of activation with PHA or exposure to the cyclooxygenase (COX) substrate arachidonic acid. Up-regulation was TCR independent and reduced by COX inhibitors at concentrations readily reached in vivo. The inducible inflammatory $CXCR^{3high}CXCR1^+$ phenotype identified nonpolarized cells, was preferentially triggered on $CCR7^+CD4^+$ T cells, and conferred increased chemotactic responsiveness. Thus, inducible CXCR3/1 expression occurs in a large fraction of $CD4^+$ T cells. Its dependency on COX may explain a number of established, and point toward novel, effects of COX inhibitors.

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Clinical Cancer Research | Clinical Cancer Research | 13, 3696–3705, 2007 IF 6,2

[Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4 Is a Highly Efficient Radiotherapeutic for Glucagon-Like Peptide-1 Receptor–Targeted Therapy for Insulinoma

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Abstract:

Purpose: Although metabolic changes make diagnosis of insulinoma relatively easy, surgical removal is hampered by difficulties in locating it, and there is no efficient treatment for malignant insulinoma. We have previously shown that the high density of glucagon-like peptide-1 receptors (GLP-1R) in human insulinoma cells provides an attractive target for molecular imaging and internal radiotherapy. In this study, we investigated the therapeutic potential of [Lys^{40}(Ahx-DTPA-^{111}In)NH2]-Exendin-4, an ^{111}In-labeled agonist of GLP-1, in a transgenic mouse model of human insulinoma.

Experimental Design: [Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4 was assessed in the Rip1Tag2 mouse model of pancreatic ß-cell carcinogenesis, which exhibits a GLP-1R expression comparable with human insulinoma. Mice were injected with 1.1, 5.6, or 28 MBq of the radiopeptide and sacrificed 7 days after injection. Tumor uptake and response, the mechanism of action of the radiopeptide, and therapy toxicity were investigated.

Results: Tumor uptake was >200% injected activity per gram, with a dose deposition of 3 Gy/MBq at 40 pmol [Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4. Other GLP-1R–positive organs showed ≥30 times lower dose deposition. A single injection of [Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4 resulted in a reduction of the tumor volume by up to 94% in a dose-dependent manner without significant acute organ toxicity. The therapeutic effect was due to increased tumor cell apoptosis and necrosis and decreased proliferation.

Conclusions: The results suggest that [Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-Exendin-4 is a promising radiopeptide capable of selectively targeting insulinoma. Furthermore, Auger-emitting radiopharmaceuticals such as ^{111}In are able to produce a marked therapeutic effect if a high tumor uptake is achieved.

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Hypertension | Hypertension | 49, 1178–1185, 2007 IF 6,0

Angiotensin II Induces Angiogenesis in the Hypoxic Adult Mouse Heart In Vitro Through an AT$_2$–B2 Receptor Pathway

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Abstract:

Angiotensin II is a vasoactive peptide that may affect vascularization of the ischemic heart via angiogenesis. In this study we aimed at studying the mechanisms underlying the angiogenic effects of angiotensin II under hypoxia in the mouse heart in vitro. Endothelial sprout formation from pieces of mouse hearts was assessed under normoxia (21% O_2) and hypoxia (1% O_2) during a 7-day period of in vitro culture. Only under hypoxia did angiotensin II dose-dependently induce endothelial sprout formation, peaking at 10–7 mol/L of angiotensin II. Angiotensin II type 1 (AT_1) receptor blockade by losartan did not affect angiotensin II–induced sprouting in wild-type mice. Conversely, the angiotensin II type 2 (AT_2) receptor antagonist PD 123319 blocked this response. In hearts from $AT_1^{-/-}$ mice, angiotensin II–elicited sprouting was preserved but blocked again by AT_2 receptor antagonism. In contrast, no angiotensin II–induced sprouting was found in preparations from hearts of $AT_2^{-/-}$ mice. Angiotensin II–mediated angiogenesis was also abolished by a specific inhibitor of the B2 kinin receptor in both wild-type and $AT_1^{-/-}$ mice. Furthermore, angiotensin II failed to induce endothelial sprout formation in hearts from $B_2^{-/-}$ mice. Finally, NO inhibition completely blunted sprouting in hearts from wild-type mice, whereas NO donors could restore sprouting in $AT_2^{-/-}$ and $B_2^{-/-}$ hearts. This in vitro study suggests the obligatory role of hypoxia in the angiogenic effect of angiotensin II in the mouse heart via the AT2 receptor through a mechanism that involves bradykinin, its B2 receptor, and NO as a downstream effector.

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The American Journal of Pathology | The American Journal of PATHOLOGY | 170, 1348–1361, 2007 | IF 5,9

Distinct Roles of Vascular Endothelial Growth Factor-D in Lymphangiogenesis and Metastasis

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Abstract:
In many human carcinomas, expression of the lymphangiogenic factor vascular endothelial growth factor-D (VEGF-D) correlates with up-regulated lymphangiogenesis and regional lymph node metastasis. Here, we have used the Rip1Tag2 transgenic mouse model of pancreatic β-cell carcinogenesis to investigate the functional role of VEGF-D in the induction of lymphangiogenesis and tumor progression. Expression of VEGF-D in β cells of single-transgenic Rip1VEGF-D mice resulted in the formation of peri-insular lymphatic lacunae, often containing leukocyte accumulations and blood hemorrhages. When these mice were crossed to Rip1Tag2 mice, VEGF-D-expressing tumors also exhibited peritumoral lymphangiogenesis with lymphocyte accumulations and hemorrhages, and they frequently developed lymph node and lung metastases. Notably, tumor outgrowth and blood microvessel density were significantly reduced in VEGF-D-expressing tumors. Our results demonstrate that VEGF-D induces lymphangiogenesis, promotes metastasis to lymph nodes and lungs, and yet represses hemangiogenesis and tumor outgrowth. Because a comparable transgenic expression of vascular endothelial growth factor-C (VEGF-C) in Rip1Tag2 has been shown previously to provoke lymphangiogenesis and lymph node metastasis in the absence of any distant metastasis, leukocyte infiltration, or angiogenesis-suppressing effects, these results reveal further functional differences between VEGF-D and VEGF-C.

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Neurology | Neurology® | 67, 804–808, 2006 | IF 5,7

Relapses and subsequent worsening of disability in relapsing-remitting multiple sclerosis

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Abstract:
Objective: To investigate whether relapses contribute to the development of subsequent sustained increase of impairment and disability in patients with multiple sclerosis (MS).

Methods: In a random sampled subset of 256 relapsing-remitting MS (RRMS) patients from the placebo arms of 20 randomized, controlled clinical trials contained in the Sylvia Lawry Centre for MS Research (SLCMSR) open database (mean follow-up time 2.66 years), the authors tested whether time to an increase of the Expanded Disability Status Scale (EDSS) score (confirmed after 6 months) was related to the occurrence of prior relapses. In the primary analysis, EDSS progressions starting within the period used to calculate the on-study relapse rate (sacrifice period) were not counted. The result obtained was then validated in an independent validation part of the SLCMSR database (n = 320).

Results: Although in the first subset of 256 RRMS patients, occurrence of relapses in the first 4 months on study appeared to be the best predictor for a shorter time to subsequent sustained increase in the EDSS score (hazard ratio [HR] 2.26 [95% CI: 1.36 to 3.75]), this finding was not confirmed in the validation dataset (HR 1.35, one-sided Wald test, lower limit of the 95% CI: 0.90).

Conclusion: Although relapses may result into permanent damage and Expanded Disability Status Scale (EDSS) progression, there is no consistent effect of on-study relapses on the subsequent development of sustained EDSS score increase during a typical clinical study observation period.

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AIDS 31, 1664–1666, 2007 IF 5,6

Increased Epstein-Barr virus-specific antibody-levels in HIV-infected individuals developing primary central nervous system lymphoma

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Research Letter:
To Primary central nervous system (PCNS)-lymphoma is an Epstein–Barr virus (EBV)-associated opportunistic malignancy of HIV-infected persons. HIV-infected individuals progressing to PCNS-lymphoma were recently found to lack EBV-specific CD4+ T cells irrespective of their absolute $CD4^+$ T cell counts. Here, we tested the hypothesis that lack of $CD4^+$ T cell-help for EBV-specific B cells impacts on EBV-specific antibody production, translating into changes in the humoral immuneresponse.

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Molecular Cancer Therapeutics 6, 773–781, 2007 IF 5,1

Combination of sublethal concentrations of epidermal growth factor receptor inhibitor and microtubule stabilizer induces apoptosis of glioblastoma cells

M. Failly, S. Korur, V. Egler, J. L. Boulay, M. M Lino, R. Imber and A. Merlo

Abstract:
The oncogenic epidermal growth factor receptor (EGFR) pathway triggers downstream phosphatidylinositol 3-kinase (PI3K)/RAS-mediated signaling cascades. In transgenic mice, glioblastoma cannot develop on single but only on simultaneous activation of the EGFR signaling mediators RAS and AKT. However, complete blockade of EGFR activation does not result in apoptosis in human glioblastoma cells, suggesting additional cross-talk between downstream pathways. Based on these observations, we investigated combination therapies using protein kinase inhibitors against EGFR, platelet-derived growth factor receptor, and mammalian target of rapamycin, assessing glioblastoma cell survival. Clinically relevant doses of AEE788, Gleevec (imatinib), and RAD001 (everolimus), alone or in combinations, did not induce glioblastoma cell apoptosis. In contrast, simultaneous inactivation of the EGFR downstream targets mitogen-activated protein/extracellular signal-regulated kinase (ERK) kinase and PI3K by U0126 and wortmannin triggered rapid tumor cell death. Blocking EGFR with AEE788 in combination with sublethal concentrations of the microtubule stabilizer patupilone also induced apoptosis and reduced cell proliferation in glioblastoma cells, accompanied by reduced AKT and ERK activity. These data underline the critical role of the PI3K/AKT and the RAS/RAF/mitogen-activated protein/ERK kinase/ERK signaling cascades in the cell-intrinsic survival program of sensitive glioblastoma cell lines. We conclude that drug combinations, which down-regulate both ERK and protein kinase B/AKT activity, may prove effective in overcoming cell resistance in a subgroup of glioblastoma.

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International Journal of Cancer | 120, 337–343, 2006 | IF 4,7

Cancer/testis antigen expression and specific cytotoxic T lymphocyte responses in non small cell lung cancer

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Abstract:
Non small cell lung cancers (NSCLC) express cancer/testis antigens (CTA) genes and MAGE-A expression correlates with poor prognosis in squamous cell carcinomas. We addressed cytotoxic T lymphocytes (CTL) responses to HLA class I restricted CTA epitopes in TIL from NSCLC in an unselected group of 33 patients consecutively undergoing surgery. Expression of MAGE-A1, -A2, -A3, -A4, -A10, -A12 and NY-ESO-1 CTA genes was tested by quantitative RT-PCR. Monoclonal antibodies (MAb) recognizing MAGE-A and NY-ESO-1 CTA were used to detect CTA by immunohistochemistry. $CD8^+$ TIL obtained from tumors upon culture with anti CD3 and anti CD28 mAb and IL-2 were stimulated with autologous mature DC (mDC) and HLA-A*0101 restricted MAGE-$A_{1161\text{-}169}$ or MAGE-$A3_{168\text{-}176}$ peptides or HLA-A*0201 restricted MAGE-$A4_{230\text{-}239}$, MAGE-$A10_{254\text{-}262}$, NY-ESO-$1_{157\text{-}165}$ or multi-MAGE-A (YLEYRQVPV) peptides or a recombinant vaccinia virus (rVV) encoding MAGE-A and NY-ESO-1 HLA-A*0201 restricted epitopes and CD80 co-stimulatory molecule. Specificity was assessed by 51Cr release and multimer staining. At least one CTA gene was expressed in tumors from 15/33 patients. In 10 specimens, at least 4 CTA genes were concomitantly expressed. These data were largely confirmed by immunohistochemistry. TIL were expanded from 26/33 specimens and CTA-specific CTL activity was detectable in 7/26 TIL. In 6, however, specific cytotoxicity was weak, (<40% lysis at a 50:1 E:T ratio) and multimer staining was undetectable. In one case, high (>60% lysis at 50:1 E:T ratio) MAGE-$A10_{254\text{-}262}$ specific, HLA-A*0201 restricted response was observed. Supportive evidence was provided by corresponding multimer staining. Although CTA genes are frequently expressed in NSCLC, detection of CTL reactivity against CTA epitopes in TIL from nonimmunized NSCLC patients represents a rare event.

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Neurobiology of Disease | 25, 473–482, 2007 | IF 4,1

Osteopontin is elevated in Parkinson's disease and its absence leads to reduced neurodegeneration in the MPTP model

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Abstract:
In the pathogenesis of Parkinson's disease (PD), oxidative and nitrosative stress, apoptosis, mitochondrial dysfunction, and excitotoxicity are involved, i.e., processes in which osteopontin (OPN) may also play a role. We have studied in PD patients serum and cerebrospinal fluid (CSF) concentrations of OPN, its immunohistochemical presence in substantia nigra (SN) and tested in OPN-null mice the impact of this protein on MPTP-induced neurodegeneration. PD was accompanied by increased OPN levels in the body fluids. Higher serum levels were associated with more severe motor symptoms. CSF levels were positively associated with concomitant dementia and negatively associated with dopaminergic treatment. In human SN, OPN was expressed in neurons, in their Lewy bodies and in microglia. Loss of tyrosine-hydroxylase-positive cells in the SN and of dopaminergic fibers in the striatum was reduced 3 weeks after MPTP intoxication in OPN-null mice. These data suggest that OPN is involved in PD-associated neurodegeneration

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ELECTROPHORESIS ELECTROPHORESIS 28, 1508–1513, 2007 IF 4,1

SDS disc electrophoresis of proteins in homogeneous, low-concentrated polyacrylamide gels

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Abstract:
In the attempt to separate in a single gel run low- and high-molecular-weight proteins, we present here a multiphasic buffer system designed for this purpose. It avoids the continuous stacking of SDS as it occurs in the classical' SDS-PAGE. The system allows complete stacking and destacking of proteins in the 3.5-250 kDa range at acrylamide concentrations as low as 4.5% T (total acrylamide concentration in %) and 2.6% C (degree of cross-linking in %). Taurine is used as the trailing ion in the cathode buffer and in the resolving zone of the gel, and two different counterions (Tris and imidazole) in the stacking zone. The gel system is easy to prepare and, due to the very low acrylamide concentrations, it is ideal for analytical as well as for preparative tasks.

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ELECTROPHORESIS ELECTROPHORESIS 27, 3889–3896, 2006 IF 4,1

Genotyping fetal paternally inherited SNPs by MALDI-TOF MS using cell-free fetal DNA in maternal plasma: Influence of size fractionation

Y. Li[1], F. Wenzel[2], W. Holzgreve[1], S. Hahn[1]

Abstract:
The determination of fetal point mutations from fetal cell-free DNA (cf-DNA) in maternal plasma is technically challenging due to the preponderance of maternal sequences. It has recently been shown that fetal cf-DNA sequences are smaller than maternal ones and that the selection of small cf-DNA fragments by size fractionation by agarose gel electrophoresis leads to the enrichment of fetal cf-DNA sequences, thereby permitting the detection of otherwise masked fetal point mutations. In a separate development, the use of MALDI-TOF MS has also been shown to facilitate the detection of fetal point mutations from cf-DNA in maternal plasma. In this study, a combination of these approaches was examined. cf-DNA was extracted from 18 maternal plasma samples, 10 taken at term and 8 obtained early in the second trimester. A total of 41 SNP loci were examined in size-fractionated and total cf-DNA using either a conventional homogeneous MassEXTEND® (hME) assay or a nucleotide-specific single allele base extension reaction (SABER) assay. The analysis of total cf-DNA indicated that size fractionation considerably enhanced the sensitivity of the standard hME assay, especially for samples taken early in pregnancy. Size fractionation also rendered the signals obtained by the SABER assay more precise.

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Rheumatology RHEUMATOLOGY 46, 403–408, 2007 IF 4,1

Bone marrow mesenchymal stromal cells (BM-MSCs) from healthy donors and auto-immune disease patients reduce the proliferation of autologous- and allogeneic-stimulated lymphocytes *in vitro*

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Abstract:

Objectives: To investigate the ability of bone marrow (BM)-derived mesenchymal stromal cells (BM-MSCs) in suppressing the proliferation of stimulated lymphocytes across a range of conditions including autologous BM-MSCs derived from autoimmune disease (AD) patients.

Methods: In vitro cultures of BM-MSCs from healthy donors and AD patients were established and characterized by their differentiation potential into adipocytes and osteoblasts, and their fibroblast-colony-forming unit (CFU-F) ability and phenotype by flow cytometry.
BM-MSCs (irradiated and non-irradiated) from healthy and AD patients were tested for their ability to suppress the in vitro proliferation of autologous and allogeneic peripheral blood mononuclear cells (PBMC) (from healthy donors and patients suffering from various ADs) stimulated with anti-CD3 antibody alone or in combination with anti-CD28 antibody. The anti-proliferative effect of the BM-MSCs from healthy donors was tested also on transformed B-cell lines as a model of non-antigen-stimulated lymphocytes.

Results: BM-MSCs from healthy donors and AD patients reduced the proliferation of autologous and allogeneic PBMCs by up to 90% in a cell dose-dependent fashion. The immunosuppression was independent of the proliferation of the BM-MSCs and was also effective on already proliferating cells. It was independent also of the clinical activity of AD.
An MSC dose-dependent pattern of suppression of proliferation was observed also with transformed B-cell lines, similar to that observed with proliferating PBMC.

Conclusions: The BM-MSCs exhibit extensive anti-proliferative properties against lymphocytes under different conditions. This property might offer a form of immunomodulatory cellular therapy for AD patients if further confirmed in animal models.

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Osteoarthritis and Cartilage Osteoarthritis and Cartilage 15, 48–58, 2007 IF 4,0

Differential cartilaginous tissue formation by human synovial membrane, fat pad, meniscus cells and articular chondrocytes

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Abstract:

Objective: To identify an appropriate cell source for the generation of meniscus substitutes, among those which would be available by arthroscopy of injured knee joints.

Methods: Human inner meniscus cells, fat pad cells (FPC), synovial membrane cells (SMC) and articular chondrocytes (AC) were expanded with or without specific growth factors (Transforming growth factor-beta1, Fibroblast growth factor-2 and Platelet-derived growth factor bb, TFP) and then induced to form three-dimensional cartilaginous tissues in pellet cultures, or using a hyaluronan-based scaffold (Hyaff®-11), in culture or in nude mice. Human native menisci were assessed as reference.

Results Cell expansion with TFP enhanced glycosaminoglycan (GAG) deposition by all cell types (up to 4.1-fold) and messenger RNA expression of collagen type II by FPC and SMC (up to 472-fold) following pellet culture. In all models, tissues generated by AC contained the highest fractions of GAG (up to 1.9% of wet weight) and were positively stained for collagen type II (specific of the inner avascular region of meniscus), type IV (mainly present in the outer vascularized region of meniscus) and types I, III and VI (common to both meniscus regions). Instead, inner meniscus, FPC and SMC developed tissues containing negligible GAG and no detectable collagen type II protein. Tissues generated by AC remained biochemically and phenotypically stable upon ectopic implantation.

Conclusions: Under our experimental conditions, only AC generated tissues containing relevant amounts of GAG and with cell phenotypes compatible with those of the inner and outer meniscus regions. Instead, the other investigated cell sources formed tissues resembling only the outer region of meniscus. It remains to be determined whether grafts based on AC will have the ability to reach the complex structural and functional organization typical of meniscus tissue.

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Experimental Cell Research | Experimental Cell Research | 313, 1024–1032, 2007 | IF 3,8

Human mature erythroblasts are resistant to apoptosis

S. Hristoskova, W. Holzgreve, S. Hahn and C. Rusterholz

Abstract:
Apoptosis plays an important role in red blood cell development, notably by regulating the fate of early erythroid progenitors. We show here that, by contrast, mature erythroblasts are resistant to apoptosis. Treatment of these cells with several apoptosis-inducing agents failed to trigger caspase activation and oligonucleosomal DNA fragmentation. Interestingly, we find that cytochrome c levels are dramatically reduced even though the cells contain mitochondria. Supplementation of cytosolic extracts from mature erythroblasts with cytochrome c, however, did not rescue caspase activation. This was not due to the presence of inhibitors of apoptosis, as these proteins were also missing in these cells. We also show that cytochrome c depletion is a normal event during erythroblast differentiation, which follows transient, developmentally induced caspase activation and correlates with the loss of response to cytokine withdrawal or drug-induced apoptosis. Our data therefore suggest that erythroblasts acquire resistance to apoptosis during maturation through the developmentally induced depletion of cytochrome c and other crucial regulators of the apoptotic machinery.

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Journal of Cellular Physiology | Cellular Physiology | 210, 167–176, 2006 | IF 3,6

Opposite effect of corticosteroids and long-acting 2-agonists on serum- and TGF-1-induced extracellular matrix deposition by primary human lung fibroblasts

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Abstract:
Asthma and chronic obstructive pulmonary disease (COPD) are characterized by chronic airway inflammation and major structural lung tissue changes including increased extracellular matrix (ECM) deposition. Inhaled corticosteroids and long-acting β_2-agonists (LABA) are the basic treatment for both diseases, but their effect on airway remodeling remains unclear. In this study, we investigated the effect of corticosteroids and LABA, alone or in combination, on total ECM and collagen deposition, gene expression, cell proliferation, and IL-6, IL-8, and TGF-β_1 levels by primary human lung fibroblasts. In our model, fibroblasts in 0.3% albumin represented a non-inflammatory condition and stimulation with 5% FCS and/or TGF-β_1 mimicked an inflammatory environment with activation of tissue repair. FCS (5%) increased total ECM, collagen deposition, cell proliferation, and IL-6, IL-8, and TGF-β_1 levels. In 0.3% albumin, corticosteroids reduced total ECM and collagen deposition, involving the glucocorticoid receptor (GR) and downregulation of collagen, heat shock protein 47 (Hsp47), and Fli1 mRNA expression. In 5% FCS, corticosteroids increased ECM deposition, involving upregulation of COL4A1 and CTGF mRNA expression. LABA reduced total ECM and collagen deposition under all conditions partly via the β_2-adrenergic receptor. In combination, the drugs had an additive effect in the presence or absence of TGF-β_1 further decreasing ECM deposition in 0.3% albumin whereas counteracting each other in 5% FCS. These data suggest that the effect of corticosteroids, but not of LABA, on ECM deposition by fibroblasts is altered by serum. These findings imply that as soon as airway inflammation is resolved, long-term treatment with combined drugs may beneficially reduce pathological tissue remodeling.

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OBESITY obesity 15, 40–49, 2007 IF 3,5

Expression and Localization of Melanocortin-1 Receptor in Human Adipose Tissues of Severely Obese Patients

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Abstract:

Objective: The melanocortin system is a key regulator in the hypothalamus of energy intake and expenditure. It is frequently linked with obesity and apparently modulates sympathetic outflow to white adipose tissues. The role of the melanocortins within adipose tissues, however, is not entirely clear. This study was aimed at determining the quantitative expression of the five melanocortin receptors (MC1-R to MC5-R) in subcutaneous and omental fat of obese patients and non-obese subjects.

Research Methods and Procedures: Expression of MC1-R to MC5-R, proopiomelanocortin, agouti signaling protein, leptin, leptin receptor, and uncoupling protein-1 was investigated in human fat samples by quantitative reverse transcription-polymerase chain reaction. MC1-R expression was also studied in preadipocytes, adipocytes, and monocytic THP-1 cells and by immunohistochemical localization in adipose tissues.

Results: Notable expression was found for MC1-R, whereas no mRNA for MC2-R and MC3-R was detected; MC4-R and MC5-R mRNA was occasionally detectable but at very low levels. MC1-R mRNA in subcutaneous fat was increased in obese patients as compared with controls; omental fat of both groups had slightly higher MC1-R expression than subcutaneous fat and did not differ between patient groups. Immunohistochemical analysis of the MC1-R in adipose tissue sections showed that MC1-R expression was higher in macrophages but also present in adipocytes.

Discussion: The expression of MC1-R and the lack of MC2-R in human adipose tissues indicate that the melanocortins may regulate cell proliferation and/or inflammatory signals rather than lipolysis. Also, the increased expression of MC1-R in subcutaneous fat of obese subjects may reflect one aspect of the pathophysiology of obesity.

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Multiple Sclerosis Multiple Sclerosis 12, 738–746, 2006 IF 2,8

Qualitative and quantitative analysis of antibody response against IFNβ in patients with multiple sclerosis.

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Abstract:

To date, inter- and intra-laboratory consistency of binding assays for measuring anti-interferon (IFN)β antibodies has not been assessed. In this investigation, two independent laboratories tested a library of 80 serum specimens obtained from multiple sclerosis (MS) patients treated with IFNβ. For binding antibodies (BAbs) evaluations, each laboratory used both a capture-ELISA (cELISA) and an enzyme-immuno-assay (EIA), which is commercially available. Samples were also tested for neutralizing antibodies (NAbs). Data demonstrated good intra-laboratory reliability ($r_{pearson} \geq 0.86$), and a good overall agreement between the results obtained from the two centers, using both the cELISA (69/80 of observed agreements) and the EIA (67/80). Accordingly, kappa coefficients (K) showed good concurrence ($K \geq 0.651$). There was also substantial agreement between cELISA and EIA measurements, as performed in both centers (Orbassano, 66/80, $K = 0.631$; Basel, 70/80, $K = 0.717$). However, by comparing NAbs and BAbs titers obtained with both assays, we found that a high degree of BAb-negative samples were positive in NAb-assay. Thus, our study does not support the usefulness of ELISA-based BAb assays as a screening tool for NAbs. Otherwise, BAb-assays can be used as a confirmation test, indicating that the decrease of the biological effects is due to antibodies. In this context, both ELISA-based assays are equally reliable techniques.

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Rapid Communication in Mass Spectometry | Rapid Communications in Mass Spectrometry | 21, 1531–1540, 2007 | IF 2,7

Determination of midazolam and its hydroxy metabolites in human plasma and oral fluid by liquid chromatography/electrospray ionization ion trap tandem mass spectrometry

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Abstract:
Midazolam (MDZ), a short-acting benzodiazepine, is a widely accepted probe drug for CYP3A phenotyping. Published methods for its analysis have used either therapeutic doses of MDZ, or, if employing lower doses, were mostly unable to quantify the two hydroxy metabolites. In the present study, a sensitive and specific liquid chromatography/electrospray ionization tandem mass spectrometry method was developed and validated for the quantitative determination of MDZ and two of its metabolites (1'-hydroxymidazolam (1'-OHMDZ) and 4-hydroxymidazolam (4-OHMDZ)) in human plasma and oral fluid. After liquid-liquid extraction with hexane/dichloromethane (73:27, v/v), the analytes were separated on a Luna C18(2) (100 × 2.1 mm) analytical column using gradient elution. Detection was achieved using tandem mass spectrometry on an ion trap mass spectrometer. Midazolam-d_6 was used as internal standard for quantification. The calibration curves were linear (R^2 >0.998) between 0.05 and 20 ng/mL for MDZ and both metabolites in both matrices. Using 1 mL samples, the limit of detection was 0.025 ng/mL and the limit of quantification was 0.05 ng/mL for MDZ and the hydroxy metabolites in both matrices. Intra- and inter-day accuracies, determined at three different concentrations, were between 92.1 and 102.3% and the corresponding coefficients of variation were <7.3%. The average recoveries were 90.6%, 86.7% and 79.0% for MDZ, 1'-OHMDZ and 4-OHMDZ in plasma and 95.3%, 96.6% and 86.8% for MDZ, 1'-OHMDZ and 4-OHMDZ, respectively, in oral fluid. The method was successfully applied to a pharmacokinetic study, showing that MDZ and its hydroxy metabolites can be determined precisely in in vivo samples obtained following a single oral or intravenous dose of 2 mg MDZ. The method appears to be useful for CYP3A phenotyping in plasma using sub-therapeutic MDZ doses, but larger studies are needed to test this assumption

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Journal of Chromatography B | 847, 205–207, 2007 | IF 2,6

Direct determination of valproic acid in biological fluids by capillary electrophoresis with contactless conductivity detection

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Abstract:
Capacitively coupled contactless conductivity detection (C^4D) is a new technique providing high sensitivity in capillary electrophoresis (CE) especially for small ions that can otherwise only be determined with indirect methods. In this work, direct determination and validation of valproic acid (VPA) in biological fluids was achieved using CE with C^4D. VPA is of pharmacological interest because of its use in epilepsy and bipolar disorder. The running electrolyte solution used consisted of 10 mM 2-(*N*-morpholino)ethane sulfonic acid (MES)/DL-histidine (His) and 50 μM hexadecyltrimethylammonium bromide (HTAB) at pH 6.0. Caproic acid (CA) was selected as internal standard (IS). Analyses of VPA in serum, plasma and urine samples were performed in less than 3 min. The interference of the sample matrix was reduced by deproteinization of the sample with acetonitrile (ACN). The effect of the solvent type and ratio on interference was investigated. The limits of detection (LOD) and quantitation (LOQ) of VPA in plasma samples were determined as 24 and 80 ng/ml, respectively. The method is linear between the 2 and 150 μg/ml, covering well the therapeutic range of VPA (50–100 μg/ml).

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Leukemia Research | Leukemia Research | 31, 1393–1402, 2007 | IF 2,5

Differentiation-promoting drugs up-regulate NKG2D ligand expression and enhance the susceptibility of acute myeloid leukemia cells to natural killer cell-mediated lysis

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Abstract:
Natural killer (NK) cells are potent effectors of innate antitumor defense and are currently exploited for immune-based therapy of human leukemia. However, malignant blood cells in acute myeloid leukemia (AML) display low levels of ligands for the activating immunoreceptor NKG2D and can thus evade NK immunosurveillance. We examined the possibility of up-regulating NKG2D-specific UL16-binding protein (ULBP) ligands using anti-neoplastic compounds with myeloid differentiation potential. Combinations of 5-aza-2′-deoxycytidine, trichostatin A, vitamin D3, bryostatin-1, and all-*trans*-retinoic acid, used together with myeloid growth factors and interferon-γ, increased cell surface ULBP expression up to 10-fold in the AML cell line HL60 and in primary AML blasts. Up-regulation of ULBP ligands was associated with induction of myelomonocytic differentiation of AML cells. Higher ULBP expression increased NKG2D-dependent sensitivity of HL60 cells to NK-mediated killing. These findings identify NKG2D ligands as targets of leukemia differentiation therapy and suggest a clinical benefit in combining a pharmacological approach with NK cell-based immunotherapy in AML.

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Journal of Immunological Methods | Journal of Immunological Methods | 321, 196–199, 2007 | IF 2,4

Investigation of alloreactive NK cells in mixed lymphocyte reactions using paraformaldehyde-silenced target cells

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Abstract:
Mixed lymphocyte reactions (MLRs) remain central to the characterization of cellular allo-interactions. Here we show that irradiation, as used to 'silence' a given cell-population in unidirectional ('one-way') MLRs, is unable to abolish cytokine-production even at doses much higher than usually applied. By contrast, using target cells silenced via a formaldehyde-based fixation-protocol, we demonstrate feasibility to detect – in a true one-way reaction – secretion of IFNγ by alloreactive NK cells. This simple, fixation-based protocol provides an accurate, robust and time-efficient means for assessing alloreactivity, avoiding cytokine-production by the MLR stimulator cells.

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Journal of Tissue Engineering and Regenerative Medicine 1, 60–65, 2007 IF NA

The osteogenicity of implanted engineered bone constructs is related to the density of clonogenic bone marrow stromal cells

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Abstract:
Reproducible osteogenicity is a key requirement for the clinical use of bone substitutes based on bone marrow stromal cells (BMSCs) and three-dimensional (3D) scaffolds. In this study we addressed whether a minimal cell density is required for ectopic osteogenicity of constructs generated using a recently developed perfusion system for seeding and culturing human BMSCs on 3D scaffolds. Cells from human bone marrow aspirates were directly seeded and expanded for 3 weeks within the pores of ceramic-based scaffolds, using a perfusion bioreactor. The resulting constructs were either implanted subcutaneously in nude mice, to determine their capacity to generate bone tissue, or digested to retrieve the expanded cells and assess their number, phenotype and clonogenic capacity. The final number of BMSCs in the constructs was correlated neither to the initial number of seeded cells, nor to the subsequent bone formation. Instead, the final number of clonogenic BMSCs in the constructs was positively correlated to the initial number of BMSCs seeded, and was significantly higher in osteogenic than in non-osteogenic constructs. These results indicate that clonogenic cells play a crucial role in determining the osteogenicity of engineered bone substitutes. Possible ways to quantify the density of clonogenic cells as a quality control parameter to predict potency of BMSC-based constructs are discussed.

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PLOS One PLoS one 2, e576, 2007 IF NA

Loss of NOTCH2 Positively Predicts Survival in Subgroups of Human Glial Brain Tumors

J.-L. Boulay[1], A. R. Miserez[2], C. Zweifel[1,3], B. Sivasankaran[1], V. Kana[1], A. Ghaffari[1,3], C. Luyken[4], M. Sabel[4], A. Zerrouqi[5], M. Wasner[3], E. Van Meir[5], M. Tolnay[6], G. Reifenberger[4], A. Merlo[1,3]

Abstract:
StreptThe structural complexity of chromosome 1p centromeric region has been an obstacle for fine mapping of tumor suppressor genes in this area. Loss of heterozygosity (LOH) on chromosome 1p is associated with the longer survival of oligodendroglioma (OD) patients. To test the clinical relevance of 1p loss in glioblastomas (GBM) patients and identifiy the underlying tumor suppressor locus, we constructed a somatic deletion map on chromosome 1p in 26 OG and 118 GBM. Deletion hotspots at 4 microsatellite markers located at 1p36.3, 1p36.1, 1p22 and 1p11 defined 10 distinct haplotypes that were related to patient survival. We found that loss of 1p centromeric marker D1S2696 within NOTCH2 intron 12 was associated with favorable prognosis in OD (P = 0.0007) as well as in GBM (P = 0.0175), while 19q loss, concomitant with 1p LOH in OD, had no influence on GBM survival (P = 0.918). Assessment of the intra-chromosomal ratio between *NOTCH2* and its 1q21 pericentric duplication *N2N* (N2/N2N-test) allowed delineation of a consistent centromeric breakpoint in OD that also contained a minimally lost area in GBM. OD and GBM showed distinct deletion patterns that converged to the *NOTCH2* gene in both glioma subtypes. Moreover, the N2/N2N-test disclosed homozygous deletions of NOTCH2 in primary OD. The N2/N2N test distinguished OD from GBM with a specificity of 100% and a sensitivity of 97%. Combined assessment of *NOTCH2* genetic markers D1S2696 and N2/N2N predicted 24-month survival with an accuracy (0.925) that is equivalent to histological classification combined with the D1S2696 status (0.954) and higher than current genetic evaluation by 1p/19q LOH (0.762). Our data propose *NOTCH2* as a powerful new molecular test to detect prognostically favorable gliomas.

[1] Laboratory of Molecular Neuro-Oncology, Department of Research, University Hospital, Basel, Switzerland
[2] Research Laboratories, Diagene Inc., Reinach, Switzerland
[3] Neurosurgical Clinic, University Hospital, Basel, Switzerland
[4] Departments of Neuropathology, and Neurosurgery, Heinrich-Heine-University, Düsseldorf, Germany
[5] Laboratory of Molecular Neuro-Oncology, Department of Neurosurgery, Emory University, Atlanta, Georgia, United States of America
[6] Institute of Pathology, University Hospital, Basel, Switzerland

Basilisken-Brunnen

In den 1880er Jahren wurde ein Wettbewerb ausgeschrieben, der den erfolgreichen Basilisken-Brunnen von Wilhelm Bubeck als Sieger hervorbrachte. Der Basilisk ist aus Bronze und der Rest aus Gusseisen hergestellt. Das Wasser strömt aus dem Maul des Basilisken in das runde Becken, das an der Aussenseite mit diversen Mustern verziert ist. Der Stockfuss ist urnenförmig und unten ist sogar ein Schälchen für Hunde angebracht worden. Heute gibt es 28 Basilisken-Brunnen, die auf öffentlichem Grund stehen und noch einige weitere auf Privatarealen.

Diverse Standorte:
Totentanz / Seite St. Johanns-Vorstadt
Gerbergasse / Rüdengasse
Schaffhauserrheinweg / Fischerweg

Dissertationen

Am 20. März 2007 hat **Bettina Flück** von der Forschungsgruppe Neurobiology (Departement Biomedizin USB) erfolgreich ihre Dissertation verteidigt. Der Titel ihrer Doktorarbeit lautete: «Particular aspects of myelin-axon interaction in health and disease».

Am 26. April 2007 hat sich **Erwin Kump** von der Forschungsgruppe Experimental Immunology (Institut für Medizinische Mikrobiologie) erfolgreich dem Dissertationskomitee präsentiert. Das Thema seiner Doktorarbeit lautete: „Apoptosis im Basalzellkarzinom".

René Marty von der Forschungsgruppe Experimental Critical Care Medicine (Departement Biomedizin USB) hat am 9. Mai 2007 seine Dissertationszeit erfolgreich abgeschlossen. Das Thema seiner Doktorarbeit war «Innate Immune Activation In Experimental Autoimmune Myocarditis».

Seit dem 15. Juni 2007 trägt **Nora Mauermann** von der Forschungsgruppe Experimental Critical Care Medicine (Departement Biomedizin USB) den Doktortitel. Sie hat sich in ihrer Dissertation mit dem Forschungsgebiet «The opposing roles of Interferon-γ and IL-17 in inflammation» auseinandergesetzt.

Am 14. Juni 2007 hat sich **Manjunath Joshi** von der Forschungsgruppe Signal Transduction (Departement Biomedizin USB) erfolgreich den Fragen des Dissertationskomitees gestellt. Er hat sich in seiner Dissertation mit «T-cadherin signaling in endothelial cells» beschäftigt.

Gao Shuping von der Forschungsgruppe Gynecological Endocrinology (Departement Biomedizin USB) hat seine Doktorarbeit dem Thema «The cloning of hBOK, Bcl2L12 and ADAMTS16 and the functional research into their regulation in physiology of the ovary and other reproductive tissues» gewidmet. Er hat seine Doktorandenzeit mit einer erfolgreichen Dissertationprüfung am 27. Juni 2007 abgeschlossen.

Seit dem 29. Juni 2007 darf sich auch **Marco Petrimpol** von der Forschungsgruppe Vascular Biology (Departement Biomedizin USB) Herr Dr. nennen. Er hat sich in seiner Dissertation mit dem Thema «Hypoxia-Induced Signaling in Angiogenesis. Role of mTOR, HIF and Angiotensin II» befasst.

Magdalena Kistowska von der Forschungsgruppe Experimental Immunology (Departement Biomedizin USB) ist am 3. Dezember 2007 mit Erfolg vor das Dissertationskomitee getreten. Sie hat ihre Doktorarbeit dem Forschungsgegenstand «Antigen recognition and thymic maturation of human TCR Vgamma9-Vdelta2 cells» gewidmet.

Herzlichen Glückwunsch an alle!

Habilitationen

An der Medizinischen Fakultät haben sich habilitiert: **Dr. Christian Kalberer** von der Forschungsgruppe Experimental Hematology (Departement Biomedizin USB) für Experimentelle Hämatologie,

Dr. Werner Krenger von der Forschungsgruppe Pediatric Immunology (Institut für Biochemie und Genetik UKBB) für Molekulare Medizin, speziell Immunologie.

SNF-Förderprofessur für Christoph Hess

PD Dr. Christoph Hess von der Forschungsgruppe Immunobiology (Departement Biomedizin USB) hat per 1. April 2007 eine SNF-Förderprofessur im Bereich Innere Medizin/Immunologie erhalten.

Herzlichen Glückwunsch!

Preise

JTGGA 2006 Award an Xaio Yan Zhong

Frau PD Dr. Xiao Yan Zhong von der Forschungsgruppe Prenatal Medicine and Gynecological Oncology (Departement Biomedizin USB) hat den Research Award 2006 des Journal of the Turkish German Gynecological Association gewonnen. Der Preis ist mit 10 000 Euro dotiert und wurde Xiao Yan Zhong auf dem siebten Internationalen Kongress der Deutsch-türkischen gynäkologischen Gesellschaft am 16. Mai 2007 für ihre Studie „Large scale analysis of circulatory fetal DNA concentrations in pregnancies which subsequently develop preeclampsia using two Y chromosome real-time PCR assays; JTGGA-19480" überreicht.

Zweiter Preis der SSPT an Katerina Novakova

Frau Dr. Katerina Novakova von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin USB) hat für ihr Poster «PGC-1a and MEF2 regulate the transcription of the organic cation and carnitine transporter OCTN2» den zweiten Preis der Schweizer Gesellschaft für Pharmakologie und Toxikologie erhalten. Der Preis wurde beim SSPT-Meeting Ende September 2007 in Bern an sie übergeben.

Roche Poster Award an Vanessa Baeriswyl und Adrian Zumsteg

Den Roche Poster Award in der Kategorie Silber konnten am Bio Valley Science Day am 23. Oktober 2007 Vanessa Baeriswyl und Adrian Zumsteg von der Forschungsgruppe Tumor Biology (Institut für Biochemie und Genetik) entgegennehmen. Der Award ist mit 1'500 Franken dotiert und wurde den Preisträgern für ihr Poster „Myeloid cells contribute to tumor lymphangiogenesis" verliehen.

Roche Poster Award an Federica Facciotti

Federica Facciotti von der Forschungsgruppe Experimental Immunology (Departement Biomedizin USB) konnte auf dem Bio Valley Science Day am 23. Oktober 2007 einen Roche Poster Award in der Kategorie Bronze entgegennehmen. Die Auszeichnung ist mit 500 Franken dotiert und wurde Federica Facciotti für ihr Poster „CD1e participates in generation of iNKT cell ligands" verliehen.

Pfizer Forschungspreis 2008 an Daniela Finke

Frau Prof. Daniela Finke von der Forschungsgruppe Developmental Immunology hat den Pfizer Forschungspreis 2008 erhalten. Der Preis wird Daniela Finke am 7. Februar 2008 an der ETH Zürich übergeben werden.

Das Departement Biomedizin gratuliert herzlich!

DEPARTEMENT BIOMEDIZIN USB

Oliver Bandschapp
Perioperative Patient Safety

Estelle Hirzel
Endocrinology

Daniela Thommen
Molecular Nephrology

Uta Helmrich
Cell and Gene Therapy

Beatrice Tonnarelli
Tissue Engineering

Rosaria Santoro
Tissue Engineering

Bettina Burger
Dermatology

Andreas Jehle
Molecular Oncology

Vera Lorenz
Myocardial Research

Xiaorong Xin
Ocular Pharmacol. & Physiol.

Frédérique Dubouloz
Cardiobiology

Christoph Berger
Exp. Critical Care Medicine

Simona Rossi
Transplantationimmunology

Pontus Lundberg
Experimental Hematology

Renate Looser
Experimental Hematology

Thomas Walpen
Vascular Biology

Eva Herrero Herranz
Neurobiology

Vera Schwierzeck
Experimental Immunology

Tamara Wenger
Animal Facility

Peter James Mullen
Clinical Pharmacology

INSTITUT FÜR BIOCHEMIE UND GENETIK

Dorothea Maass
Tumor Biology

Lorenz Waldmeier
Tumor Biology

INSTITUT FÜR ANATOMIE

Susanne Drews
Macroanatomy

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE

Klaus-Dieter Molle
Experimental Oncology

Gabriele Huber
Molecular Diagnostics

Ausserdem haben angefangen:

DEPARTEMENT BIOMEDIZIN USB

Andrea Steinhuber, Infect. Diseases
Marc Wolf, Experimental Critical Care Medicine
Nathan Wolfensberger, Experimental Critical Care Medicine
Rahel Bänziger Keel, Experimental Critical Care Medicine
Lea Landolt, Infection Biology
Stephan Moser, Prenatal Medicine
Thomas Peters, Endo nology
Olav Lapaire, Prenatal Medicine
Peter Meyer, Ocular Pharmacology and Physiology
Martin Sailer, Neurooncology
Irina Banzola, Prenatal Medicine
Oliver Sterthaus, Ocular Pharmacology and Physiology

INSTITUT FÜR ANATOMIE

Magdalena Müller-Gerbl, Macroanatomy
Melanie Brito, Animal Facility
Simone Probst, Developmental Genetics
Rosmarie Jucker, Anatomisches Museum
Peter Zimmermann, Zentrale Dienste Lehre

INSTITUT FÜR BIOCHEMIE UND GENETIK

Daniela Müller, Animal Facility
Angelika Jacobs, Molecular Genetics
Stefan Weis, Molecular Genetics
Markus Buschle, Cancer- & Immunobiology
Parthena Fotiadou, Cancer- & Immunobiology
Zoë Alvarado, Human Genetics
Robert Blatter, Human Genetics
Michal Kovac, Human Genetics
Dominique Vanhecke, Developmental and Molecular Immunology

INSTITUT FÜR PHYSIOLOGIE

Nadine Hardel, Synapse Formation
Klara Susankova, Synaptic Plasticity
Rostislav Turecek, Synaptic Plasticity
Xue Gongda, Synapse Formation

Interne Wechsel:

DEPARTEMENT BIOMEDIZIN USB

Emmanuel Traunecker, Flowcytometry

Austritte:

DEPARTEMENT BIOMEDIZIN USB

Maurizio Anselmi, Oncology Surgery
Sreekanth Bandaru, Cell and Gene Therapy
Cuddapah Sunku Chennakesava, Molecular Nephrology
Stefan Diermayr, Experimental Hematology
Mona Ali, Hepatology
Bettina Flück, Neurobiology
Célia Groeper, Oncology Surgery
Antoine Heinis, Proteomics
Matthias Hoch, Endocrinology
Kerstin Wunderlich, Endocrinology
Mihai-Constantin Ionescu, Neurooncology
Andrea Knapp, Clinical Pharmacology
René Marty, Experimental Critical Care Medicine
Nora Mauermann, Experimental Critical Care Medicine
Marco Petrimpol, Vascular Biology
Maurizio Provenzano, Oncology Surgery
Tea Rekviashvili, Prenatal Medicine
Jens Schümann, Experimental Immunology
Dalma Seboek, Metabolism
Vivian Suarez Domenech, Cardiobiology
Sonja Ursic, Infection Biology
Esther Vögtli, Animal Facility
Katri Waldhauser, Clinical Pharmacology
Jingqing Yang, Pneumology
Yi Song, Prenatal Medicine
Pascal Urwyler, Transplantationimmunology

Pensionierung:

Esther Vögtli geht in Pension

Am 30. Juni 2007 ist Esther Vögtli in Pension gegangen. Viele werden Esthi in ihrer fast zwanzigjährigen Tätigkeit in der Tierversuchsstation des Departements Forschung begegnet sein: Mit flottem Rossschwanz, voller Energie und Temperament. An ihrem Arbeitseifer hinderten sie auch ihre permanenten Schulterschmerzen nicht, nach ihrer Teilpensionierung im Alter von sechzig Jahren war es für sie klar, noch mit einem Pensum von 50% bis zum 63. Lebensjahr weiterzumachen, ein Alter, das man ihr absolut nicht ansieht. Jeden Morgen um sieben stand Esthi ihre Frau, zuvor hatte sie bereits ihren Spaziergang mit ihren beiden Hunden hinter sich, ihre Chinchillas, ihr Meerschweinchen und ihr Kaninchen versorgt. Doch was Esthi neben ihrer exakten Arbeitsweise und ihrem Pflichtbewusstsein am meisten auszeichnete, war ihre grenzenlose Tierliebe. Niemals verlor sie die Würde der Tiere in der Versuchsstation aus den Augen. Sie schaute nach jedem Insassen und kümmerte sich. Wenn es einem Tier nicht gut ging, Esthi war da.

Heute widmet Esthi ihre ganze Energie dem Tierfriedhof in Läufelfingen. Wenn es sein muss, rund um die Uhr: Nimmt verstorbene Tiere auf, bereitet ihnen einen würdevollen Abschied und spendet den menschlichen Angehörigen Trost.

Liebe Esthi, wir danken Dir für Dein liebevolles Wirken am Departement Forschung und wünschen Dir für den neuen Lebensschnitt noch lange soviel Energie, weiterhin dieses Dir eigene Temperament und eine gute Gesundheit!

Heidi Hoyermann

Congratulations

Das DBM gratuliert ganz herzlich!

Pimprenelle Schlicklin -Traunecker

Geboren am 13.04.2007

Sascha Kurz mit Schwester Vanessa

Geboren am 9.5.2007

Eliah Ströbel Geboren am 14.05.2007

Amelia Blyszczuk (Kania)
Geboren am 12.8.2007

Samuel Martin (Facompré)
Geboren am 9.9.2007

Lucie Ehret-Juge
Geboren am 20.9.2007

Rebecca Delfini (Braccini)

Geboren am 22.10.2007

Herzlich willkommen, allerseits!

Ein milder Wintertag

**An jenes Waldes Enden,
wo still der Weiher liegt
und längs den Fichtenwänden
sich lind Gemurmel wiegt;**

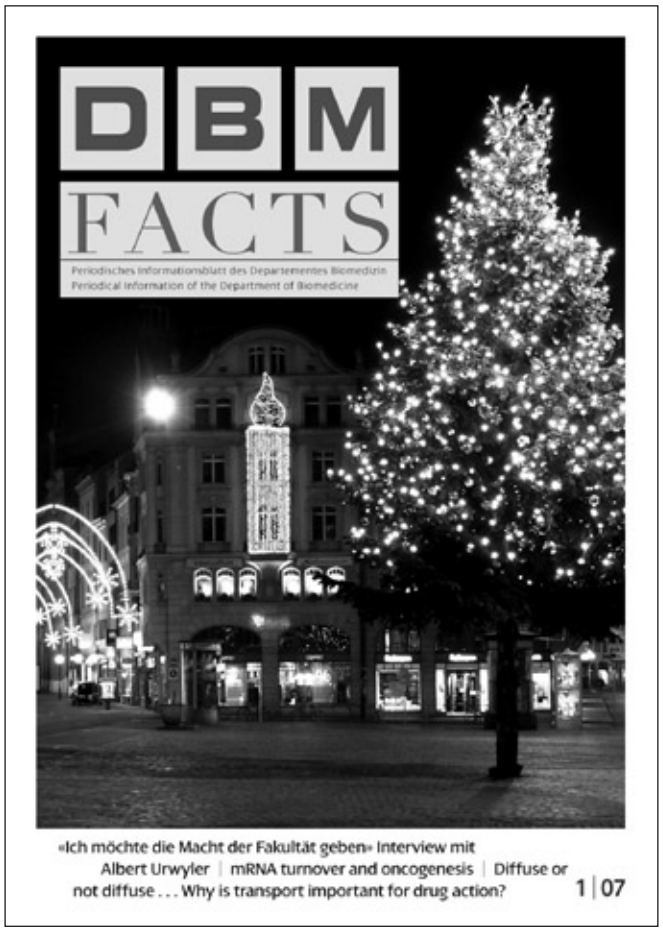
**wo in der Sonnenhelle,
so matt und kalt sie ist,
doch immerfort die Welle
das Ufer flimmernd küsst.**

**Wenn ich den Mantel dichte
nun legen übers Moos,
mich lehnen an die Fichte
und dann auf meinem Schoß.**

**Gezweig' und Kräuter breiten,
so gut ich's finden mag:
Wer will mir's übel deuten,
spiel ich den Sommertag?**

**Und hat Natur zum Feste
nur wenig dargebracht:
Die Luft ist stets die beste,
die man sich selber macht.**

(Annette von Droste-Hülshoff)



Liebe Leserinnen und Leser

Nun liegt sie vor Ihnen. Die erste Ausgabe der DBM Facts. Lange geplant, viel diskutiert, und nun nach bestem Wissen und Gewissen umgesetzt, als Newsletter für alle Institute des Departements Biomedizin Basel. Information und Unterhaltung haben wir uns auf unsere Fahnen geschrieben, auch möge DBM Facts uns alle gegenseitig näher bringen, uns teilhaben lassen am Leben der jeweils anderen Institute. Das eine oder andere mag noch nicht perfekt sein, geben Sie und wir uns ein wenig Zeit, aus der Forschung wissen Sie ja nur zu gut, gut Ding will Weile haben.

Wir wünschen Ihnen viel Freude bei der Lektüre

Ihre DBM Facts Redaktion

Dear Readers

Here it is in front of you - the first edition of the DBM Facts! Long planned, much discussed and now, with the best of our knowledge and belief, implemented as the newsletter for all institutions of the Department of Biomedicine Basel. In addition to its main objective of providing information and entertainment, DBM Facts is intended to draw people closer and facilitate greater participation in the activities of the different institutions. Achievement of the goals is probably not yet perfect, and will take a little while yet. As you all know too well from research, good things do not happen in haste.

We wish you very pleasant reading

Your DBM Facts editors

Die Redaktion stellt sich vor

Name: Heidi Hoyermann-Welinsky
Geboren: 1964 in Köln
Ausbildung: Studium der Soziologie und Politischen Wissenschaften an der Universität Konstanz, daran anschliessend Ausbildung zur Journalistin am Medienausbildungszentrum Luzern (MAZ), später berufsbegleitende Weiterbildung im Bereich Human Resources.
Bisherige Tätigkeiten: Redaktorin (Ressort Politik), freie Journalistin in Sofia/Bulgarien, seit 1997 am Departement Forschung, seit 2001 Personalleiterin des DF, seit 2007 Übernahme diverser zusätzlicher Aufgaben im Personalbereich des Departements Biomedizin Basel.
Aufgaben bei DBM-Facts: Planung und Organisation allgemein, Auswahl und redaktionelle Bearbeitung der Beiträge, Verfassen von eigenen Artikeln und allgemeinen Texten, Schlussredaktion.
Meine Freizeit verbringe ich gerne mit Hund, Mann, Freunden, Familie, politischer Arbeit, Lesen, Schwimmen, Träumen und Nichtstun.

Grüezi, mein Name ist Verena Jäggin. Ich wurde 1952 geboren. Nach einer Ausbildung zur Biomedizinischen Analytikerin HF bin ich seit 1979 am Departement Biomedzin USB tätig, mit sehr vielfältigen Aufgaben: In der Forschungsgruppe Endokrinologie beschäftige ich mich momentan mit Fluoreszenzmikroskopie, im Rahmen meiner Infrastrukturaufgaben für das ganze Institut betreue ich den Facssorter und die Flowzytometrie-Facility. Auch bei der Departementszeitung bin ich von Anfang an mit dabei. Hauptsächlich widme ich mich hier der Planung, dem Layout und der Fotografie. In meiner Freizeit fröne ich am liebsten meinen beiden Passionen Alpinismus und Reisen.

Wenn ich beides miteinander verbinden kann umso besser. Aber auch ein Marathonlauf lässt mein Herz höher schlagen.

Hi, I'm Paula and my job here is to edit the English articles submitted DBM-Facts (and translate the odd German one). I'm Irish, and yes I've got the red hair (from a bottle !) and freckles to prove it ! Mornings you'll find me in the Dept of. Experimental Immunology where I work on project administration. But after that I have any number of interests to keep me more than busy. I trained as a freshwater biologist, and I still do a fair bit of research with my university in Galway. On top of that I have plenty of hobbies that keep me busy. One of my favourites has to be food – there's not much I don't love about it. I like to grow unusual vegetable varieties, purple Brussels sprouts anyone? When I'm not looking after the garden I'm planning ways to use the produce. I adore cooking, I love inventing new dishes, but best of all is cooking for friends. There is nothing like a big get-together over some good food. I think dinner with 41 friends is the most I've done so far ! With all this inventing comes no end of new recipes so every few year myself and some friends get together and write ourselves a cookbook. After all that good food one has to do something to work it off. I like walking, but nothing beats a nice swim, preferably outdoors of course! My other big passion is crafting. I knit, I crochet, and my favourite of all is my sewing. No I don't just mean sewing on some buttons or making up some clothes. I do a lot of cross stitch. Funnily when I tell people that they think, how boring – stitching flowers and vases like my grandmother used to do! Far from it ! I stitch wizards, dragons, angels and fairies, moonlight and snowfall scenes, Christmas designs, Beatrix Potter, Winnie the Pooh and even my own designs: Celtic knots and b&w photos of family mostly. Yup, stitched photos. Far from boring I think ! So that's a little about me. I guess in a nutshell you could sum me up by saying that if you give me some water (river, lake or sea) I'll be happy. I can study it, swim in it, cook from it, and when all else it done, sit by it and stitch !

Mein Name ist Thomas Stebler. Geboren wurde ich 1967 in Basel. Nach meiner Lehre als Schriftsetzer, habe ich mich in verschiedenen Gebieten weitergebildet. Unter anderem als Lehrlingsbetreuer oder auch in der Sachbearbeitung.
Über zwölf Jahre war ich Experte bei den Abschlussprüfungen der Polygrafen.
Kennengelernt habe ich das damalige Departement Forschung, mit den beiden Frauen Heidi Hoyermann und Verena Jäggin, im Frühjahr 2001. Wie heute auch noch, waren meine Tätigkeiten im Layout

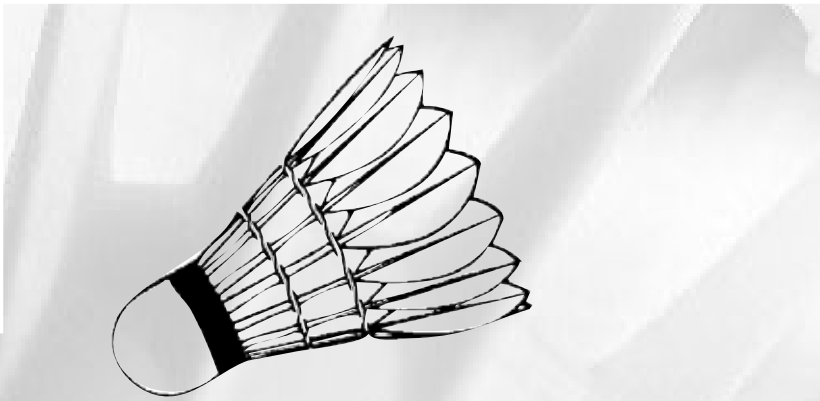
und der Mithilfe in technischen Fragen. Und die gab es anfangs zuhauf.
Ich hoffe, dass die heutige, neue Aufmachung des DBM-Facts Gefallen bei Ihnen findet.
Wenn ich nicht gerade überlegen muss, was ich über mich schreiben soll, ist Trommeln eines meiner grössten Hobbys. Aber auch Kochen für Freunde oder selbst bekocht werden gehören dazu. Für ein gutes Buch oder für süsses Nichtstun bin ich auch zu haben.

1. DF Badminton Open 2007

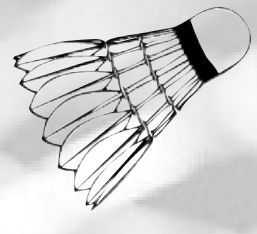
28 members of the Department of Research and guests participated in the first DF Badminton Tournament on Friday November 2nd 2007.

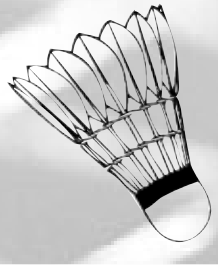
Badminton is an increasingly popular sport in the Basel area. There are more than 300 licensed members playing regularly in 5 clubs and many more recreational players go to the four badminton centers in town. The semi-professional "Team Basel" is one of the best in Switzerland and was second in the 2006/07 championship of the Swiss Badminton League.

Being a badminton player myself for more than 20 years, I realized that there were quite a few people in the DF that shared my hobby. Thus arose the idea of organising a tournament to bring these people together for a fun evening. On Friday November 2nd 2007 18 DF members and 10 guests (mainly from the University Hospital), constituting 14 teams (6 men doubles, 3 women doubles and 5 mixed), met in the Badminton Halle in Oberwil where we had rented all 5 courts for our tournament. Not surprisingly the badminton skills were rather broad: some participants hardly knew the rules and had not played for a long time while others were well trained. But it quickly became evident that everybody played with a lot of enthusiasm.



Pan Dejing, Lab 312, stated: "Everybody enjoyed the atmosphere of the tournament. Personally I was surprised that I did so well." The drawing in each round was done such that teams with the same number of wins played against each other, thus the chance to compete against a team of similar strength increased with each round. The most exciting games, however, occurred when teams of the same lab played against each other. Didi/Evita against Michel/Anja, Gideon/Marek against Stephanie/Pit or Christian/Stefan against Heike/Gabriela were just a few examples of the numerous "lab derbies". F. and R. (full names known to the author) complained with a smile that "it was unfair that not everybody had a beer during the tournament, otherwise we would have had a better chance". After the third round two teams led the ranking with 3 wins. Jakub/Hendrik (a guest team from the university Basel) won in the deciding set against Ulrich and Emmanuel. After the final game the prizes were distributed among the





teams by drawing. Indeed some of the teams which did not do so well could pick Shuttles and Sweets from the Herbstmesse as prize.
As the organizer I would like to thank all the participants for making this event a great success.

Christian Kalberer

Final ranking:

1. Jakub/Hendrik (guests): 4 wins,
2. Ulrich/Emmanuel (310/sorter): 3 wins,
3. Pan/David (310/guest): 2 wins, 5:2 sets.

«Geschenke in letzter Minute»

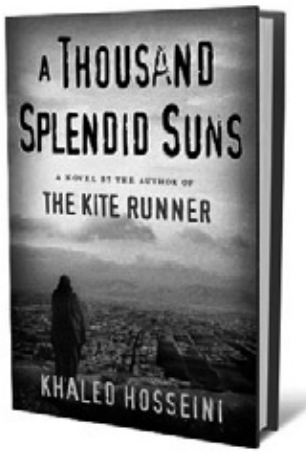
„Last minute presents“

Für alle, die noch keine Zeit hatten oder noch nicht richtig wissen, was sie ihren Lieben zu Weihnachten schenken können, hier eine kleine Auswahl an CD-, DVD- und Bücher-Tipps. Exklusiv empfohlen von Mitarbeitenden des Departements Biomedizin USB.

For all of you who had no time or still no ideas what kind of christmas present you will organize for your loved ones, here a small CD-, DVD-, and book selection exclusively recommended from DBM colleagues.

Oliver Bandschapp recommends : “Back to black” (Amy Winehouse) (CD)

Amy Winehouse “back to black”: my personal favourite for the year. The only problem as a present, it may already be in the CD rack of the person you want to make a present. Otherwise a safe tip. Really cool sound, retro but in the same time very much up to date with it’s beat and piano licks. The tracks written and sung by the artist herself. Incredible Voice. Too good. A must have.



Aleksandra Filipowicz recommends: „A thousand splendid suns“ (book)

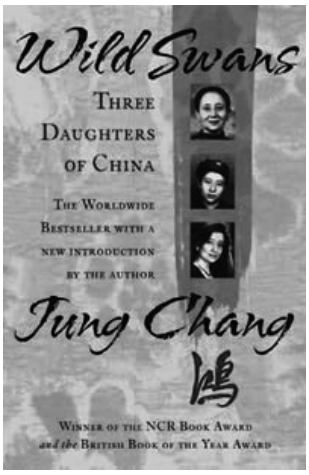
Have you read “The Kite Runner” (Drachenläufer), the novel by Khaled Hosseini? If not, it is a must. Even though the movie by Marc Forster is under way, the soft poetic language and the love of an afghan writer for his country are best to experience directly from the original. After you finished “The Kite Runner” (in 1 and 1/2 days) you will certainly rush to the bookstore and get the Khaled Hosseini’s 2007 book “A thousand splendid suns” (Tausend strahlende Sonnen) and spent 2 days (since thicker) with it. Breathtaking stories, likely authentic, will remain long in your head and contribute to better understanding of the soft and the barbarian sites of the troubled country of Afghanistan.

Corinne Rusterholz recommends: „La Llorana“ and „The Living Road“ (Lhasa) (CD)

Lhasa was born in a family of artists, of a Mexican father and an American mother of Russian Jewish descent. Her first decade was spent criss-crossing the United States and Mexico in a converted school bus with her parents and three sisters. Her two albums, La Llorona and The Living Road, mix traditional South American songs with original songs in spanish, english and french, and are strongly influenced by Mexican music, but also Eastern European gypsy music and alternative rock. Her music is like her, roaming and free. She sings moments of her life, and maybe ours: love, melancholy, passion, sadness. Her songs speak to our soul.

Naja Jann recommends: Crash (german: L.A. Crash) by Paul Haggis (DVD)

„Any real cities you walk, you know, you brush past people, people bump into you. In L.A., nobody touches you. We’re always behind this metal and glass“. Crash is about the collision of cars, the machinery on which L.A. is built. But it’s also about the collision of races, cultures, and classes — another kind of L.A. experience. It begins as it ends, with the discovery of a man’s body sprawled beside a freeway, then winds back 24 hours to the events that led to his death. 12 lives violently crash into each other and from then on nothing happens as we think it will. „It’s the sense of touch. I think we miss that touch so much that we crash into each other so we can feel something.“ Brilliant movie with unexpected and astonishing twists which make you think about your own everyday acting.



Simona Rossi recommends: "White Swans from Jung Chang" (book)

During the long dark winter nights, sitting in front a good cup of tee, the story of 3 generations of Chinese women: grandmother, mother and daughter is going to fascinate you and keep your mind busy thinking. If it wouldn't be a real history I would say that the violence is to exaggerate, that no one can survive such life conditions. I'm horrified. But to describe the book only in this way is absolutely reductive. The beauty, the violence, the culture, the tradition, the force, the commitment and the power of an entire nation is pictured like a huge dark painting with few shy rays of light. I didn't know much about China history and this story touched me because is not only „historical-facts", but is alive and call for attention.If China is a big mystery for you reader, and you always wanted to know more... this book is for you!

Uta Helmrich empfiehlt: «Die Reklamation» (Wir sind Helden) (CD)

Für alle, die sich für Berliner Elektropop begeistern, ist das Album «Die Reklamation» von «Wir sind Helden» genau das Richtige. Mit spritzigen kritischen Texten prägen die vier Musiker einen Musikstil, welcher auch unter dem Namen der «Neuen neuen deutschen Welle» bekannt wurde. Das Album überzeugt mit Titeln wie «Rüssel an Schwanz» oder «Guten Tag».

Gerry Brunner empfiehlt: The Simpsons Movie (DVD)

Nach achtzehn erfolgreichen Jahren im Fernsehen gibt es nun endlich den ersten, langersehnten Kinofilm auf DVD. Für eingefleischte Fans der gelben Familie ein absolutes Muss! Der Film eignet sich jedoch auch für „Neueinsteiger", welche so die Chance erhalten, doch noch zum rechten Glauben zu finden! USA2007 / 87 Minuten

Anne-Kathrin John recommends: Becoming Jane (DVD)

Becoming Jane is a film inspired by the early life of author Jane Austen and her possible flirtation with Thomas Lefroy. Both heading actors had performed a powerful chemistry that made the love story between Jane and Thomas so genuine.When you like the books of Jane Austen you will love this movie.

Andrea Steinhuber empfiehlt: «White Album» (Handsome Hank & His Lonesome Boys) (CD)

Auch wenn Country und Bluegrass sonst nicht euer Ding sind, give your Howdie to Handsome Hank & His Lonesome Boys. Die Band, 1946 in Nashville gegründet und inzwischen nach Basel übergesiedelt, ist und war das heimliche musikalische Vorbild von The Ramones, Robbie Williams und Boney M., was zahlreiche Coverversionen ihrer Songs eindrucksvoll beweisen. Meine Empfehlung speziell zu Weihnachten ist ihr «White Album», doch auch das «Best of» und «Live in Murmansk» sind mein bewährter Geheimtipp gegen eingeschlafene Füsse und hängende Mundwinkel.

Jean-Louis Boulay recommends: «Antoine, La plus belle île du monde» (book)

Where is the most beautiful island in the world? In the West Indies? In Polynesia? In the Mediterranean Sea? In the Indian Ocean? To answer this question, Antoine, a French singer of the sixties decided to retire at the age of 30, to sail over the seas and oceans of the world. His answer is clear: the most beautiful island in the world is the one which appears day after day in front of his sailing boat. A magnificient mix of pictures.

Einstein's Christmas

Do you belong to the 2% of the most intelligent people of the world?

There is no trick to solving this enigma, only pure logic. So: good luck and don't give up!

1. There are five houses of five different colours.
2. In each house lives one of the children.
3. Each child prefers a certain drink, eats a Christmas speciality and holds a certain pet.
4. Not one of the five children drinks the same drink, eats the same speciality or holds the same animal as one of their neighbours.

Illustration: Rok Humar

enigma

The Christmas enigma was adapted from the model of the enigma that was supposedly composed by Einstein. Einstein is said to have stated that 98% of the people in the world could not solve this problem. Have fun!

Little hint: It is easier, if you imagine the houses in a line, even if this is not mentioned.

Colour of the houses: blue, yellow, green, red, white
Names: Friedrich, Max, Maxi, Paul, Pauline
Drinks: Cola, Limo, Milk, Tea, Water
Specialities: Orange, Brezel, Gingerbread, Stollen, Walnuts
Pets: fish, dog, cat, horse, bird

Please send your answer to the DBM Facts editorial: **redaktion-dfacts@unibas.ch** by January 15, 2008. Those with the corrected answer will be entered in a draw to win cinema tickets.

Question: Who keeps the fish?

1. Paul lives in the red house.
2. Maxi keeps a dog.
3. Friedrich drinks tea.
4. The green house is just on the left of the white house.
5. The child in the green house drinks limo.
6. The child, who eats Brezel, keeps a bird.
7. The child, who lives in the house in the middle, drinks milk.
8. The child in the yellow house eats Stollen.
9. Max lives in the first house.
10. The gingerbread-eater lives beside the child with a cat.
11. The child, who keeps a horse, lives beside the child, who eats stollen.
12. The orange-eater drinks cola.
13. Max lives beside the blue house.
14. Pauline eats walnuts.
15. The child who eats gingerbread, has a neighbour, who drinks water.

Die Redaktion von DBM Facts wünscht allen Leserinnen und Lesern schöne Weihnachten und ein gutes neues Jahr!

The Editorial team of DBM Facts wishes all its readers a Merry Christmas and a Happy New Year!


2008